Mortality of IgA Nephropathy Patients: A Single Center Experience over 30 Years

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Abstract

Research on the prognosis of IgA nephropathy (IgAN) has focused on renal survival, with little information being available on patient survival. Hence, this investigation aimed to explore long-term patient outcome in IgAN patients. Clinical and pathological characteristics at the time of renal biopsy were reviewed in 1,364 IgAN patients from 1979 to 2008. The outcomes were patient death and end stage renal disease (ESRD) progression. Overall, 71 deaths (5.3%) and 277 cases of ESRD (20.6%) occurred during 13,916 person-years. Ten-, 20-, and 30-year patient survival rates were 96.3%, 91.8%, and 82.7%, respectively. More than 50% patient deaths occurred without ESRD progression. Overall mortality was elevated by 43% from an age/sex-matched general population (GP) (standardized mortality ratio [SMR], 1.43; 95% confidence interval [CI], 1.04–1.92). Women had comparable mortality to GP (SMR, 1.22; 95% CI, 0.82–1.75), but, in men, the mortality rate was double (SMR, 2.17; 95% CI, 1.21–3.57). Patients with renal risk factors such as initial renal dysfunction (estimated glomerular filtration rate < 60 ml/min per 1.73m²; SMR, 1.70; 95% CI, 1.13–2.46), systolic blood pressure ≥ 140 mmHg (SMR, 1.88; 95% CI, 1.19–2.82) or proteinuria ≥ 1 g/day (SMR, 1.66; 95% CI, 1.16–2.29) had an elevated mortality rate. Patients with preserved renal function, normotension, and proteinuria < 1 g/day, however, had a similar mortality rate to GP. When risk stratification was performed by counting the number of major risk factors present at diagnosis, low-risk IgAN patients had a mortality rate equal to that of GP, whereas high-risk patients had a mortality rate higher than that of GP. This investigation demonstrated that overall mortality in IgAN patients was higher than that of GP. Women and patients with renal risk factors had a higher mortality than that of GP. Therefore, strategies optimized to alleviate major renal risk factors are warranted to reduce patient mortality.

Introduction

IgA nephropathy (IgAN) is the most common form of glomerular disease worldwide, with an incidence that ranges from 20% to 40% in patients with primary glomerulonephritis [1]. The relative incidence of IgAN has increased recently, especially in Korea [2]. Despite the well-known heterogeneity of the disease and a generally slow course of disease progression, IgAN is a significant contributor to end stage renal disease (ESRD) progression [1,3,4]. Indeed, numerous studies have addressed the clinical [3–9] and pathological [3,10–14] risk factors linked to the risk of progression. These include initial renal impairment [3,5,9], heavier or prolonged proteinuria [4–6,8], hypertension [6,8,9], and several histological changes [3,6,8,14]. However, the mortality data are not reported in most IgAN survival studies. Patient death has been considered as one part of a composite outcome [8,12,15] or analyzed only descriptively [16]. The mortality rate or its predictors have not been addressed in previous studies. Therefore, according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for glomerulonephritis (to be published), there is an assumption that IgAN patients had higher mortality than the general population (GP), and that cardiovascular morbidity and mortality increase in these patients, as in others with chronic kidney disease.

IgAN patients are usually diagnosed at a relatively young age, and most have a benign clinical course in our clinical practice. Moreover, these patients are thought to be more likely to receive transplantation because of their relatively younger age even after ESRD progression compared to their diabetic ESRD counterparts. Such clinical experiences suggest a favorable patient outcome in IgAN patients. Therefore, the rate of IgAN progression to patient death needs to be clarified, as do the clinical or pathological risk factors involved. The main purpose of this retrospective observational study was to describe the definitive patient outcome and analysis of their predictive factors, compared with renal outcome and its indicators.

Materials and Methods

Ethics statement

This investigation was approved by the institutional review board in Seoul National University Hospital and was in accordance with the principle of the Helsinki Declaration II (H-
Study subjects

From 1979 to 2008, a kidney biopsy registry was constructed using 4,998 kidney needle biopsy cases among patients aged ≥15 years at the Seoul National University Hospital. Allograft biopsy cases were excluded from this cohort. Among the retrospective cohort, a primary diagnosis of IgAN was made in 1,379 patients. Fifteen of these patients who had less than 5 glomeruli in their biopsy specimen had insufficient information for diagnosis and were excluded from this study [11,17]. The diagnosis was based on immunofluorescence microscopy showing mesangial IgA deposition as the predominant or co-dominant immunoglobulin, and on the lack of clinical or laboratory evidence of systemic lupus erythematosus, Henoch-Schonlein nephritis, or liver cirrhosis. In case of lupus nephritis, only the patients with clinical suspicion for lupus nephritis were further tested for lupus autoantibodies.

