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Efficacy of tonsillectomy for the treatment of immunoglobulin A nephropathy recurrence after kidney transplantation

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Abstract

Background: Post-transplant recurrent nephritis is the third common complication that leads to graft loss, which affects the long-term graft survival of kidney transplant patients. Immunoglobulin A nephropathy (IgAN) is the most common for recurrent nephritis, with a recurrence rate of 13–53%. In this study, 12 patients diagnosed with recurrent IgAN were divided into two groups, one which underwent tonsillectomy and another which did not, to analyze the effect of treating IgAN recurrent with or without tonsillectomy.

Methods: Urinary findings, estimated GFR (eGFR), and histopathological alteration (Banff and Oxford classifications) were examined for >5 years after kidney transplantation.

Results: We found that tonsillectomy protected graft function and prevented pathological alterations. The levels of urinary proteins increased in the no tonsillectomy group, whereas no difference was observed in the severity of hematuria between two groups. eGFR declined and mesangial hypercellularity score increased in the no tonsillectomy group.

Conclusions: Tonsillectomy not only results in a favorable clinical outcome but also protects against the histological damage caused by recurrent IgAN after kidney transplantation.

Keywords: Immunoglobulin A nephropathy (IgAN), Kidney transplantation, Recurrent nephritis, Tonsillectomy

Background

The recurrence rate of IgAN in renal graft is 13–53% among transplant recipients with IgAN, which affects long-term graft survival [1, 2]. In recent trials of immunosuppression therapy, mycophenolate mofetil was expected to suppress IgAN after transplantation; however, it failed to enhance graft survival [3]. In another study of 532 transplant recipients by Esther et al., graft loss due to IgAN recurrence occurred in as many as 9.7% patients at 10 years. Among these, IgAN accounted for 22% of the total cases of graft loss, IgAN recurrence was the third major cause of graft loss after chronic rejection and death with a functioning graft [4]. Establishing a treatment for recurrent nephritis, particularly recurrent IgAN, is crucial for improving the renal graft survival. Berger et al. first described IgAN in 1968 [5]; it is now the most frequent form of chronic glomerulonephritis in Japan. In another study, Xie et al. compared patients with primary IgAN that did or did not undergo tonsillectomy, and renal survival rates for the two groups at 240 months were 89.6 and 63.7%, respectively; this difference was statistically significant [6]. Tonsillectomy monotherapy or steroid pulse therapy following tonsillectomy is commonly used to treat primary IgAN in Japan [6–9]. This therapy achieves particularly beneficial effects in the early stages of IgAN. Protocol graft biopsy can reveal important findings regarding the onset and extension of IgAN, which might explain why tonsillectomy has particularly favorable effects on early stage recurrent IgAN. To our knowledge, few reports have assessed the natural progression of recurrent IgAN using protocol graft biopsies.

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In this study, we evaluated the efficacy of tonsillectomy for the treatment of IgAN recurrence after kidney transplantation.

Methods

Between 1984 and 2008, kidney transplantation was performed on 520 patients at our department. Among these recipients, 76 (14.6%) were diagnosed with primary IgAN that was confirmed pathologically. Among these, 23 (30.3%) had recurrent IgAN in the kidney graft. After excluding individuals who we were unable to follow-up for 5 years or more, 12 patients were included in the final analysis. All 12 patients received immunosuppressive therapy including tacrolimus, cyclosporine, azathioprine, mycophenolate mofetil (MMF), and methylprednisolone during the study period. IgAN recurrence was defined as follows:

1. The confirmation of primary IgAN using a native kidney biopsy.
2. The new appearance of urinary findings (proteinuria and/or hematuria)
3. New-onset histological IgA deposition without previous IgAN deposition at 1-h biopsy.

Tonsillectomy was offered to all 12 patients as a treatment option, and it was only performed on patients who provided consent. After given the informed consent, five patients (tonsillectomy group) underwent tonsillectomy, whereas the remaining seven patients (no tonsillectomy group) did not. Protocol biopsies were routinely performed at 1 h, 3 months, 12 months, 36 months, 60 months, and 84 months after kidney transplantation. One nephrologist and one or two pathologists evaluated the pathological findings using the Banff classification 2007 [10] and the Oxford classification [11, 12]. Informed consent was obtained from all patients regarding the use of their pathological specimens in this study before each graft biopsy.

