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Original Article

ORIGINAL ARTICLE

Increasing prescription of renin–angiotensin–aldosterone system blockers associated with improved kidney prognosis in Korean IgA nephropathy patients

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ABSTRACT

Background. We aimed to describe the characteristics of immunoglobulin A nephropathy (IgAN) in Korea with assessment for time trends.

Methods. We performed a multicenter retrospective observational cohort study including biopsy-confirmed native IgAN cases from four tertiary hospitals in Korea. Time eras of diagnosis were stratified into 1979–2003, 2004–9 and 2010–17. The prognostic variable was progression to end-stage kidney disease (ESKD) analyzed by multivariable Cox regression analysis.

Results. We included 1366 (from 1979 to 2003), 1636 (from 2004 to 2009) and 1442 (from 2010 to 2017) IgAN patients in this study. In the recent periods, IgAN had relatively better clinical characteristics, as patients had higher estimated glomerular

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filtration rates and lower baseline blood pressures than before. The use of renin–angiotensin–aldosterone system (RAAS) blockers increased from 57.7% in 1979–2003 to 80.0% in 2010–17. During a median follow-up duration of 11.3 years, 722 patients progressed to ESKD with an incidence rate of 12.5 per 1000 person-years. The 10-year risk of progression to ESKD was lower in 2010–17 compared with that of 1979–2003 [adjusted hazard ratio 0.692 (95% confidence interval 0.523–0.915)], even after adjustment for multiple clinicopathologic characteristics. The use of RAAS blockers was a significant mediator ($P < 0.001$) for the association between time trends and lower 10-year ESKD risk.

Conclusions. Clinicopathologic characteristics of IgAN in Korea have changed over time. Although the limitation of a retrospective observational study remains, the result showed that the prognosis of IgAN has improved over the study period, possibly related to increased prescription of RAAS blockers.

Keywords: aldosterone receptor blockade, angiotensin-converting enzyme inhibitor, end-stage kidney disease, glomerulonephritis, IgA nephropathy

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is one of the most common primary glomerulonephritis globally [1, 2]. As the disease is a major etiology of end-stage kidney disease (ESKD), many studies have focused on the pathophysiology, characteristics and prognosis of the disease. However, as a disease-specific biomarker or treatment has not been firmly established, IgAN continues to be an important disease category to be studied in the field of nephrology.

IgAN has been widely recognized since the 1970s [3, 4] and previous studies have since improved clinical practices and reported useful treatment strategies for the disease, particularly the maximum usage of renin–angiotensin–aldosterone system (RAAS) blockers as a standard of care [5–8]. Although the understanding of the disease has advanced, there has been limited research investigating the time trends of characteristics and prognosis of IgAN with a sufficient number of patients [9, 10]. As the population structure is changing and clinical guidelines have been developed [11], a study investigating whether any distinct features are present in the different time periods regarding IgAN may provide insights regarding future disease trends. In addition, as IgAN is relatively more common and shows a worse prognosis in Asians compared with other ethnicities, such evidence would be particularly important in this region [12].

In this study we aimed to evaluate the temporal trends of characteristics and prognoses of IgAN in Korea, where a high prevalence of IgAN is reported [13], using a large-scale, multicenter cohort. We hypothesized that a time trend would be present in the cohort and that the trend would be associated with the introduction of treatment strategies for IgAN.

MATERIALS AND METHODS

Ethics approval

The institutional review boards (IRBs) of the four study hospitals [Seoul National University Hospital (IRB No. H-1802-102-924), Seoul National University Bundang Hospital (SNUBH; IRB No. B-1707-408-106), Asan Medical Center (IRB No. 2017-0317) and Severance Hospital (IRB No. 4-2017-0646)] approved the study. The study was performed in accordance with the principles of the Declaration of Helsinki.

Study design and study population

This study employed a multicenter retrospective cohort including IgAN patients from the four government-designated tertiary hospitals in Korea. We included pathology-confirmed IgAN cases from 1979 to 2017 in the study. We excluded those who were on maintenance kidney replacement therapy without baseline or follow-up information. The included patients were divided according to three time periods, which were determined to include similar numbers of IgAN patients: 1979–2003, 2004–9 and 2010–17.

