Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

# Impact of recurrent disease and chronic allograft nephropathy on the long-term allograft outcome in patients with IgA nephropathy

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**Keywords**
chronic allograft nephropathy, graft survival, IgA nephropathy, recurrence.

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Received: 22 June 2009
Revision requested: 14 July 2009
Accepted: 22 August 2009

doi:10.1111/j.1432-2277.2009.00966.x

## Summary

Although recurrent IgA nephropathy (IgAN) may lead to graft dysfunction after transplantation, donation from living related donor (LRD), with whom the risk of recurrence may be higher, is not a contraindication. Herein, we evaluated the natural history of allograft in recipients with IgAN and the risk factors influencing long-term allograft outcome. Recurrence rate and graft survival were assessed retrospectively in 221 IgAN patients, including transplants from 139 LRDs (62.9%). Ten-year cumulative rate for recurrent IgAN was 30.8%. The operation at younger age and donation from LRD were significant for the recurrence by multivariate analysis. Ten-year graft survival was affected by recurrent IgAN (61.0% in recurrent IgAN group vs. 85.1% in nonrecurrent, $P < 0.01$). However, transplants from LRDs did not show poor graft survival when compared with those from other types of donors. In transplants from LRDs, the incidence of chronic allograft nephropathy (CAN) was lower than those in grafts from deceased donors (10.8% vs. 19.5%, $P < 0.05$). When CAN was considered in addition to recurrence, the variance of graft survival was affected significantly by the development of CAN than by the recurrence. These results suggest that the detection and adequate management of CAN could improve graft outcome in transplant recipients with IgAN.

## Introduction

The major causes of end-stage renal disease (ESRD) which is a rapidly increasing global burden are diabetes, hypertension, and chronic glomerulonephritis (GN) [1]. Immunoglobulin A nephropathy (IgAN) is the most common form of chronic GN, both globally and in Korea [2,3]. The clinical manifestations of IgAN are diverse and a curative treatment for IgAN is not yet available [4]. The prognosis of IgAN is not benign, and thus ESRD develops in as many as 30% of patients after 20–30 years [5,6].

Recurrent GN after kidney transplantation is a major threat to graft survival after the first year. Although it does not occur as frequently as death with function or chronic allograft nephropathy (CAN), it is significantly more common than acute rejection [7]. However, because of the fact that the introduction of newer immunosuppressive agents has reduced graft loss by decreasing the incidence of acute rejection and CAN, recurrent GN may be a significant cause of graft loss in current clinical practice. Since recurrent IgAN in kidney transplants was first described by Berger *et al.* in 1975 [8], the recurrence rate reported in the literature has ranged from 15 to 60% depending on the duration of follow up and biopsy policy [9]. Kidney recipients who had recurrent disease showed worse graft survival rates than the nonrecurrent group [10,11]. A graft from living related donor (LRD) is the most well-known risk factor for recurrent IgAN. [10–14]. However, the graft

 

survival rate was not different with respect to types of donor in kidney recipients by IgAN [12,13]. The reason for this discrepancy is not well understood.

The purposes of this study were to delineate the natural history of allograft in recipients with IgAN and to investigate the risk factors influencing the long-term outcome of allograft.

## Patients and methods

### Patients

Two hundred twenty-one kidney recipients, who suffered from ESRD attributable to biopsy-proven IgAN, were recruited from three institutes (Seoul National University Hospital, Asan Medical Center, and Samsung Medical Center, Seoul, Korea). We excluded the recipients who had multi-organ transplantation. Medical records were reviewed retrospectively. Clinical parameters such as age at transplantation, gender, history of hypertension and diabetes mellitus, time from kidney biopsy until development of ESRD, and duration of dialysis before transplantation were collected. Donor factors such as age at transplantation, gender, and types of donor [LRD, living unrelated donor (LUD), or deceased donor (DD)] were evaluated. Degree of HLA matching was also assessed.