The degree of urinary findings, histopathological alterations, the decline slope of 1/Cr, and estimated glomerular filtration (eGFR) were analyzed retrospectively in the two patient groups. Microhematuria was defined as five or more erythrocytes per high-power microscopy field (×400) in urinary sediment, according to the Japanese Urological Association guidelines. Proteinuria was evaluated using the protein/creatinine ratio (g/gCr) in a urine sample obtained in the morning at the outpatient clinic. eGFR was calculated using serum creatinine levels on the day or the day before the renal biopsy. Clinical data are expressed as mean ± standard deviations (SDs). Statistical comparisons between the two groups were performed using Wilcoxon rank sum test, and individual pairs of specimens were analyzed using matched-pair t tests. $P < 0.05$ was considered to denote statistical significance in all tests.

This study was approved by the Ethics Committee of Toho University Omori Medical Center, Tokyo, Japan (approval number: 26–60), and was performed in adherence with the Declaration of Helsinki. Informed consent was obtained from all patients.

Results

In the tonsillectomy group, two patients were male and three were female, and the mean age was 33.7 ± 9.7 years at kidney transplantation. The mean period from transplantation to IgAN recurrence was 37.4 ± 25.7 months, and the median time between IgAN recurrence and tonsillectomy was 3.1(1.4–28.9) months. The mean follow-up period after kidney transplantation was 146.8 ± 30.1 months. At the time of the diagnosis of IgAN recurrence, the mean serum creatinine (SCr) levels were 1.15 ± 0.28 mg/dl (eGFR was 47.7 ± 14.6 ml/min/1.73 m^2). Three of the five patients (60%) had hematuria, and the mean proteinuria was 0.33 ± 0.52 g/gCr. All patients were administered antihypertensive agents such as angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) after IgAN recurrence was confirmed. The no tonsillectomy group included six males and one female with mean age of 36.6 ± 8.6 years. The mean period from transplant to IgAN recurrence was 31.8 ± 19.3 months, and the mean follow-up period was 193.6 ± 105.1 months. The mean SCr and eGFR at the time of diagnosis of IgAN recurrence was 1.29 ± 0.17 mg/dl and 39.1 ± 5.8 ml/min/1.73 m^2, respectively. Four of seven patients (57%) had hematuria, and the mean proteinuria was 0.07 ± 0.19 g/gCr. ACE-I or ARB therapy was initiated after IgAN recurrence was confirmed in all but one patient. All patients were re-evaluated for IgAN recurrence or not by repetitive protocol biopsy (Table 1).

We showed a recurrence rate in each protocol graft biopsy within all cases: 1 h, 0%; 3 months, 8.3%; 12 months, 25%; 3 years, 41.7%; 5 years, 25%; 7 year, 0%. Among 3 years after transplantation, 66% of recurrence was noted.

The therapeutic response was measured by assessing hematuria and proteinuria in each group. The tonsillectomy group exhibited more proteinuria than did the no tonsillectomy group at recurrence. However, no significant differences were observed in the degree of proteinuria between groups (0.33 ± 0.52 vs. 0.07 ± 0.19 g/gCr, respectively; $p = 0.33$). In the no tonsillectomy group, the mean proteinuria at recurrence was 0.07 ± 0.19 g/gCr, which increased significantly to 0.97 ± 1.09 g/gCr at 60 months after recurrence ($p = 0.043$). However, no significant change was observed in proteinuria in the tonsillectomy group (0.33 ± 0.52 vs. 0.40 ± 0.53 g/gCr, $p = 0.87$) during the same observation period (Fig. 1a, b). No significant differences were observed in the degree of hematuria between groups.

In terms of the histological damage caused by IgAN in the tonsillectomy group, no significant differences were