Data collection

The following clinicopathologic characteristics were collected at the time of the initial biopsy for diagnosing IgAN: age, sex and baseline systolic and diastolic blood pressure (BP), with calculations of mean arterial pressure (MAP; one-third of systolic BP + two-thirds of diastolic BP). History of diabetes mellitus or hypertension was recorded. Collected laboratory parameters included estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine values. The amount of baseline proteinuria (PU) was measured from a 24-h urine sample; as these data were frequently absent, the random urine protein:creatinine ratio (uPCR) was used instead in such cases. Treatment history after the diagnosis of IgAN was reviewed. The treatment approaches included RAAS blockers or immunosuppressants, mainly corticosteroids, cyclophosphamide and calcineurin inhibitors. Pathological characteristics, including the degree of cellular or fibrocellular crescent formation, global sclerosis, segmental sclerosis, tubular atrophy and interstitial fibrosis, were recorded. As the Oxford classification had not been implemented, for global sclerosis and segmental sclerosis we used the cutoffs to grade the findings by the criterion that was used in our previous study, which validated the predictive role of cellular or fibrocellular crescents [14]. The degree of cellular or fibrocellular crescents in the biopsied tissue was stratified according to the following C scores: C0 (none), C1 (>0–<25%) and C2 (≥25%) [15]. The severity of tubular atrophy or interstitial fibrosis was graded as none (0%), mild (>0–≤25%), moderate (>25–≤50%) and severe (>50%).

Clinical outcome assessment

The prognostic outcome was progression to ESKD defined by the initiation of kidney replacement therapy. We reviewed the nationwide kidney replacement therapy registry maintained by the Korean Society of Nephrology [16]. Since the data included information about the initiation date of the kidney replacement therapy and modalities, we were able to identify the nationwide outcomes. Considering that the follow-up duration was significantly different between the time periods, the 10-year ESKD

data that were right truncated were analyzed as the main outcome. We also collected the ESKD outcome during the total follow-up period. Right censoring was performed when patient death was recorded or on 31 December 2019. The death events were collected from Statistics Korea, which records data regarding deaths for Koreans, with appropriate approval from the organization.

Statistical analysis

Categorical variables were presented as frequencies (percentages) and analyzed by the chi-squared test. Continuous variables were shown as medians (interquartile ranges) and analyzed by the Kruskal–Wallis test. We plotted Kaplan–Meier survival curves and the log-rank method was used to calculate P-values. We also constructed multivariable Cox proportional hazards models and the hazard ratios (HRs) for the ESKD outcome were calculated and adjusted for the following variables: age, sex, baseline body mass index, eGFR (categorical, ≥60, ≥30 –<60, <30 mL/min/1.73 m^2), presence of a high BP (MAP ≥100 mmHg), significant PU (random uPCR or 24-h protein ≥1 g/g or 1 g/day), serum uric acid level, total cholesterol level and degree of interstitial fibrosis (none, mild, moderate and severe) and tubular atrophy (none, mild, moderate and severe). The details regarding other subgroup investigations are described in the Supplemental Methods.

Whether the differences in groups of patients who received RAAS blockers or immunosuppressants as treatment for IgAN in different time periods mediated the differences in prognosis was analyzed with mediation analysis. In the analysis, a univariable model and the above fully adjusted multivariable model were used and the presence of a significant mediation effect of the medication (RAAS blockers or immunosuppressants) was tested with the 'mediation' package in R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

As there was missing information in the data set (Supplemental Methods); for multivariable investigation, multiple imputation was performed for the missing variables by the chained equations method. The imputation was performed with the 'mice' package in R. The imputation process was used only for multivariable adjustments and not for reporting descriptive statistics or dividing subgroups. The patients with missing information for the variables used to determine subgroups were disregarded in the corresponding subgroup analysis.

All statistical analyses were performed with R and a two-sided P-value <0.05 was considered statistically significant.