### Immunosuppression

Calcineurin inhibitors, steroids, and inhibitors of purine metabolism were used as the basic immunosuppressive agents in most of the recipients. In some recipients, induction therapy utilizing anti-thymocyte globulin (ATG) or anti-CD25 antibody (basiliximab) was applied wherever indicated. The administration of angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) was also evaluated.

### Graft biopsy

We performed graft biopsies in the case of significant proteinuria (>1.0 g/day), persistent microscopic hematuria, or a progressive deterioration of renal function. Protocol biopsies were not performed routinely. Biopsy tissue was examined by light-, electron-, and immunofluorescent microscopy. For immunofluorescence analysis, fresh renal tissue was frozen in ornithine-carbamoyltransferase embedding compound and stained with fluorescein isothiocyanate-conjugated antisera. IgAN was defined by standard criteria, which included the typical immunofluorescence features [15]. CAN (previously termed chronic rejection) was diagnosed when the biopsy specimen showed double contours on glomerular capillaries, diffuse interstitial fibrosis and arteriolar thickening determined by the renal ones. The definition of graft loss was stipulated as a requirement for maintenance dialysis or an estimated glomerular filtration rate (GFR) of less than 15 ml/min/1.73 $m^2$; the latter was estimated using the Modification of Diet in Renal Disease (MDRD) equation [16].

### Statistical analysis

All analyses and calculations were performed using the SPSS software (SPSS version 16.0, Chicago, IL, USA). Data were presented as the median (interquartile range) for continuous variables and as the proportion for categorical variables. Continuous and categorical data were compared using the Mann–Whitney *U*-test and the chi-squared test respectively. Graft survival rates were calculated using the Kaplan-Meier method, and comparison between groups was performed using the log-rank test. The Cox regression model was used to calculate unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI) for factors that affected the recurrent IgAN and graft loss. The interactions among variables for adjustments were determined using the general linear model. To compare the effects of variables on graft survival, we used the backward stepwise selection in the Cox regression model. To assess the effect of donor type, transplants from one donor type were compared with all those that were not from that donor type (e.g., LRD versus non-LRD). A $P$ value less than 0.05 was considered significant.

## Results

### Demographic characteristics of the recipients

Of the two hundred twenty-one recipients, 128 were male and 93 were female patients. The median age of the recipients was 33 years old (range: 9–64), and the median age of the donor was 38 years old (range: 9–67). All transplants were ABO-compatible. In 62.9% of the cases, the donor was related to the recipients, while 37.1% of the transplants were from unrelated donors (18.5% from living unrelated donors and 18.6% from deceased donors). Whereas 187 recipients (84.6%) had dialysis therapy before transplantation, pre-emptive transplantation was performed in 34 recipients (15.4%). The patients were followed for a median duration of 70.7 months (range: 1–262 months) (Table 1). The median follow-up duration according to types of donor was 70.0 months (range: 6–262 months) in LRD and 101.0 months (range: 0–180 months) in DD, both of which were longer than the mean follow-up duration of 58.6 months (range: 1–180 months) in LUD. The immunosuppressive agents used depended on the period/date of surgery. Before year

**Table 1.** Baseline characteristics of recipients and donors.

| | Male (*n* = 128) | Female (*n* = 93) | Total (*n* = 221) |
|---|---|---|---|
| Recipient age (years) | 32 (27–40) | 36 (26–46) | 33 (27–43) |
| Hypertension (%) | 88.1 | 86.0 | 87.2 |
| Diabetes mellitus (%) | 2.4 | 1.1 | 1.8 |
| Donor age (years) | 37 (28–48) | 39 (26–49) | 38 (27–48) |
| Donor gender ratio (male:female) | 69:59 | 54:39 | 123:98 |
| Living related donor (%) | 60.2 | 66.7 | 62.9 |
| Living unrelated donor (%) | 19.5 | 17.2 | 18.5 |
| Deceased donor (%) | 20.3 | 16.1 | 18.6 |
| Time to develop ESRD (months) | 39.5 (17.1–65.9) | 40.5 (10.0–88.3) | 39.5 (14.0–72.8) |
| Dialysis duration before TPL (months) | 6.0 (2.0–15.8) | 5.0 (1.0–14.8) | 6.0 (1.5–15.0) |
| Median follow up (months) | 72.9 (41.3–118.6) | 68.0 (43.0–111.0) | 70.7 (42.2–111.7) |

