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# Recurrence of IgA Nephropathy after Kidney Transplantation in Adults

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## Abstract

**Background and objectives** In patients with kidney failure due to IgA nephropathy, IgA deposits can recur in a subsequent kidney transplant. The incidence, effect, and risk factors of IgA nephropathy recurrence is unclear, because most studies have been single center and sample sizes are relatively small.

**Design, setting, participants, & measurements** We performed a multicenter, international, retrospective study to determine the incidence, risk factors, and treatment response of recurrent IgA nephropathy after kidney transplantation. Data were collected from all consecutive patients with biopsy-proven IgA nephropathy transplanted between 2005 and 2015, across 16 "The Post-Transplant Glomerular Disease" study centers in Europe, North America, and South America.

**Results** Out of 504 transplant recipients with IgA nephropathy, recurrent IgA deposits were identified by kidney biopsy in 82 patients; cumulative incidence of recurrence was 23% at 15 years (95% confidence interval, 14 to 34). Multivariable Cox regression revealed a higher risk for recurrence of IgA deposits in patients with a pre-emptive kidney transplant (hazard ratio, 3.45; 95% confidence interval, 1.31 to 9.17) and in patients with preformed donor-specific antibodies (hazard ratio, 2.59; 95% confidence interval, 1.09 to 6.19). After kidney transplantation, development of *de novo* donor-specific antibodies was associated with subsequent higher risk of recurrence of IgA nephropathy (hazard ratio, 6.65; 95% confidence interval, 3.33 to 13.27). Immunosuppressive regimen was not associated with recurrent IgA nephropathy in multivariable analysis, including steroid use. Graft loss was higher in patients with recurrence of IgA nephropathy compared with patients without (hazard ratio, 3.69; 95% confidence interval, 2.04 to 6.66), resulting in 32% (95% confidence interval, 50 to 82) graft loss at 8 years after diagnosis of recurrence.

**Conclusions** In our international cohort, cumulative risk of IgA nephropathy recurrence increased after transplant and was associated with a 3.7-fold greater risk of graft loss.

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## Introduction

In patients who received a kidney transplantation for kidney failure due to IgA nephropathy, IgA deposits can recur in the transplanted kidney. The clinical course of recurrent IgA nephropathy is variable because it can be diagnosed in patients on a protocol biopsy who are asymptomatic, in patients with mild hematuria or proteinuria, or in patients with rapidly deteriorating kidney function. As a result, reported rates of recurrence vary significantly between 9% and 61%, mainly due to diverse biopsy protocols and differences in follow-up (1).

Recent studies have shown that recurrence of IgA nephropathy usually manifests a couple of years after transplantation, and longer follow-up studies showed lower survival rates after 5–10 years (2). Reported graft loss due to recurrent IgA nephropathy varies from 2% to 14% in studies with medium follow-up (3), but increase up to 29% in patients with symptomatic recurrent disease in long follow-up studies (2). A number of risk factors for IgA nephropathy recurrence have been described, including younger age at transplant, transplant without an induction agent, higher HLA-mismatch, and early steroid withdrawal immunosuppressive regimens (4–13). Because most performed studies are single center with relatively small sample sizes, outcomes are difficult to generalize and risk factors often cannot be validated in subsequent studies (Supplemental Table 1).

As part of The Post-Transplant Glomerular Disease (TANGO) project, we analyzed detailed retrospective

clinical data from patients with biopsy-proven IgA nephropathy in 16 centers located in three continents. In this study, we report IgA nephropathy recurrence rates, risk factors for recurrence, treatment strategies, and outcomes.

## Materials and Methods

### Study Design, Objectives, and Risk Factors

We performed a multicenter, international, retrospective study in patients from 16 TANGO kidney transplant centers in Europe, North America, and South America (14). The primary objective was to determine the incidence of recurrent IgA nephropathy after kidney transplantation in patients with a biopsy-proven native diagnosis of IgA nephropathy. Secondary objectives included identification of risk factors for IgA nephropathy recurrence, clinical outcomes of patients with and without IgA nephropathy recurrence, and treatment strategies of IgA nephropathy recurrence (see Supplemental Methods for further details).

### Patient Selection and Data Collection

In participating centers, all adult (aged >16 years) kidney transplant recipients between January 2005 and December 2015, with a biopsy-proven native diagnosis of IgA nephropathy were included. Detailed patient information was extracted from medical records. Patients were censored at the time of graft loss, patient death, loss to follow-up, or in January 2020.

In the primary analysis on incidence and risk factors for IgA nephropathy recurrence, one participating center in Brazil was excluded because biopsies on native kidneys were not routinely performed. However, we included patients with recurrent IgA nephropathy and pretransplant clinical course suspect for IgA nephropathy (*e.g.*, active urine sediment, proteinuria, no other explanation of symptoms) from this center ($n=26$) in the analysis to treatment and outcomes of recurrent IgA deposits.

### Statistical Analysis

Data are shown as frequencies (percentages) for categorical variables, and medians (interquartile range) or mean±SD for continuous variables. Statistical analysis of Table 1 was done by complete case analysis. Continuous variables were analyzed by *t* test; binary and categorical variables by chi-squared or Fisher's exact test, depending on group size.

Cumulative incidence, Kaplan–Meier curves and 95% confidence intervals (95% CIs) were graphed by Prism 7.02 software (GraphPad software, Inc). Log-rank test or Log-rank test for trend was used to compare two groups or three or more groups, respectively. Missing data are shown in Supplemental Table 2. STATA's multiple imputation by chained equations procedure was used to impute missing data (Supplemental Methods).

Univariable and multivariable Cox proportional hazards regression was performed with imputed data (Table 2). Categorical variables were entered as binary variables. Schoenfeld residuals were evaluated to assess the proportional-hazard assumption, and deviance residuals were used to examine model accuracy and outliers (Supplemental Methods). In Cox regression to graft failure, IgA nephropathy recurrence was treated as a time-varying covariate. In Cox regression analysis of Table 3, adverse events after kidney transplantation (acute rejection, cytomegalovirus [CMV], cancer, BK viremia, and *de novo* donor-specific antibodies [dnDSA]) were treated as time-varying covariates to assess the association between the occurrence of adverse events and subsequent development of recurrent IgA nephropathy. A two-sided *P* value of $<0.05$ was deemed significant in all tests. Statistical analyses were performed using Prism 7.02 software (GraphPad software, Inc) and STATA (v. 15.1, StataCorp LLC). Sensitivity analyses are described in the Supplemental Methods.

## Results

### Cohort Demographics

A total of 577 patients fulfilled the inclusion criteria and were included in a dedicated online database. In total, 47 patients were subsequently excluded because of patient death or loss to follow-up within 1 year after transplant, or primary nonfunction of the kidney transplant (Supplemental Figure 1). Patients from one Brazilian center who had post-transplant IgA deposits without a native biopsy-proven diagnosis of IgA nephropathy were excluded from the primary analysis, but included in secondary analyses ($n=26$). Finally, 504 patients with a biopsy-proven native diagnosis of IgA nephropathy were included for primary analysis. Patient and donor characteristics are shown in Table 1.

