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ORIGINAL ARTICLE

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Glomerular crescents are associated with worse graft outcome in allograft IgA nephropathy

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The prognosis of patients with allograft IgA nephropathy (IgAN) requires further investigation. We performed a bicenter retrospective cohort study on kidney transplant recipients diagnosed with IgAN in allograft biopsy. Recipients without allograft IgAN but with known IgAN before transplantation were included as the control group. We investigated the associations between clinicopathological characteristics, including allograft crescents, and the risk of death-censored graft failure. In total, 1256 IgAN patients in both pre- and posttransplant stages were included. Among them, 559 were diagnosed with allograft IgAN, which was a time-dependent risk factor for worse prognosis (adjusted hazard ratio = 5.009 [3.610-6.951]; $P < .001$) during a median of 8.1 years of follow-up. Of the patients with allograft IgAN, 88 (15.9%) had glomerular crescents, including 40 patients (7.2%) with >10% crescent formation in the total biopsied glomeruli. The presence of glomerular crescents in IgAN was associated with a worse graft prognosis, and the association was still valid with the C scores of the current Oxford classification. In conclusion, allograft IgAN is a time-dependent event and is associated with worse graft outcomes. The pathological characteristics of allograft, particularly the degree of glomerular crescent formation, may represent important risk factors for a poor prognosis.

KEYWORDS
clinical research/practice, graft survival, kidney (allograft) function/dysfunction, kidney transplantation/nephrology, pathology/histopathology

Abbreviations: AMC, Asan Medical Center; DCGF, death-censored graft failure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; sCr, serum creatinine; SNUH, Seoul National University Hospital.

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1 | INTRODUCTION

Recurrent glomerulonephritis is an important cause of graft failure after kidney transplantation.[1] IgA nephropathy (IgAN), one of the most prevalent forms of primary glomerulonephritis worldwide, represents a substantial burden to end-stage renal disease (ESRD).[2,3] As IgAN patients receive transplantation at a relatively young age with few comorbidities, they have a better transplant outcome than do those with other causes of ESRD.[4] On the other hand, this raises the importance of considering the long-term prognosis for IgAN. In this respect, recurrent IgAN represents a critical issue, as the recurrence of IgAN adversely affects transplantation outcome.[4,5] Several risk factors have been reported for IgAN recurrence, although a general consensus has yet to be established. In addition, the prognosis of posttransplantation IgAN with uncertain primary disease, which clinicians may commonly encounter during practice, requires further investigation.

Pathologic findings in native kidney biopsy of IgAN have a significant prognostic value. Previous studies have described useful scoring criteria, known as MEST scores or the Oxford Classification, for IgAN, which have become widely adopted in clinical practice.[6] More recent research has highlighted the importance of crescent formation in native IgAN pathology; as a result of these findings, the original scoring system was updated to become the MEST-C scoring system.[7] However, although the clinical significance of MEST scoring for allograft IgAN has been demonstrated,[8] there is only limited knowledge as to whether crescent formation in allograft IgAN bears prognostic information. Previous studies have reported rapid deterioration of graft function in crescentic allograft IgAN; however, the number of cases in these studies was small and additional robust comparison with a control group was warranted.[9,10]

In the present study, we investigated a large number of patients diagnosed with allograft IgAN in order to assess the risk factors and clinical impact of this disease. In addition, we collated a range of clinical and pathological parameters at the time of posttransplantation IgAN diagnosis that were used to evaluate the clinical association between glomerular crescents in allograft IgAN patients and death-censored graft failure (DCGF).

2 | METHODS

2.1 | Ethical considerations

The institutional review board (IRB) of Seoul National University Hospital (SNUH, IRB No: H-1701-008-819) and Asan Medical Center (AMC, IRB No: S2017-0369-0001) approved this study. The study was conducted in accordance with the principles of the Declaration of Helsinki and informed consent was waived under IRB approval because of the retrospective nature of this study.

2.2 | Study design and study population

This was a retrospective cohort study carried out in 2 tertiary teaching hospitals in Korea: SNUH and AMC. Patients with confirmation

TABLE 1 Donor and recipient characteristics according to presence of allograft IgAN

	Only native IgAN (+) (N = 697)	Allograft IgAN (+) (N = 559)	*P* value
Recipient characteristics			
Age at transplantation (Y)	39 (32-48)	37 (29-45)	<.001
≥40	335 (48.1)	221 (39.5)	.003
<40	362 (51.9)	338 (60.5)	
Sex (male)	390 (56.0)	377 (67.4)	<.001
Body mass index (kg/m^2)	21.4 (19.6-23.5)	22.1 (20.2-24.2)	.001
History of hypertension	598 (85.8)	387 (69.2)	<.001
History of diabetes mellitus	111 (15.9)	61 (10.9)	.013
RRT type before TPL			.002
No RRT	44 (7.1)	14 (2.6)	
Hemodialysis	467 (75.1)	427 (79.7)	
Peritoneal dialysis	111 (17.8)	95 (17.7)	
Era of transplantation			<.001
Before 1990	13 (1.9)	1 (0.2)	
1990~1999	70 (10.0)	235 (42.0)	
2000~2009	182 (26.1)	244 (43.6)	
After 2010	432 (62.0)	79 (14.1)	
Donor characteristics			
Donor age	42 (33-51)	39 (30-48)	<.001
Donor sex (male)	382 (55.0)	298 (53.4)	.622
Donor type			.986
Living related donor	414 (59.4)	330 (59.0)	
Living unrelated donor	147 (21.1)	120 (21.4)	
Deceased donor	136 (19.5)	109 (19.5)	
ABO incompatible	109 (16.7)	51 (11.4)	.018
HLA mismatch			.011
Ag mismatch 4-6	348 (55.8)	198 (47.9)	
Ag mismatch 1-3	222 (35.6)	159 (38.5)	
No mismatch	54 (8.7)	56 (13.6)	
Peritransplant immunosuppressant			
Cyclosporine	196 (28.2)	308 (55.2)	<.001
Tacrolimus	505 (72.6)	202 (36.2)	<.001
Mycophenolate mofetil or sodium	573 (82.3)	283 (50.7)	<.001
Azathioprine	87 (12.5)	122 (27.8)	<.001
Steroid	688 (98.9)	555 (99.5)	.395
Induction treatment (Basiliximab, ATG etc.)	488 (70.1)	190 (34.1)	<.001