Table 1 Patient characteristics

	Tonsillectomy ($n = 5$)	No tonsillectomy ($n = 7$)	p
Recipient gender (M/F)	2/3	6/1	0.10
Recipient age at transplantation (mean ± SD)	33.7 ± 9.7	36.6 ± 8.6	0.75
Donor age at transplantation (mean ± SD)	57.7 ± 15.5	53.1 ± 17.1	1.00
Duration of pre-transplant dialysis (months)	41.3 ± 42.1	9.6 ± 3.6	0.10
Living/deceased	5/0	6/1	1.00
ABO compatible/incompatible	3/2	7/0	0.15
Immunosuppressant use (CsA/FK)	3/2	6/1	0.52
SCr at recurrence (mg/dl)	1.15 ± 0.28	1.29 ± 0.17	0.33
eGFR at recurrence (ml/min)	47.7 ± 14.6	39.1 ± 5.8	0.33
Urinary findings at recurrence			
Hematuria	3/5 (60%)	4/7 (57%)	1.00
Proteinuria (g/g·Cr)	0.33 ± 0.52	0.07 ± 0.19	0.39
Use of RASI	5/5 (100%)	6/7 (85.7%)	1.00
Period between transplant and IgAN recurrence (months)	37.4 ± 25.7	31.8 ± 19.3	0.94
Median time between IgAN recurrence and tonsillectomy (months)	3.1(1.4 – 28.9)	–	–
Time between IgAN recurrence and the next protocol biopsy (months)	57.4 ± 10.1	61.4 ± 8.5	0.76
Follow-up period (months)	146.8 ± 30.1	193.6 ± 105.1	0.75

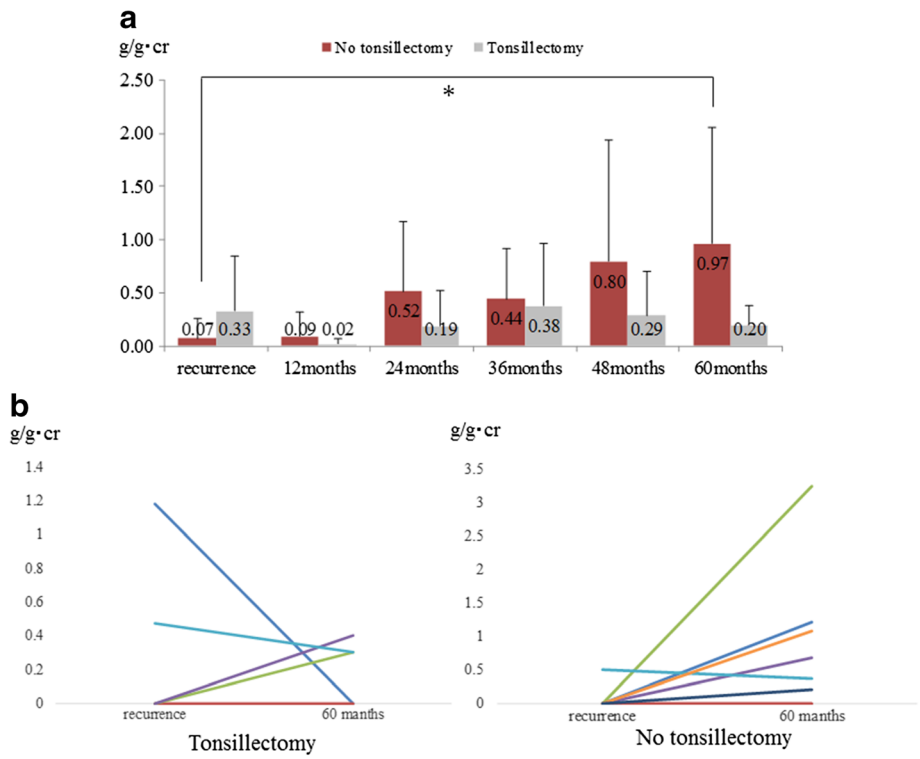

Fig. 1 **a** Changes in urinary protein excretion in patients with or without tonsillectomy. *$p < 0.05$, urinary protein excretion at 60 months vs. at recurrence in patients with no tonsillectomy. **b** Changes in urinary protein by individuals with or without tonsillectomy

observed in the histopathological alterations before and after tonsillectomy. However, in the no tonsillectomy group, the mesangial matrix score (mm) in the Banff classification 2007 increased from 0.14 ± 0.38 to 2.14 ± 0.69 ($p = 0.002$), the mesangial hypercellularity score (MS) in the Oxford classification increased from 0.20 ± 0.36 to 0.69 ± 0.37 ($p = 0.003$), and the segmental glomeruloscreosis score (SS) in the Oxford classification increased from 0 to 0.57 ± 0.54 ($p = 0.03$) (Table 2). Pathological rejection, except for borderline changes, was not observed during the study period.