### Recurrence of IgA Deposits in the Transplanted Kidney

Over a median follow-up period of 8.7 (interquartile range, 5.5–11.2) years, biopsy-proven recurrence of IgA nephropathy occurred in 82 patients. The incidence of IgA nephropathy recurrence increased gradually after transplant (Figure 1), with a cumulative incidence of 19% at 10 years (95% CI, 12 to 26), and 23% at 15 years (95% CI, 14 to 34) after kidney transplantation. Among patients who experienced IgA nephropathy recurrence, median time to recurrence was 3.4 years (interquartile range, 1.4–5.7 years). Four patients had IgA deposits found on protocol biopsy (5%), whereas 78 recurrences were detected on a clinically indicated biopsy (95%).

In patients with IgA nephropathy recurrence compared with patients without, median age at time of transplant was lower (41 and 46, respectively; $P=0.02$), median time from IgA nephropathy diagnosis to kidney failure was lower (48 and 72 months, respectively; $P=0.04$), DSA at time of transplant was observed more frequently (8% versus 3%, respectively; $P=0.03$), and more patients with recurrent IgA nephropathy had received a pre-emptive transplant (30% versus 16%, respectively; $P=0.002$). Other variables did not differ between groups (Table 1).

A sensitivity analysis was performed to the recurrence rate of IgA nephropathy in patients who underwent a post-transplant kidney biopsy. Out of 455 patients (as detailed in Supplemental Methods), a post-transplant kidney biopsy was performed in 209 patients (46%). The cumulative incidence of IgA nephropathy recurrence in these patients was 42% (95% CI, 34 to 50) at 10 years after kidney transplantation.

### Risk Factors for IgA Nephropathy Recurrence

In univariable Cox regression, IgA nephropathy recurrence was associated with time on dialysis, age at

**Table 1. Baseline characteristics of participants in The Post-Transplant Glomerular Disease project with kidney failure due to IgA nephropathy and their kidney donors**

| Baseline Characteristic | Overall Cohort ($n$=504) | No Recurrence ($n$=422) | Recurrence ($n$=82) |
|---|---|---|---|
| Follow-up, yrs | 8.7 (5.5–11.2) | 8.8 (5.5–11.3) | 8.2 (5.7–10.6) |
| Age at transplantation, yrs | 46 (37–55) | 46 (38–56) | 41 (32–54) |
| Age at diagnosis, yrs | 33 (26–44) | 34 (26–44) | 31 (25–41) |
| Male sex | 362 (72) | 302 (72) | 60 (73) |
| **Race/Ethnicity** | | | |
| White | 354 (70) | 294 (70) | 60 (73) |
| Black | 13 (3) | 12 (3) | 1 (1) |
| Hispanic | 16 (3) | 14 (3) | 2 (2) |
| Asian | 33 (7) | 28 (7) | 5 (6) |
| Mixed | 5 (1) | 5 (1) | 0 (0) |
| Other/unknown | 83 (16) | 69 (16) | 14 (17) |
| BMI at transplantation, kg/m$^2$ | 25.8±4.6 | 25.9±4.6 | 25.1±4.4 |
| **Diseases associated with IgA nephropathy** | | | |
| Symptoms of Henoch-Schönlein purpura | 27 (5) | 23 (5) | 4 (5) |
| Autoimmune disease | 22 (4) | 18 (4) | 4 (5) |
| Liver disease | 7 (1) | 7 (2) | 0 (0) |
| Time from diagnosis to KF, mos | 66 (15–135) | 72 (17–143) | 48 (12–96) |
| Time on dialysis, mos | 17 (4–44) | 19 (5–44) | 11 (0–43) |
| **Type of dialysis** | | | |
| Hemodialysis | 283 (56) | 239 (57) | 44 (54) |
| Peritoneal dialysis | 94 (19) | 87 (21) | 7 (9) |
| Both | 35 (7) | 29 (7) | 6 (7) |
| None (pre-emptive transplant) | 92 (18) | 67 (16) | 25 (30) |
| First degree family member with kidney disease | 11 (2) | 11 (3) | 0 (0) |
| **Number of prior transplants** | | | |
| None | 434 (86) | 362 (86) | 72 (88) |
| 1 | 63 (13) | 55 (13) | 8 (10) |
| 2 | 7 (1) | 5 (1) | 2 (2) |
| PRA >50% | 35 (8) | 30 (8) | 5 (7) |
| DSA at time of transplant | 17 (4) | 11 (3) | 6 (8) |
| Deceased donor | 279 (56) | 238 (57) | 41 (51) |
| Extended criteria donor (KDPI>85%) | 48 (18) | 42 (19) | 6 (16) |
| Cold ischemia time, hours | 16±7 | 16±7 | 16±6 |
| Living donor | 222 (44) | 182 (43) | 40 (49) |
| Living related donor | 131 (60) | 107 (60) | 24 (62) |
| Donor age, years | 49 (39–58) | 50 (40–58) | 49 (35–57) |
| HLA-A/B/DR mismatch | 3.1±1.7 | 3.1±1.7 | 3.3±1.7 |
| **Induction therapy** | | | |
| None | 74 (15) | 61 (15) | 13 (16) |
| Basiliximab | 203 (41) | 171 (41) | 32 (39) |
| Antithymocyte globulin | 176 (35) | 143 (34) | 33 (40) |
| Daclizumab | 39 (8) | 38 (9) | 1 (1) |
| Other | 8 (2) | 5 (1) | 3 (4) |
| **Baseline immunosuppressive regimen** | | | |
| Tacrolimus + MMF + steroids | 355 (71) | 296 (70) | 59 (73) |
| Cyclosporine + MMF + steroids | 89 (18) | 77 (18) | 12 (15) |
| Tacrolimus + MMF | 19 (4) | 15 (4) | 4 (5) |
| Other | 40 (8) | 34 (8) | 6 (7) |
| Steroid free/ early steroid withdrawal | 76 (15) | 59 (14) | 17 (21) |

Values represent frequency (percentage), mean±SD or median (interquartile range). BMI, body mass index; KF kidney failure; PRA, panel reactive antibody; DSA, donor-specific antibody; KDPI, Kidney Donor Profile Index; MMF, mycophenolate mofetil.

