**Table 2** Baseline characteristics according to the category of proteinuria at 1 year of follow-up

| Variables | Category of UPE at 1 year of follow-up (g/day) | | | | *p* value |
|---|---|---|---|---|---|
| | *Disappeared* (<0.3) | *Mild* (0.30–0.39) | *Moderate* (0.40–0.99) | *Severe* (≥1.00) | |
| Number of patients | 80 | 23 | 22 | 16 | |
| Age (years) | 35 (26–44) | 30 (25–42) | 32 (26–36) | 35 (26–42) | >0.2 |
| Female | 39 (48.8) | 11 (47.8) | 12 (54.5) | 9 (56.3) | >0.2 |
| Current smokers | 18 (22.5) | 5 (21.7) | 6 (27.3) | 5 (31.3) | >0.2 |
| BP >130/80 mmHg | 25 (31.3) | 9 (39.1) | 5 (22.7) | 4 (25.0) | >0.2 |
| UPE (g/day) | 0.82 (0.57–1.28) | 0.80 (0.64–2.17) | 1.58 (0.97–2.28) | 1.90 (1.25–2.80) | <0.001[#] |
| U-RBC >30/hpf | 48 (60.0) | 12 (52.2) | 8 (36.4) | 9 (56.3) | >0.2 |
| eGFR (ml/min/1.73 $m^2$) | 75.1 ± 27.1 | 73.7 ± 29.1 | 68.2 ± 29.5 | 66.3 ± 29.1 | >0.2 |
| eGFR <60 | 25 (31.3) | 10 (43.5) | 10 (45.5) | 6 (37.5) | >0.2 |
| Tonsillectomy | 40 (50.0) | 10 (43.5) | 12 (54.5) | 6 (37.5) | >0.2 |
| RAAS inhibitors | 35 (43.8) | 9 (39.1) | 11 (50.0) | 7 (43.8) | >0.2 |

Values are presented as numbers (%), medians (IQR) or mean ± SD

*BP* blood pressure, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *eGFR* estimated glomerular filtration rate.
[#] $p < 0.05$

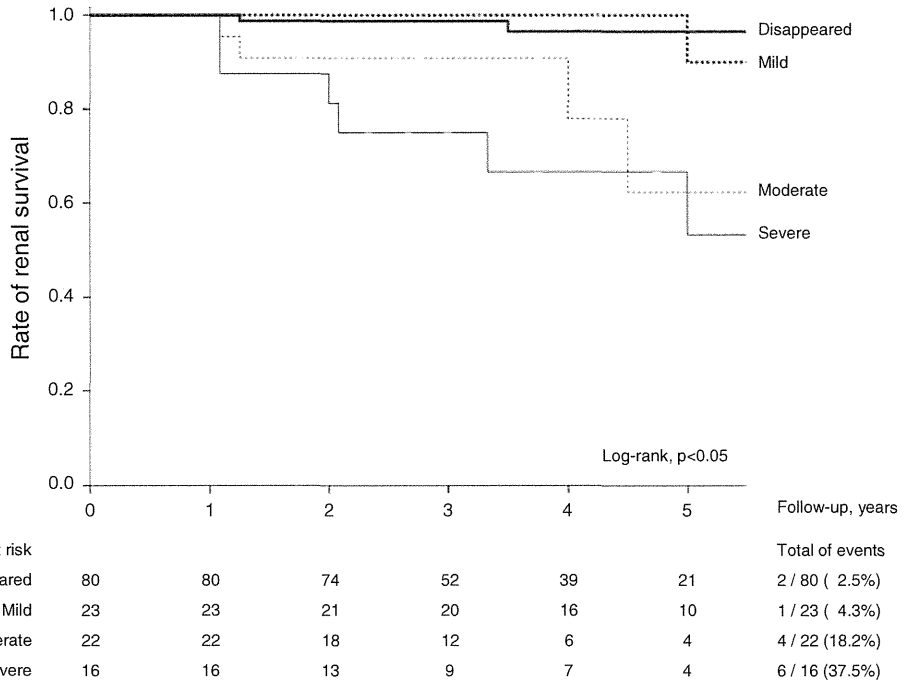


**Fig. 3** Renal survival determined by the Kaplan–Meier method, stratified by the category of UPE at 1 year after 6 months of steroid therapy. These unadjusted curves demonstrate that, in addition to the *Disappeared* category, the *Mild* category showed significantly better renal survival compared to that in the *Moderate* or *Severe* categories (log-rank, $p < 0.05$ for both strata)

relative to the absence of endocapillary hypercellularity (E0). T1 or T2 tubular atrophy/interstitial fibrosis was significantly associated with impaired renal survival relative to T0. In addition, HG 2 was significantly associated with favorable renal outcome relative to HG 3 plus HG 4. Although HG 1 was not significantly associated with favorable outcome, no event was observed in 32 patients of HG 1.

The multivariate model A and model B in Table 4 examined the predictive power of UPE <0.4 g/day at 1 year for renal survival after adjusting for pathological predictors in the Oxford classification and HG, respectively. A UPE <0.4 g/day at 1 year was selected as an independent predictor in both model A and model B.

## Adverse effects

Serious adverse events were not observed during the study period. Although three patients developed type 2 diabetes during the 6 months of treatment, they showed normal levels of glycosylated HbA1 at 1 year with diet therapy alone. Seven patients developed infections during the