Values are expressed as the median (interquartile range) or the percentage.
ESRD, end-stage renal disease; TPL, transplantation.

**Table 2.** Hazard ratios for the development of recurrent IgA nephropathy calculated from clinical and immunologic factors.

| | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Tertiles in recipient age | | | | |
| <29 years old | 1 (Referent) | | 1 (Referent) | |
| 29–37 years old | 0.40 (0.20–0.79) | 0.009 | 0.41 (0.20–0.85) | 0.017 |
| >37 years old | 0.18 (0.07–0.46) | <0.001 | 0.21 (0.08–0.55) | 0.002 |
| Tertiles in donor age | | | | |
| <31 years old | 1 (Referent) | | 1 (Referent) | |
| 31–45 years old | 0.54 (0.23–1.28) | 0.159 | 0.62 (0.24–1.57) | 0.615 |
| >45 years old | 1.56 (0.79–3.09) | 0.203 | 1.44 (0.66–3.17) | 0.363 |
| Male recipient (versus female) | 1.36 (0.73–2.56) | 0.337 | 1.40 (0.72–2.72) | 0.316 |
| Time to develop ESRD ≥40 months (vs. <40) | 0.94 (0.86–1.02) | 0.151 | 0.76 (0.39–1.49) | 0.421 |
| Dialysis duration before TPL ≥6 months (vs. <6) | 1.07 (0.58–1.98) | 0.818 | 0.75 (0.38–1.48) | 0.401 |
| Degree of HLA match | | | | |
| HLA mismatch ≥3 (vs. <3) | 0.84 (0.43–1.64) | 0.611 | 1.49 (0.51–4.38) | 0.468 |
| Full HLA match (versus not) | 0.94 (0.37–2.41) | 0.896 | 0.99 (0.25–3.91) | 0.983 |
| HLA A2 | 1.70 (0.89–3.24) | 0.109 | 1.96 (0.98–3.90) | 0.056 |
| HLA B35 | 0.45 (0.06–3.31) | 0.432 | 0.55 (0.07–4.15) | 0.559 |
| HLA DR4 | 0.87 (0.46–1.62) | 0.651 | 0.84 (0.44–1.62) | 0.608 |
| Use of immunosuppressive agent | | | | |
| Azathioprine | 1.32 (0.71–2.45) | 0.389 | 1.35 (0.69–2.61) | 0.381 |
| Mycophenolate mofetil | 0.77 (0.41–1.43) | 0.399 | 0.56 (0.28–1.09) | 0.089 |
| Cyclosporine | 0.93 (0.41–2.12) | 0.858 | 0.79 (0.31–1.96) | 0.605 |
| Tacrolimus | 1.55 (0.83–2.91) | 0.171 | 1.35 (0.68–2.68) | 0.392 |
| Donor type | | | | |
| Living related donor | 3.16 (1.40–7.12) | 0.005 | 2.44 (1.01–5.87) | 0.047 |
| Living unrelated donor | 0.12 (0.02–0.87) | 0.036 | 0.14 (0.02–1.06) | 0.056 |
| Deceased donor | 0.59 (0.25–1.42) | 0.240 | 0.88 (0.35–2.20) | 0.788 |

*Adjusted for following variables: recipient age, gender, donor type, and degree of HLA class mismatch.
ESRD, end-stage renal disease; TPL, transplantation; HLA, human leukocyte antigen.