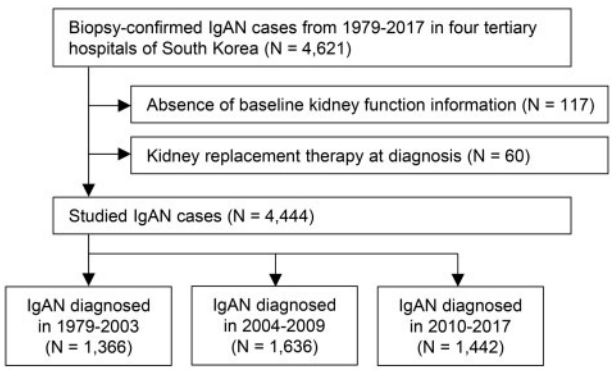

FIGURE 1: Study population.

RESULTS

Study population

We screened 4621 biopsy-confirmed IgAN patients in the study hospitals (Figure 1). After excluding those without baseline or follow-up information ($n = 117$) or patients with established ESKD ($n = 60$), a total of 4444 patients were studied. When we divided the study patients according to time periods, 1366, 1636 and 1442 patients were diagnosed in 1979–2003, 2004–9 and 2010–17, respectively.

Clinicopathologic characteristics of IgAN according to time periods

The clinicopathologic characteristics for each of the time periods are presented in Table 1. The median age at the time of diagnosis tended to be older; in particular, the proportion of patients ≥60 years of age greatly increased in the later periods in contrast with the earlier period. The baseline BP was lower in the more recent periods; however, the proportion of patients with combined hypertension increased more in the recent periods than from 1979 to 2003. The amount of PU at the time of IgAN diagnosis tended to be lower in the recent periods. The proportion of patients initially treated with RAAS blockers was <60% in 1979–2003, but it notably increased with time and reached up to 80% in 2010–17. The use of immunosuppressants also increased with time, from 21.0% in 1979–2003 to 29.1% in 2010–17. Pathological characteristics and the degree of glomerular changes, including global sclerosis, segmental sclerosis and crescent formation, were not different based on time periods. Interestingly, in terms of histologic changes in the tubulointerstitial area, the number of patients with moderate or severe interstitial fibrosis increased with time; meanwhile, the number of patients with moderate or severe tubular atrophy decreased.

Prognosis of IgAN according to time periods

During the total follow-up of the 48 314 person-years with a median follow-up of 11.3 (interquartile range 7.5–15.4) years, 722 patients progressed to ESKD with an incidence rate of 12.5/1000 person-years. The total number of identified ESKD cases within 10 years was 560.

The number of IgAN patients who progressed to ESKD was 384 (incidence rate 14.4/1000 person-years), 239 (incidence rate 12.4/1000 person-years) and 99 (incidence rate 10.1/1000 person-years) in the time periods of 1979–2003, 2004–9 and 2010–17, respectively (Figure 2). The difference in prognosis, both in terms of ESKD during the total follow-up and in terms of ESKD within 10 years, was significant in both univariable and multivariable analyses, and the prognosis of IgAN patients diagnosed in 2010–2017 showed improvement compared with that in 1979–2003, even after multivariable adjustment (Table 2). This trend was also identified when we separated the study patients into five groups according to the year of diagnosis and the HRs compared with the previous time period showed consistently decreasing patterns (Supplementary data, Table S1). The difference in prognosis was significant between IgAN patients diagnosed in 1979–2000 and 2005–7 or afterward in the univariable analysis and between 1979–2000 and 2008–11 or afterward in the multivariable analysis.