transplantation, pre-emptive transplant, presence of preformed DSA, and time to kidney failure (Table 2). In multivariable analysis, pre-emptive transplant (hazard ratio [HR], 2.56; 95% CI, 1.59 to 4.17; $P$<0.001) and presence of DSA before transplant (HR, 2.74; 95% CI, 1.22 to 6.14; $P$=0.01) remained associated with recurrent IgA nephropathy. Because pre-emptive transplantation was associated with IgA nephropathy recurrence, we analyzed subgroups for better interpretation of data. In 92 patients with a pre-emptive transplantation, there was no difference in recurrence between deceased or living donation (HR, 2.33; 95% CI, 0.61 to 8.81), or between related and unrelated living donation (HR, 0.93; 95% CI, 0.37 to 2.31), analyzed by Cox regression adjusted for time to kidney failure and DSA. In 412 patients treated with dialysis pretransplant, time on dialysis was not associated with recurrence (HR, 1.05 per month; 95% CI, 0.82 to 1.36; $P$=0.69). Interestingly, peritoneal dialysis was associated with lower recurrence rates (HR, 0.42; 95% CI, 0.19 to 0.94; $P$=0.03) compared with hemodialysis. The geographical location (Europe, United States, or Brazil) of the patient was not associated with recurrence (Table 2). Furthermore, the

**Table 2. Associations of clinical characteristics with recurrence of IgA nephropathy**

| Variable | Missing Values (%) | Total Number of Events | Unadjusted Analysis Hazard Ratio (95% Confidence Interval) | Multivariable Analysis Hazard Ratio (95% Confidence Interval) |
|---|---|---|---|---|
| **Geographic location of center** | 0 (0) | | | |
| Brazil | | 6 | ref | ref |
| Europe | | 48 | 0.78 (0.33 to 1.84) | 0.93 (0.37 to 2.36) |
| United States | | 28 | 0.96 (0.39 to 2.32) | 0.91 (0.33 to 2.49) |
| Age at diagnosis IgA nephropathy, per 10 yrs | 37 (7) | 77 | 0.94 (0.79 to 1.12) | 1.14 (0.78 to 1.67) |
| White race | 79[a] (16) | 68 | 1.25 (0.61 to 2.54) | 1.59 (0.70 to 3.62) |
| BMI, per kg/m$^2$ | 0 (0) | 82 | 0.96 (0.91 to 1.01) | 0.96 (0.91 to 1.01) |
| Time on dialysis, per mo (log)[b] | 10 (2) | 82 | 0.84 (0.73 to 0.97)* | 1.13 (0.84 to 1.53) |
| Age at transplantation, per 10 yrs | 1 (0) | 81 | 0.81 (0.68 to 0.96)* | 0.79 (0.53 to 1.18) |
| Pre-emptive transplant | 0 (0) | 82 | 2.27 (1.41 to 3.57)* | 3.45 (1.31 to 9.17)* |
| Living donor | 3 (1) | 81 | 1.34 (0.87 to 2.08) | 1.03 (0.57 to 1.87) |
| Age donor, per 10 yrs | 55 (11) | 72 | 0.93 (0.79 to 1.10) | 0.99 (0.82 to 1.21) |
| **HLA mismatch >3** | 68 (13) | | | |
| 0 | | 7 | ref | ref |
| 1–3 | | 35 | 1.06 (0.47 to 2.39) | 1.10 (0.45 to 2.65) |
| 4–6 | | 29 | 1.03 (0.46 to 2.33) | 1.08 (0.43 to 2.69) |
| Presence of DSA at transplantation | 43 (9) | 73 | 3.11 (1.38 to 7.00)* | 2.59 (1.09 to 6.19)* |
| **Induction** | 8 (2) | | | |
| None | | 13 | ref | ref |
| Basiliximab/caclizumab | | 33 | 0.83 (0.44 to 1.58) | 0.97 (0.48 to 1.96) |
| ATG/alemtuzumab | | 34 | 1.21 (0.63 to 2.29) | 1.12 (0.54 to 2.31) |
| IgA associated autoimmune diseases[c] | 0 (0) | 82 | 0.86 (0.40 to 1.88) | 0.73 (0.32 to 1.64) |
| Immunosuppression with tacrolimus + MMF + steroids | 1 (0) | 81 | 1.28 (0.78 to 2.09) | 1.20 (0.68 to 2.13) |
| Time to KF, per mo (log)[b] | 32 (6) | 80 | 0.88 (0.77 to 1.00)* | 0.90 (0.75 to 1.08) |
| Steroid free/early steroid withdrawal | 3 (1) | 82 | 0.78 (0.37 to 1.64) | 1.53 (0.80 to 2.90) |

ref, reference; BMI, body mass index; DSA, donor-specific antibody; MMF, mycophenolate mofetil; KF, kidney failure.
[a]Most patients with missing race come from France, where race/ethnicity is not allowed to be reported.
[b]Variables "time on dialysis" and "time to kidney failure" were natural log-transformed; hazard ratios are to be interpreted per natural log unit increase.
[c]IgA associated autoimmune diseases: Henoch-Schönlein purpura, infective bowel disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, diabetes mellitus type 1, Hashimoto's thyroiditis. *P* value is *statistically significant.

presence of systemic autoimmune diseases associated with IgA nephropathy did not affect recurrence of IgA nephropathy, neither did early steroid withdrawal or a younger age at kidney transplantation.

Among 70 patients with a prior kidney transplantation, 23 patients had lost a prior graft due to recurrent IgA nephropathy ($n$=19) or a combination of recurrent IgA nephropathy and rejection ($n$=4). In these patients, the incidence of recurrent IgA nephropathy in the new transplanted kidney was similar to the full cohort ($n$=4, 17%).

## Graft Failure

Graft loss occurred in 16 patients (20%) with recurrent IgA nephropathy, compared with 49 (12%) in patients without

**Table 3. Associations of post-transplantation time-dependent adverse events with development of IgA nephropathy recurrence**

| Adverse Event, Treated as Time-Varying Covariate | Overall Cohort ($n$=455) | No Recurrence ($n$=378) | Recurrence ($n$=77) | Number of Recurrences after Adverse Event | Hazard Ratio (95% Confidence Interval) |
|---|---|---|---|---|---|
| Acute rejection | 67 (15) | 49 (13) | 18 (23) | 17 | 1.77 (0.97 to 3.21)[a] |
| Cellular-mediated | 53 (12) | 40 (11) | 13 (17) | | |
| Antibody-mediated | 13 (3) | 8 (2) | 5 (6) | | |
| CMV | 74 (16) | 64 (17) | 10 (13) | 6 | 0.50 (0.22 to 1.15) |
| Cancer | 101 (22) | 83 (22) | 18 (23) | 11 | 1.53 (0.77 to 3.05) |
| BK viremia | 36 (8) | 27 (7) | 9 (11) | 6 | 1.51 (0.66 to 3.50) |
| *De novo* DSA | 51 (11) | 35 (9) | 16 (21) | 12 | 6.65 (3.33 to 13.27)[a] |

In one European center, not all post-transplant complications were registered, therefore analysis of Table 3 was limited to 455 patients from 14 centers. Hazard ratios to the effect of adverse events on development of IgA nephropathy recurrence were calculated by Cox regression, treating the adverse event (acute rejection, CMV, cancer, BK viremia, and *de novo* DSA, respectively) as time-varying covariate. CMV, cytomegalovirus; DSA, donor-specific antibodies.
[a]Hazard ratio is corrected for pretransplant DSA and pre-emptive kidney transplant.