2000, azathioprine (72.2% of transplants) and cyclosporine (96.2%) were used more commonly, whereas mycophenolate mofetil (80.1%) and tacrolimus (50.4%) were applied more often after year 2000. As the induction therapy, 4.1% and 9.7% of recipients were administered with ATG and anti-CD25 antibody respectively.

 

### Predictors of recurrent IgA nephropathy

Forty-four recipients (19.9%) showed recurrent IgAN upon subsequent renal biopsy. The 5- and 10-year cumulative rates for recurrent IgAN were 15.0% and 30.8% respectively. Table 2 shows the predictors for the development of recurrent IgAN after kidney transplantation. In univariate analysis, the risk factors for recurrent IgAN were found to be younger recipient age and donation from LRD. In contrast, LUD seemed to protect against recurrent IgAN. The presence of anti-HLA antibodies before transplantation and the induction therapy were not associated with recurrent IgAN (data not shown). When multiple variables such as recipient age, gender, types of donor, and degree of HLA mismatch were adjusted, the operation at younger age and the donation from LRD were significant for disease recurrence. The interactions between variables for adjustments were not evident. We found that kidney transplants from LRDs were 2.5 times more likely to show recurrent IgAN than those from other types of donor. It is known that certain HLA types in the recipient such as -A2, -B35, and -DR4 are associated with recurrent IgAN [11]. Therefore, we evaluated the impact of HLA-A2, -B35, and -DR4 on recurrent IgAN. However, our study did not find any correlation between the above HLA types and recurrent IgAN.

### Graft outcome

The incidence of recurrent IgAN, CAN, and acute rejection according to the types of donor were evaluated. In transplants from LRDs, the incidence of recurrent IgAN was higher, but the incidences of CAN and acute rejection were higher in grafts from DD than those in grafts from other types of donor (incidence of recurrent IgAN in LRD versus LUD versus DD: 26.6% vs. 2.4% vs. 14.6%, $P < 0.01$; incidence of CAN, 10.8% vs. 2.4% vs. 19.5%, $P < 0.05$; incidence of acute rejection 23.0% vs. 29.3% vs. 34.1%, $P > 0.05$) (Fig. 1).

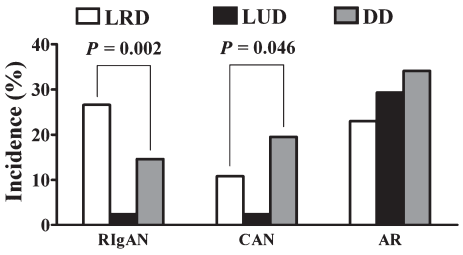


**Figure 1** Incidence of recurrent IgA nephropathy, chronic allograft nephropathy, and acute rejection with respect to types of donor during the follow-up period. Recurrence of IgAN was more prevalent in recipients from living related donors, whereas chronic allograft nephropathy was more often prevalent in deceased donor transplantation. LDR, living related donor; LUD, living unrelated donor; DD, deceased donor; RIgAN, recurrent IgA nephropathy; CAN, chronic allograft nephropathy; AR, acute rejection.

During the period of follow up, 32 patients (14.5%) lost their grafts. The overall graft survival rate was 92.5% at 5 years and 78.1% at 10 years. When the graft survival was plotted according to the disease recurrence, 10-year graft survival rate in the recurrent IgAN group was 61.0%, which was significantly lower than that of the nonrecurrence group (85.1%, $P < 0.01$) (Fig. 2). The presence of CAN was also associated with poor 10-year graft survival rate (survival rate with CAN versus survival rate without: 38.9% vs. 86.6%, $P < 0.01$). We further evaluated the hazard ratios for graft loss that were calculated from baseline clinical and immunologic data. The use of different immunosuppressive agents (induction and maintenance) or of ACEi/ARB did not affect the 10-year graft survival. In multivariate analysis using the Cox regression model, grafts from LRDs, in whom the risk of recurrent IgAN was higher, showed a better graft survival rate when compared with grafts from other types of donor. However, transplants from DDs were associated with a poor graft survival rate even though they had lower rate of disease recurrence (Table 3).