The clinical characteristics were collected upon the time of renal transplantation. Missing values were present in the donor age (n = 5), donor sex (n = 3), HLA mismatch (n = 219), ABO incompatibility (n = 196), and medication usage history (n = 2). ATG, antithymoglobulin; RRT, renal replacement therapy; TPL, transplantation.

TABLE 2 Risk factors associated with allograft IgAN

	[a]Univariable analysis		[b]Multivariable analysis	
	HR (95% CI)	*P* value	[c]Adjusted HR (95% CI)	*P* value
Age at transplantation (1 y increment)	1.001 (0.993-1.009)	.766	0.999 (0.991-1.007)	.881
Male sex (vs female)	1.283 (1.075-1.532)	.006	1.289 (1.077-1.542)	.006
Donor age (1 y increment)	1.005 (0.998-1.012)	.190	1.215 (0.998-1.012)	.195
Donor male sex (vs female)	0.836 (0.708-0.988)	.035	0.834 (0.702-0.992)	.040
Donor type (vs living related)				
Living unrelated	1.040 (0.844-1.282)	.714	1.011 (0.808-1.266)	.923
Deceased	1.145 (0.922-1.422)	.221	1.225 (0.969-1.549)	.089
ABO incompatible (vs compatible)	1.040 (0.776-1.395)	.792	1.120 (0.836-1.450)	.448
HLA mismatch (vs. full match)				
Mismatch 1-3	0.800 (0.590-1.085)	.152	0.783 (0.590-1.038)	.088
Mismatch 4-6	0.987 (0.732-1.330)	.930	0.914 (0.687-1.214)	.533
Peri-transplantation medication				
Induction therapy (vs no)	1.022 (0.847-1.234)	.820	1.074 (0.844-1.367)	.560
Tacrolimus (vs no)	0.906 (0.757-1.084)	.279	0.871 (0.703-1.081)	.210
Mycophenolate mofetil or sodium (vs no)	0.946 (0.795-1.124)	.527	0.932 (0.763-1.138)	.489
[d]Specific recipient HLA type				
HLA A2	1.026 (0.806-1.307)	.834	0.950 (0.756-1.192)	.643
HLA B35	1.020 (0.685-1.520)	.923	1.259 (0.929-1.705)	.136
HLA DR4	0.960 (0.753-1.225)	.744	1.033 (0.860-1.240)	.731
Zero mismatch	1.121 (0.846-1.487)	.426	1.137 (0.822-1.571)	.427
[e]Donor and recipient sex (vs. both female)				
Recipient only male	1.366 (1.042-1.791)	.024	1.404 (1.064-1.853)	.016
Donor only male	0.926 (1.080-0.688)	.611	0.918 (0.679-1.243)	.581
Both male	1.110 (0.848-1.455)	.448	1.102 (0.837-1.450)	.489

[a]Univariable analysis was performed using the complete-case method.
[b]For multivariable analysis, missing values were imputed using the multivariate imputation with classification and regression trees method.
[c]Adjusted with age at transplantation, recipient sex, donor age, donor sex, donor type (categorical, living related, living unrelated, deceased), ABO compatibility, HLA mismatch (categorical, full match, mismatch 1-3 Ag, mismatch 4-6 Ag), peritransplantation use of medication including use of tacrolimus, mycophenolate mofetil or sodium, induction therapy).
[d]HLA A2, B35, DR4, HLA-full match was additionally tested base on literature review.
[e]Donor and recipient sex was additionally tested as previous analysis revealed the risk of allograft IgAN was dependent on sex.

of IgAN in their allograft biopsies (allograft IgAN) were included in the study group. Patients who had biopsy-proven IgAN as an initial cause of ESRD, but confirmed to be devoid of recurrent IgAN, were included in the control group. Patients who had multiorgan transplantations were not considered.

2.3 | Allograft IgAN and graft biopsy

Allograft IgAN following kidney transplantation was pathologically confirmed by graft biopsy. We performed allograft biopsies in cases showing a progressive decline in renal function, persistent hematuria, or significant proteinuria of more than 1.0 g/day.[5] Routine protocol biopsy was not always performed, although some of the transplant recipients underwent biopsy at time zero and then again 2 weeks after transplantation. Biopsied tissues were examined using light, electron, and immunofluorescence microscopy by experienced hospital pathologists. The pathological diagnosis of allograft IgAN was made when the biopsied tissue specimens showed a typical immunofluorescence pattern of IgA ± C3 dominant staining in the glomerulus mesangial space. Other pathological characteristics were also investigated in the kidney allografts and used for the diagnosis of allograft IgAN. For example, the degree of pathological change in the glomeruli was classified as none, mild to moderate, or severe. Cutoff values were as follows: global sclerosis (0, >0% and ≤40%, >40%), segmental sclerosis (0, >% and ≤20%, >20%), and crescent formation (0, >0% and ≤10%, and >10%). Only the cellular or fibrocellular crescents were included in the study, as suggested by the Oxford classification.[7] The main cutoff value for the degree of