Table 1. Baseline characteristics according to time periods of IgAN diagnosis

Characteristics	1979–2003 ($n = 1366$)	2004–09 ($n = 1636$)	2010–17 ($n = 1442$)	P-value
Demographics				
Year of biopsy, median (IQR)	1998 (1991–2001)	2007 (2005–2008)	2012 (2011–2014)	<0.001
Age (years), *n* (%), median (IQR)	31 (21–42)	35 (24–46)	39 (27–51)	<0.001
<20	281 (20.6)	289 (17.7)	208 (14.4)	
≥20–<40	662 (48.4)	716 (43.8)	519 (36.0)	
≥40–<60	365 (26.7)	533 (32.6)	535 (37.1)	
≥60–<80	57 (4.2)	95 (5.8)	173 (12.0)	
≥80	1 (0.1)	3 (0.2)	7 (0.5)	
Male, *n* (%)	767 (56.2)	775 (47.4)	702 (48.7)	<0.001
Body mass index (kg/m^2), median (IQR)	22.7 (20.6–24.9)	22.9 (20.9–25.4)	23.2 (20.8–25.6)	0.006
Comorbidities, *n* (%)				
Diabetes mellitus	59 (5.0)	67 (4.7)	81 (6.6)	0.061
Hypertension	463 (38.4)	551 (38.3)	603 (47.6)	<0.001
BP (mmHg), median (IQR)				
Systolic	127 (115–140)	122.5 (113–135)	120 (111–133)	<0.001
Diastolic	80 (70–90)	79 (70–85)	77 (70–85)	<0.001
Mean arterial pressure	97 (87–106)	93 (84–102)	92 (83–100)	<0.001
<100, *n* (%)	765 (58.4)	1045 (69.4)	1016 (73.9)	
≥100, *n* (%)	546 (41.7)	461 (30.6)	359 (26.1)	
Lab findings				
Serum Cr (mg/dL), median (IQR)	1.10 (0.90–1.40)	1.00 (0.80–1.40)	0.96 (0.74–1.29)	<0.001
eGFR (mL/min/1.73 m^2), median (IQR)	79.42 (55.05–104.03)	79.52 (55.70–103.41)	86.31 (57.28–112.06)	<0.001
≥60, *n* (%)	966 (70.7)	1167 (71.3)	1053 (73.0)	
≥30–<60, *n* (%)	285 (20.9)	350 (21.4)	282 (19.6)	
<30, *n* (%)	115 (8.4)	119 (7.3)	107 (7.4)	
uPCR (g/g), median (IQR)	1.45 (0.67–2.73)	1.00 (0.46–2.02)	1.12 (0.51–2.23)	<0.001
≥1, *n* (%)	778 (64.0)	676 (50.2)	723 (54.0)	
Total cholesterol (mg/dL), median (IQR)	194 (162–230)	180 (156–210)	186 (160–215)	<0.001
Triglycerides (mg/dL), median (IQR)	138.5 (93–208)	116 (81–171)	118 (82–173)	0.001
Uric acid (mg/dL), median (IQR)	5.9 (4.7–7.1)	5.7 (4.5–7.0)	5.8 (4.7–7.1)	0.064
Treatment, *n* (%)				
RAAS blockers	788 (57.7)	1215 (77.0)	1004 (80.0)	<0.001
Immunosuppressants	287 (21.0)	422 (26.7)	365 (29.1)	<0.001
Pathologic findings, *n* (%)				
Global sclerosis				0.089
None	338 (27.4)	445 (27.8)	351 (24.6)	
>0–<40	683 (55.4)	924 (57.6)	832 (58.4)	
≥40	212 (17.2)	234 (14.6)	242 (17.0)	
Segmental sclerosis				0.812
None	556 (45.1)	750 (46.8)	649 (45.6)	
>0–<20	528 (42.8)	651 (40.6)	598 (42.0)	
≥20	149 (12.1)	203 (12.7)	177 (12.4)	
Crescent formation				0.090
None	973 (79.0)	1243 (77.6)	1157 (81.3)	
>0–<25	238 (19.3)	321 (20.1)	235 (16.5)	
≥25	21 (1.7)	37 (2.3)	31 (2.2)	
Tubulointerstitial changes				
Tubular atrophy				<0.001
None	231 (19.9)	299 (19.0)	259 (19.8)	
Mild	419 (36.1)	938 (59.7)	793 (60.5)	
Moderate	313 (27.0)	256 (16.3)	208 (15.9)	
Severe	197 (17.0)	78 (5.0)	50 (3.8)	
Interstitial fibrosis				<0.001
None	176 (15.1)	308 (19.6)	179 (14.0)	
Mild	946 (81.1)	1130 (72.0)	857 (67.0)	
Moderate	35 (3.0)	111 (7.1)	196 (15.3)	
Severe	10 (0.9)	21 (1.3)	47 (3.7)	

There was the following numbers of missing information in the studied data set: BP, $n = 252$; comorbidities for diabetes, $n = 616$; hypertension, $n = 530$; treatment history, $n = 244$; proteinuria, $n = 543$; pathologic findings, $n = 183$; medication history, $n = 244$; total cholesterol, $n = 540$; triglycerides, $n = 2623$; and uric acid, $n = 877$.
IQR: interquartile range.