### Development of CAN and graft outcome

We further probed the importance of disease recurrence and presence of CAN on the graft outcome. Recipients were divided into the following four groups according to the recurrence of IgAN and the development of CAN; (i) nonrecurrent IgAN without CAN, (ii) nonrecurrent IgAN

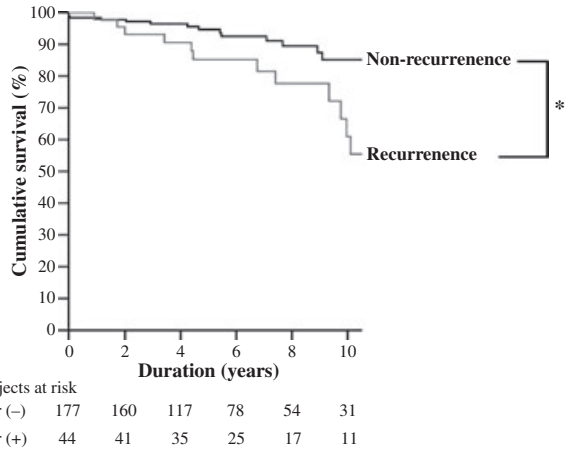


**Figure 2** Comparison of graft survival rates with respect to recurrent IgA nephropathy. When the graft survival was plotted according to the disease recurrence, 10-year graft survival rate in the recurrent IgAN group was significantly lower than that of the nonrecurrence group (*$P < 0.001$).


 

**Table 3.** Univariate and multivariate analyses of the hazard ratios for graft loss within a 10-year period after kidney transplantation

| | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Tertiles in recipient age | | | | |
| <29 years old | 1 (Referent) | | 1 (Referent) | |
| 29–37 years old | 0.59 (0.24–1.43) | 0.240 | 2.74 (0.88–8.56) | 0.083 |
| >37 years old | 0.44 (0.15–1.24) | 0.120 | 1.23 (0.37–4.10) | 0.733 |
| Tertiles in donor age | | | | |
| <31 years old | 1 (Referent) | | 1 (Referent) | |
| 31–45 years old | 0.37 (0.10–1.41) | 0.146 | 1.36 (0.30–6.14) | 0.691 |
| >45 years old | 1.77 (0.74–4.23) | 0.197 | 6.73 (1.82–24.89) | 0.004 |
| Male recipient (versus female) | 1.57 (0.68–3.64) | 0.294 | 1.93 (0.74–5.05) | 0.181 |
| HLA mismatch ≥3 (vs. <3) | 1.09 (0.42–2.85) | 0.856 | 1.25 (0.46–3.37) | 0.665 |
| Use of immunosuppressive agent | | | | |
| Azathioprine | 1.54 (0.65–3.69) | 0.330 | 1.38 (0.52–3.67) | 0.524 |
| Mycophenolate mofetil | 0.71 (0.31–1.62) | 0.411 | 0.46 (0.18–1.21) | 0.116 |
| Cyclosporine | 0.56 (0.20–1.57) | 0.268 | 0.40 (0.12–1.28) | 0.122 |
| Tacrolimus | 1.86 (0.80–4.29) | 0.148 | 2.57 (0.96–6.85) | 0.060 |
| Use of ACEi/ARB | 0.83 (0.36–1.94) | 0.668 | 0.94 (0.35–2.53) | 0.905 |
| Donor type | | | | |
| Living related donor | 0.74 (0.33–1.62) | 0.445 | 0.34 (0.12–0.93) | 0.035 |
| Living unrelated donor | 0.48 (0.11–2.06) | 0.325 | 0.58 (0.13–2.56) | 0.467 |
| Deceased donor | 2.08 (0.92–4.72) | 0.081 | 4.57 (1.70–12.25) | 0.003 |

*Adjusted for following variables: recipient age, gender, donor type, and degree of HLA class mismatch.