Figure 2 shows the change in eGFR between groups. The decreases in eGFR before and 60 months after transplantation were as follows: tonsillectomy group, 47.7 ± 14.6 to 34.8 ± 12.2 ml/min/1.73 m^2 ($p = 0.11$); no tonsillectomy group, 39.1 ± 5.8 to 30.4 ± 10.2 ml/min/1.73 m^2 ($p = 0.03$). In terms of the change in 1/Cr between groups, the decreases in 1/Cr before and 60 months after transplantation were as follows: tonsillectomy group, 0.91 ± 0.21 to 0.73 ± 0.26 mg/dl ($p = 0.14$); no tonsillectomy group, 0.79 ± 0.11 to 0.65 ± 0.22 ml/min/1.73 m^2 ($p = 0.03$). Although eGFR and 1/Cr reduced in both groups, the decline was only significant in the no tonsillectomy group. No patients in the tonsillectomy group experienced renal graft loss, while three (42.3%) patients lost their graft in the no tonsillectomy group (Fig. 3). Among these, the mean graft survival was 11.3 ± 6.8 years, and the reason for graft loss was followed, two patients for IgAN recurrence, one patient for interstitial fibrosis and tubular atrophy (IF/TA).

Table 2 Changes in renal pathological findings in patients with or without tonsillectomy according to the Banff classification and the Oxford classification

		At recurrence	Post tonsillectomy	*p*
Tonsillectomy group				
Banff classification	t	0.60 ± 0.89	0.20 ± 0.45	0.48
	i	0.60 ± 0.89	0.20 ± 0.45	0.48
	v	0	0.20 ± 0.45	0.37
	g	0.20 ± 0.45	0.20 ± 0.45	1.00
	ci	0	0.60 ± 0.55	0.07
	ct	0.40 ± 0.55	0.80 ± 0.45	0.37
	mm	0.40 ± 0.55	0.80 ± 0.45	0.37
	cg	0	0	–
	cv	0.40 ± 0.55	0.40 ± 0.89	1.00
	ah	0.20 ± 0.45	0.60 ± 0.89	0.18
	ptc	0.20 ± 0.45	0.60 ± 0.89	0.48
	Scl (%)	6.20 ± 6.46	18.06 ± 22.02	0.19
Oxford classification	M	0.24 ± 0.21	0.32 ± 0.29	0.59
	S	0.40 ± 0.55	0.40 ± 0.55	1.00
	E	0.20 ± 0.45	0	0.37
	T	0	0.20 ± 0.45	0.37
No tonsillectomy group				
Banff classification	t	0.14 ± 0.38	0.14 ± 0.38	1.00
	i	0.14 ± 0.38	0	0.36
	v	0	0	–
	g	0	0.14 ± 0.38	0.36
	ci	0.14 ± 0.38	0.29 ± 0.49	0.60
	ct	0.43 ± 0.53	0.71 ± 0.49	0.17
	mm	0.14 ± 0.38	2.14 ± 0.69	0.002
	cg	0	0.29 ± 0.49	0.17
	cv	0.43 ± 0.53	0.71 ± 0.76	0.17
	ah	0.29 ± 0.38	0.71 ± 0.49	0.20
	ptc	0.14 ± 0.38	0.14 ± 0.38	1.00
	Scl (%)	6.43 ± 11.43	14.5 ± 13.45	0.25
Oxford classification	M	0.20 ± 0.36	0.69 ± 0.37	0.003
	S	0	0.57 ± 0.54	0.03
	E	0	0.14 ± 0.38	0.36
	T	0.24 ± 0.21	0.14 ± 0.38	0.25

Discussion

We found that tonsillectomy is an effective treatment for IgAN recurrence after kidney transplantation both clinically and pathologically. Hotta et al. reported that tonsillectomy and steroid pulse therapy had a significant effect in patients with primary IgAN. In addition, patients with early to mid-stage primary IgAN with relatively preserved renal function were more likely to respond satisfactorily [13]. In the current study, the tonsillectomy group exhibited no significant differences in the degree of proteinuria and eGFR. Graft loss did not occur during the observation period, and there were no remarkable changes in mesangial hypercellularity score (MS in the Oxford classification) or matrix expansion (mm score in the Banff classification 2007).

