

Research Article

Recurrence of IgA Nephropathy in Protocol Kidney Biopsies After Renal Transplantation and Its Impact on Prognosis

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Abstract

Objectives: IgA nephropathy (IgAN) is a common primary glomerulonephritis with a wide clinical spectrum ranging from asymptomatic urinary abnormalities to rapidly progressive disease and is a major cause of chronic kidney failure. Although kidney transplantation is an effective treatment for primary IgAN, recurrence and graft loss remain significant concerns.

Methods: This study investigated predictors of post-transplant IgAN recurrence and graft loss. Seventy-six patients who underwent kidney transplantation due to end-stage kidney disease secondary to primary IgAN were retrospectively analyzed. First-year protocol biopsy results (6-month and 12-month) were evaluated using light microscopy and immunofluorescence. Baseline demographic, clinical, and laboratory data, along with post-transplant parameters, indication biopsies after the first year, graft loss, and mortality were analyzed.

Results: Binary logistic regression was used to identify predictors of recurrence, and Kaplan–Meier analysis assessed graft survival. Group comparisons were performed using appropriate statistical tests, with $p < 0.05$ considered significant.

Conclusion: Recurrence rates were 9.3% at 6 months and 26.3% at 12 months. Isolated IgA deposition detected by immunofluorescence was common. Age at transplantation was independently associated with recurrence; each additional year reduced risk by 6%. No association was found between recurrence and 10-year graft survival. Younger age was strongly associated with recurrence.

Keywords: Biopsy, IgA nephropathy, kidney transplantation, prognosis, recurrence

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IgA nephropathy (IgAN) is one of the most common primary glomerulonephritides worldwide. The clinical course of IgAN may range from mild disease presenting with asymptomatic hematuria and proteinuria detected during routine screening to severe disease, such as acute rapidly progressive glomerulonephritis.

Previous studies have reported that a considerable propor-

tion of patients with IgAN may progress to kidney failure during long-term follow-up.^[1]

In patients who undergo kidney transplantation, close monitoring of transplant kidney function during follow-up is of great importance. Especially in the first year after transplantation, and subsequently at regular intervals, graft function should be closely monitored for possible allograft rejection,

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recurrence of the native kidney disease, or infections. Even when laboratory values are normal, rejection may be detected in follow-up biopsies (protocol biopsies), and this condition, referred to as subclinical rejection, has been reported to be associated with poorer kidney survival in subsequent years.

In our center, as in many centers worldwide, in addition to indication biopsies (performed for impaired kidney function, active urinary findings, etc.), protocol biopsies are performed in eligible patients to evaluate graft function and adjust treatments accordingly.

In this retrospective study, we aimed to determine the frequency of IgAN recurrence using sequential protocol biopsies in the population of patients who underwent kidney transplantation due to IgAN at a tertiary care center, to identify predictive factors, and to evaluate the clinical course of patients with IgA deposition without clinical evidence of disease.

Materials and Methods

This retrospective, single-center study included 76 patients who had follow-up records at a tertiary care kidney transplant outpatient clinic between June 2000 and June 2019. Pathological results of kidney biopsies were evaluated from retrospective follow-up files.

Sociodemographic characteristics and clinical and laboratory data at the time of transplantation and at the 6-month and 12-month post-transplant follow-up periods were recorded in a case report form, and a database was created. Six-month and 1-year protocol biopsy data were evaluated and entered into the database.

Patients aged ≥ 18 years with primary IgAN who underwent kidney transplantation due to end-stage kidney disease, had a post-transplant follow-up duration of at least 6 months, and had immunofluorescence staining performed in both the 6-month and 1-year protocol biopsies were included in the study. Exclusion criteria were the absence of immunofluorescence staining in protocol biopsies, missing clinical/laboratory data, or initiation of treatment at an external center. Clinical, laboratory, and treatment-related data were obtained from electronic medical records.