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Subgroup analysis for prognosis of IgAN

In the subgroup analysis (Table 3), time-dependent 10-year ESKD outcome improvement was significant only in those with a daily PU ≥1 g or 1 g/g but not in those witha lower degree of PU. When the subgroups were divided according to treatment history recorded during the time of diagnosis, IgAN patients treated with immunosuppressants did not show any prognosis improvement, but those not treated by immunosuppressants showed improved prognoses in the recent time periods. Regarding RAAS blocker use, better prognoses were noted in the recent periods both in those who did and did not receive initial RAAS blocker treatment in the univariable analysis. However, such statistical significance was not observed in those diagnosed in 2010–17 but not prescribed RAAS blockers, but the patients consist of only a small number so statistical power was not secured for the multivariable investigation.

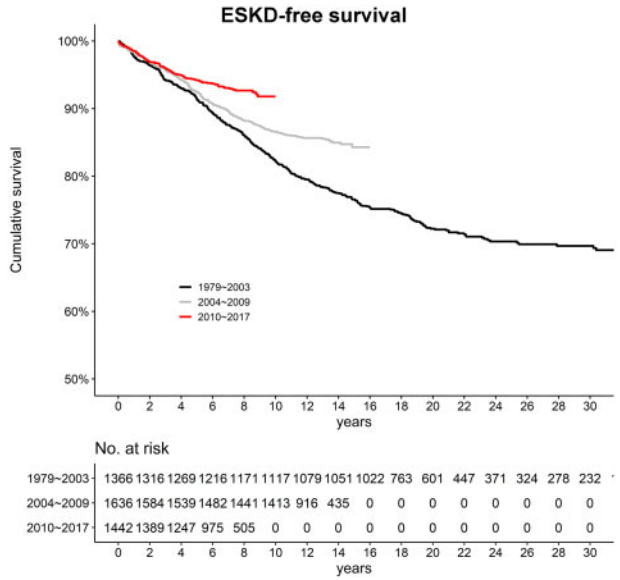

FIGURE 2: Kaplan–Meier survival curve showing kidney survival. The *x*-axis indicates the time from initial biopsy (years) and the *y*-axis indicates the cumulative survival. The black line indicates the survival curve of the IgAN patients diagnosed in 1979–2003, gray line in 2004–09 and red line in 2010–17. Tables containing the number at risk are shown in the chart below the survival graph.

Significance of RAAS blocker use

Among those with data regarding treatment history, treatment with RAAS blockers was a significant mediation factor for associations in both the univariable model ($P < 0.001$) and the multivariable model ($P = 0.04$). Treatment with immunosuppressants showed a suspected mediation effect only on the association between time periods and 10-year ESKD outcomes in the univariable model ($P = 0.006$); however, the effect was insignificant when the model accounted for other clinicopathologic factors ($P = 0.16$). The improvement of IgAN prognosis was more strongly associated with changes in other factors accompanying the prescription of immunosuppressants than to the medication itself.

Considering the significance of RAAS blocker use, we additionally tested the association between RAAS blocker treatment and 10-year progression to ESKD risk in subgroups categorized based on the presence of high MAP (≥100 mmHg) or a high amount of PU (≥1 g/g or 1 g/24 h; Table 4). The univariable and age-/sex-adjusted model showed that RAAS blocker use was associated with lower 10-year ESKD risk only in those with both high MAP and a high amount of PU. On the other hand, a history of RAAS blocker use was insignificantly associated with 10-year ESKD risk in the other subgroups with lower MAP or a lower amount of PU.

DISCUSSION

In this study we showed the characteristics and prognoses of IgAN in South Korea for different time periods. The number of IgAN patients diagnosed at relatively older ages or with preserved kidney function has increased with time. RAAS blockers and immunosuppressants have been more frequently prescribed in recent times. The prognosis of IgAN has improved recently and this improvement was associated with the increasing use of RAAS blockers for treatment.