Clinical data

Baseline demographic and clinical characteristics were obtained from a review of the medical records at the time of biopsy. Demographic and clinical parameters including age, sex, blood pressure, blood chemistry analysis and 24-h urine protein were obtained. Information about co-morbidities was also collected. Hypertension was defined as a reported history of hypertension, a diastolic blood pressure ≥90 mmHg, or a diastolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as a reported history of diabetes or as the active use of an oral hypoglycemic agent or insulin. Anemia was defined as a hemoglobin level <13 g/dL for men and <12 g/dL for women. The estimated glomerular filtration rate (eGFR) was calculated by the modified modification of diet in renal disease equation after measuring serum creatinine. Data on medication were collected if any of the following was started within 6 months of renal biopsy and was prescribed for more than 3 months: renin-angiotensin system blockades, including any kind of angiotensin-converting enzyme inhibitor and angiotensin receptor

### Table 1. Baseline demographic and clinical characteristics.

| Parameters                     | Total (n=1,364) | Death (n=60) | ESRD (n=1,007) |
|--------------------------------|-----------------|--------------|----------------|
| **At the time of biopsy (n)**  | 1,364           | 60           | 1,007          |
| Age (years)                    | 33(25–45)       | <0.001       | <0.001         |
| Sex (male)                     | 862(50.0)       | 0.087        | 513(48.1)      |
| SBP (mmHg)                     | 120(110–130)    | <0.001       | 120(110–130)   |
| Co-morbidity                   |                 |              |                |
| Diabetes                       | 25(2.0)         | 0.120        | 181(1.9)       |
| Cancer                         | 10(0.8)         | <0.001       | 7(0.7)         |
| Hypertension                   | 484(38.7)       | <0.001       | 319(32.4)      |
| Laboratory tests               |                 |              |                |
| Hemoglobin (g/dL)              | 13.3(11.8–14.6) |              | 13.5(12.1–14.7)|
| Albumin (g/dl)                 | 3.9(3.5–4.2)    | <0.001       | 3.9(3.6–4.2)   |
| Cholesterol (mg/dl)            | 186(158–220)    | 0.125        | 184(157–216)   |
| Creatinine (mg/dl)             | 1.10(1.00–1.50) | <0.001       | 1.10(1.00–1.30)|
| eGFR (mL/min/1.73m²)           | 67.6(72.6)      | <0.001       | 73.5(25.2)     |
| 24-hour proteinuria (g/day)    | 1.30(0.56–2.50) | <0.001       | 1.11(0.50–2.12)|
| During follow-up (n)           | 1223            |              | 965            |
| Development of cancer          | 47(3.8)         | <0.001       | 303(1.1)       |
| Development of diabetes        | 73(6.0)         |              | 21(0.8)        |
| Medical treatment (%)          | 1050(7.9)       | 0.084        | 505(2.0)       |
| Antiplatelet agents            | 695(64.8)       | 0.017        | 265(30.9)      |
| Statin                         | 146(13.8)       |              | 117(13.6)      |
| RAS blockade                   | 328(30.6)       | 0.014        | 557(64.9)      |
| Immunosuppressant              | 137(12.7)       | 0.002        | 103(12.0)      |

All continuous variables are shown as mean (SD) for normal distributions, or median (interquartile range) for non-parametric variables. Categorical variables were frequency per observation (N (%)). Baseline characteristics for patients who progressed to the primary outcome were compared with those who did not using Z² test for dichotomous variables, and student t-test for parametric continuous variables.

Abbreviations: ESRD, end stage renal disease; BMI, body mass index; AUA, asymptomatic urinary abnormalities; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; TA, tubular atrophy; RAS, renin-angiotensin system.

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1010-055-336). As the study was retrospective in design and did not include any interventions, informed consent was waived.
blocker; any kind of glucocorticoid; statins; and antiplatelet agents such as aspirin or clopidogrel.