Independent variables included recipient age, sex, duration of kidney failure, transplantation type, number of transplantations, degree of tissue matching, donor age, donor sex, donor relationship, post-transplant medications, serum urea and creatinine levels, urinalysis findings, spot urine protein/creatinine ratio, presence of microscopic or macroscopic hematuria, and blood pressure values. Dependent variables were the presence of IgAN recurrence in follow-up kidney biopsies and graft survival.

Statistical Analysis

Binary logistic regression analysis was used to identify variables predicting post-transplant IgA recurrence. Kaplan–Meier analysis was used to determine the relationship between IgA recurrence and graft survival. SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for descriptive statistics and group comparisons. Student's t-test and the Mann–Whitney U test were used for parametric and non-parametric variables, respectively, and the chi-square test was used for categorical variables. A p-value <0.05 was considered statistically significant.

Ethics Approval

Ethical approval was obtained on Ege University Medical Research Ethics Committee January 21, 2021 (decision number: 21-1.1T/57).

This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Patient Characteristics

Data from 76 patients were retrospectively analyzed. The mean age at transplantation was 37.2 ± 9.7 years. Seventy-nine percent of the patients were male. Preemptive transplantation was performed in 45% of cases. Before transplantation, 51% of patients were receiving chronic hemodialysis and 3% were on peritoneal dialysis (Table 1).

The mean duration of dialysis before transplantation was 14.6 ± 29.5 months. Eleven percent of the patients underwent a second kidney transplantation.

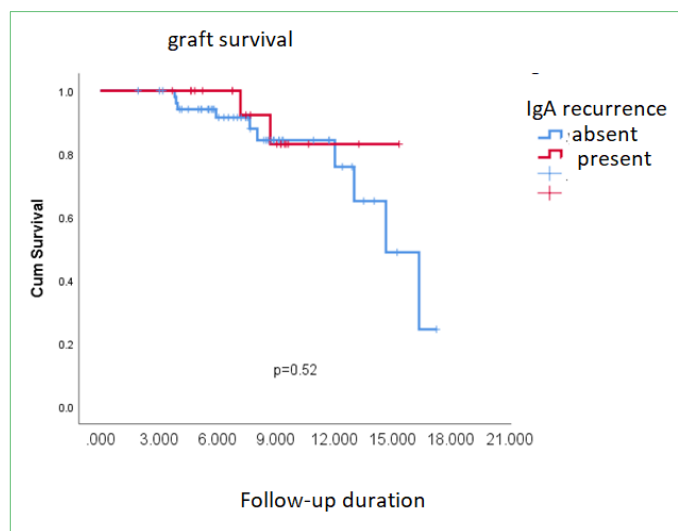


Figure 1. Shows graft survival in patients with and without IgA recurrence detected in the 1-year protocol biopsies.

Table 1. Characteristics of all patients and comparison between patients with and without IgA nephropathy recurrence in 1-year protocol biopsies after transplantation

	Overall group (n=76)	IgA recurrence negative (n=56)	IgA recurrence positive (n=20)	p
Follow-up duration (years)	7.4±2.2	7.2±2.3	7.7±2.1	0.53
Age at transplantation (years)	37.2±9.7	38.5±8.6	33.4±11.2	0.10
Gender (M, %)	79	78	85	0.15
Pre-transplant hemodialysis duration (months)	14.6±29.5	15.5±31.8	13.3±24.2	0.46
Pretransplant RRT modality				
Hemodialysis (%)	51	50	55.0	0.77
Peritoneal dialysis (%)	3	1.9	5.0	
Hemodialysis -Peritoneal dialysis (%)	1	1.9	-	
Preemptive Transplant (%)	45	46.3	40.0	0.61
Number of transplants (%)				
Transplant	89	85	100	0.02
Transplant	11	15	-	
Donor type (%)				
Living Related	63	59.3	80.0	0.05
Living-unrelated	21	20.4	15.0	0.12
Cadaveric	16	20.4	5	0.02
Age at donation (years)	50.1±11.8	51.8±12.0	45.6±11.0	0.46
Donor gender (M, %)	51	50	55	0.45
Haplotype match (%)				
1-haplotype match	88	90	85	0.84
Fullmatch	7	7	7	
immunosuppression)(%)				
Corticosteroids	100	100	100	-
Mycophenolate mofetil	97.3	100	90	0.07
Cyclosporine	52.7	53.7	50.0	0.77
Tacrolimus	45.9	44.4	50.0	0.79
Rapamycin	1.6	1.9	-	-
Induction therapy (%)				
ATG (%)	77.5	75.0	84.2	0.56
Basiliximab (%)	11.3	13.5	5.3	
None	11.3	11.5	10.5	