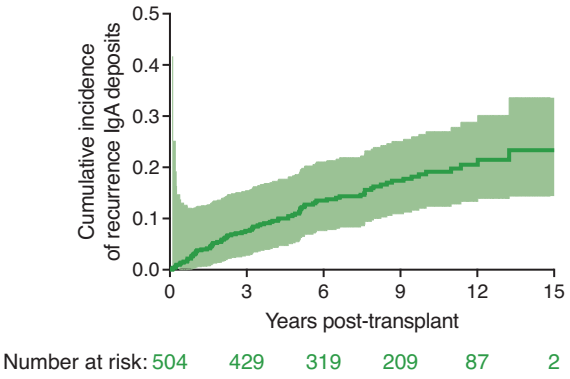


**Figure 1.** | **Recurrent IgA postkidney transplantation.** Cumulative incidence curve of IgA recurrence in kidney transplant recipients with biopsy-proven IgA nephropathy. Cumulative incidence of recurrence of IgA deposits was 19% at 10 years and 23% at 15 years. Among patients with IgA nephropathy recurrence, median time to recurrence was 3.4 years. Shaded area around the curve represents the 95% confidence interval.

recurrence. The 10-year death-censored graft survival was 76% in patients with and 89% in patients without recurrence. However, because many patients with IgA nephropathy recurrence experienced recurrence several years after transplant, the analysis comparing recurrence groups is likely to be biased due to immortal time bias. We therefore performed subsequent analyses with IgA nephropathy recurrence as a time-varying covariate. A multivariable Cox regression to graft failure, treating IgA nephropathy recurrence as a time-varying variable and adjusted for HLA mismatch, pretransplant DSA, donor type, donor age, and pre-emptive transplant, revealed an HR 3.69 (95% CI, 2.04 to 6.66; $P<0.001$) in patients with recurrent IgA nephropathy compared with patients without. Kaplan–Meier analysis to graft failure after diagnosis of IgA nephropathy recurrence revealed graft survival of 94% at 1 year, 83% at 5 years, and 68% at 8 years after diagnosis (Figure 2).

In patients with IgA nephropathy recurrence, graft failure was attributed to recurrent IgA nephropathy alone ($n=7$; 44%), a combination of chronic rejection and recurrent IgA nephropathy ($n=2$), graft rejection ($n=2$), and unknown cause ($n=5$). In patients without recurrence, graft failure was attributed to (chronic) rejection ($n=26$), BK nephropathy ($n=5$), *de novo* glomerular disease ($n=1$), infection ($n=2$), calcineurin inhibitor nephropathy ($n=2$), or unknown or other ($n=13$) etiology.

In total, 53 patients died with a functioning graft during follow-up: 46 (11%) in patients without versus seven patients (9%) with IgA nephropathy recurrence ($P=0.66$).

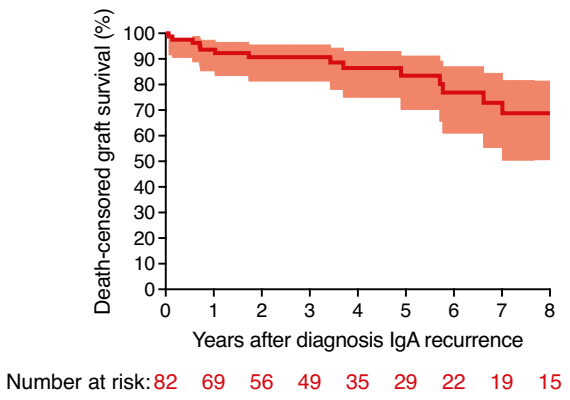


**Figure 2.** | **Graft survival in patients with recurrent IgA nephropathy post-transplantation**. Kaplan–Meier graft survival curve of patients with IgA nephropathy recurrence after diagnosis. Area around the curve represents 95% confidence intervals.

### Events Postkidney Transplantation

As native IgA nephropathy is associated with dysregulation of the immune system (15), we investigated the incidence of IgA nephropathy recurrence after development of immune-related events post-transplantation. In unadjusted analysis, the occurrence of CMV, BK viremia, or cancer was not associated with subsequent IgA nephropathy recurrence, although the number of IgA nephropathy recurrences after CMV, BK, or cancer was low and adjusted analysis was therefore not possible (Table 3). In multivariable analysis, adjusted for pre-emptive transplantation and preformed DSA, occurrence of acute rejection was not associated with subsequent IgA nephropathy recurrence; however, IgA nephropathy recurrence rates were higher in patients after development of dnDSA (HR, 6.65; 95% CI, 3.33 to 13.27; $P<0.001$).

Because IgA deposits could be a coincidental finding as a result of increased surveillance and number of biopsies performed in patients with dnDSA, we performed two sensitivity analyses. Assessing only patients who had undergone a kidney biopsy, occurrence of dnDSA was associated with subsequent IgA nephropathy recurrence (HR, 3.41; 95% CI, 1.74 to 6.70; $P<0.001$). Post-transplant DSA testing was performed at least once in 270 patients (59%), and in this analysis, development of dnDSA was associated with subsequent IgA recurrence (HR, 6.05; 95% CI, 2.91 to 12.61; $P<0.001$).

### Clinical Signs, Treatment, and Outcomes in Patients with Recurrent IgA Nephropathy

A total of 108 patients were included for analysis of clinical signs and treatment of IgA nephropathy recurrence: 82 from the general cohort and 26 patients with recurrent IgA nephropathy without native biopsy from one center in Brazil. At time of recurrence, 32 (30%) patients had proteinuria with or without hematuria, 30 (28%) patients only had a rise in creatinine, whereas 42 (39%) patients experienced a rise in creatinine with proteinuria or hematuria. Four patients had no significant kidney manifestations (IgA deposits found on protocol biopsy) and did not experience graft loss during follow-up. Patients with proteinuria at time of recurrence were more likely to develop graft failure after diagnosis compared with patients with only a rise in creatinine ($P=0.002$, Figure 3).

In 95 out of 105 kidney biopsy reports, a score was given to the amount of mesangial proliferation (no, mild, moderate, severe). No difference in graft survival between groups was found (Supplemental Figure 2). Additionally, the strength of IgA staining (1+ to 4+) did not correlate with graft outcome (data not shown).