To evaluate histopathological change, 2 pathologists reviewed the renal biopsy slides. In the glomerular area, the numbers of glomeruli, proportions of global sclerosis, segmental sclerosis, and crescent lesion were calculated. The percentages of glomeruli with these lesions were deduced and categorized. In the tubulointerstitial area, tubular atrophy and interstitial fibrosis, interstitial inflammatory cell infiltration, and vascular change were graded. The histopathological grades were also analyzed using the WHO grading system for IgAN.

Outcome measurement

The outcomes were the death from any cause and ESRD progression (permanent hemodialysis, peritoneal dialysis or renal transplantation) after renal biopsy. Data on mortality and cause of death were obtained from the Korean National Statistical Office (KNSO), and ESRD data were collected from the Korea ESRD registry [18]. We combined all these data according to the unique identification number held by all Koreans. In addition, the medical records were searched retrospectively to obtain additional information related to the primary outcome and the recent renal function of the patients. It was assumed that patients who had no follow-up with our institution and no follow-up creatinine values, and who did not undergo any renal replacement therapy or a reported death did not meet the primary endpoint at the time the database closed.

Statistical analysis

The data are presented as frequencies and percentages for categorical variables. Continuous variables with normal distribution are indicated as mean ± SD, while those without normal distribution are shown as median and interquartile range (IQR). Comparisons between the outcome group and other groups were performed using the \( \chi^2 \) test for dichotomous variables, Student t-test for parametric continuous variables, and Mann-Whitney test for non-parametric continuous variables. Survival rates for ESRD, death, and composite outcome were analyzed using the Kaplan-Meier method. Survival differences were tested by the log-rank procedure. Cox proportional hazards models were used for prognostic factor assessment. Proportional hazards assumption for Cox models were tested by using log-minus-log plots. Variables that failed to satisfy the proportional hazards assumptions were analyzed by using time-dependent Cox regression analysis. Variables that showed a significant association (\( P < 0.10 \)) in the univariate analysis or that were of considerable theoretical relevance were retained as potential predictors in the multivariate model. In the forward conditional multivariate

| Parameters | Total (n = 1,270) | Death (n = 1,190) | Yes (n = 67) | P | ESRD (n = 858) | Yes (n = 219) | P |
|------------|-----------------|------------------|-------------|----|---------------|----------------|----|
| Number of glomerulus | 64(21–55) | 35(22–56) | 26(18–43) | 0.007 | 38(23–58) | 26(17–40) | <0.001 |
| Global sclerosis (%) | 14.8(3.7–34.9) | 14.3(3.4–34.2) | 25(5.6–46.2) | 0.020 | 11.3(2.4–27.2) | 37.5(19.2–59.3) | <0.001 |
| Segmental sclerosis (%) | 6.8(0–14.3) | 6.9(0–14.3) | 3.3(0–16.7) | 0.193 | 6.1(0–13.0) | 11.2(3.4–19.1) | <0.001 |
| Crescent (yes) | 268(21.3) | 246(20.7) | 22(32.8) | 0.022 | 210(21.2) | 58(21.8) | 0.866 |
| TA/Interstitial fibrosis | 0.004 | <0.001 |
| None | 119(9.6) | 114(9.7) | 5(7.9) | 0.001 | 106(10.8) | 13(5.0) |
| Mild | 517(41.8) | 498(42.4) | 19(30.2) | 0.472(48.3) | 45(17.2) |
| Moderate | 375(30.3) | 358(30.5) | 17(27.0) | 0.29(23.5) | 84(32.1) |
| Severe | 228(18.3) | 205(17.4) | 22(34.9) | 0.108(11.1) | 120(45.8) |
| Interstitial inflammation | 0.014 | <0.001 |
| None | 163(13.2) | 155(13.2) | 7(11.1) | 0.133(13.6) | 30(11.5) |
| Mild | 485(39.1) | 467(39.7) | 18(26.6) | 0.447(45.8) | 38(14.5) |
| Moderate | 380(30.7) | 362(30.8) | 18(26.6) | 0.293(30.0) | 87(22.9) |
| Severe | 211(17.0) | 191(16.3) | 20(31.7) | 0.104(10.6) | 107(40.8) |
| Vascular change | 0.042 | <0.001 |
| None | 769(62.0) | 736(62.7) | 32(50.0) | 0.657(67.2) | 112(43.1) |
| Hyalinosis | 215(17.4) | 199(17.0) | 16(25.0) | 0.148(15.1) | 66(25.4) |
| Atherosclerotic change | 255(20.6) | 239(20.3) | 16(25.0) | 0.173(17.7) | 82(31.6) |
| WHO pathologic grade (n) | 1077 | 1027 | 50 | 858 | 219 |
| I | 31(2.9) | 31(3.0) | 0(0.0) | 293(3.4) | 2(0.9) |
| II | 272(25.3) | 267(26.0) | 5(10.0) | 265(30.9) | 7(3.2) |
| III | 464(43.1) | 446(43.5) | 18(36.0) | 398(46.4) | 66(30.1) |
| IV | 191(17.8) | 178(17.3) | 13(26.0) | 124(14.5) | 67(30.6) |
| V | 118(11.0) | 104(10.1) | 14(28.9) | 42(4.9) | 77(35.2) |