Regarding donor type, 63% received grafts from living related donors, 21% from living unrelated donors, and 16% from deceased donors. The mean donor age was 50.1±11.8 years, and 51% of donors were male. In terms of tissue matching, the full-match rate was 7%, and the 1-haplotype match rate was 88%.

The mean follow-up duration was 7.4±2.2 years. All patients received corticosteroid treatment after kidney transplantation; mycophenolate mofetil was used in 97%, cyclosporine in 45%, and tacrolimus in 45%. Induction therapy consisted of ATG in 77.5% and basiliximab in 11.3%, while 11.3% received no induction therapy.

The 3-month, 6-month, and 12-month post-transplant follow-up data are presented in Table 2. During the first 3 months after transplantation, the mean baseline creatinine level was 1.44±0.31 mg/dL, the mean proteinuria level was

0.21±0.19 g/day, and the frequency of microscopic hematuria was 13%.

At the 6-month protocol biopsy, the mean serum creatinine level was 1.44±0.34 mg/dL, proteinuria was 0.19±0.23 g/day, and the frequency of hematuria was 19%. Mean systolic and diastolic blood pressures were 131±17 mmHg and 83±10 mmHg, respectively. IgA recurrence was detected in 9.3% (n=7) of 6-month protocol biopsies (Table 3). Among these 7 patients, 5 (71%) had IgA deposition detected only by immunofluorescence staining, while 2 patients were diagnosed with IgA recurrence by both light microscopy and immunofluorescence. In the remaining 69 patients (90.7%), no IgA recurrence was detected in the 6-month biopsies. Among patients without recurrence at 6 months, focal tubulointerstitial nephritis was detected in 7, polyoma nephropathy in 2, and findings consistent with thrombotic

Table 2. First-year follow-up data of patients with and without IgA nephropathy recurrence

	All group	IgA recurrence negative	IgA recurrence positive	p
3 months				
Creatinine (mg/dL)	1.44±0.31	1.45±0.31	1.38±0.36	0.32
Proteinuria (g/day)	0.21±0.19	0.20±0.20	0.23±0.18	0.97
Hematuria (%)	13	10	23	0.23
6 months				
Systolic BP (mmHg)	131±17	130±17	133±17	0.69
Diastolic BP (mmHg)	83±10	82±10	84±11	0.30
Creatinine (mg/dL)	1.44±0.34	1.47±0.36	1.39±0.27	0.17
Proteinuria (g/day)	0.19±0.23	0.18±0.23	0.21±0.25	0.33
Hematuria (%)	19	12	30	0.06
12 months				
Systolic BP (mmHg)	130±14	130±14	130±13	0.99
Diastolic BP (mmHg)	83±9	82±6	83±11	0.63
Creatinine (mg/dL)	1.43±0.36	1.46±0.37	1.34±0.32	0.20
Proteinuria (g/day)	0.18±0.21	0.19±0.25	0.16±0.14	0.58
Hematuria (%)	21	22	15	0.53

Table 3. Distribution of IgA nephropathy recurrence rates in 6-month and 12-month protocol biopsies

	IgA nephropathy recurrence positive			IgA nephropathy recurrence negative
	Total (n)	IM + IF	IF	Total (n)
6-month biopsy	7 (9.3%)	2 (29%)	5 (71%)	69 (90.7%)
12-month biopsy	20 (26.3%)	3 (15%)	17 (85%)	56 (73.7%)

microangiopathy in 1, while the remaining biopsies were considered nonspecific.