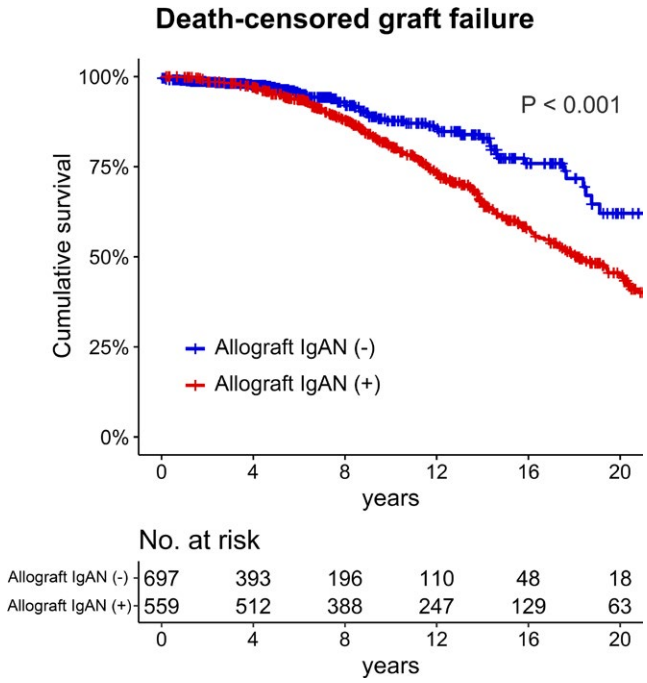

FIGURE 1 Kaplan-Meier survival curve showing death-censored graft failure according to the presence of allograft IgAN. The *x*-axis indicates the time from transplantation and the *y*-axis indicates cumulative survival [Color figure can be viewed at wileyonlinelibrary.com]

crescent formation was defined in order to distribute the number of patients with the findings similarly between the >0% and ≤10%, and >10% subgroups, as the number of patients with a high degree of crescents was small. We also performed an analysis using the C and S scores suggested in the MEST-C scoring system.[7,11] Coexisting evidence of acute rejection was also collated. In SNUH, allograft pathology was additionally reviewed for this study, and MEST scores were recorded in accordance with the Oxford classification.[6] This practice, however, was not performed in AMC.

2.4 | Data collection

The following baseline demographic data were collected for the entire study population at the time of renal transplantation: age, sex, and body mass index (BMI). Baseline history of hypertension and diabetes mellitus was also recorded, as was the type of renal replacement therapy prior to transplantation. We also collated information relating to donor age, sex, whether the donor was cadaveric or not, the relationship of the donor to the recipient, the presence/absence of ABO mismatch and the number of HLA antigen mismatches. We also obtained information on the use of immunosuppressive agents including cyclosporine, tacrolimus, mycophenolate mofetil or sodium, azathioprine, and maintenance steroids and on whether immunosuppressive induction therapy, including the use of basiliximab or antithymocyte globulin, had been performed. Peritransplantation medication history was recorded until 6 months after transplantation, and the use of medications was reviewed for the same duration before and after the diagnosis of allograft IgAN.

We recorded the following characteristics at the time of biopsy in patients diagnosed with allograft IgAN: age, graft age, BMI, serum creatinine (sCr), estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[12] albuminuria and hematuria measured using the dipstick method. In addition, we recorded the treatment history for acute rejection prior to the diagnosis of allograft IgAN, including steroid pulse therapy, antithymocyte globulin, rituximab, and bortezomib treatment.

2.5 | Clinical outcomes

The main clinical outcome was death-censored-graft failure (DCGF). Irreversible graft failure was defined as a return to long-term dialysis (or retransplantation), and events of death with a functioning graft were censored. When investigating the prognosis of patients with allograft IgAN, we recalculated survival duration from the date of the diagnosis of allograft IgAN.

2.6 | Statistical analysis

Categorical variables are presented herein as frequencies and percentages and were analyzed by chi-square tests. Continuous variables are expressed as medians (interquartile ranges) and analyzed by the Mann-Whitney U test because such continuous variables were not normally distributed. Using the survival data, we plotted Kaplan-Meier survival curves and calculated the associated *P* values using the log rank test. To assess the risk factors for allograft IgAN, we performed multivariable Cox analysis adjusted for age at transplantation, recipient sex, donor age, donor sex, donor type (categorical, living related, living unrelated, deceased), ABO compatibility, HLA mismatch (categorical, full-match, 1-3 mismatch, 4-6 mismatch), and peritransplantation use of medication (including use of tacrolimus, mycophenolate mofetil or sodium, induction therapy).

To evaluate the association between allograft IgAN and DCGF, we used multivariable time-dependent Cox analysis, including allograft IgAN diagnosis as a time-dependent variable. The Cox model was adjusted for the same variables as with the multivariable model, except for medication histories. Additional sensitivity analyses were performed, within patients who (1) had or (2) did not have initially confirmed IgAN as the cause of ESRD, (3) excluding patients who were diagnosed for allograft IgAN within 2 weeks in which donor origin IgAN might be possible, and (4) excluding the patients who did not receive allograft biopsy because of possible unknown diseases.

Finally, clinicopathological factors at the time of allograft IgAN diagnosis that were associated with poor DCGF were specifically investigated with a multivariable Cox analysis adjusted for age at allograft IgAN diagnosis (continuous, years); recipient sex; donor relationship; HLA mismatch; ABO incompatibility; eGFR (continuous, 1 mL/min/1.73 m^2 increment); and coexisting acute rejection. Four sensitivity analyses were performed: (1) using the C and S scores in the Oxford classification with exclusion of patients whose number of biopsied glomeruli was less than 8,[7,11] for those (2) with and