All continuous variables are shown as mean (SD) for normal distributions, or median (interquartile range) for non-parametric variables. Categorical variables were frequency per observation (N (%)). Pathological characteristics for patients who progressed to the primary outcome were compared with those who did not using \( \chi^2 \) test for dichotomous variables, and student t-test for parametric continuous variables. Abbreviations: ESRD, end stage renal disease; TA, tubular atrophy; DOI:10.1371/journal.pone.0051225.t002
models, the orders of variable selection and the values of Wald statistics helped to determine the rankings of the risk factors.

From the results of Cox-regression analyses, we identified 3 major risk factors: SBP $\geq 140$ mmHg, proteinuria $\geq 1$ g/day, and baseline renal insufficiency with eGFR $< 60$ ml/min per 1.73m$^2$. These major risk factors were simplified as a sum of present risk factors as follows: low-risk group for none or one of the risk factors; intermediate-risk group for any 2 of the risk factors, and high-risk group for all their simultaneous presence. Patient survival and renal survival analyses were also performed according to the risk stratification.

To clarify the mortality rate associated with IgAN, the standardized mortality ratio (SMR) was calculated as the ratio between the observed and the expected number of deaths. The expected number of deaths was calculated by person-year methods as follows: (1) The sum of annual observed person-years was calculated during the observation period (1992–2008). (2) The expected number of deaths was calculated by multiplying the sum of annual expected person-years by sex-adjusted national mortality data in 5-year calendar periods and 5-year age groups. (3) The sum of annual expected number of deaths was calculated. Information about the annual mortality rates of the general Korean population was collected from the KNSO. Because national mortality statistics were available from 1992, SMR was calculated in the patients who had a renal biopsy after 1992. An SMR $> 1.0$ was considered to be an excess mortality. To calculate the 95% confidence intervals (CIs) for the SMR of each group, the Poisson-distributed number of observed cases was assumed [19]. Two-sided $P$ values are reported, with the level of statistical significance set at 0.05. The SPSS Statistics (version 19.0, Chicago, IL, USA) package was used for statistical analysis.

**Results**

Baseline characteristics according to outcome development

Overall, 1,364 patients were included in the final analysis. Initial demographic and clinical data are listed in Table 1. The median age at the time of biopsy was 33 years (IQR, 25–45). The proportion of men and women was equal, although age distribution according to sex was quite different. Median age was lower in men (31 years; IQR, 22–45) than in women (35 years; IQR, 27–45). Gross hematuria was present in 33.2% of patients.
The mean eGFR was 67.6 ml/min per 1.73m² and proteinuria was 1.3 g/day. In all, 137 patients were treated with immunosuppressive agents, of which 25 were treated with intravenous steroids; 130 with oral steroids; 36 with oral cyclophosphamide; 9 with cyclosporine; and 9 with mycophenolate mofetil.

The patients who died were significantly older, and had higher blood pressure, more nephrotic features and more depressed renal function at the time of biopsy than did the survivors. A higher proportion of the patients who died was managed with immunosuppressive agents before death. Patients with ESRD progression were slightly older and included a higher proportion of men than did the non-ESRD group. Nephrotic features, higher blood pressure, lower hemoglobin level and initial renal dysfunction were significantly higher in patients with renal progression. Table 2 summarizes the pathological data of the study population. The pathological changes were more severe in both glomerular and tubulointerstitial areas in ESRD patients and in those who died.