**Table 3** Clinical predictors for a 50 % increase in serum creatinine from the baseline level in the Cox–hazard model

| Predictors | Univariate model | | Multivariate model[a] | |
|---|---|---|---|---|
| | HR (95 % CI) | *p* value | HR (95 % CI) | *p* value |
| At 1 year | | | | |
| Category of proteinuria[b] | | | | |
| *Disappeared*[c] | 0.07 (0.01–0.33) | 0.001[#] | 0.06 (0.01–0.57) | 0.014[#] |
| *Mild*[c] | 0.10 (0.12–0.80) | 0.030[#] | 0.02 (0.00–0.29) | 0.003[#] |
| *Moderate*[c] | 0.55 (0.16–1.98) | >0.2 | 0.24 (0.04–1.25) | 0.089 |
| U-RBC <5/hpf[d] | 2.59 (0.71–9.42) | 0.148 | – | – |
| Clinical remission[d] | 0.35 (0.08–1.57) | 0.170 | – | – |
| At baseline | | | | |
| Age (years) | 1.04 (0.99–1.08) | 0.092 | 1.00 (0.94–1.06) | >0.2 |
| Female[d] | 1.06 (0.36–3.16) | >0.2 | – | – |
| Current smoking[d] | 3.96 (1.33–11.8) | 0.013[#] | 1.27 (0.28–5.58) | >0.2 |
| BP ≥130/80 mmHg[d] | 1.31 (0.36–4.79) | >0.2 | – | – |
| UPE (g/day) | 2.09 (1.43–3.07) | <0.001[#] | –[e] | –[e] |
| U-RBC ≥30/hpf[d] | 0.22 (0.06–0.79) | 0.021[#] | 0.34 (0.06–1.99) | >0.2 |
| eGFR <60 ml/min/1.73 $m^2$ [d] | 11.5 (2.55–52.3) | 0.002[#] | 24.3 (2.72–217) | 0.004[#] |
| Concurrent treatment | | | | |
| Tonsillectomy[d] | 0.37 (0.11–1.21) | 0.099 | 1.23 (0.27–5.55) | >0.2 |
| RAAS inhibitors[d] | 2.06 (0.67–6.29) | >0.2 | – | – |

*HR* hazard ratio, *CI* confidence interval, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *NE* not enrolled in the multivariate model, *eGFR* estimated glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system

[a] If the *p* value of the variable was <0.1 in the univariate model, the predictor was selected for the multivariate model

[b] The category is shown in Table 2

[c] Reference = *Severe* category

[d] Yes versus no

[e] As it was related to category of UPE at 1 year (see Table 2), it was not enrolled in the multivariate model

[#] $p < 0.05$

**Table 4** Pathological predictors and UPE <0.4 g/day at 1 year for a 50 % increase in the serum creatinine level from baseline in the Cox model

| Predictors | Univariate model | | Multivariate model A | | Multivariate model B | |
|---|---|---|---|---|---|---|
| | HR (95 % CI) | *p* value | HR (95 % CI) | *p* value | HR (95 % CI) | *p* value |
| Oxford classification | | | | | | |
| M1 versus M0 | 0.93 (0.24–3.61) | >0.2 | – | – | – | – |
| E1 versus E0 | 0.23 (0.06–0.89) | 0.033[#] | 0.44 (0.10–1.91) | >0.2 | – | – |
| S1 versus S0 | 2.03 (0.26–16.0) | >0.2 | – | – | – | – |
| T1 versus T0 | 6.97 (1.66–29.2) | 0.008[#] | 4.35 (1.02–18.5) | 0.047[#] | – | – |
| T2 versus T0 | 12.8 (2.12–77.1) | 0.005[#] | 19.1 (2.55–144) | 0.004[#] | – | – |
| Ext, present versus absent | 0.44 (0.09–2.06) | >0.2 | – | – | – | – |
| HG | | | | | | |
| HG1 versus HG3 + 4 | 0.00 (0.00–100<) | >0.2 | – | – | 0.00 (0.00–100<) | >0.2 |
| HG2 versus HG3 + 4 | 0.24 (0.06–0.92) | 0.038[#] | – | – | 0.36 (0.08–1.51) | 0.161 |
| UPE at 1 year <0.4 g/day[a] | 0.10 (0.03–0.36) | <0.001[#] | 0.08 (0.01–0.45) | 0.004[#] | 0.06 (0.01–0.29) | 0.001[#] |

*HR* hazard ratio, *CI* confidence interval, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental sclerosis, *T* tubulointerstitial atrophy/fibrosis, *Ext* extracapillary lesion, *HG* histological grade, *UPE* urinary protein excretion volume

[#] $p < 0.05$

[a] Yes versus no

steroid therapy: five bacterial infections (tonsillitis, pharyngitis) and two viral infections (influenza). Two females became pregnant during the follow-up and maintained a stable renal function.

## Discussion

The goal of this study was to identify the level of proteinuria after steroid therapy associated with a favorable renal outcome in IgAN patients. Previous studies by Reich et al. [4], Hwang et al. [5], or Le et al. [6] have demonstrated that the average level of proteinuria during the whole period of follow-up (A-P) was significantly associated with the renal outcome, providing a targeted proteinuria during long-term follow-up. In contrast, we identified a therapeutic indicator of a favorable renal outcome as an early response to the steroid therapy, which might be more practical than A-P, whereas it was not analyzed in the previous studies. We adopted 1 year as the time to assess the attenuated proteinuria, since another Cox model in our cohort revealed that the values for proteinuria at 1 year were significantly associated with the outcome, whereas those at baseline or 6 months were not (data not shown).

In this study, the spline model revealed that the threshold UPE predicting the outcome was approximately 0.4 g/day. In addition, a multivariate Cox model including the categorized UPE at 1 year revealed that not only the *Disappeared* category but also the *Mild* category were significantly associated with favorable renal survival relative to the *Severe* category. Therefore, attenuated proteinuria <0.4 g/day at 1 year after treatment can lead to a favorable outcome, as well as the disappearance of proteinuria. The predictive power of UPE <0.4 g/day at 1 year for renal survival was confirmed even after adjusting for pathological predictors determined by the multivariate model (Table 4).

Concerning the impact of clinical remission at an early phase on the renal outcome, Tatematsu et al. [20] showed that clinical remission within 2 years after 6 months of steroid therapy was associated with limiting the eGFR decline. In contrast, clinical remission at 1 year was not significantly associated with the endpoint in our univariate Cox model (Table 3). Although the reasons for the discrepancy between the two studies are unknown, there might be several factors responsible. For example, the timing for assessment of clinical remission was different: during the first 2 years in Tatematsu's study and at 1 year after the intervention in our study. Furthermore, the fact that the incidence of the endpoint in our patients achieving clinical remission at 1 year after the therapy was not significantly different from that in those without clinical remission (4.1 vs. 12.0 %, respectively, $p > 0.2$) may have affected the results shown in Table 3.