After diagnosis of recurrent IgA nephropathy, most patients with available information on treatment regimen,

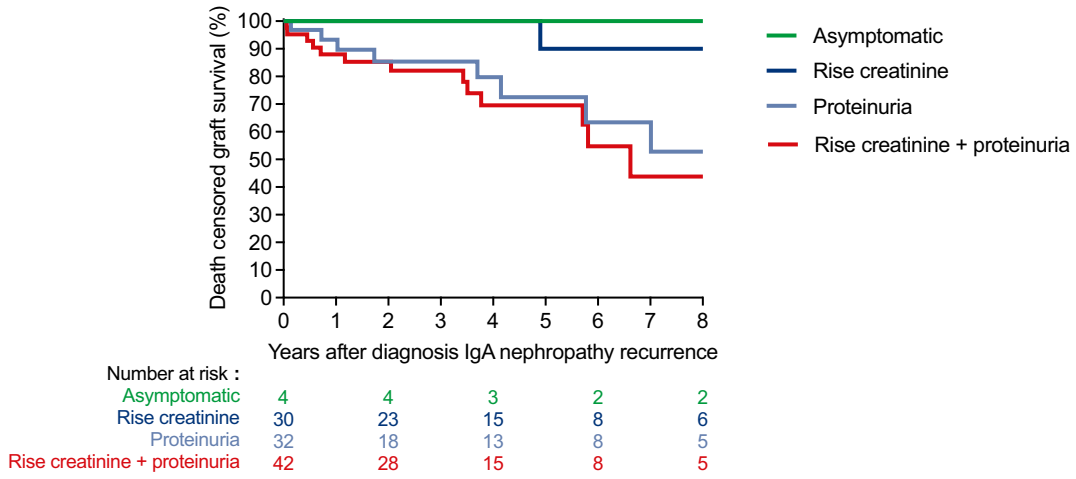


**Figure 3.** | **Clinical signs at time of IgA nephropathy recurrence and graft survival.** Death-censored Kaplan–Meier analysis to graft survival in patients with IgA nephropathy recurrence, stratified by the presence of proteinuria and/or rise in creatinine.

received angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) ($n$=78, 75%). Other treatments included pulse steroids ($n$=25; 24%), increased dose of mycophenolate mofetil or adding steroids to the immunosuppressive regimen ($n$=10, 10%), cyclophosphamide ($n$=4, 4%), and/or treatment for concurrent rejection ($n$=8, 8%). A total of 11 patients (11%) received no treatment for IgA recurrence. Patients who received ACEi/ARB did not have better graft outcomes after diagnosis of IgA nephropathy recurrence ($P$=0.86) (Supplemental Figure 3).

## Discussion

In this multicenter international cohort of kidney transplant recipients, because of IgA nephropathy, cumulative incidence of recurrent IgA nephropathy was 19% at 10 years and 23% at 15 years after kidney transplantation. If only patients who had undergone a post-transplant kidney biopsy are analyzed, the recurrence rate was 42% after 10 years. In multivariable analysis to risk factors, a pre-emptive transplant and presence of DSA at time of transplantation were associated with recurrence of IgA deposits. Post-kidney transplantation, development of dnDSA was also associated with subsequent IgA nephropathy recurrence. Recurrent IgA nephropathy was mostly found on clinically indicated biopsy (95%), and was independently associated with a 3.7-fold higher risk of graft loss. Clinical presentation at time of recurrence was of importance for graft survival because patients with proteinuria had worse outcomes compared with patients without. Management of recurrent IgA deposits was mainly focused on starting or increasing ACEi or ARB.

The incidence of recurrent IgA nephropathy found in our cohort is in accordance with previous literature, because it lies within most confidence intervals of other studies (Supplemental Table 1). The incidence is, however, on the lower side, which might be explained by the fact that most centers in this study did not perform protocol biopsies post-kidney transplantation. Patients with Henoch-Schönlein purpura in our cohort had equal recurrence rates compared with patients with solely IgA nephropathy, which is also in accordance with prior studies (16).

We found a strong association between a pre-emptive transplant and recurrence of IgA deposits. To our knowledge, a pre-emptive transplant has not been linked to IgA nephropathy recurrence before, possibly because this variable was usually not included in prior studies. Because most pre-emptive transplants were from living donors (85%) and few previous studies had found an association between living (related) donation and IgA nephropathy recurrence (6,17,18), it is important to exclude any bias regarding donor type. In our cohort, the association between pre-emptive transplantation and IgA nephropathy recurrence was not affected by type of donation (deceased, living related, living unrelated), both in the general cohort and in patients with a pre-emptive transplant. The reason why pre-emptive transplanted patients had an associated higher risk of recurrence is not clear. It could be hypothesized that, similar to lupus nephritis, active and/or aggressive IgA nephropathy disease may "burn-out" on dialysis (19), although there was no effect of length of dialysis on recurrence.

The association between pretransplant DSA and recurrence of IgA nephropathy should be interpreted with caution. The outcomes of patients with DSA could be confounded by the increased surveillance that these patients might have had. However, we also found a post-transplant association between dnDSA and subsequent IgA nephropathy recurrence, which makes a possible relation between IgA nephropathy recurrence and DSA more likely. Although our results cannot be used to state any definitive conclusion due to the low number of patients with preformed or dnDSA who experienced IgA nephropathy recurrence, they do provide a rationale for subsequent studies testing the relationship between DSA and IgA nephropathy recurrence. Both IgA nephropathy recurrence and dnDSA could reflect a primary lack of sufficient immunosuppression. Nonetheless, we found no evidence for an effect of baseline immunosuppression and induction therapy on IgA nephropathy recurrence. Of note, immunosuppressant use was homogeneous

with 89% of patients receiving calcineurin inhibitors, mycophenolate mofetil, and steroids. Few prior studies have reported an association between early steroid withdrawal and IgA nephropathy recurrence, although these studies have important limitations, such as large differences in groups at baseline (including immunosuppression), no or only limited multivariable analysis, and/or possibility of bias due to biopsy practices or patient selection (10,13,20,21). In agreement with other studies (7,22,23), we did not find an association between early steroid withdrawal and IgA nephropathy recurrence in multivariable analysis.

There are no universally accepted guidelines for the treatment of recurrent IgA nephropathy (24). ACEi/ARB treatment was often used after IgA nephropathy recurrence and was not associated with graft outcomes, but the control group of patients not receiving such therapies was small. Additional therapies, such as pulse steroids or intravenous cyclophosphamide, lack strong evidence in literature. Nonetheless, in >25% of patients, one of these treatments was used.

The main limitations of this study comprise the retrospective design, noncentralized pathology, and the possibility of patients with undiagnosed recurrent IgA nephropathy due to the absence of protocol biopsy. A retrospective study inherently has the potential of bias regarding selection, imputation of missing data, and adjustment of confounders. Because of the large number of centers, we were only able to correct for continent, not for center-to-center variability and different practices. Pathology was not centralized and, therefore, differences across centers could be present, although detailed history and biopsy reports were obtained to minimize variation. A clinical limitation of the study entails the variety in which IgA nephropathy recurrence can manifest, which can be very similar to other pathology, such as transplant glomerulopathy, and therefore can be missed. Lastly, because most patients in our cohort had kidney manifestations at presentation, our data can only be extracted to IgA nephropathy recurrence with clinical signs, not to IgA nephropathy recurrences found on protocol biopsy.

In conclusion, our study shows patients with recurrent IgA deposits detected on clinically indicated biopsy are at higher risk of graft failure. Additionally, our findings reveal an association between recurrence of IgA nephropathy and a pre-emptive transplantation, preformed DSA, and dnDSA after kidney transplantation. In contrast to previous studies, steroid withdrawal did not correlate with higher incidence of IgA nephropathy recurrence. Future studies are needed to test ideal management and treatment strategies to improve the outcomes of affected individuals.