Figure 1 compares the overall renal and patient survival rates. In cases of renal survival, 277 (20.6%) patients advanced to renal death. Ten, 20- and 30-year renal survival rates were 82.0%, 70.8% and 67.3%, respectively during a median observation period of 96 (IQR, 56–187) months with 14,495 person-years. The median time to ESRD was 71 (IQR, 32–123) months. Seventy-one (5.3%) patients died during the median observation period of 100 (IQR, 51–210) months, with 13,916 person-years. The median time to death was 101 (IQR, 38–189) months. Ten, 20-, and 30-year patient survival rates were 96.3%, 91.8%, and 82.7%, respectively. For composite outcome, the significant predictors were similar to those of ESRD.

The results of the multivariate analysis for the indicators of ESRD and patient death are summarized in Table 3. In the case of renal survival, initial renal function was the most important determinant, followed, as expected, by hypertension. Segmental sclerosis and hypoalbuminemia remained as significant predictors of renal progression. Gross hematuria was associated with a favorable renal outcome. For patient outcome, advanced age, SBP $\geq 140$ mmHg, hypoalbuminemia and combined malignancy were identified as independent determinants. Interestingly, predictors of patient and renal death appeared to be similar, with hypoalbuminemia and hypertension (or SBP $\geq 140$ mmHg) being common risk factors for both outcomes. Moreover, determinants of the composite outcome seemed to be the combination of the predictors of mortality and ESRD progression. When the simplified risk stratification was applied, it predicted both renal and patient outcome in IgAN patients well (Figure 2).

Subgroup analysis for patient death

Among the 71 deaths, 39 (55.7%) patients died before ESRD progression. These 39 patients were significantly older (median age 49 [IQR, 38–64] vs.61 [IQR, 53–66] years, $P=0.049$) and showed relatively conserved renal function (median eGFR 55.8 [IQR, 39.1–71.5] vs. 37.0 [IQR, 18.3–53.7] ml/min per 1.73m², respectively).
Table 3. Univariate and multivariate time dependent cox regression analyses for patient death and renal death.

| Death | Univariate analysis | Multivariate analysis |
|-------|---------------------|----------------------|
|       | Wald HR 95% CI P    | Wald HR 95% CI P     |
| Age <40 years | Ref. Ref. Ref. | Ref. Ref. Ref. |
| 40–59 | 20.440 3.718 2.104–6.571 <0.001 | 4.626 2.229 1.074–4.626 0.031 |
| ≥60  | 101.088 24.493 13.130–45.691 <0.001 | 49.267 15.627 7.253–33.670 <0.001 |
| SBP ≥140 mmHg | 28.157 3.730 2.294–6.065 <0.001 | 9.121 2.484 1.376–4.482 0.003 |
| Albumin <3.5 g/dL | 39.264 4.778 2.930–7.794 <0.001 | 8.481 2.470 1.344–4.539 0.003 |
| Cancer | 28.999 5.745 3.040–10.855 <0.001 | 3.943 2.224 1.010–4.894 0.047 |
| Composite | Ref. Ref. Ref. | Ref. Ref. Ref. |
| Age <40 years | Ref. Ref. Ref. | Ref. Ref. Ref. |
| 40–59 | 16.913 1.695 1.318–2.180 <0.001 | 1.520 0.672 0.358–1.264 0.218 |
| ≥60  | 60.809 4.582 3.125–6.718 <0.001 | 14.317 5.351 2.244–12.757 <0.001 |
| Cancer | 23.350 2.760 1.828–4.166 <0.001 | 13.545 2.882 1.640–5.064 <0.001 |

Multivariate time-dependent cox regression analysis for patient-death was included age, sex, clinical manifestations of edema/gross hematuria, co-morbidities of hypertension/cancer, BMI, GFR, anemia, albumin <3.5 g/dL, SBP ≥140 mmHg, DBP ≥90 mmHg, proteinuria ≥1 g/day, pathologic change of segmental sclerosis, and treatment history with statin and renin-angiotensin system blockades. Sex and age were considered changes of proportional hazard according to time progression. Global sclerosis interacted with GFR and interstitial inflammatory cell infiltration. BMI interacted with age. Therefore such interactions were considered in this model.