Our retrospective study has several limitations. First, we did not include control patients who were followed by supportive therapy alone. Second, the study population and statistical power were small, and the observation period was relatively short to evaluate the outcome in IgAN, leading to the small number of outcomes. Since a limited number of outcomes would generally restrict the number of explanatory variables in multivariate models, we additionally tested the Cox–hazard model for the outcome with two explanatory variables: UPE at 1 year <0.4 g/day and propensity score. The propensity model for UPE at 1 year <0.4 g/day was constructed with the baseline characteristics or pathological parameters. After adjusting the propensity score, we also found the predictive power of UPE at 1 year <0.4 g/day for the outcome (data not shown), suggesting the consistency of the significance of UPE at 1 year <0.4 g/day. Nevertheless, the value of UPE at 1 year <0.4 g/day as a favorable predictor should be ascertained in other studies with longer observation periods and a larger number of outcomes. Third, the role of recurrent proteinuria after 1 year on the progression of IgAN should be examined, since clinical remission was not associated with the endpoint in this study.

In conclusion, the achievement of proteinuria <0.4 g/day at 1 year after 6 months of steroid therapy is an optimal goal for achieving a subsequent favorable renal survival, independent of the baseline renal function or renal pathological changes. Further investigations of the impact of recurrence during follow-up on the endpoint are now in progress.

**Acknowledgments** We are grateful to Mrs. Tomoko Hayakawa for technical assistance. This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, Research on Intractable Disease, from the Ministry of Health, Labour and Welfare of Japan.

**Conflict of interest** None.



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Clin Exp Nephrol (2012) 16:580–588
DOI 10.1007/s10157-012-0598-2

ORIGINAL ARTICLE

# ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes

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Received: 15 November 2011 / Accepted: 13 January 2012 / Published online: 18 February 2012


**Abstract**
*Background* This study was conducted to standardize treatment and determine patient and renal outcome in Japanese anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis/rapidly progressive glomerulonephritis (AAV/RPGN) patients, because the prognosis of AAV/RPGN patients in Japan had been poor compared with that of other countries.
*Methods* The participants in this retrospective cohort study were 824 ANCA-positive RPGN patients, 705 of whom were only myeloperoxidase (MPO)-ANCA positive.
*Results* Among the early-years cohort (group A; cases diagnosed between 1988 and 1998), patients frequently died due to opportunistic infection. Therefore, we recommended a reduced dose of prednisolone (oral prednisolone dose <0.8 mg/kg/day) with or without cyclophosphamide for initial treatment of Japanese RPGN patients. After this recommendation, 1-year survival of the patients improved: 75% in group A, 79% in group B (between 1999 and 2002), and 81% in group C (after 2003). During the entire observation period, average serum creatinine level at the start of treatment decreased, and improvement of 1-year renal survival was also found (72% in group A, 83% in group B, and 83% in group C), while the recurrence rate was significantly increased in group C (0.05/patient-year in group A, 0.07/patient-year in group B, and 0.13/patient-year in group C).
*Conclusions* Oral prednisolone dose <0.8 mg/kg/day with or without cyclophosphamide as an initial treatment could improve patient survival in older Japanese AAV/RPGN patients. However, maintenance treatment avoiding relapse should be established to improve renal outcomes.

**Keywords** Anti-neutrophil cytoplasmic auto-antibody (ANCA) · Immunosuppression · Prognosis changes · Rapidly progressive glomerulonephritis (RPGN) · Vasculitis

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## Introduction

Recently, the wider availability of anti-neutrophil cytoplasmic auto-antibody (ANCA) assays, improved recognition of ANCA-associated vasculitis (AAV), and evidence-based treatment for AAV have resulted in longer life expectancy and avoidance of renal replacement therapy (RRT) in patients with AAV. ANCAs have been detected in patients with pauci-immune crescentic glomerulonephritis, microscopic polyangitis (MPA), granulomatosis with polyangitis (Wegener's) (GPA), and other systemic vasculitis syndromes [1, 2]. There are two major subclasses of ANCA: perinuclear (p-)ANCA and cytoplasmic (c-)ANCA [1]. The main epitope of p-ANCA is myeloperoxidase

(MPO), and that of c-ANCA is proteinase-3 (PR3) [2]. MPO-ANCA is regarded as a useful serum marker for MPA and idiopathic pauci-immune crescentic glomerulonephritis (renal limited form of MPA), and PR3-ANCA is regarded as a serum marker for GPA and MPA [2, 3]. Furthermore, enzyme-linked immunosorbent assay (ELISA)-based serum examination for MPO-ANCA, PR3-ANCA, and anti-glomerular basement membrane (a-GBM) antibody titer tests were available in clinical settings. Several reports have suggested that, compared with PR3-ANCA-positive patients, MPO-ANCA-positive patients were older and showed predominantly chronic sclerotic lesions on histologic analysis [4, 5].

To improve the outcome of rapidly progressive glomerulonephritis (RPGN) patients in Japan, we conducted a nationwide survey of RPGN including AAV from 1998, by sending a questionnaire to 351 nephrology departments. From this survey, we concluded that 64.7% of Japanese RPGN patients had ANCAs, and among ANCA-positive patients, approximately 90% had MPO-ANCA [6].

In this study, we report the changes in treatment and outcome of Japanese AAV/RPGN patients during the last 20 years. Furthermore, we discuss the differences in clinical characteristics of ANCA subgroups in our AAV/RPGN patients.

## Subjects and methods

### Subjects

We retrospectively collected records of patients with RPGN from 1989 to 1998 and prospectively collected the clinical records of RPGN patients from 1999 to 2007 by sending a questionnaire annually by post to 351 nephrology departments of tertiary hospitals in Japan. This study was approved by the medical ethics committee at the Graduate School of Comprehensive Human Sciences, University of Tsukuba, in accordance with the guidelines for epidemiological research by the Ministry of Health, Labor, and Welfare of Japan. The definition of RPGN was based on clinical findings of rapidly progressing renal failure over several weeks to a few months, accompanied by the following nephritic urinary abnormalities: hematuria (mostly microscopic hematuria, but occasionally gross hematuria), proteinuria, and red blood cell cast or granular cast in urine sediment. In total, 171 nephrology departments responded and presented 1772 RPGN cases for this study. During the study period, the Japanese government decided that the PR3-ANCA test was covered by medical insurance in 1993, the MPO-ANCA test in 1998, and the a-GBM antibody test in 1999 for diagnosis of RPGN and vasculitis. Among the RPGN patients, although 1203 patients (67.9%) had ANCA [6], 824 patients received all three serological tests and presented outcome data. To analyze the effect of ANCA subclasses on patient outcomes, we selected these 824 patients for further analysis.