At the 12-month protocol biopsy, the mean serum creatinine level was 1.43±0.36 mg/dL, proteinuria was 0.18±0.21 g/day, and the frequency of hematuria was 21% (Table 2). Mean systolic and diastolic blood pressures were 130±14 mmHg and 83±9 mmHg, respectively. The recurrence rate of IgA nephropathy in the 1-year protocol biopsies was 26.3% (n=20), which was approximately three times higher than the rate detected at 6 months (Table 3). Among the 20 patients with recurrence, 17 (85%) had isolated IgA deposition detected only by immunofluorescence staining, while 3 patients were diagnosed by both light microscopy and immunofluorescence. In the remaining 56 patients (73.7%), no IgA recurrence was detected in the 12-month biopsies. Among those without recurrence, tubulointerstitial nephritis was reported in 9, polyoma nephropathy in 1, and glomerulitis with peritubular capillaritis in 1.

The baseline clinical and laboratory characteristics of pa-

tients with and without recurrence detected in the first year are presented in Table 1. When patients with IgA nephropathy recurrence in the 1-year follow-up biopsies were compared with those without recurrence, no differences were observed between the two groups in terms of pre-transplant dialysis duration, donor age, donor sex, haplotype matching, baseline immunosuppression, or induction therapies. Although patients with IgA nephropathy recurrence were younger and had a higher proportion of males, these differences were not statistically significant. Preemptive transplantation rates were similar between the two groups. The proportion of first-time transplantation was significantly higher among patients with IgA nephropathy recurrence, and the frequency of living-related donor transplantation was also significantly higher in this group. In addition, the use of mycophenolate mofetil as baseline immunosuppressive therapy tended to be less frequent in the recurrence group, approaching statistical significance.

First-year Data of Patients with and without IgA Nephropathy Recurrence

When parameters related to IgAN recurrence were examined, adjusted regression analysis including recipient age, recipient sex, number of transplantations, and donor type identified age at transplantation as an independent predictor of IgA recurrence on the 1-year biopsy (RR: 0.94, 95% CI: 0.88–0.99, $p=0.04$). Each additional year of age was associated with a 6% reduction in the risk of IgA recurrence.

Ten-year graft survival was 90% in the group with IgA recurrence and 87% in the group without IgA recurrence. During the study period, only one patient died, and at the end of the study, 87% of the patients continued follow-up with a functioning graft.

Discussion

IgAN is the most common primary glomerulonephritis and leads to end-stage kidney disease in 30–50% of patients within 20 to 30 years after diagnosis.^[2] Because patients with IgAN are typically younger and have fewer comorbidities, they are among the most suitable candidates for kidney transplantation. However, recurrence of the original disease in the graft is a known complication of IgAN and often results in decreased graft function. Other glomerular or vascular lesions due to acute or chronic graft rejection may also negatively affect graft function.^[2,3]

In previous studies, the male-to-female ratio has been reported to vary from less than 2:1 in Asian populations to as high as 6:1 in Europe and the United States. In our study, the vast majority of patients were male (79%), with an approximate male-to-female ratio of 4:1.^[4-7]

While some studies have suggested that kidney disease progression occurs faster in men than in women, others have argued that sex differences are not determinants of the risk of renal progression.^[4,8,9] In studies concluding that IgAN progresses more rapidly in men, possible mechanisms underlying the renal protective role of female sex are thought to be related to estrogen.^[10] In our study, the frequency of male sex was moderately higher in the recurrence group (85% vs. 78%, $p=0.15$). Similarly, in the study by Maixnerova et al., 80% of patients with recurrence were male.^[2] In some studies in the literature, male sex has been associated with a higher risk of recurrence, consistent with our findings.^[11-13] In the study by Pippias et al. reporting 15-year post-transplant follow-up results, 71.2% of patients were male, and the median age was 47.5 years.^[14] In our study, the mean age was 37.2 ± 9.7 years. Overall, the sociodemographic characteristics of our cohort appear consistent with the literature. Additionally, younger age was

identified as a significant risk factor for IgAN recurrence in 1-year protocol biopsies.