Multivariate time-dependent cox regression analysis for renal-death was included age, sex, clinical manifestations of edema/gross hematuria, co-morbidities of diabetes/hypertension/cancer, GFR, anemia, albumin <3.5 g/dL, SBP ≥140 mmHg, DBP ≥90 mmHg, proteinuria ≥1 g/day, pathologic change of segmental sclerosis, and treatment history with statin and renin-angiotensin system blockades. Sex and age were considered changes of proportional hazard according to time progression. Global sclerosis and other tubulointerstitial changes were excluded in the final model because of severe interaction with GFR.

Abbreviations: SBP, systolic blood pressure; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; CI, confidence interval.

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As expected, ESRD progression was a significant predictor of mortality [hazard ratio, 2.593; 95% CI, 1.609–4.177; P <0.001]. After ESRD progression, 25.3% patients received renal transplantation. Among the patients who received transplantation, only 3 patients died, 1 from infection and the other 2 after allograft failure and resumption of dialysis. All of them were dead by 12 years after ESRD progression. As a result, although the 10-year survival rate after ESRD was higher in all ESRD patients including transplantation recipients, than in those excluding transplantation recipients, the 20-year survival rate of ESRD was similar in both groups at about 65% (Figure 3).

Thirteen patients who were managed by immunosuppressive agents had died. Among them, 5 patients died from infection and two patients died from malignancy. Three patients whose cause of death was infection had underlying cancer (Table 5). There was no relationship between the cumulative dose of immunosuppressive agents and any death or infection-associated death (data was not shown).
Standardized mortality ratio in IgAN

Table 6 summarizes the overall and sex-specific SMR results. The overall relative mortality rate of IgAN patients was significantly higher by 43% than that of age/sex-matched GP (SMR, 1.43; 95% CI, 1.04–1.92). Interestingly, the mortality rate was different according to subgroups. An excess mortality rate was found in women (SMR, 2.17; 95% CI, 1.21–3.57), but not in men (SMR, 1.22; 95% CI, 0.82–1.75) with IgAN. Moreover, patients with lower eGFR (<60 ml/min per1.73m²; SMR, 1.70; 95% CI, 1.13–2.46), higher proteinuria (≥1 g/day; SMR, 1.66; 95% CI, 1.16–2.29), or higher SBP (≥140 mmHg; SMR, 1.88; 95% CI, 1.19–2.82) had an elevated mortality rate compared with their age/sex-matched GP, whereas patients without such risk factors had a similar mortality rate.

When the SMR was further classified by the simplified risk stratification, IgAN patients in the low-risk group had a similar mortality rate to the GP. In the intermediate-risk group, IgAN patients’ mortality appeared higher than that in the GP, although insignificant. However, in the high-risk group, IgAN patients’ mortality was significantly higher than that in the GP. Interestingly, this relationship was different according to sex. Thus, risk stratification did not have any influence on the SMR in men, but SMR in women was affected significantly (Figure 4).

Discussion

Until recently, investigations on IgAN have focused on renal prognosis because it is the most common primary glomerulonephritis and a significant contributor to the development of ESRD, despite the slow rate of progression [1,20]. However, there has been no information about death, which is more definitive outcome than ESRD. In this investigation, we demonstrated that the 30-year mortality of IgAN patients was 82.7%. Moreover, we showed that mortality of IgAN patients was higher than that of the age/sex-matched GP by 43%. To the best of our knowledge, this is the first study to investigate patient survival and its predictive factors as distinguished from renal survival in IgAN patients.

The most notable finding in our survival analyses is that although the overall relative mortality of IgAN, expressed by SMR, was shown to be higher than that of the GP, the absolute mortality rate was not very high when considering the significant renal progression to ESRD. More than half of the deaths occurred even before ESRD progression and the most common cause of death was malignancy. In particular, the patients who survived and progressed to ESRD had a better survival rate than the general dialysis patients did. According to the Korean ESRD registry, the 10-year survival rate of the overall dialysis patients was about 45%, and the 10-year survival rate of the non-diabetic dialysis patients within this group was 58.5% [21]. In the 2011 US Renal Data System data, survival over the first 5 years of therapy was only 45% in the patients with glomerulonephritis [22]. Compared with the above data, the ESRD patients with IgAN in this investigation have a favorable survival rate. The relatively young age of the ESRD population in this study may have explained the favorable survival. In this study, the mean age of the 277 patients who progressed to ESRD was 45 years, which was lower than the mean age (52.1 years) of the 5,550 glomerulonephritis-induced ESRD patients in the Korean ESRD registry [21].