## Disclosures

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## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

## Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00910121/-/DCSupplemental.

Supplemental Methods.

Supplemental Table 1. Published nonregistry studies on incidence of recurrence of IgA nephropathy since 2000 including >50 subjects.

Supplemental Table 2. Missing data per variable in patients without and with recurrent IgA nephropathy.

Supplemental Figure 1. Flow chart of the study population .

Supplemental Figure 2. Kaplan–Meier analysis to death-censored graft survival in patients with IgA nephropathy recurrence after time of diagnosis, stratified by degree of mesangial expansion on kidney biopsy.

Supplemental Figure 3. Kaplan–Meier analysis to graft survival in patients with recurrent IgA after time of diagnosis, treated with or without ACEi/ARB.

Supplemental References.

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## Supplemental Material

**Supplemental Methods**

**Supplemental Table 1.** Published non-registry studies on incidence of recurrence of IgA nephropathy since 2000 including >50 subjects

**Supplemental Table 2**. Missing data per variable in patients without and with recurrent IgA

**Supplemental Figure 1.** Flow chart of the study population

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**Supplemental Figure 3.** Kaplan Meier analysis to graft survival in patients with recurrent IgA treated with or without ACEi/ARB

**Supplemental References**

## Supplemental methods

Patient selection and data collection (continued)

Collected patient information comprised demographics, past medical history, information on native biopsy, transplantation characteristics, immunosuppressive regimen and yearly follow-up visits after transplant including clinical parameters, rejection, IgA recurrence and other complications.

Predictor selection

We selected and collected data on the following potential predictors of recurrent IgA deposits, based on prior literature and clinical practice: age at diagnosis, race, BMI, time on dialysis, age at transplantation, pre-emptive transplant, living donor, age of donor, HLA-mismatch, presence of DSA at time of transplant, induction therapy, IgA associated diseases (e.g., auto-immune and Henoch-Schönlein Purpura), immunosuppressive regimen, time to ESKD and steroid free regimen/early steroid withdrawal. To account for the different geographical regions in which the patients were followed up, continent of residence was added as a predictor.

Definitions

Recurrence of IgA was defined as mesangial IgA deposits in kidney biopsy, with or without mesangial expansion and/or endocapillary hypercellularity. If IgA deposits were present in other parts of the biopsy without mesangial deposition, the patient was considered as non-recurrent. Patients with potential IgA recurrence because of proteinuria, hematuria or a rise in creatinine, but without confirmatory kidney biopsy, were also considered non-recurrent.

eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) study equation. Acute antibody- or T cell mediated rejection was recorded if confirmed on renal biopsy by the pathologist of the corresponding center. Borderline rejection was not considered acute rejection. New onset diabetes was defined as a new and persistent elevation of blood glucose levels post-transplantation requiring glucose lowering medication. Early steroid withdrawal was defined as the withdrawal of steroids within 3 months after kidney transplantation. Non-

compliance was recorded if this was highly suspected or confirmed by the patient's physician, noted in the charts. De novo DSA was recorded if MFI (mean fluorescent intensity) of anti-HLA antibodies exceeded the center's threshold for positivity. Proteinuria was checked by spot urine, protein to creatinine ratio, or 24-hour urine collection, depending on transplant center's clinical practice.

Biopsy assessment of IgA nephropathy and scoring of mesangial proliferation and/or intensity of IgA staining was performed in each center by the local pathologist. Biopsy reports were thoroughly reviewed.

Statistical analysis (continued)

Little's missing completely at random (MCAR) test was performed on all predictors and outcome to investigate randomness of missing data and resulted in a significant outcome ($p<0.001$), which implies that the pattern of missing data was not completely at random. However, detailed analysis of missing data showed a low frequency of missing data (overall 4%) and Fisher's exact test showed no difference per predictor between recurrence groups. We therefore proceeded with imputation for missing data.

STATA's multiple imputation by chained equations (MICE) procedure was used to impute missing categorical, ordinal, normal continuous and non-normal continuous variables by logistic regression, ordinal regression, linear regression and predictive mean matching, respectively. For each missing value, 100 values were imputed, using all predefined predictors, including recurrence and graft failure. In case of perfect prediction, augmentation was performed to avoid bias in imputations. Imputations were graphically assessed on outliers and variances and coefficients of the imputed cox-models were checked on agreement with complete case analysis.

Schoenfeld residuals were evaluated to assess the proportional-hazard assumption. In our predictor analysis (Table 2), the proportional-hazard assumption was violated in analyses with the variables "pre-emptive transplant" and "recurrence", tested by Schoenfeld residuals. We therefore proceeded with adding a time-interaction (time after

transplant) to the model and performing stratified analysis to perform a better interpretation of the data. Indeed, for the variables “pre-emptive transplant” and “recurrence”, an interaction with time was significant ($p<0.001$), after which we concluded that proportional hazards for these variables changed over time. Deviance residuals were used to examine model accuracy and outliers, after which time on dialysis and time to kidney failure were log-transformed to improve random scatter of residuals.

Sensitivity analyses

We performed a sensitivity analysis to determine the impact of the chosen method for imputation of missing data. Complete case analysis on the final multivariable model (DSA at time of transplant and pre-emptive kidney transplantation) resulted in an analysis on 461 patients with 73 IgA recurrences. Similar to the imputed model, significant p-values for all variables were observed. Furthermore, univariable complete case analysis for each variable showed similar significance and hazard ratios compared to univariable analysis with imputed values.

We furthermore performed sensitivity analyses limited to patients who were biopsied or who were tested for DSA. These analyses were performed in 455 patients, since in one center, post-transplant information regarding complications, de novo DSA and biopsies were not complete. We therefore decided to remove all data from this center for post-transplant analysis.

Lastly, we performed an analysis to patients who were excluded from the cohort because they died or had follow-up less than one year. In the group of patients lost to follow-up, 19 out of 32 patients did not have any follow-up information entered to the online database, only baseline data, and were therefore excluded. The other 13 patients were lost to follow-up with a median time of 1.6 months (range 2 weeks - 5.8 months) after transplant. Seven patients died within 8 months of transplant. To investigate whether excluding these 7 patients who died and 13 who were lost to follow-up would change our primary outcome, we calculated cumulative incidence of the total cohort with these 20 patients included. Ten-year graft survival was 19% (95%CI 12-27), and increased to 23% (95%CI 14-34) at 15 years, which is in accordance with the numbers of the final cohort.

Data storage

All data was stored in an ad hoc designed database using REDCapTM (Research Electronic Data Capture); a secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure and Services (ERIS) group. (S1,S2) Investigators received access to the secured website to enter and access patient data online, but were only able to access their individual centers' data, not from other centers. Upon downloading of the dataset, specific dates were date-shifted to complete de-identification of the dataset to ensure confidentiality of participants.