Kennoki et al. conducted a retrospective study of 28 transplant recipients with IgAN recurrence and persistent proteinuria. Of the 16 and 12 patients with or without tonsillectomy during a mean follow-up period of 60 months, proteinuria decreased significantly in all tonsillectomized patients but did not in no tonsillectomy patients. No significant differences were observed in the degree of hematuria and eGFR between the groups [14]. In other study, Ushigome et al. analyzed four transplant recipients with IgAN recurrence who underwent tonsillectomy. The urinary findings were improved in all patients after tonsillectomy, including a histologically severe case, for a mean period of 13.5 months [15]. Furthermore, Koshino et al. reported date from seven transplant recipients with IgAN recurrence who underwent tonsillectomy. Both of urinary findings and SCr levels improved in the mild-grade recurrent IgAN cases

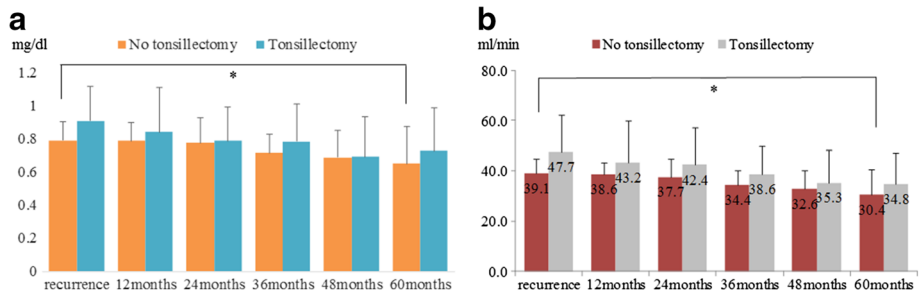

Fig. 2 **a** Changes in renal function (1/Cr) in patients with or without tonsillectomy. *$p < 0.05$, 1/Cr at 60 months vs. at recurrence in patients with no tonsillectomy. **b** Changes in estimated glomerular filtration rate (eGFR) in patients with or without tonsillectomy. *$p<0.05$, eGFR at 60 months vs. at recurrence in patients with no tonsillectomy

after tonsillectomy over a mean observation period of 48.4 months [16].

In the current study, patients with tonsillectomy group exhibited improved urinary findings, whereas proteinuria increased significantly in the no tonsillectomy group. Consistent with previous studies, tonsillectomy treatment reduced proteinuria. We hypothesize that tonsillectomy alone protects graft function and pathology. In the tonsillectomy group, the slope of eGFR seemed to be greater, but SD was higher in tonsillectomy than no tonsillectomy group, higher SD might result in no statistical different during 60 months observation. We therefore tried to show graft function by other parameter instead of eGFR (Fig. 2a), the slope of 1/Cr was similar as the slope of eGFR. Although the decline of eGFR (from 47.7 to 34.8ml/min) was 27.0% during 60 months (less than 30%) in the tonsillectomy group (Fig. 2b), the most important factor for IgAN progression depends on the amount of proteinuria at the same kidney function [17].

Ohya and Shigematsu et al. showed that the efficacy of tonsillectomy in IgAN in native kidney [18]. Mean age (34.6 years) and levels of serum creatinine (0.9 mg/dl) and proteinuria (0.87 g/dl) were similar to our study population. They concluded that tonsillectomy resulted in lower relapse after achieving remission compared to steroid therapy alone. In order to reveal the effect of tonsillectomy alone, our results as well as other reports [18] made possible this hypothesis. The mechanism of tonsillectomy is an antigenic stimulation of immune system by the tonsillar mucosa via the mucosa-bone marrow axis [19].

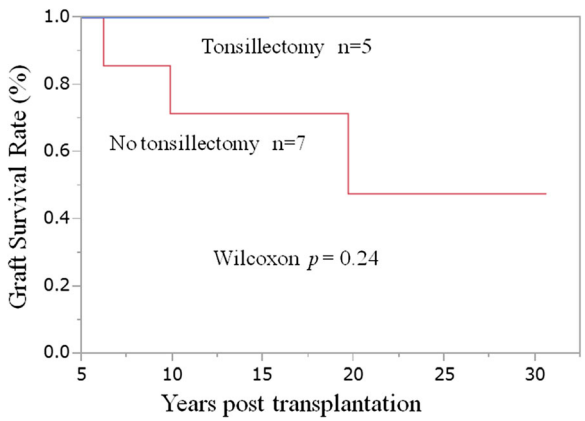

Fig. 3 Kaplan-Meier analysis of graft survival in patients with or without tonsillectomy

Histological evidence is required to confirm that tonsillectomy exhibits a graft-protecting effect. In the current study, there was no change in mesangial cell proliferation in the tonsillectomy group. In contrast, the mm, MS, and SS scores significantly increased in the no tonsillectomy group. This suggests that tonsillectomy improves mesangial cell proliferation and matrix expansion. Hotta et al. reported that both of urinary findings and graft pathology were improved in 15 transplant recipients with IgAN recurrence who underwent tonsillectomy [20]. Although their results were consistent with those of the current study, they were unable to confirm IgAN as a primary disease in those recipients.