TABLE 3 Clinical characteristics associated with DCGF in the total cohort

	[a]Univariable analysis		[b]Multivariable analysis	
	HR	***P***	[c]**Adjusted HR**	***P***
Allograft IgAN (as a time-dependent variable)	5.222 (3.772-7.228)	<.001	5.009 (3.610-6.951)	<.001
[d]Sensitivity analysis 1-1	5.810 (3.888-8.684)	<.001	5.082 (3.350-7.709)	<.001
[e]Sensitivity analysis 1-2	4.112 (2.926-5.777)	<.001	4.039 (2.864-5.696)	<.001
[f]Sensitivity analysis 1-3	5.595 (4.007-7.812)	<.001	5.369 (3.780-7.520)	<.001
[g]Sensitivity analysis 1-4	5.633 (3.805-8.340)	<.001	5.611 (3.834-8.311)	<.001
Other variables included in the multivariable analysis				
Age at transplantation (1 y increment)	0.988 (0.976-1.000)	.052	0.986 (0.973-0.999)	.034
Male sex (vs. female)	1.346 (1.024-1.766)	.033	1.302 (0.980-1.729)	.067
Donor age (1 year increment)	1.015 (1.005-1.026)	.005	1.013 (1.001-1.024)	.027
Donor male sex (vs female)	0.695 (0.543-0.891)	.004	0.754 (0.580-0.980)	.035
Donor type (vs living related)				
Living unrelated	1.022 (0.741-1.411)	.893	1.138 (0.810-1.598)	.456
Deceased	1.189 (0.863-1.637)	.290	1.447 (1.026-2.042)	.035
ABO incompatibility	1.144 (0.701-1.865)	.591	1.033 (0.463-2.307)	.929
HLA mismatch (vs. full-match)				
Mismatch 1-3	1.287 (0.815-2.030)	.279	1.071 (0.702-1.632)	.747
Mismatch 4-6	0.938 (0.572-1.539)	.800	1.020 (0.666-1.564)	.927

[a]Univariable analysis was performed using the complete-case method.
[b]For multivariable analysis, missing values were imputed using the multivariate imputation with classification and regression trees method. Time-dependent Cox regression analysis was performed, treating allograft IgAN as a time-dependent variable.
[c]Multivariable analysis was adjusted with recipient age at transplantation, recipient sex, donor age, donor sex, HLA mismatch (categorical, full-match, 1-3 mismatch, 4-6 mismatch), ABO incompatibility, donor relation (living related, living unrelated, deceased) and allograft IgAN as a time-dependent variable.
[d]The analysis was done within those who had known initial diagnosis as IgAN (n = 817).
[e]The analysis was done within those who had unknown or other initial diagnosis than IgAN (n = 439).
[f]The analysis was done excluding the allograft IgAN cases who were diagnosed within 2 weeks from the transplantation (n = 46), as donor origin IgAN was possible.
[g]The analysis was done excluding the patients who did not receive allograft biopsy (n = 366), as hidden IgAN was possible and the excluded patients had relatively stable posttransplant clinical course.

(3) without known initial IgAN, and (4) simultaneously adding the degree of global sclerosis, segmental sclerosis, and crescent formation into the multivariable model within patients who had initial IgAN. Values were missing for donor age (n = 5), donor sex (n = 3), the number of HLA mismatches (n = 219), ABO incompatibility (n = 196) and the history of medication usage (n = 2). As missing values tended to appear in a random manner, such data underwent multivariate imputation by classification and the regression trees method with "mice" package in R (version 3.4.2, The R Foundation).[13] All other statistical analyses were also performed with R. A 2-sided $P < .05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Study population

We identified 1258 kidney transplant recipients with pre- or posttransplant IgAN from SNUH and AMC. Two patients were excluded because of noninterpretable records. Thus, a total of 1256 IgAN kidney transplant recipients were included in the final study with a median follow-up duration of 8.1 (3.8-14.9) years. There were 817 patients with initial confirmed IgAN and 439 patients had unknown or other diagnosis as the cause for ESRD.

When we further stratified the study and the control groups per the diagnosis of allograft IgAN, the control group consisted of the 697 patients with IgAN as the confirmed cause for their ESRD but with no diagnosis of posttransplant IgAN recurrence. The study group featured 559 patients with allograft IgAN. Of these, 120 patients had initial IgAN and pathologically confirmed IgAN recurrence. Eleven patients had initial diagnoses other than IgAN but were diagnosed with allograft IgAN during the posttransplantation period; 4 with focal segmental glomerular sclerosis, 3 who underwent nephrectomy for kidney malignancy, 1 with membranoproliferative glomerulonephritis, 2 with chronic reflux nephropathy, and 1 with tubulo-interstitial nephritis. The other 428 patients had unknown primary disease or only clinical diagnoses (eg, hypertension nephropathy, diabetic nephropathy, or chronic glomerulonephritis) and were consequently diagnosed for their allograft IgAN.

TABLE 4 Characteristics of the patients with allograft IgAN according to crescent proportion