Among the 76 patients included, 89% underwent a first transplantation. The mean age at transplantation was 37.2 ± 9.7 years. In the retrospective analysis of 62 patients who underwent transplantation due to IgAN by Avasare et al.^[15], the mean age at transplantation was 38.1 ± 12.2 years, and the duration of dialysis was approximately 10 months. In our study, the mean dialysis duration in 42 patients receiving hemodialysis or peritoneal dialysis before transplantation was 14.6 ± 29.5 months. In Pippias's study^[16], although the mean age at transplantation (47.5 years) was slightly higher than ours, the mean pre-transplant dialysis duration was similar at approximately 13 months. In the study by Maixnerova et al.^[2], including 313 patients, the mean age at transplantation was 46 years, similar to Pippias's findings.

In our study, the living-donor transplantation rate was 84%, the mean donor age was 50.1 ± 11.8 years, and the most common donor type was living-related donors (63%). In the study by Boğa^[16], the living-donor rate was 63.2%, 54.3% of living donors were first-degree relatives, and the mean donor age was 32.2 ± 11.7 years. In Ünsal's^[17] study, the mean donor age was 44 ± 14.5 years, and 59% were living donors. According to the Turkish Nephrology, Dialysis and Transplantation Registry 2015 report, the predominance of male recipients and the highest transplantation frequency in the 20–45 age group are consistent with our findings.^[16,18] Similarly, Avasare et al.^[15] reported that 74% of transplants were from living donors. In Ünsal's^[17] study, unlike ours, 53% of donors were female.

In the article by Şantaş evaluating the current status of organ donation in Türkiye, it was stated that organs used for transplantation are largely obtained through donation from relatives, whereas in developed countries, most organ needs are met through deceased donors. A major issue in developing countries, including Türkiye, is the insufficient number of deceased donor transplants.^[19]

In our cohort, the most frequently used medications after transplantation were corticosteroids, mycophenolate mofetil, cyclosporine, and tacrolimus. Most patients received ATG as induction therapy. In the literature, early initiation of immunosuppressive regimens in patients with IgAN at risk of progression has been reported to slow progression to end-stage kidney disease.^[2] In the study by Ordin et al.^[20], patients used an average of 6.72 ± 1.92 (min–max: 2–13) medications daily; 76% received tacrolimus, 48% received cyclosporine, and 8% received everolimus-containing immunosuppressive therapy, and 36.7% used triple therapy consisting of corticosteroids, tacrolimus, and mycophenolate mofetil.

Although immunosuppression protocols vary between centers, the goal is to achieve the lowest acute rejection rate and the highest patient and graft survival. Therefore, except for transplants between identical twins, continuous immunosuppressive therapy is essential for long-term graft function, either as induction or maintenance therapy.^[21] In our study, no significant difference was found between patients with and without IgAN recurrence in 1-year protocol biopsies in terms of immunosuppressive treatment regimens.

In our study, the graft loss rate was 10.8% during a mean follow-up period of 7.4 ± 2.2 years, and no significant association was found between IgAN recurrence in protocol biopsies and 10-year graft survival. Graft survival was similar between patients with and without recurrence. Only one patient death occurred. In the literature, graft loss due to IgAN recurrence has been reported to be approximately 3–4%.^[15–22] Moroni et al.^[12] reported graft loss due to IgAN recurrence at a rate of 8.4%, which is similar to our findings. Clayton et al.^[23] also reported that recurrent IgAN was the cause of graft loss in 12.6% of patients transplanted for primary IgAN, which is close to our result.