IgAN became widely recognized in the medical literature from historical studies in the 1970s reporting glomerulonephritis with mesangial IgA disposition [3, 4, 17]. Later studies identified that IgAN is one of the most common primary glomerulonephritis worldwide [1, 2, 18] and the prognosis of the disease has been reported in various regions [19, 20]. Clinical prognostic factors, including high BP, decreased baseline kidney function or a large amount of PU, were initially reported [21, 22],

Table 2. Prognosis of IgAN patients according to different time periods of the diagnosis

		Univariable		Multivariable	
Outcomes/groups	Outcomes, *n* (%)	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
ESKD during total follow-up					
1979–2003	384 (28.1)	Reference		Reference	
2004–09	239 (14.6)	0.659 (0.557–0.780)	<0.001	0.874 (0.722–1.059)	0.169
2010–17	99 (6.9)	0.479 (0.380–0.604)	<0.001	0.593 (0.447–0.785)	<0.001
10-year ESKD					
1979–2003	242 (17.7)	Reference		Reference	
2004–09	219 (13.4)	0.744 (0.620–0.893)	0.002	1.043 (0.851–1.278)	0.687
2010–17	99 (6.9)	0.506 (0.400–0.641)	<0.001	0.692 (0.523–0.915)	0.010

Multivariable model was adjusted for age, sex, baseline body mass index, eGFR (categorical, ≥60, ≥30–<60, <30 mL/min/1.73 m^2), presence of a high BP (MAP ≥100 mmHg), significant proteinuria (random uPCR or 24-h protein ≥1 g/g or 1 g/day), serum uric acid level, total cholesterol level, degree of interstitial fibrosis (none, mild, moderate and severe) and tubular atrophy (none, mild, moderate and severe). Multiple imputation was performed for missing variables using the multivariate imputation by chained equations method.

Table 3. Risks of progression to ESKD within 10 years in various subgroups

Groups	Outcome number/ subgroup number (%)	Univariable		Multivariable	
		HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
eGFR ≥60 mL/min/1.73 m^2					
1979–2003	77/966 (8.0)	Reference		Reference	
2004–09	42/1167 (3.6)	0.441 (0.303–0.642)	<0.001	0.651 (0.458–0.925)	0.017
2010–17	21/1053 (2.0)	0.398 (0.244–0.649)	<0.001	0.547 (0.320–0.936)	0.028
eGFR <60 mL/min/1.73 m^2					
1979–2003	165/400 (41.2)	Reference		Reference	
2004–09	177/469 (36.2)	0.910 (0.736–1.125)	0.384	1.064 (0.842–1.343)	0.604
2010–17	78/389 (17.0)	0.601 (0.458–0.789)	< 0.001	0.659 (0.475–0.914)	0.013
MAP <100 mmHg					
1979–2003	93/762 (12.2)	Reference		Reference	
2004–09	97/1039 (9.3)	0.760 (0.572–1.001)	0.058	0.789 (0.593–1.049)	0.103
2010–17	51/1009 (5.1)	0.583 (0.412–0.823)	0.002	0.549 (0.370–0.817)	0.003
MAP ≥100 mmHg					
1979–2003	136/549 (24.8)	Reference		Reference	
2004–09	106/467 (23.6)	0.957 (0.744–1.230)	0.729	1.011 (0.781–1.309)	0.932
2010–17	42/366 (11.5)	0.577 (0.407–0.817)	0.002	0.598 (0.405–0.883)	0.010
Proteinuria <1 g/g or g/day					
1979–2003	30/436 (6.9)	Reference		Reference	
2004–09	37/671 (5.5)	0.802 (0.495–1.298)	0.368	0.849 (0.538–1.342)	0.484
2010–17	15/615 (2.4)	0.518 (0.277–0.969)	0.040	0.551 (0.276–1.099)	0.091
Proteinuria ≥1 g/g or g/day					
1979–2003	193/781 (24.7)	Reference		Reference	
2004–09	148/676 (21.9)	0.920 (0.744–1.137)	0.439	0.852 (0.683–1.063)	0.156
2010–17	62/723 (8.6)	0.563 (0.431–0.734)	<0.001	0.483 (0.354–0.660)	<0.001
ISD positive					
1979–2003	54/287 (18.8)	Reference		Reference	
2004–09	105/422 (24.9)	1.385 (0.997–1.923)	0.052	1.106 (0.814–1.503)	0.520
2010–17	35/365 (9.6)	0.703 (0.458–1.081)	0.108	0.633 (0.397–1.009)	0.055
ISD negative					
1979–2003	188/1079 (17.4)	Reference		Reference	
2004–09	104/1157 (9.0)	0.496 (0.390–0.630)	< 0.001	0.762 (0.592–0.982)	0.035
2010–17	48/890 (5.4)	0.400 (0.291–0.551)	< 0.001	0.573 (0.396–0.828)	0.003
RAAS blocker positive					
1979–2003	146/788 (18.5)	Reference		Reference	
2004–09	195/1215 (16.0)	0.866 (0.699–1.074)	0.190	0.894 (0.724–1.104)	0.299
2010–17	75/1004 (7.5)	0.540 (0.407–0.715)	<0.001	0.580 (0.425–0.791)	<0.001
RAAS blocker negative					
1979–2003	96/578 (16.6)	Reference		Reference	
2004–09	14/364 (3.8)	0.218 (0.125–0.382)	<0.001	0.532 (0.282–1.007)	0.052
2010–17	8/251 (3.2)	0.240 (0.116–0.495)	<0.001	0.545 (0.244–1.216)	0.138