	No crescents (N = 471)	Crescents >0% and ≤10% (N = 48)	Crescents >10% (N = 40)	*P* value
Characteristics at diagnosis of allograft IgAN				
Recipient age (y)	42 (34-50)	44 (34-51)	43 (37-48)	.774
Sex (male)	319 (67.7)	31 (64.6)	27 (67.5)	.907
Creatinine (mg/dL)	1.7 (1.4-2.1)	1.6 (1.3-2.2)	1.8 (1.4-2.6)	.613
eGFR (mL/min/1.73 m^2)	44.2 (33.6-57.8)	48.7 (34.0-59.2)	41.8 (26.6-57.5)	.616
Albuminuria (dipstick)				.064
negative	250 (53.8)	19 (39.6)	14 (35.0)	
1^+	46 (10.0)	7 (14.6)	4 (10.0)	
$\geq 2^+$	168 (36.4)	22 (45.8)	22 (55.0)	
Hematuria (dipstick)	84 (18.1)	14 (29.2)	5 (12.5)	.100
Duration from transplantation to diagnosis of allograft IgAN (y)	4.1 (1.1-7.9)	4.2 (2.7-8.9)	6.1 (3.3-8.8)	.024
Transplant-related characteristics				
Recipient age at transplantation	37 (29-45)	38 (29-44)	35 (30-42)	.736
Donor age	40 (31-48)	37 (28-46)	34 (26-50)	.217
Donor type				.910
Living related	275 (58.4)	31 (64.6)	24 (60.0)	
Living unrelated	102 (21.7)	10 (20.8)	8 (20.0)	
Deceased donor	94 (20.0)	7 (14.6)	8 (20.0)	
Donor sex (male)	253 (53.8)	25 (52.1)	20 (50.0)	.881
ABO incompatibility	42 (11.1)	4 (9.1)	5 (17.9)	.492
HLA mismatch				.322
Ag mismatch 4-6	172 (49.4)	17 (44.7)	9 (33.3)	
Ag mismatch 1-3	127 (36.5)	17 (44.7)	15 (55.6)	
No mismatch	49 (14.1)	4 (10.5)	3 (11.1)	
Cause of ESRD				.690
Known IgAN	100 (21.2)	13 (27.1)	7 (17.5)	
Other primary disease	10 (2.1)	1 (2.1)	0 (0.0)	
Unknown or other suspected diagnoses	361 (76.6)	34 (70.8)	33 (82.5)	
Medication usage before allograft IgAN diagnosis				
RAAS blockade	207 (43.9)	22 (45.8)	21 (52.5)	.572
Cyclosporine	295 (62.6)	28 (58.3)	31 (77.5)	.130
Tacrolimus	156 (33.1)	21 (41.8)	6 (15.0)	.015
Azathioprine	15 (3.2)	1 (2.1)	2 (5.0)	.738
Mycophenolate mofetil or sodium	266 (56.5)	26 (54.2)	16 (40.0)	.131
Steroid	417 (88.5)	42 (87.5)	34 (85.0)	.792
Treatment history of rejection				
Steroid pulse	124 (26.3)	17 (35.4)	6 (15.0)	.096
Antithymocyte globulin	3 (0.6)	1 (2.1)	0 (0.0)	.451

(Continues)

TABLE 4 (Continued)

	No crescents (N = 471)	Crescents >0% and ≤10% (N = 48)	Crescents >10% (N = 40)	*P* value
B-cell depletion therapy				
Rituximab	3 (0.6)	0 (0.0)	0 (0.0)	.754
Bortezomib	1 (0.2)	0 (0.0)	0 (0.0)	.911
Histopathologic findings				
Global sclerosis				.106
0%	140 (29.7)	9 (18.8)	5 (12.5)	
>0 and ≤40%	260 (55.2)	30 (62.5)	28 (70.0)	
>40%	71 (15.1)	9 (18.8)	7 (17.5)	
Segmental sclerosis				<.001
0%	346 (73.5)	26 (54.2)	18 (45.0)	
>0 and ≤20%	98 (20.8)	18 (37.5)	15 (37.5)	
>20%	27 (5.7)	4 (8.3)	7 (17.5)	
Coexisting acute rejection	145 (30.8)	12 (25.0)	9 (22.5)	.413

There were 2 patients with missing value of eGFR at allograft IgAN diagnosis and 146 patients with HLA mismatching, and 140 patients with ABO incompatibility in the table. RAAS, renin-angiotensin-aldosterone-system.

3.2 | Baseline characteristics

Table 1 shows the baseline characteristics of the study population according to the presence of allograft IgAN. Patients with allograft IgAN tended to be younger in age ($P < .001$) and were more frequently male ($P < .001$). The study group received transplantation in an earlier era ($P < .001$) and cyclosporine was more commonly used ($P < .001$) as the maintenance immunosuppressants. In contrast, tacrolimus ($P < .001$) and mycophenolic acid ($P < .001$) were less commonly prescribed in the patients with allograft IgAN. In addition, allograft IgAN occurred in a time-dependent manner with a median time to diagnosis of 4.4 years (Figure S1). Donor type ($P = .986$), donor sex ($P = .622$), and the use of maintenance steroid treatment ($P = .395$) were not significantly different when compared between the study and the control group.

3.3 | Risk factors for allograft IgAN

Age of recipient or donor, donor relationship, HLA mismatch, ABO incompatibility, or peritransplant immunosuppression medications were not significantly associated with the risk of allograft IgAN (Table 2). We also assessed specific recipient HLA types (A2, B35, DR4, or zero mismatch) that were considered in previous studies [5,14–16] but could not identify significant association. On the other hand, when the recipient was male and the donor was female, the risk of allograft IgAN was significantly increased (adjusted hazard ratio [HR]: 1.404; 95% confidence interval [CI]: 1.064-1.853; $P = .016$). We further analyzed this association excluding the control patients who did not receive posttransplant biopsies (n = 366), as these patients might have had indolent IgAN but missed the opportunity for the diagnosis of allograft IgAN (Table S1). Within this group of patients, none of the clinical characteristics that we investigated were associated with the risk of allograft IgAN including the particular sex relation.

3.4 | Prognosis of allograft IgAN

The 5-year and 10-year graft survival of the study population was 804/829 (97.0%) and 451/518 (87.1%), respectively. The patient graft failure rate for allograft IgAN appeared to be similar to that for the control group during the early posttransplantation period but worsened over time from 7 to 8 years after transplantation (Figure 1). The median time to DCGF, when occurred, from the diagnosis of allograft IgAN was 3.1 (1.4-6.8) years. In our multivariable model (Table 3), allograft IgAN, as a time-dependent variable, was strongly associated with the risk of DCGF (adjusted HR: 5.009; 95% CI: 3.610-6.951; $P < .001$). When we performed sensitivity analyses, the significant acceleration of the consequent DCGF after allograft IgAN diagnosis was repetitively confirmed.