HR, hazard ratio; HLA, human leukocyte antigen; IgA, immunoglobulin A; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

with CAN, (iii) recurrent IgAN without CAN, and (iv) recurrent IgAN with CAN. 10-year graft survival rates of the four groups were 91.0%, 34.0%, 70.0%, and 48.6% respectively ($P < 0.01$) (Fig. 3). The variance of graft survival rates was affected more by the development of CAN than by the recurrence of IgAN. When backward stepwise selection in the Cox regression model was used, the occurrence of CAN but not recurrent IgAN affected the adjusted graft survival rate [recurrent IgAN, HR 2.52, 95% CI (0.86–7.33), $P > 0.05$; development of CAN, HR 4.07, 95% CI (1.40–11.85), $P < 0.05$].

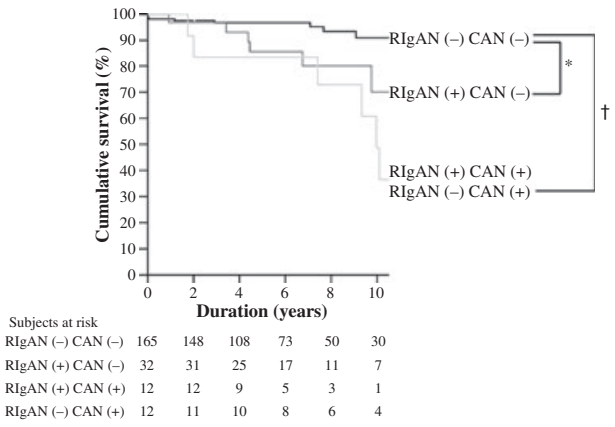


**Figure 3** Effect of recurrent IgA nephropathy and chronic allograft nephropathy on graft survival. Development of chronic allograft nephropathy influenced the graft survival more significantly than the development of recurrence (*$P = 0.016$, †$P < 0.001$). RIgAN, recurrent IgA nephropathy; CAN, chronic allograft nephropathy.

## Discussion

Among two hundred twenty-one recipients, the 10-year cumulative rate of recurrent IgAN was 30.8%, and the risk of recurrence was higher in younger recipients, as also those who received grafts from LRDs. The overall 10-year graft survival rate was 78.1% and this rate was affected by the presence of recurrent IgAN. The effect of recurrent IgAN on the outcome of renal allograft was worsened by CAN. Multivariate analysis showed that the impact of CAN on the graft survival was more significant than that of IgAN recurrence. This result may explain the discrepancy between disease recurrence and graft survival for transplants from LRDs. To date, although recurrent IgAN in renal allografts has been known to affect graft outcome, no published report has compared the effects of recurrent IgAN and CAN during an extended follow-up period of two decades.

Since the initial report from Berger, there have been many reports about recurrent IgAN [9]. The wide range of recurrence rates may be explained by the different baseline characteristics of the populations in each study,

 

and differences in biopsy policies. The 10-year cumulative rate for recurrent IgAN in our study was 30.8%, which might have been underestimated because we did not perform protocol biopsies. Kim *et al.* reported a higher risk of recurrent IgAN (44%) after 10 years in a different Korean population [17]. The pooled data showed that there was a higher risk of disease recurrence among transplant recipients with related donors (HR 2.14, $P < 0.001$) as compared to unrelated donors [9]. However, each study included a small number of patients, or patients of multiple ethnicities, and different biopsy policies were implemented. Although our study included only Korean recipients, the data that we obtained with regard to the risk of recurrent IgAN, are more reliable as we performed multivariate analysis and included relatively large number of recipients.