| Causes of death (N) | Death before ESRD (n = 39) | Death after ESRD (n = 31) | Total |
|--------------------|-----------------------------|---------------------------|-------|
| Renal disease      | 2                           | 11                        | 13    |
| Cardiovascular disease | 5                           | 5                          | 10    |
| Cancer             | 12                          | 1                         | 13    |
| Infection          | 6                           | 4                          | 10    |
| Traffic accident or injury | 3                           | 1                          | 4     |
| Miscellaneous      | 2                           | 3                          | 5     |
| Unknown            | 9                           | 6                          | 15    |

Abbreviations: ESRD, end-stage renal disease.

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Figure 3. Cumulative patient survival after ESRD progression according to the all ESRD patients (A) and excluding transplantation recipients (B). The primary outcome is patient survival. The numbers of patients remaining at 60, 120, 180, 240, 300, and 360 months of follow-up are shown at the bottom. ESRD, end stage renal disease.
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With regard to transplantation, this may have contributed to the improved survival in the ESRD patients with IgAN for 10-year survival rate, but not the 20-year survival rate. To clarify the precise mechanisms of the fair survival rate for IgAN patients with ESRD, further well-designed investigations are needed.

Interestingly, the survival patterns differed according to the sex, renal function, proteinuria and blood pressure. Patients who were male, with preserved renal function, normotension, and proteinuria <1 g/day had a similar mortality rate compared with the GP, whereas female patients, or patients with renal dysfunction, higher blood pressure and proteinuria ≥1 g/day had significantly higher mortality, compared with the GP. The results for the 3 subgroups (renal dysfunction, higher blood pressure, and proteinuria ≥1 g/day) were similar, although the difference according to sex was unexpected result. In the regression analysis, a sex difference was not detected even in the univariate analysis. However, men showed a comparable survival rate, whereas women tended to have a higher mortality rate compared with the age-matched Korean GP, although the actual number of patients who died was higher in men. On average, men had a 20% higher death rate than did women. The difference was increased up to 3-fold in their 40s and 50s compared with Korean GP (http://kostat.go.kr).

### Table 5. Causes of death according to use of immunosuppressive agents.

|                | Steroid IV | Steroid PO | Cyclophosphamide | Calcineurin inhibitor | Mycophenolate |
|----------------|------------|------------|-------------------|-----------------------|---------------|
| **No of prescription** | 25         | 130        | 36                | 9                     | 9             |
| **Cumulative dose** | 1187(450–2437) | 3115(1519–4308) | 6487(4087–10050) | 1833       | 107000        |
| **Duration** | 3(1.8–6.0) | 122(75–168) | 80(48–123)        | 107               | 111           |
| **No of death** | 3          | 12         | 6                 | 2                    | 1             |
| **Cause of death** |            |            |                   |                      |               |
| Renal disease | 0          | 0          | 1                 | 0                    | 0             |
| Cardiovascular disease | 0          | 1          | 1                 | 0                    | 0             |
| Cancer | 0          | 2          | 0                 | 0                    | 0             |
| Infection | 2          | 5          | 2                 | 2                    | 1             |
| Unknown | 1          | 4          | 2                 | 0                    | 0             |

Abbreviations: IV, intravenous; PO per oral; doi:10.1371/journal.pone.0051225.t005