Other variables that were significantly associated with outcome included deceased donor (adjusted HR: 1.447; 95% CI: 1.026-2.042; $P = .035$), age at transplantation (adjusted HR: 0.986; 95% CI: 0.973-0.999; $P = .034$), and male donation (adjusted HR: 0.754; 95% CI: 0.580-0.980; $P = .035$). Male recipients were associated with a worse outcome (HR 1.346: 95% CI: 1.024-1.766; $P = .033$), but this did not reach statistical significance in the multivariable model (adjusted HR: 1.302; 95% CI: 0.980-1.729; $P = .067$).

3.5 | Clinicopathological characteristics of allograft IgAN patients with crescent formation

The clinicopathological characteristics of allograft IgAN patients, according to crescent formation, is shown in Table 4. Patients with a severe degree (>10%) of crescents had an older graft age

TABLE 5 Clinical characteristics of allograft IgAN patients and their association with DCGF

Clinical characteristics	[a]Adjusted HR (95% CI)	*P* value
Age at allograft IgAN diagnosis (continuous, y)	1.000 (0.986-1.015)	.996
Sex (vs female)	1.290 (0.938-1.773)	.117
Donor relation (vs living related)		
Living unrelated	1.242 (0.854-1.806)	.256
Deceased	0.899 (0.611-1.324)	.591
ABO incompatibility	0.913 (0.549-1.518)	.720
HLA mismatch (vs zero mismatch)		
1-3	1.023 (0.621-1.686)	.927
4-6	0.725 (0.446-1.178)	.192
Laboratory values at recurrence		
eGFR (continuous, 1 mL/min/1.73 m^2 increment)	0.977 (0.970-0.985)	<.001
Albuminuria (vs negative)		
1+	0.986 (0.589-1.652)	.957
≥2+	1.100 (0.813-1.490)	.536
Hematuria (vs no)	0.967 (0.618-1.516)	.882
History of acute rejection treatment (vs none)	1.045 (0.730-1.494)	.811
Presence of coexisting acute rejection (vs none)	1.160 (0.838-1.608)	.371
Initial diagnosis as IgAN (vs unconfirmed or other)	1.942 (1.390-2.714)	<.001
Pathologic parameters		
Crescent formation (vs. none)		
>0 and ≤10%	2.091 (1.279-3.417)	.003
>10%	2.336 (1.490-3.662)	<.001
Global sclerosis (vs. none)		
>0 and ≤40%	2.041 (1.393-2.992)	<.001
>40%	3.545 (2.273-5.528)	<.001
Segmental sclerosis (vs. none)		
>0 and ≤20%	2.035 (1.430-2.894)	<.001
>20%	1.667 (0.993-2.800)	.053

[a]Adjusted with recipient age (continuous, y), recipient sex (categorical), donor relationship (categorical, living related, living unrelated, deceased), HLA mismatch (categorical, full-match, 1-3 mismatch, 4-6 mismatch), ABO incompatibility, eGFR (continuous, 1 mL/min/1.73 m^2 increment), and coexisting acute rejection. The laboratory values and pathologic parameters were collected at the time of diagnosis for allograft IgAN.

when their allograft IgAN was diagnosed; however, renal function parameters, including serum creatinine levels (*P* = .613), eGFR (*P* = .616), or urinalysis abnormalities did not show any significant difference between subgroups. Donor or transplant-related characteristics were also similar among patients with different degrees of crescent formation, except that patients with a severe degree of crescent formation were treated with tacrolimus less frequently than the others. Analysis of the degree of global

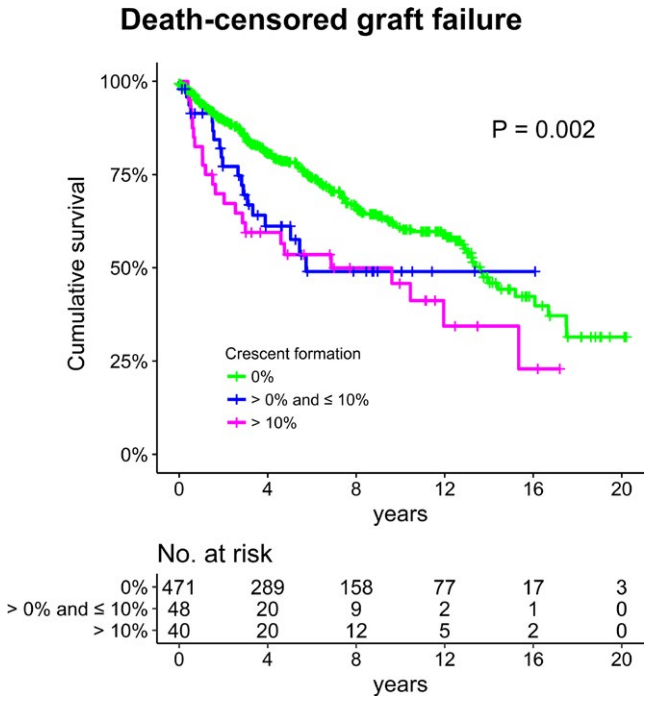

FIGURE 2 Kaplan-Meier survival curve showing death-censored graft failure according to the presence of crescent formation in the allograft IgAN. The *x*-axis indicates time from the diagnosis of allograft IgAN and the *y*-axis indicates cumulative survival [Color figure can be viewed at wileyonlinelibrary.com]

sclerosis (*P* = .106) or the presence of coexisting acute rejection (*P* = .413) did not reveal any statistically significant difference among the subgroups, although a severe degree of segmental sclerosis was identified more frequently in patients with a higher degree of crescent formation.