We evaluated AAV cases by stratifying patients into three periods depending on the year of diagnosis of AAV as previously described. Briefly, patients who were diagnosed between 1989 and 1998 were classified as group A, and data were collected retrospectively. Patients diagnosed between 1999 and 2001 were classified as group B, when we had started the analysis of Japanese cases of RPGN and part of the results had been announced in Japan during this period. Patients diagnosed between 2002 and 2007, after we had published the Japanese guideline for RPGN in 2002 [6, 7], were classified as group C.

### Clinical evaluation and treatment methods

Baseline characteristics including age, sex, comorbid conditions, features of prodromal illness, and clinical, biochemical, serological, and urinary features at presentation were obtained from clinical records. Follow-up clinical data including serum creatinine level, ANCA subclasses, C-reactive protein (CRP), recurrence and survival outcome, dialysis dependence (after 1, 2, 3, 6, 12, and 24 months), start date of dialysis therapy, final follow-up date, and cause of death were also recorded. Relapse was defined as an increase in creatinine concentration with nephritic sediment and other signs or symptoms of vasculitis. The initial dose of oral prednisolone, the duration of the initial dose, and immunosuppressive treatment were also recorded.

### Statistical analysis

Unpaired Student's $t$ test was used, after a symmetrical distribution was confirmed, to determine differences in the continuous variables between groups. Otherwise, the Mann–Whitney $U$ test was used. We used the chi-square test to analyze the frequencies of categorical variables. Both renal and patient survival rates were estimated by the Kaplan–Meier method. Prognostic factors were determined by the chi-square test, and then hazard ratios of patient outcome were estimated by the Cox regression model after confirming the proportionality in each model. To evaluate prognostic factors among the subjects at the start of treatment, we selected age, renal function (serum creatinine, urinary volume), glomerular damage (hematuria, proteinuria, cast formation), general status (serum albumin, serum total protein, hemoglobin), systemic inflammation (CRP, erythrocyte sedimentation rate, white blood cell count), and extrarenal complications (blood pressure, presence of lung involvement). Lung involvement indicates the existence of

chest X-ray abnormality, interstitial pneumonitis, or lung bleeding. We used two sets of models for analysis. The first set included age, gender, serum creatinine level at start of treatment, CRP, presence of lung involvement, and ANCA subclass. For the second set, we added initial dosage of prednisolone and cyclophosphamide usage in addition to the above variables. A $p$ value <0.05 was considered significant. Parts of the statistical analyses were performed using SPSS software 17.0.

## Results

### Differences among ANCA subclasses

The study participants were 824 ANCA-positive patients, and 94.6% of the subjects had MPO-ANCA. During the last 20 years, 705 AAV patients were only MPO-ANCA positive, 34 patients were only PR3-ANCA positive, 37 patients were both MPO- and PR3-ANCA positive, 44 patients had both MPO-ANCA and a-GBM antibody, and four patients had both PR3-ANCA and a-GBM antibody. Table 1 presents the number of patients, their age, and the male-to-female ratio. Patients with only PR3-ANCA were significantly younger than those with only MPO-ANCA, and both ANCAs and a-GBM. Patients with PR3-ANCA only were predominantly male; however, patients with both ANCAs and a-GBM were predominantly female.

**Table 1** Patient profile and ANCA type

| ANCA type | $n$ | Mean age (years)[a,b] | Male[a,b,c] (%) |
|---|---|---|---|
| MPO-ANCA only | 705 | 64.4 | 42.6 |
| PR3-ANCA only | 34 | 53.6 | 70.6 |
| Both ANCA | 37 | 61.5 | 54.1 |
| ANCA + a-GBM | 48 | 65.3 | 29.2 |

[a] Statistically significant between MPO-ANCA only and PR3-ANCA only

[b] Statistically significant between PR3-ANCA only and ANCA + a-GBM

[c] Statistically significant between both-ANCA only and ANCA + a-GBM

Patients with PR3-ANCA had significantly more affected organs than both patients with MPO-ANCA and patients with both ANCAs. In particular, 65.7% of PR3-ANCA patients had ear, nose, and throat lesions, 34.3% had gut lesions, and 34.3% had skin lesions, and these involvement rates were significantly higher than in patients with MPO-ANCA. Serum creatinine levels at presentation were significantly higher in patients with both ANCAs and a-GBM antibody than for other patients (MPO-ANCA only 4.67 ± 2.84 mg/dl, PR3-ANCA only 4.51 ± 2.74 mg/dl, both ANCAs 5.08 ± 2.96 mg/dl, both ANCAs and a-GBM antibody 6.96 ± 4.08 mg/dl). CRP concentration at presentation was significantly higher in patients with PR3-ANCA only than in those with MPO-ANCA only (MPO-ANCA only 6.30 ± 6.56 mg/dl, PR3-ANCA only 9.11 ± 7.69 mg/dl, both ANCAs 6.65 ± 8.70 mg/dl, both ANCAs and a-GBM antibody 8.30 ± 8.52 mg/dl). Crescent formation rate was calculated from renal biopsy samples; patients with both ANCA and a-GBM antibody had a significantly higher crescent formation rate than patients with other types of AAV (MPO-ANCA only 57.9 ± 32.6%, PR3-ANCA only 54.4 ± 29.8%, both ANCAs 57.7 ± 28.7%, both ANCAs and a-GBM antibody 77.6 ± 22.3%).

Among the patients who were diagnosed from 1989 to 1998 (group A), from 1999 to 2002 (group B), or after 2003 (group C), ANCA subclass patterns and the proportion of patients with lung involvement were similar. The average age of the patients in both groups B and C was significantly higher than that of group A patients, and the serum creatinine level of group C patients was significantly lower than that of group A patients (Table 2).