Ethical considerations

The overall protocol of TANGO-study was submitted and approved by the ethical committee of the Partners Human Research Committee (PHRC) at the Brigham and Women's hospital in Boston (protocol number: 2015P000993), and at each participating center. In one participating center, the University Medical Center Groningen, ethical approval was waived by the Medical Ethics review Board (METc UMCG). All protocols are in accordance with International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.(S3)

Potential sources of bias

We implemented the following strategies to avoid potential sources of bias: Centers were instructed to chronologically add patients according to their date of transplant, to avoid selection bias towards patients who had a recurrence. We recorded detailed medical histories and review of histories and biopsies of patients included in our database was done in a blinded fashion for the primary outcome of post-transplant IgA recurrence. Each case of post-transplant recurrence or graft loss was reviewed and when questions were raised (e.g., important missing information, inconsistencies in data), clarification was asked from the specific center to verify the data. Analyses to graft failure and complications post-transplant were corrected for the most important confounders known from literature. The multi-center setup of this study over multiple continents was done to make sure many ethnical

groups were present to avoid population bias. Unfortunately, some ethnical groups (especially patients with an African-American background) were still underrepresented. An analysis plan with clearly defined outcome and predictors (selected from literature) was made before the start of data-analysis and was followed throughout the analysis of data.

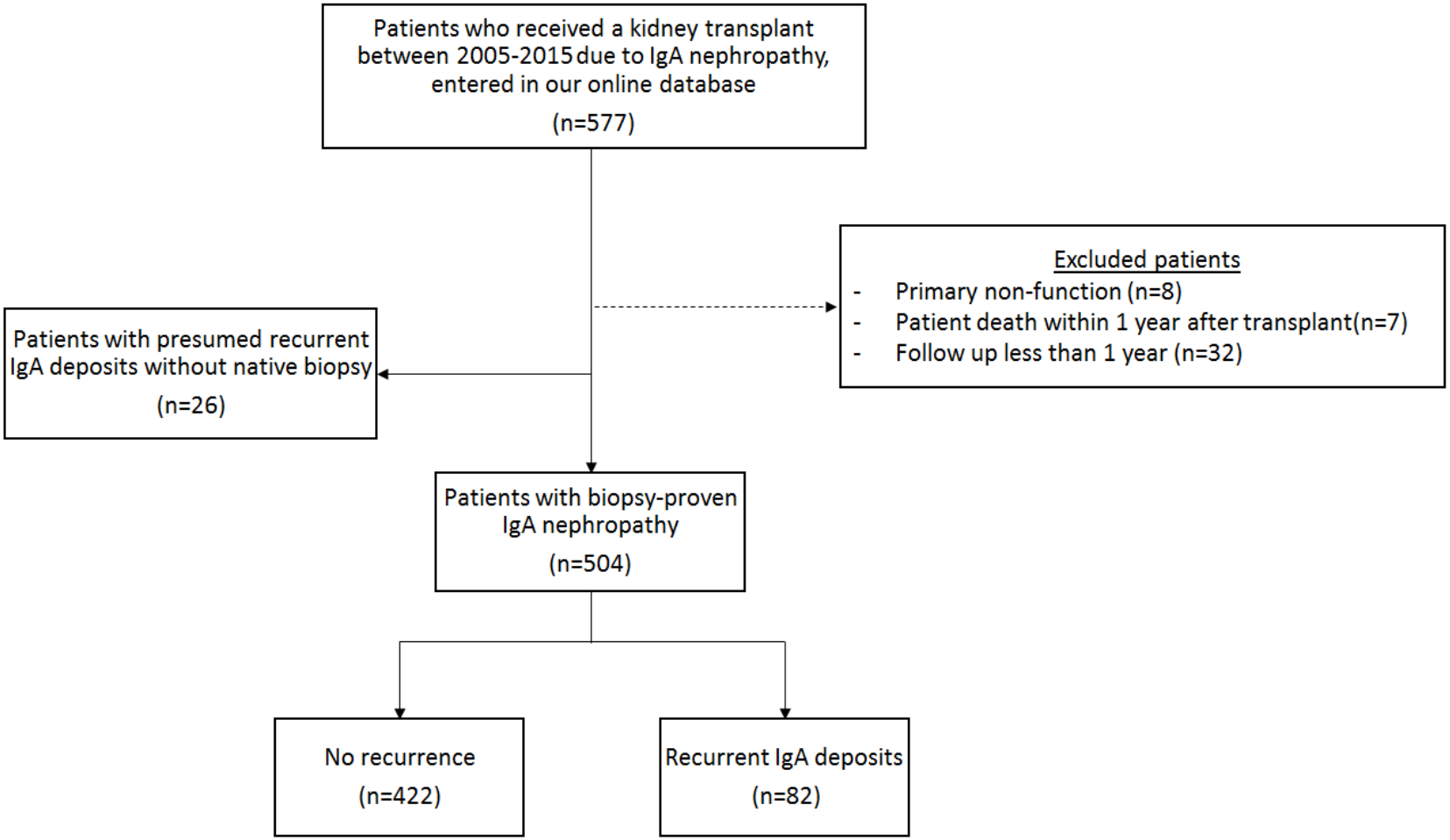
**Supplemental Table 1.** Published non-registry studies on incidence of recurrence of IgA nephropathy since 2000 including >50 subjects

| Year | Population | Total n | Incidence | 95% CI | Analysis | Clinical or protocol biopsy | Ethnicity | Risk factors |
|---|---|---|---|---|---|---|---|---|
| 2001(S4) | Adults | 106 | 35% | 26-44 | Multivariable | Mixed | Mainly white | Younger age at transplant |
| 2001(S5) | Adults | 79 | 22% | 12-31 | Univariable | Mixed | Mainly white | Living related donor |
| 2001(S6) | Adults | 90 | 21% | 13-30 | Univariable | Clinical | Asian | None |
| 2003(S7) | Adults | 75 | 19% | 10-27 | Univariable | Clinical | Asian | None |
| 2005(S8) | Adults | 152 | 13% | 8-19 | Univariable | Clinical | Mainly white | None |
| 2006(S9) | Adults | 75 | 17% | 9-26 | Univariable | Clinical | Mainly white | None |
| 2008(S10) | Adults | 116 | 28% | 20-37 | Multivariable | Clinical | Mainly white | No induction compared to ATG |
| 2009(S11) | Adults | 221 | 20% | 15-25 | Multivariable | Clinical | Mainly Asian | Younger age at transplant, living related donor |
| 2012(S12) | Adults | 65 | 32% | 21-44 | Univariable | Mixed | Mainly white | Younger donor age, use cyclosporine protective |
| 2012(S13) | Adults | 142 | 18% | 11-24 | Univariable | Clinical | Mainly white | None |
| 2013(S14) | Adults | 190 | 22% | 16-28 | Multivariable | Clinical | Mainly white | Younger age at transplant, triple immunosuppressive therapy |
| 2014(S15) | Adults | 78 | 15% | 7-23 | Multivariable | Mixed | Mainly Asian | Unclear (data conflicting) |
| 2014(S16) | Adults | 124 | 22% | 15-29 | Multivariable | Clinical | Mixed | Steroid free regimen, no induction compared to ATG, sirolimus based regimen, use of MMF protective |
| 2015(S17) | Children and Adults | 56 | 30% | 18-42 | Univariable | Clinical | Asian | Younger age at transplantation, shorter time on dialysis |
| 2016(S18) | Adults | 104 | 19% | 12-27 | Univariable | Clinical | Mixed races | Younger age at transplantation |
| 2017(S19) | Adults | 96 | 35% | 26-45 | NA | Clinical | Unknown | NA |
| 2017(S20) | Adults | 62 | 23% | 12-33 | Multivariable | Clinical | Mixed races | Younger age at diagnosis, crescents on native biopsy, acute rejection |
| 2018(S21) | Adults | 123 | 23% | 15-30 | Univariable | Clinical | Mainly white | Early steroid withdrawal |
| 2018(S22) | Adults | 67 | 21% | 11-31 | Univariable | Clinical | Unknown | Serum IgA level |