### Table 6. Standardized mortality ratios (SMRs) in overall and subpopulation of IgAN patients.

|                | N       | Initial age | Final age | Person-year | Observed | Expected | SMR(95% CI) |
|----------------|---------|-------------|-----------|-------------|----------|----------|-------------|
| **Overall**    | 1009    | 36.8±13.7   | 6         | 45.0±14.0   | 8134.2   | 44       | 30.7        | 1.43(1.04–1.92) |
| eGFR ≥60       | 606     | 32.9±12.2   | 7         | 41.3±13.2   | 5077.4   | 15       | 13.8        | 1.08(0.61–1.79) |
| <60            | 374     | 43.4±13.6   | 6         | 50.9±13.2   | 2825.6   | 28       | 16.5        | 1.70(1.13–2.46) |
| Proteinuria <1 g/day | 341     | 33.8±13.1   | 4         | 41.0±13.3   | 2445.5   | 6        | 6.2         | 0.97(0.36–2.12) |
| ≥1 g/day       | 572     | 39.1±13.7   | 6         | 47.7±13.7   | 4941.5   | 36       | 21.7        | 1.66(1.16–2.29) |
| SBP <140       | 768     | 35.2±13.1   | 4         | 42.8±13.4   | 5911.3   | 18       | 18.3        | 0.98(0.58–1.56) |
| ≥140           | 230     | 42.2±14.1   | 5         | 51.4±13.9   | 2125.2   | 23       | 12.3        | 1.88(1.19–2.82) |
| **Men**        | 495     | 36.1±14.7   | 7         | 45.0±15.0   | 4403.6   | 29       | 23.8        | 1.22(0.82–1.75) |
| eGFR ≥60       | 309     | 31.6±12.9   | 5         | 40.7±13.6   | 2827.9   | 10       | 10.2        | 0.98(0.47–1.81) |
| <60            | 173     | 44.6±14.0   | 6         | 53.1±13.5   | 1482.8   | 18       | 13.4        | 1.34(0.80–2.13) |
| Proteinuria <1 g/day | 143     | 31.5±13.7   | 4         | 40.1±14.0   | 1225.5   | 3        | 1.9         | 1.57(0.32–4.58) |
| ≥1 g/day       | 307     | 38.7±14.4   | 4         | 47.8±14.3   | 2791.7   | 12       | 4.6         | 2.60(1.35–4.55) |
| SBP <140       | 356     | 34.4±14.3   | 4         | 43.0±14.5   | 3092.0   | 12       | 14.1        | 0.85(0.44–1.49) |
| ≥140           | 135     | 40.6±14.9   | 8         | 50.2±14.6   | 1299.1   | 15       | 9.7         | 1.55(0.87–2.56) |
| **Women**      | 514     | 37.5±12.6   | 5         | 45.0±13.0   | 3730.6   | 15       | 6.9         | 2.17(1.21–3.57) |
| eGFR ≥60       | 297     | 34.4±11.3   | 5         | 41.9±12.7   | 2249.5   | 5        | 3.7         | 1.36(0.44–3.18) |
| <60            | 201     | 42.4±13.2   | 5         | 49.0±12.8   | 1342.8   | 10       | 3.1         | 3.24(1.55–5.95) |
| Proteinuria <1 g/day | 198     | 35.5±12.4   | 4         | 41.6±2.9    | 1220.0   | 3        | 4.2         | 0.71(0.15–2.07) |
| ≥1 g/day       | 265     | 39.4±12.7   | 4         | 47.5±13.0   | 2149.8   | 24       | 17.1        | 1.40(0.90–2.08) |
| SBP <140       | 412     | 35.9±12.0   | 6         | 42.7±12.4   | 2819.3   | 6        | 4.2         | 1.43(0.53–3.12) |
| ≥140           | 95      | 44.5±12.5   | 8         | 53.1±12.7   | 826.1    | 8        | 2.6         | 3.09(1.34–6.10) |

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

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may cause the discordance between the relative and absolute mortality in IgAN patients. The precise mechanisms of the sex difference in relative mortality remain to be defined.

The survival pattern of IgAN patients described in this analysis suggests the need for some changes in clinical practice. Despite the high prevalence of IgAN, adequate and specific treatment intervention in the early stage of IgAN remains controversial. Therefore, both clinicians and patients tend to hesitate before following an active therapeutic approach to individual IgAN patients, even at high risk for progression. However, the decreased age at diagnosis, reduced cardiovascular risk factors and increased average life expectancies have allowed more IgAN patients to live with ESRD state for a relatively longer duration, compared with other causes of ESRD including diabetes. ESRD treatment clearly incurs a considerable burden to both society and the patients [22]. The cost per person-year of ESRD was the highest and that of transplantation was the fourth highest among the 500 common causes of ESRD, more meticulous and active management to mitigate renal progression is warranted in IgAN patients.

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