3.6 | Crescent formation and DCGF in allograft IgAN

We performed multivariable analysis to identify prognostic factors for allograft IgAN (Table 5). As expected, eGFR, at the time of allograft IgAN diagnosis, was significantly associated with subsequent DCGF (adjusted HR: 0.977; 95% CI: 0.970-0.985; *P* < .001). Patients with IgAN as the known cause of ESRD had a worse prognosis (adjusted HR: 1.942; 95% CI: 1.390-2.714; *P* < .001) than those with unconfirmed or other initial diagnoses. With regards to pathological parameters, a Kaplan-Meier survival curve showed that the presence of crescent formation was significantly associated with a worse prognosis (log rank *P* = .002; Figure 2). Moreover, our multivariable model indicated that the presence of crescents, in both the > 0 and ≤ 10% subgroup (adjusted HR: 2.091; 95% CI: 1.279-3.417; *P* = .003), and the > 10% subgroup (adjusted HR: 2.336; 95% CI: 1.490-3.662; *P* < .001), was associated with an increased risk of DCGF.

Next, we performed 4 sensitivity analyses, as described previously (Table 6). When the current Oxford classification criteria were implemented, both C1 (adjusted HR: 2.243; 95% CI:

TABLE 6 Sensitivity analysis for clinical significance of pathologic glomerular changes in allograft IgAN

	[a]Adjusted HR (95% CI)	*P*
[b]Sensitivity analysis 2-1 (.vs none)		
S1 (presence of segmental sclerosis)	2.030 (1.453-2.837)	<.001
C1 (crescent >0 and <25%)	2.243 (1.526-3.297)	<.001
C2 (crescent ≥25%)	4.306 (1.875-9.889)	<.001
[c]Sensitivity analysis 2-2 (.vs none)		
Crescent > 0 and ≤10%	2.189 (1.333-3.595)	.002
Crescent >10%	2.631 (1.663-4.163)	<.001
Global sclerosis >0 and ≤40%	1.925 (1.264-2.931)	.002
Global sclerosis >40%	3.417 (2116-5.518)	<.001
Segmental sclerosis >0 and ≤20%	2.139 (1.481-3.089)	<.001
Segmental sclerosis >20%	1.760 (1.001-3.096)	.049
[d]Sensitivity analysis 2-3 (vs none)		
Crescent >0 and ≤10%	2.317 (1.309-4.101)	.004
Crescent >10%	1.964 (1.155-3.342)	.013
Global sclerosis >0 and ≤40%	1.976 (1.265-3.084)	.002
Global sclerosis >40%	3.846 (2.342-6.317)	<.001
Segmental sclerosis >0 and ≤20%	2.201 (1.441-3.363)	<.001
Segmental sclerosis > 20%	1.625 (0.892-2.962)	.123
[e]Sensitivity analysis 2-4 (.vs none)		
Crescent >0 and ≤10%	1.731 (0.632-4.744)	.286
Crescent >10%	13.324 (4.337-40.930)	<.001
Global sclerosis >0 and ≤40%	1.782 (0.824-3.856)	.142
Global sclerosis >40%	2.134 (0.770-5.920)	.145
Segmental sclerosis >0 and ≤20%	0.945 (0.478-1.867)	.870
Segmental sclerosis >20%	0.690 (0.214-2.223)	.534

[a]Multivariable model was adjusted with recipient age (continuous, y), recipient sex (categorical), donor relationship (categorical, living related, living unrelated, deceased), HLA mismatch (categorical, full-match, 1-3 mismatch, 4-6 mismatch), ABO incompatibility, eGFR (continuous, 1 mL/min/1.73 m^2 increment), and coexisting acute rejection. The laboratory values and pathologic parameters were collected at the time of diagnosis for allograft IgAN.

[b]Analysis was done with the S and the C score using the criteria of the Oxford classification, and those with biopsied glomeruli less than 8 were excluded. Within the subset, there were 494 allograft IgAN patients, and among them, 161 patients had the S1 score, and 76, 8 patients had the C1 and C2 score, respectively.

[c]Multivariable analysis was done within those who had known initial diagnosis as IgAN, the recurrent IgAN cases (n = 120).

[d]Multivariable analysis was done within those who had unknown or other initial diagnosis than IgAN (n = 439).

[e]With those who had known initial diagnosis as IgAN (n = 120), degree of 3 pathologic parameters, crescent formation (categorical, 0%, >0% and ≤ 10%, >10%), global sclerosis (categorical, 0%, > 0% and ≤40%, > 40%) and segmental sclerosis (categorical, 0%, >0% and ≤20%, >20%) were simultaneously added to the multivariable model.

1.526-3.297; *P* < .001) and C2 (adjusted HR: 4.306; 95% CI: 1.875-9.889; *P* < .001) were associated with an increased risk of DCGF in allograft IgAN. Also, S1 (adjusted HR: 2.030; 95% CI: 1.453-2.837; *P* < .001) was an independent predictor for an adverse outcome. As there were few patients (n = 10 or n = 8 after excluding those with fewer than 8 biopsies) with such a high proportion of crescents (≥ 25%), further sensitivity analyses in the subgroups were performed with a cutoff value of 10%. The presences of glomerular crescents, both less or equal to 10% or above 10% were significant risk factor for worse allograft prognosis when studied patients were divided according to whether their initial cause of ESRD was proven IgAN. Moreover, the presence of crescents in > 10% of biopsied glomeruli remained significantly associated with graft outcome (adjusted HR: 13.324; 95% CI: 4.337-40.930; *P* < .001) even after simultaneously adjusted for the proportion of global sclerosis or segmental sclerosis, within the confirmed recurrent IgAN cases. The global sclerosis and segmental sclerosis also showed substantial association with a worse graft outcome (Figure S2). However, the statistical significance of those variables became weak or was lost in the sensitivity analysis.

In the SNUH cohort in which the information of MEST score was available, those with higher MEST scores had worse graft outcome, except for endocapillary hypercellularity as this parameter was not associated with DCGF in the cohort (Table S2 and Figure S3).