ISD: immunosuppressive drug.

Multivariable model was adjusted for age, sex, baseline eGFR (categorical, ≥60, ≥30–<60, <30 mL/min/1.73 m^2), presence of a high BP (MAP ≥100 mmHg), significant proteinuria (random uPCR or 24-h protein ≥1 g/g or 1 g/day), degree of interstitial fibrosis (none, mild, moderate and severe) and tubular atrophy (none, mild, moderate and severe). Missing values were imputed using a multivariate imputation by the chained equation method.

along with the implementation of pathologic risk scoring for the disease, leading to the development of the Oxford classification [15, 23]. Clinical trials have shown the benefits of RAAS blockers in improving the prognosis of IgAN [5–8]; however, the benefits of immunosuppressant use have not been firmly established [24–26]. In recent times, genomic studies have investigated potential disease-specific biomarkers or treatment targets [15, 27, 28]. In addition, understanding of the IgAN pathophysiology, through formation of IgA1-containing immune complexes, has expanded [29, 30]. With the extension of knowledge of disease pathophysiology, novel treatment strategies have been recently trialed for the treatment of IgAN [31–33].

Along with the above historical progress and changes in population structure in the modern era we hypothesized that the epidemiology of IgAN would be different in recent periods when compared with the past. Through this study, which includes one of the largest IgAN cohorts, we identified that the proportion of relatively older IgAN patients has increased. However, the proportion of patients with impaired baseline kidney function or established high BP has not increased, implying that the range of indications for biopsies might have been widened for the older population before they show overt kidney function impairment. Additionally, changes in the general population structure might have led to the increasing trend of

Table 4. Association between RAAS blockade usage and risks of progression to ESKD within 10 years in various subgroups

Groups and explanatory variable	Outcome number/ subgroup number (%)	Univariable		Multivariable	
		HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
MAP <100 mg and PU <1 g/g or 1 g/24 h					
No RAAS blocker use	10/404 (2.5)	Reference		Reference	
RAAS blocker use	33/756 (4.4)	1.881 (0.927–3.819)	0.080	1.645 (0.781–3.464)	0.191
MAP ≥100 mg and PU <1 g/g or 1 g/24 h					
No RAAS blocker use	7/99 (7.1)	Reference		Reference	
RAAS blocker use	25/313 (8.0)	1.143 (0.494–2.643)	0.755	0.997 (0.422–2.358)	0.995
MAP <100 mg and PU ≥1 g/g or 1 g/24 h					
No RAAS blocker use	29/251 (11.6)	Reference		Reference	
RAAS blocker use	136/951 (14.3)	1.280 (0.857–1.911)	0.228	1.038 (0.682–1.581)	0.861
MAP ≥100 mg and PU ≥1 g/g or 1 g/24 h					
No RAAS blocker use	59/145 (40.7)	Reference		Reference	
RAAS blocker use	172/477 (26.5)	0.610 (0.454–0.820)	0.001	0.680 (0.500–0.924)	0.014