In our study, the characteristics of patients with and without recurrence in 1-year protocol biopsies were compared. Although there were numerical differences between the two groups in variables such as follow-up duration, age at transplantation, recipient sex, pre-transplant hemodialysis, RRT type, preemptive transplantation, donor sex, haplotype matching, immunosuppressive treatment, and induction therapy, these differences were not statistically significant. Chailimpamontree et al.^[24] reported that age at transplantation was not associated with recurrence risk. In contrast to our findings, Avasare et al.^[15] reported that age at transplantation was higher in patients with recurrence, and this difference was statistically significant.

In our results, a statistically significant association was found between recurrence and the number of transplantations and donor type. Similar to our findings, Han et al.^[13] reported a significant relationship between living-related donation and recurrence, and Choy et al.^[25] stated that living-related donation increased the likelihood of IgAN recurrence 2.5-fold. Conversely, in Han's^[13] study, the presence of anti-HLA antibodies was not associated with recurrent IgAN, and chronic allograft nephropathy was more frequent in deceased-donor transplantation. In our study, similarly, no significant association was found between haplotype matching and recurrence.

In adjusted analyses, each additional year of recipient age was associated with a 6% reduction in the risk of IgA recurrence. In the study by Moroni et al.^[12], transplant year,

younger age, and immunosuppressive use were identified as predictive variables for recurrence. Han et al.^[13] also reported that younger age at transplantation was associated with a higher risk of recurrence.

Since Berger's first report,^[102] many studies have evaluated recurrent IgAN.^[13,15,24–26] In our study, the IgAN recurrence rate was 26.3% in 1-year protocol biopsies and 65% in indication biopsies performed beyond the first year. Kim et al.^[27] reported a 44% risk of recurrent IgAN after 10 years, while Han et al.^[13] reported 30.8%. We believe these differences may be due to the ethnic characteristics of the studied populations and the frequent use of indication biopsies in our center when graft dysfunction or active urinary findings are detected.

Conclusion

In our study, 10-year graft loss was found to be 10%. This rate was similar in patients with and without IgAN recurrence in 1-year protocol biopsies. The rate of living-donor transplantation was higher among patients with IgAN recurrence. Younger age at the time of transplantation was a risk factor for IgAN recurrence (RR: 0.94, 95% CI: 0.88–0.99, $p=0.04$). Each additional year of age was associated with a 6% reduction in the risk of IgA recurrence.

In our study, the recurrence rate of IgAN was 26.3% in 1-year protocol biopsies among all patients and 65% in indication biopsies during the study period. The wide range of recurrence rates reported in the literature may be explained by differences in the baseline characteristics of study populations and biopsy policies. In addition, the inclusion of small sample sizes and/or patients from multiple ethnic backgrounds, as well as varying biopsy strategies, may lead to differences in reported findings. Although our study includes data from a single center, our findings regarding the risk of recurrent IgAN are considered reliable due to multivariable analyses, long-term follow-up results, and the relatively large sample size compared with the existing literature. Our data also showed that immunosuppressive use and induction therapy were not associated with the prevention of recurrent IgAN. Moreover, no significant association was found between haplotype matching and recurrent IgAN.

Although our results contribute to the literature, our study has several limitations. The study design was retrospective, and all patients in our dataset were from a single center.

Although further prospective, well-designed studies are needed, our data may help evaluate risk factors for IgAN recurrence in protocol biopsies and determine prognosis in recurrent IgAN among kidney transplant recipients.

Disclosures

Ethics Committee Approval: This study was approved by The Ege University Medical Research Ethics Committee (January 21, 2021 / 21-1.1T/57).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

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Authorship Contributions: Concept: EZG; Design: EZG, GA; Supervision: GA; Materials: SŞ, BSK, SUB; Data Collection and/or Processing: EZG; Analysis and/or Interpretation: EZG, GA; Literature Search: EZG; Writing: EZG; Critical Reviews: GA, EZG.

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