**Table 2** Patient profile by treatment period

| $n$ | ANCA subclass MPO:PR3:both:+a-GBM | Mean age (years)*# | Lung involvement (%) | Mean serum creatinine (mg/dl)# | Recurrence ($n$)/patient (year)#$ | Initial prednisolone dose (mg/kg/day)*#$ | Cyclophosphamide usage (%) |
|---|---|---|---|---|---|---|---|
| Group A | | | | | | | |
| 347 | 284:15:27:21 | 60.56 | 50.70 | 5.11 | 0.05 | 0.85 | 41.69 |
| Group B | | | | | | | |
| 136 | 116:5:6:9 | 65.01 | 55.00 | 4.52 | 0.07 | 0.79 | 45.16 |
| Group C | | | | | | | |
| 341 | 305:14:4:18 | 66.88 | 58.80 | 4.19 | 0.13 | 0.71 | 33.67 |

* $p < 0.05$ between groups A and B

# $p < 0.05$ between groups A and C

$ $p < 0.05$ between groups B and C

## Renal and patient survival

Cumulative patient survival rate and renal survival rate by Kaplan–Meier analysis are shown in Fig. 1. The median follow-up duration was 19.1 months (range 0–211.8 months). Cumulative patient survival rate at 12 months was 79.1%, and cumulative renal survival at 12 months was 78.4%. We further analyzed both patient survival rate and renal survival rate separated by treatment period by Kaplan–Meier analysis (Fig. 2). The median follow-up durations were 42.9, 33.2, and 10.3 months in groups A, B, and C, respectively. Patient survival rate in group C was significantly improved compared with that in group A (6-month cumulative patient survival rate: group A 77.5%, group B 81.0%, group C 85.1%; 12-month cumulative patient survival rate: group A 75.0%, group B 79.3%, group C 81.3%; $p < 0.05$). Cumulative renal survival rates in groups B and C were significantly higher than that in group A (6-month renal survival rate: group A 73.3%, group B 84.3%, group C 83.9%; 12-month renal survival rate: group A 71.7%, group B 83.3%, group C 82.8%; $p < 0.05$). Patient survival rate was slightly improved in group B compared with group C; however, renal survival was slightly exacerbated. Furthermore, the recurrence rates were 0.05, 0.07, and 0.13/patient-year in groups A, B, and C, respectively (Table 3).

Table 4 presents multivariate analysis for patient survival and renal survival. Age, lung involvement (as interstitial pneumonitis or lung bleeding), renal function, and CRP level were predictors of mortality in AAV patients. ANCA subclass did not affect patient survival. Serum creatinine level at presentation was the best predictor of renal survival; in addition, age between 60 and 69 years, and a-GBM antibody positivity among AAV patients were predictors of reduced renal survival.

## Treatment methods and outcome changes

As shown in Table 4, renal function was the best predictor of renal survival; we compared renal outcome according to renal function at the start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A. However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was similar during the entire study period. Patients with serum creatinine levels >6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (Fig. 3). Figure 4 shows the initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. In patients with serum creatinine levels <3 mg/dl, the initial prednisolone dosage in both groups B and C was significantly lower than that in group A. In patients with serum creatinine levels of 3–6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in group A. In patients with serum creatinine levels >6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in either group A or B. The proportion of initial cyclophosphamide usage was similar among groups A, B, and C in patients with serum creatinine levels <3 and >6 mg/dl. The proportion of initial cyclophosphamide usage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl.

As shown in Table 2, the initial prednisolone dosage was significantly reduced recently (group C). We further analyzed the initial dosage of prednisolone and the proportion of cyclophosphamide usage, in addition to the above variables, by forward selection methods of

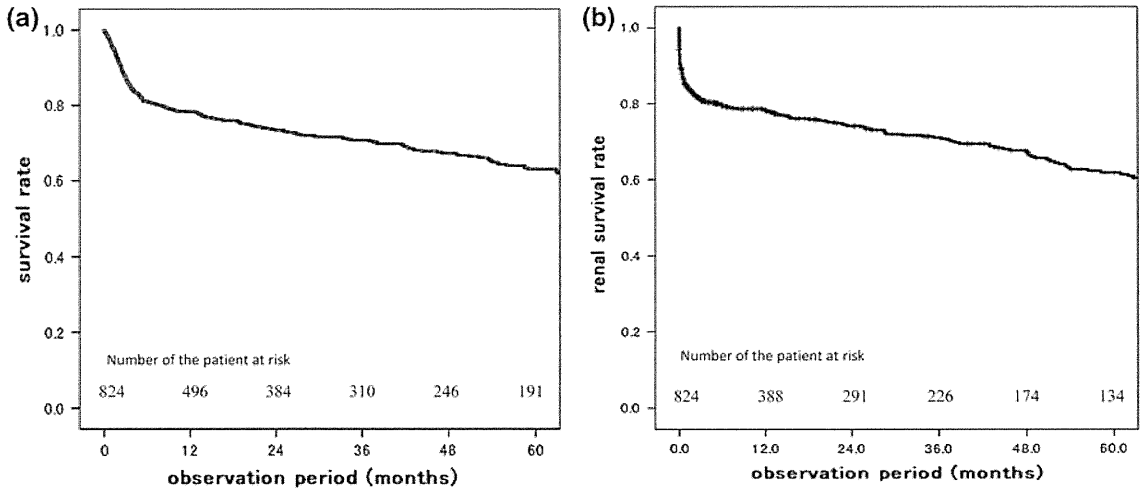


**Fig. 1** Cumulative patient survival and renal survival by Kaplan–Meier analysis. **a** Patient survival: 6-month, 12-month, and 5-year cumulative patient survival rates were 81.8%, 79.1%, and 63.6%, respectively. **b** Renal survival: the 6-month, 12-month, and 5-year cumulative renal survival rates were 79.7%, 78.4%, and 62.0%, respectively