The multivariable model was adjusted for age and sex.

elderly IgAN patients as the Korean population ages [11], and clinicians may chose more active diagnostic or therapeutic strategies for older IgAN patients. Together with a previous report, also showing the increasing prevalence of IgAN among the elderly [10], this study suggests that IgAN in elderly patients could be an important clinical issue in the future. Conversely, regarding the prognosis of IgAN, the risk of progression to ESKD has been reduced in recent periods compared with that in the past; the progression to ESKD rate was 10.6/1000 person-years for the cases diagnosed from 2010 to 2017. Our study provides epidemiological evidence showing that the characteristics of IgAN patients have been changing and the prognosis has improved between time periods.

Another notable finding was that the prescription of RAAS blockers has been widely introduced recently in Korea. Evidence since the 1990s demonstrating the benefits of RAAS blockers in terms of IgAN prognosis is likely attributable to this phenomenon [6, 7]. Moreover, the improvement in prognosis of IgAN patients was significantly associated with the increased prescription of RAAS blockers. As identified in our results, those with both high MAP (≥100 mmHg) and a high-degree PU (≥1 g/g or 1 g/24 h) may be actively prescribed RAAS blockers as suggested in the current clinical guideline [34].

However, increased use of immunosuppressants was not a significant mediator for the association between time periods and prognosis in the multivariable model. In addition, among those who received immunosuppressive medications, improvement of prognosis according to time periods was not observed. This may imply that the prognosis of those who required immune suppression, possibly the high-risk group with rapid clinical deterioration, has not been improved. In addition, the benefits of immunosuppressive medication have yet to be firmly established, which may partially explain the lack of prognostic improvement in this patient group [24, 25]. This suggests the necessity of a future study investigating treatment strategies for IgAN patients with rapidly progressing kidney dysfunction or who are at high risk of ESKD.

Our study has several limitations. First, the recent time era had a relatively short follow-up duration. We made efforts to compensate for this by establishing ESKD within 10 years as an outcome; however, the difference could not be completely compensated for. Nonetheless, when we divided the study population into five groups, patients diagnosed from 2005 to 2007 who completed the 10-year follow-up showed a better prognosis than those diagnosed in 2000 or earlier. A future study with a longer follow-up period may enable us to robustly compare the prognosis between time periods and evaluate whether the prognostic risk factors have been altered. Second, as the study evaluated outcomes over a long period of time, heterogeneity in terms of certain factors, including socioeconomic characteristics or clinical behaviors, might have been present. In addition, up-to-date pathologic information (e.g. Oxford classification or vascular lesions [35]) was not available in the past pathologic records. Third, although the study included a large number of IgAN patients comparable to that of other large cohorts globally, there were still IgAN patients in other major hospitals in the nation who were not included. In addition, the study included a limited number of patients of ethnicities other than Asian. Therefore the possibility of selection bias should be considered when interpreting the results of our study and additional external validation may be necessary to confirm the findings. Lastly, due to its retrospective, observational nature, there could be hidden confounders that were not included in the current study. In addition, the prescribed medications for RAAS blockade were uncontrolled and heterogeneous among the study patients, so information of RAAS blocker dosage, compliance or withdrawal could not be included in this study.

In conclusion, temporal trends in the characteristics of biopsy-confirmed IgAN in the Korean cohort were noted and the proportion of elderly IgAN patients is increasing. The overall prognosis of IgAN showed a trend of improvement, particularly in those without reduced eGFR but with significant PU, and this was associated with the increasing proportion of patients treated with RAAS blockers. Clinicians may utilize the results of this study for understanding the recent trends of IgAN and preparing future strategies for the disease.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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