4 | DISCUSSION

Our present study showed that allograft IgAN was predominantly a time-dependent event and was associated with a significantly higher risk of DCGF. Besides this time dependency, other clinical factors did not show any notable association with the risk of allograft IgAN. Glomerular crescent formation was associated with a worse graft outcome, even when the C score was tested per the Oxford classification. Our study has strength that we confirmed this association in a large cohort of patients with allograft IgAN.

Kidney transplantation recipients with underlying IgAN are usually considered to have an excellent prognosis when compared to patients with other etiologies.[4] However, recurrence of the primary disease is consistently reported to cause negative effects upon long-term graft survival.[1,4,5,14,17] Existing studies show notable variability in the incidence of IgAN recurrence, first because centers did not use the same protocol for allograft biopsies and second because such studies varied in their approach to confirming IgAN only in the posttransplantation period. Clinicians commonly encounter ESRD patients without confirmation of an underlying disease or with only a suspected diagnosis; thus, clearly differentiating events related to recurrent IgAN and de novo IgAN after transplantation is challenging. As IgAN is one of the most common forms of primary glomerulonephritis, both in the pre- and posttransplant era, we considered that the identification of predictors for the prognosis of allograft

IgAN would be helpful for clinical practice. In the present study, we demonstrated that allograft IgAN is a significant risk factor for poor graft outcome, and additional risk factors for a worse prognosis within allograft IgAN were investigated. A particular strength of our study is that we included, to the best of our knowledge, the largest number of allograft IgAN patients evaluated so far and used this cohort to assess the prognostic importance of graft pathology.

The risk of DCGF was increased when allograft IgAN patients had cellular or fibrocellular crescent formation in the allograft. A recent meta-analysis showed that each score on the Oxford classification, except for endocapillary hypercellularity, was associated with patient prognosis.[18] Interestingly, the presence of crescents was also an important risk factor for poor prognosis, and a recent report suggested a clinically meaningful cutoff value of 10% for crescents within biopsied glomeruli.[19] Although some debate still remains,[20] the clinical significance of crescentic lesions in IgAN is now generally accepted, and the implementation of MEST-C scores has been suggested.[7,11] The usefulness of MEST scores for allograft IgAN has already been confirmed,[8] although the prognostic value of crescents in allografts requires further investigation in large cohorts of patients.[9,10] In our present study, we showed that cellular or fibrocellular crescents in allograft IgAN were associated with a worse posttransplant outcome, and this was also true with the Oxford criteria C scores. In addition, with the exception of endocapillary hyperfiltration, we showed that MEST scores were potentially associated with transplant prognosis. Therefore, components of the MEST-C scoring system may also represent an important predictor of the prognosis of allograft IgAN, and routine reporting and consideration of these pathological parameters may be warranted for posttransplantation biopsy.[18, 20]

Previous studies have investigated a range of risk factors for posttransplantation IgAN. A young age, male sex, living related donor, steroid withdrawal, and specific HLA subtypes have all been previously reported as factors associated with the risk of recurrent IgAN, although a consistent consensus has yet to be established.[1,21–23] In our study, the sex of the donor and the recipient, in cases where the recipient was male and the donor was female, was identified as a factor associated with the risk of allograft IgAN. However, this may be a biased result as this specific sex relation would be associated with poor graft function, which leads to a higher possibility of allograft biopsies.[24] The fact that the association was not reproduced within patients who received graft biopsies support our previous assertion. Steroid withdrawal, which could hardly be assessed in our cohort as most of the patients maintained with steroids, younger recipient age, nor donor relation showed association with the risk of allograft IgAN. Still, we could see that allograft IgAN was strongly a time-dependent event.

Our study also showed that allograft IgAN was associated with an increased risk of DCGF. During the first 10 years from transplantation, the renal survival between the allograft IgAN patients and the controls seemed similar.[25] However, as allograft IgAN occurred in a time-dependent manner, the worse prognosis in allograft IgAN became prominent over time. Interestingly, patients who had known initial IgAN were associated with a worse prognosis than those with unconfirmed or other causes of ESRD. The reason may be that patients without pretransplantation IgAN diagnosis had slowly progressing underlying IgAN, which subsequently led to a relatively milder course of disease after recurrence. Furthermore, de novo IgAN, which may have been included in allograft IgAN cases, may have a different clinical prognosis from recurrent IgAN. Nevertheless, as allograft IgAN patients without known initial IgAN diagnoses also had a worse prognosis than IgAN patients without recurrence, clinicians should consider the adverse effects of allograft IgAN on posttransplantation graft survival regardless of the primary cause of ESRD.

Our study has several limitations that need to be considered. First, we did not include pathological findings from native graft biopsies because such data were frequently unavailable. Consequently, it was not possible to investigate the link between posttransplant prognosis and pathological parameters in native IgAN herein. Second, the definitive separation of de novo IgAN and recurrent IgAN was not possible in our study. Yet, we believe that clinicians will encounter a mixture of de novo and recurrent IgAN cases and we therefore included data from all of our allograft IgAN patients. In addition, our sensitivity analysis revealed the importance of allograft crescents in patients with recurrent IgAN. Third, because of the nature of our retrospective study, it is possible that hidden confounding variables may exist. This also was a reason that we could not investigate possible treatment strategy for allograft IgAN. Lastly, clinical management or pathological diagnostics were not standardized between the 2 study hospitals. In addition, transplantations in the past period were included in our analysis, and it was therefore inevitable that allograft IgAN was mostly diagnosed after a long duration of follow-up.

In conclusion, allograft IgAN was shown to be a time-dependent event and was significantly associated with a worse posttransplant prognosis. In particular, allograft crescents may represent important predictive parameters for the outcome of posttransplantation IgAN. Pathological parameters associated with allograft IgAN should therefore be carefully interpreted and reported in order to identify patients at risk of a poor prognosis.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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