Many trials have been carried out on the prevention of recurrent IgAN. In relation to maintenance immunosuppression, Chandrakantan *et al.* reported the impact of mycophenolate mofetil on the rate of recurrence [18]. Analysis showed that recurrent IgAN developed in 20% of the azathioprine group and in 7.7% of the mycophenolate mofetil group. However, after the follow-up interval had been adjusted for, there was no significant difference in the rate of incidence between the azathioprine (10%) and mycophenolate mofetil (8.1%) groups. Maes *et al.* also reported no beneficial effect upon renal function of treatment for 3 years with mycophenolate mofetil ($n = 21$) as compared with a placebo ($n = 13$) in a prospective placebo-controlled randomized trial [19]. Our data also showed that the use of any of the immunosuppressive agents analysed was not associated with the prevention of recurrent IgAN. In respect to induction therapy, Berthoux *et al.* revealed retrospectively the superiority of ATG to anti-CD25 antibody for reducing the recurrence rate [20]. However, their study was not a randomly controlled design and had different baseline data from our subjects (e.g., in Berthoux's study, most of donor type was from deceased one). We assumed that a low proportion of living related donor in their study could lead to different outcome. Certain HLA types have been examined with respect to their association with IgAN recurrence but no consistent relationship was found [10,11,21]. Our data showed no correlation between the risk of recurrent IgAN and certain HLA types, including HLA-A2, B35, and -DR4.

It is known that long-term graft survival in recipients whose primary renal disease is IgAN, is comparable to that for other etiologies of renal failure [11,17]. Although we did not compare long-term graft outcome between recipients with IgAN as the primary disease and those with disease of another etiology, 10-year graft survival rate showed better survival when compared with previous report [17]. This excellent graft survival rate could be attributable to the relatively low proportion of deceased donors, which was 18.6% in our patient cohort. Several studies have reported that recurrent IgAN after kidney transplantation affects the long-term survival of grafts [10,11]. Another report did not find an effect of donor type on the long-term graft survival [17]. In our study, univariate analysis showed that the presence of recurrent IgAN had a significant effect on graft survival. However, after multivariate analysis, the impact of recurrent IgAN on graft survival was reduced, particularly relative to CAN. This result was not surprising because CAN is the most common cause of graft loss [7]. Sumethkul *et al.* reported that the 2-year graft survival rate for recipients with recurrent IgAN was 12.5%; this was significantly less than that for recipients who had CAN (55.5%, $P = 0.04$) [22]. This finding as well as our data indicates that if a further decline of renal function occurs in recurrent IgAN allograft the potential contribution of other insults, such as CAN, should be considered.

Although our results are informative, our study has some limitations. First, the study design was retrospective and did not involve protocol kidney biopsy. However, this would have required us to gather data in a clinical setting because of the invasive nature of protocol biopsy. Second, all the recipients in our data set were Korean. Therefore, inferences from our data may not be applicable to other ethnicities. Third, Cox regression model has a limitation as it does not reflect the change of HR over a period of time. It has been known that recurrence is a time-dependent event [7].

It is expected that the number of kidney transplants performed will increase, and that long-term survival rates will be improved by the introduction of new immunosuppressive agents. To the best of our knowledge, this paper provides the largest-scale analysis with the most extended follow up to date of kidney transplantation resulting from IgAN. Furthermore, it could lead to new insights about graft survival in the presence of recurrent disease following kidney transplantation: CAN was found to have a greater impact than recurrent IgAN on graft survival. Consequently, although additional well-designed research, especially of prospective design is required, our data may be helpful in evaluating risk factors for recurrent disease and determining prognosis in the case of recurrent IgAN and CAN.

## Authorship

SSH: collected data, analysed results, performed study, wrote manuscript. WH and SKP: designed study, collected data. CA, JSH and SK: collected data. YSK: designed study, analysed results, wrote and edited the manuscript.

## Acknowledgements

This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A084001).

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