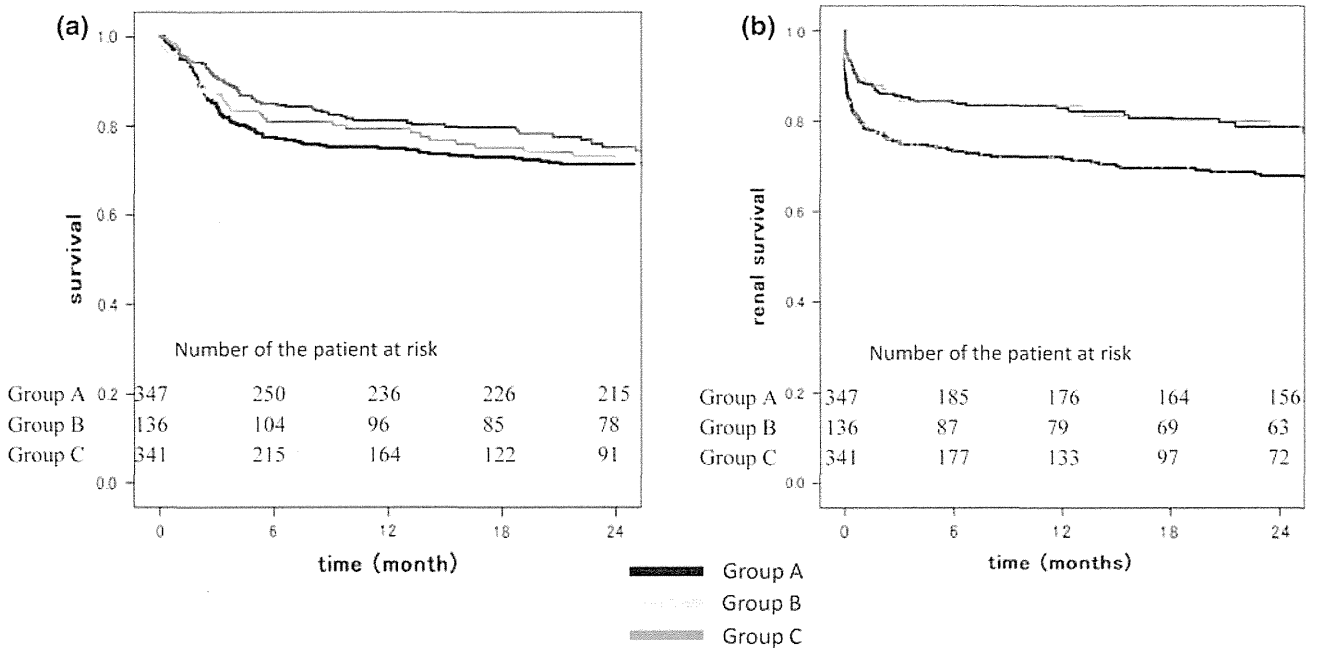


**Fig. 2** Patient survival and renal survival by treatment period. **a** Patient survival: patient survival rate in group C was significantly higher than that in group A. **b** Renal survival: renal survival in groups B and C was significantly higher than that in group A. Comparing group B with group C, patient survival rate was slightly improved; however, there was no improvement in renal survival

**Table 3** Multivariate Cox proportional regression analysis on predictor of death and ESRD

| Factors | Death | | ESRD | |
|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Age (ref. <59 years) | | | | |
| 60–69 years | 2.20 (1.54–3.16) | 0.000 | 1.38 (0.99–1.92) | 0.056 |
| >70 years | 3.32 (2.35–4.68) | 0.000 | 1.20 (0.85–1.68) | 0.301 |
| Sex (ref. male) | 1.14 (0.91–1.42) | 0.265 | 0.92 (0.71–1.19) | 0.536 |
| Lung involvement (ref. negative) | 1.94 (1.51–2.48) | 0.000 | 0.83 (0.63–1.10) | 0.199 |
| Number of affected organs | 0.98 (0.90–1.07) | 0.621 | 0.98 (0.89–1.08) | 0.725 |
| Serum creatinine (ref. <3 mg/dl) | | | | |
| 3–6 mg/dl | 1.85 (1.39–2.47) | 0.000 | 3.26 (2.17–4.90) | 0.000 |
| >6 mg/dl | 2.53 (1.88–3.38) | 0.000 | 11.77 (7.96–17.40) | 0.000 |
| CRP (ref. <2.6 mg/dl) | | | | |
| 2.6–10 mg/dl | 0.95 (0.73–1.24) | 0.717 | 0.72 (0.53–0.98) | 0.036 |
| >10 mg/dl | 1.46 (1.10–1.95) | 0.010 | 1.22 (0.88–1.69) | 0.243 |
| ANCA subclass (ref. PR3-ANCA only) | | | | |
| MPO-ANCA only | 0.69 (0.42–1.14) | 0.144 | 1.50 (0.79–2.83) | 0.214 |
| Both ANCA | 0.59 (0.29–1.18) | 0.135 | 1.72 (0.74–3.96) | 0.205 |
| ANCA + a-GBM | 0.61 (0.30–1.24) | 0.173 | 3.27 (1.50–7.11) | 0.003 |

*ESRD* end-stage renal disease, *CI* confidence interval, *HR* hazard ratio

multivariate stepwise Cox proportional hazard analysis. An increase in the oral prednisolone dosage significantly reduced patient survival. The initial prednisolone dosage did not affect renal survival; however, cyclophosphamide use significantly improved renal outcome (Table 4).

## Discussion

We began this survey of AAV/RPGN cases in Japan in 1998 to determine patient outcome, evaluate standard treatment patterns, and enable us to propose suitable

**Table 4** Multivariate stepwise Cox proportional hazard analysis on predictor of death and ESRD (forward selection method, critical $F_{in} = 0.05/F_{out} = 0.1$)

| | HR (95% CI) | *p* |
|---|---|---|
| **Death** | | |
| Age (ref. <59 years) | | |
| 60–69 years | 2.284 (1.383–3.772) | 0.001 |
| >70 years | 4.286 (2.649–6.936) | 0.000 |
| CRP (ref. <2.6 mg/dl) | | |
| 2.6–10 mg/dl | 0.776 (0.538–1.120) | 0.176 |
| >10 mg/dl | 1.315 (0.886–1.951) | 0.175 |
| Lung involvement (ref. negative) | 2.169 (1.508–3.119) | 0.000 |
| Serum creatinine (ref. <3 mg/dl) | | |
| 3–6 mg/dl | 2.250 (1.474–3.434) | 0.000 |
| >6 mg/dl | 2.492 (1.636–3.797) | 0.000 |
| Initial prednisolone dose (ref. <0.6 mg/kg/day) | | |
| 0.6–0.8 mg/kg/day | 1.555 (0.996–2.429) | 0.052 |
| 0.8–1.0 mg/kg/day | 1.645 (1.005–2.692) | 0.048 |
| >1.0 mg/kg/day | 2.132 (1.296–3.506) | 0.003 |
| Other variables considered: gender, ANCA subclass, cyclophosphamide usage | | |
| **ESRD** | | |
| Serum creatinine (ref. <3 mg/dl) | | |
| 3–6 mg/dl | 2.811 (1.595–4.957) | 0.000 |
| >6 mg/dl | 11.513 (6.827–19.416) | 0.000 |
| ANCA subclass (ref. PR3-ANCA only) | | |
| Both ANCA | 2.891 (0.788–10.611) | 0.110 |
| MPO-ANCA only | 2.224 (0.699–7.077) | 0.176 |
| ANCA + a-GBM | 5.403 (1.474–19.806) | 0.011 |
| Cyclophosphamide usage (ref. none) | | |
| CYC | 0.683 (0.474–0.986) | 0.042 |