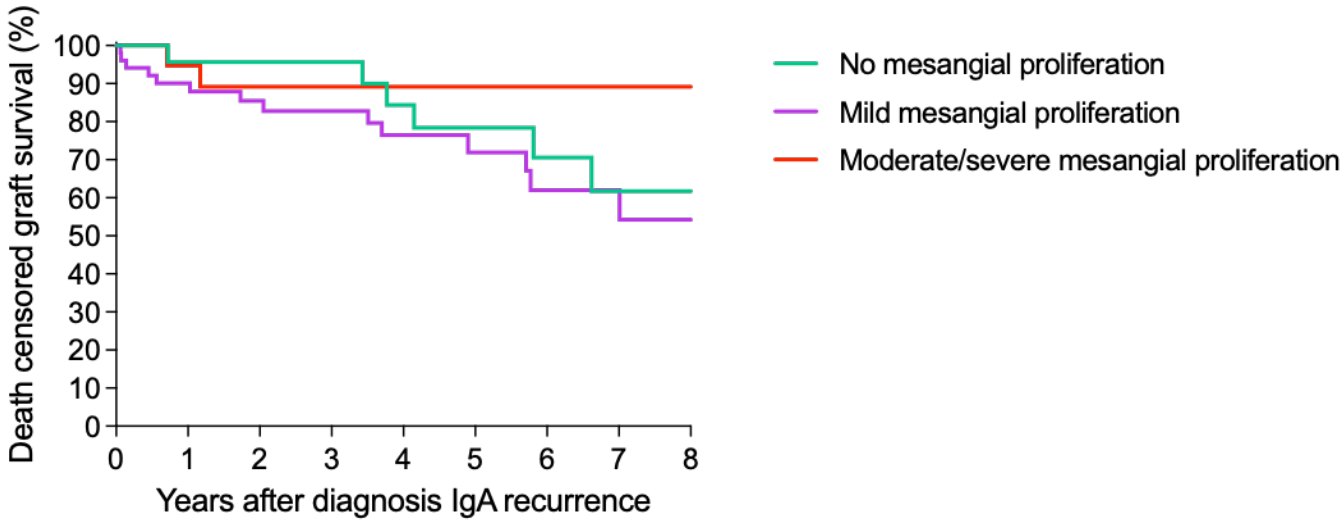
**Supplemental Table 2.** Missing data in variables comparing patients without and with recurrent IgA

| Variable | No recurrence (n=422) | Recurrence (n=82) | P-value |
|---|---|---|---|
| Age at diagnosis | 32 (6) | 5 (6) | 0.81 |
| White race | 65 (15) | 14 (17) | 0.74 |
| BMI | 0 (0) | 0 (0) | NA |
| Time on dialysis | 10 (2) | 0 (0) | 0.38 |
| Age at kidney transplantation | 0 (0) | 1 (1) | 0.16 |
| Age donor | 45 (11) | 10 (12) | 0.70 |
| Steroid withdrawal/ steroid free regimen | 3(1) | 0 (0) | 1.00 |
| Induction | 7 (2) | 1 (1) | 0.64 |
| Immunosuppression with Tac +MMF + st | 0 (0) | 1 (1) | 0.16 |
| Geographic location of center | 0 (0) | 0 (0) | NA |
| Living transplant | 2 (0) | 1 (1) | 0.41 |
| Pre-emptive transplant | 0 (0) | 0 (0) | NA |
| Time to kidney failure | 30 (7) | 2 (2) | 0.14 |
| DSA at time of transplant | 34 (8) | 9 (11) | 0.39 |
| HLA-mismatch | 57 (14) | 11 (13) | 1.00 |
| IgA associated diseases | 0 (0) | 0 (0) | NA |
| **Total missing values (% of all data)** | 285 (4) | 55 (4) | |

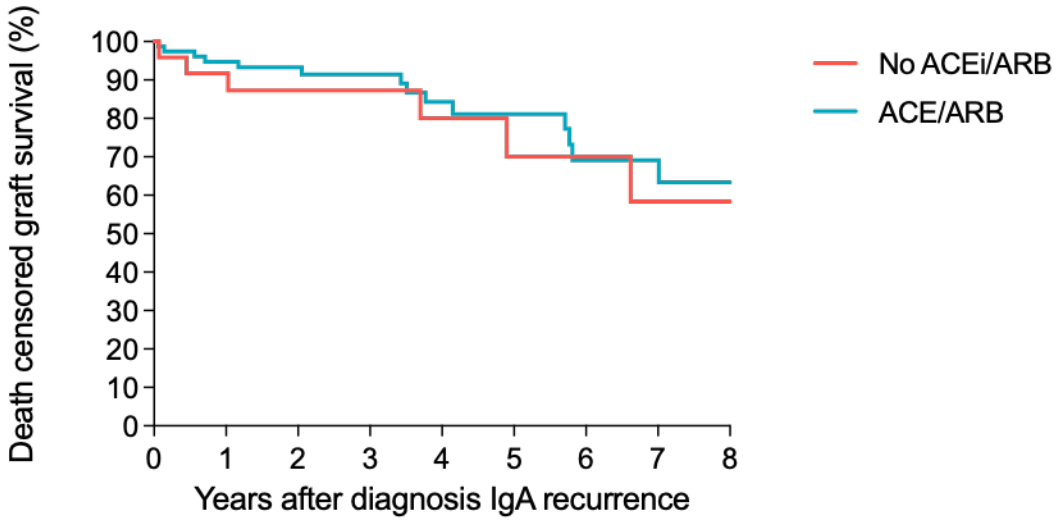
**Supplemental Figure 1.** Flow chart of the study population



**Supplemental Figure 2.** Kaplan-Meier analysis to death-censored graft survival in patients with IgA recurrence after diagnosis, stratified by degree of mesangial expansion on kidney biopsy



**Supplemental Figure 3.** Kaplan Meier analysis to graft survival in patients with recurrent IgA treated with or without ACEi/ARB. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.



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