When considering the effects of tonsillectomy, it is necessary to compare a tonsillectomy group to no tonsillectomy group. It is also important to confirm any changes pathologically using protocol graft biopsies. However, several previous studies [14–16, 20] did not perform long-term evaluations using protocol graft biopsies. We can also evaluate rejection according to the Banff classification and aggravation of the IgAN process for long-term observation about 10 years. The Banff classification is a useful tool for standardizing to evaluate rejection, but it is not designed to evaluate the recurrence of nephritis. On the other hand, the Oxford classification was announced in 2009 by a working group of the International IgAN Network and Association of International Kidney Pathology. It analyzes the reproducibility of lesions in IgAN by every pathologist, and it then can be confirmed as the responsible lesion for the prognosis of IgAN. This classification also takes into consideration the mesangial cells proliferation, which is an important reason why this classification system was

generated [21]. IgAN recurrence in renal grafts is generally categorized with mild histological findings; therefore, lesions such as cellular crescents, fibrocellular crescents, and intraluminal lesions are usually not considered. Therefore, we utilized the Oxford classification system with the Banff classification to determine IgAN recurrence in the current study. Even if just mild lesion seen at protocal biopsy, tonsillectomy resulted in favorable outcome based on repetitive biopsies in our study.

The effectiveness of tonsillectomy and steroid pulse combined-therapy, for improving mesangial cell proliferation and fibrosis, has been reported previously [13, 22]. However, there is concern that the additional steroid pulse therapy might lead to over-immunosuppression. Therefore, many physicians hesitate steroid pulse therapy in patients with recurrent IgAN after transplantation. Although, the postoperative use of immunosuppressive agents might suppress the development of IgAN, the addition of steroid pulse therapy is doubted for taking a side effect into account. Immunosuppressive therapy might not successfully prevent from IgAN recurrence even in this era after kidney transplantation [23]; therefore, we evaluated the efficacy of tonsillectomy alone in the current study.

Study limitations

This study has three limitations: First, the number of cases was insufficient in both groups. In order to make a diagnosis of recurrent IgAN, both pre- and post-transplant renal biopsy diagnosis is required. Unfortunately, there were few patients who diagnosed IgAN as primary disease. We extensively recruited patients since 1984 because of above reason. Second, more patients with proteinuria were included in the tonsillectomy group; therefore, there is a selection bias in this retrospective study. Third, most of patients introduce our hospital to transplant purpose; we could not take information about IgAN activity in detail.

Conclusions

This study demonstrated that tonsillectomy protected clinical and pathological alteration in patients with IgAN recurrence after kidney transplantation. However, a large sample size and more long-term observation are necessary to determine the effectiveness of tonsillectomy in case of IgAN recurrence after kidney transplantation.

Abbreviations

Ah: Arteriolar hyaline thickening score; Cg: Allograft glomerulopathy score; ci: Interstitial fibrosis score; CsA: Cyclosporin A; Ct: Tubular atrophy score; Cv: Fibrous intimal thickening score; E: Endocapillary hypercellularity score; eGFR: Estimated glomerular filtration rate; g: Early allograft glomerulitis score; i: Mononuclear cell interstitial inflammation score; IgAN: Immunoglobulin A nephropathy; M: Mesangial hypercellularity score; Mm: Mesangial matrix increase score; Ptc: Peritubular capillaritis score; RASI: Renin-angiotensin system inhibitors; S: Segmental glomerulosclerosis score; Scl: Glomerular sclerosis; SCr: Serum creatinine; SD: Standard deviation; T: Tubular atrophy/interstitial fibrosis score; T: Tubulitis score; V: Intimal arteritis score

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Availability of data and materials

The data will be shared.

Authors' contributions

HN and KS (corresponding author) planned the study, searched the literature, assessed studies, extracted data, analyzed data, and wrote the manuscript. HE assisted the study operation and data collection. SS, KS, and AA assessed studies and assisted in the data analysis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

We have also obtained consent to publish from the participant to report individual patient data.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Toho University Omori Medical Center, Tokyo, Japan (approval number: 26–60), and was performed in adherence with the Declaration of Helsinki. Informed consent was obtained from all patients.

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