Other variables considered: age, gender, CRP, lung involvement, initial prednisolone dose

treatment guidelines for Japanese AAV/RPGN patients. During the early years of this study, we considered that the prognosis of AAV/RPGN patients in Japan was very poor compared with that of patients of different races and countries. A 1-year survival rate in AAV patients of 89% was reported in the USA [8], and 84% was reported in Europe [9], whereas the rate was 75% in our cohort during the same period (group A). We analyzed the etiology of these differences. We found that more than 90% of Japanese AAV patients had MPO-ANCA, the average age of Japanese AAV patients was high, and the most frequent cause of death was infectious complications. The standard treatment for AAV/RPGN in Europe and the USA was a combination of 1 mg/kg prednisolone and 100–200 mg cyclophosphamide [10, 11]. However, the prognosis of patients treated with high-dose prednisolone was significantly worse than that of patients treated with an oral prednisolone dose <0.8 mg/kg/day in our cohort. Furthermore, 95% of our AAV patients had MPO-ANCA (85.5% of patients were only MPO-ANCA positive), and the average age was 64.4 years. Gayraud et al. [9] reported that MPA patients above 65 years of age showed poorer outcome with use of cyclophosphamide. Based on our analysis of patients with group A and published reports, we proposed treatment guidelines for Japanese RPGN patients in 2002 [7] (Fig. 5). The guidelines emphasized the need for reduced immunosuppressive treatment, such as an initial oral prednisolone dose reduction with or without immunosuppressant, for Japanese MPO-ANCA-positive AAV/RPGN patients. With this treatment recommendation, the oral dose of prednisolone was significantly reduced and the number of patients using cyclophosphamide as an immunosuppressant was decreased.

Patient age was one of the prognostic factors for AAV/RPGN patients, and the average age of our patients was significantly increased with time; however, patient survival was significantly improved. There were several possible reasons for this. First, serum creatinine level at start of treatment was a good predictor of patient survival, and was also the strongest predictor of renal survival. Serum creatinine level at start of treatment was gradually decreased by early diagnosis and early treatment start during our observation period. Second, prophylaxis with trimethoprim/sulfamethoxazole combinations or other agents was generally used to avoid pneumocystis pneumonia in AAV/RPGN patients using immunosuppressant [12]. This prophylactic treatment was recommended in the Japanese RPGN/AAV treatment guideline [7], and was effective in reducing opportunistic infection in our most recent cohort (group C). Third, a significant reduction in prednisolone dosage and selective usage of cyclophosphamide according to treatment guideline for Japanese RPGN patients resulted in increased patient survival [6].

Although patient survival was improved with time, renal outcome of the Japanese AAV/RPGN patients was not improved. Although patients with both ANCAs and anti-GBM showed significantly poorer renal outcomes than other ANCA-positive patients, the proportion of patients with both ANCAs and anti-GBM was the same throughout our observation period. As shown in Fig. 3, renal outcome was improved by an initial serum creatinine level below 3 mg/dl; however, renal outcome was the same in the three groups in patients with serum creatinine levels of 3–6 mg/dl, and was worse in group C than in group B in those with a serum creatinine level >6 mg/dl. As shown in Fig. 5, a significant reduction in the initial prednisolone dosage resulted in a reduction in early mortality, but poorer renal outcome. de Lind van Wijngaarden et al. [13] reported a 1-year survival rate of 75% in dialysis-dependent AAV patients, and Day et al. [14] reported a rate of

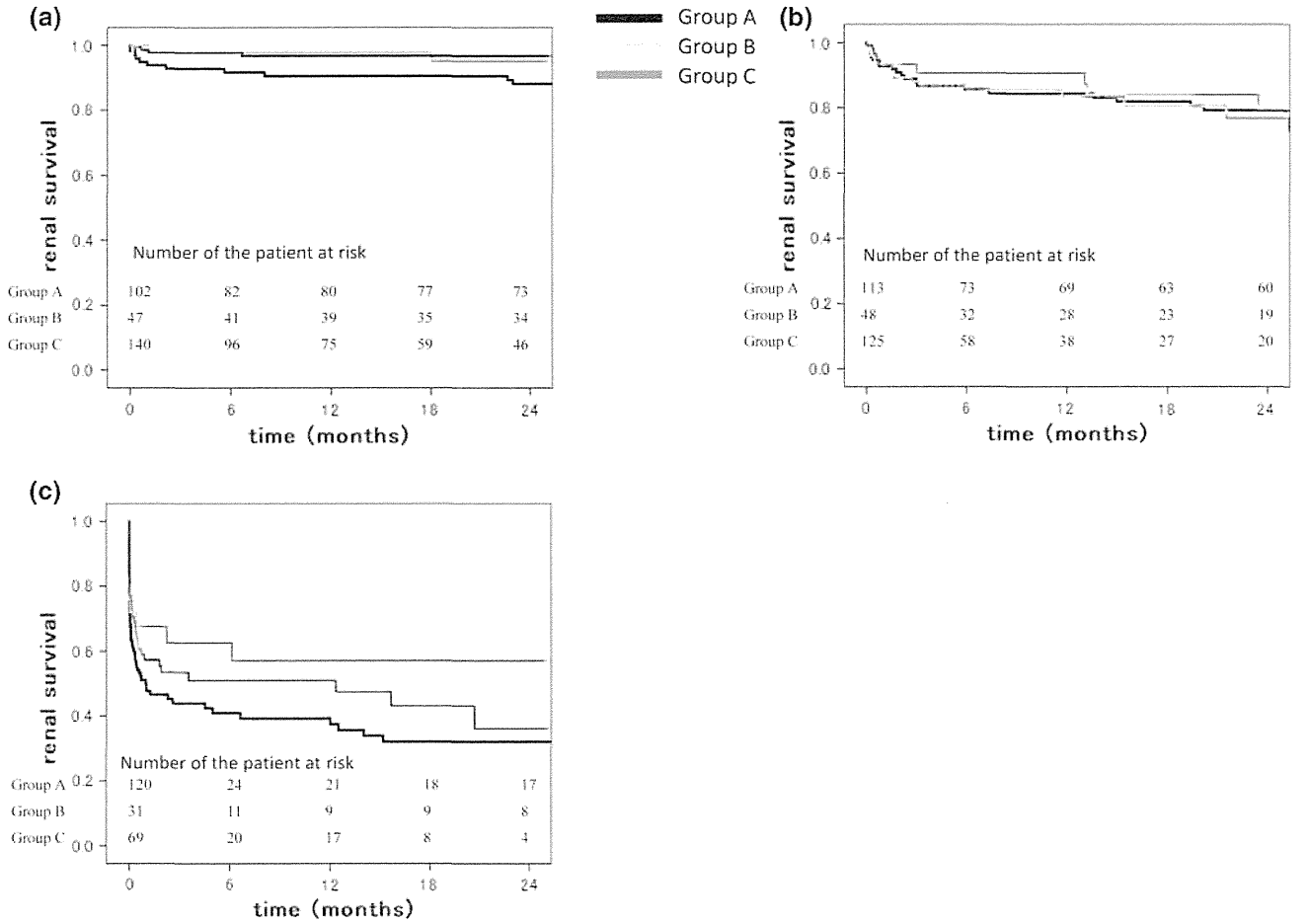


**Fig. 3** Renal survival by renal function at start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A (6-month cumulative renal survival rate: group A 91.6%, group B 97.8%, group C 97.7%; 12-month cumulative renal survival rate: group A 90.5%, group B 97.8%, group C 96.7%; $p < 0.05$). However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was not statistically different throughout the study period (6-month cumulative renal survival rate: group A 85.6%, group B 90.7%, group C 85.5%; 12-month cumulative renal survival rate: group A 84.4%, group B 90.7%, group C 83.3%; not significant). Patients with serum creatinine levels above 6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (6-month cumulative renal survival rate: group A 40.9%, group B 62.7%, group C 52.6%; 12-month cumulative renal survival rate: group A 37.4%, group B 57.0%, group C 52.6%; not significant). **a** Serum creatinine <3 mg/dl at treatment start, **b** serum creatinine 3–6 mg/dl at treatment start, **c** serum creatinine <6 mg/dl at treatment start

77% in AAV patients with an average serum creatinine level of 3.9 mg/dl, whereas in our group C patients with serum creatinine level >6 mg/dl, the 1-year survival rate was 71% and was similar in the other two cohorts. However, in our patients with serum creatinine levels >6 mg/dl in group C, the 1-year renal survival rate was 51%. Thus, renal outcome in our cohort was worse or equal to that of previously reported cohorts [13, 14, 15]. It is possible that recent patient survival improvement resulted in longer life expectancy in patients with advanced renal insufficiency, and those patients may have progressed to end-stage renal disease (ESRD). However, it is also possible that a significant reduction in prednisolone dosage in our group C patients with serum creatinine levels >6 mg/dl might result in insufficient treatment to restore their renal function.

It was reported that the recurrence rate of patients with MPO-ANCA was lower than that of patients with PR3-ANCA [3]. However, recently the selective usage of cyclophosphamide according to treatment guidelines for Japanese RPGN patients resulted in a 1.5-fold increase in the recurrence rate in Japanese AAV/RPGN patients. For treatment of active renal vasculitis, to avoid relapses, and to improve long-term renal outcomes, treatment with cyclophosphamide may be recommended; however, prolonged immunosuppression with a safer immunosuppressive agent, such as azathioprine [16], mycophenolate mofetil [17], or mizoribine [18], should be considered. We conducted a prospective randomized controlled trial with and without mizoribine for maintenance treatment of MPO-ANCA-positive RPGN (UMIN000000708). From

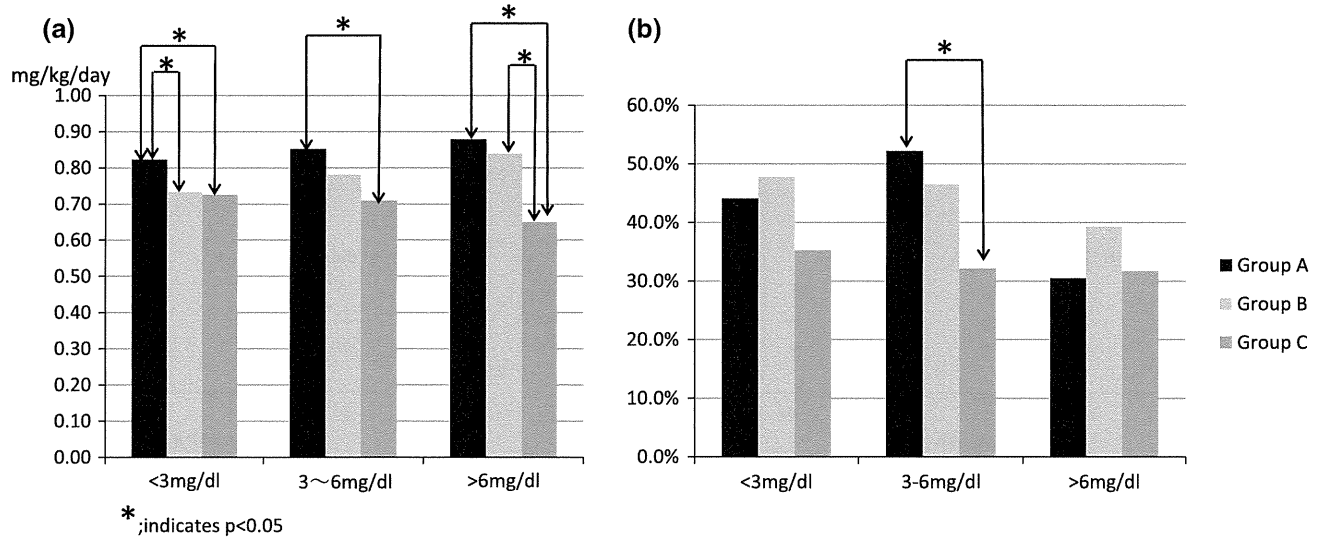


**Fig. 4** Initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. The initial prednisolone dosage in groups B and C was significantly lower than that in group A in patients with serum creatinine levels <3 mg/dl. The initial prednisolone dosage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl. The initial prednisolone dosage in group C was significantly lower than that in both groups A and B in patients with serum creatinine levels >6 mg/dl (**a**). The proportion of initial cyclophosphamide usage was not statistically different among the three groups in patients with serum creatinine levels <3 or >6 mg/dl. The proportion of initial cyclophosphamide usage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl (**b**)

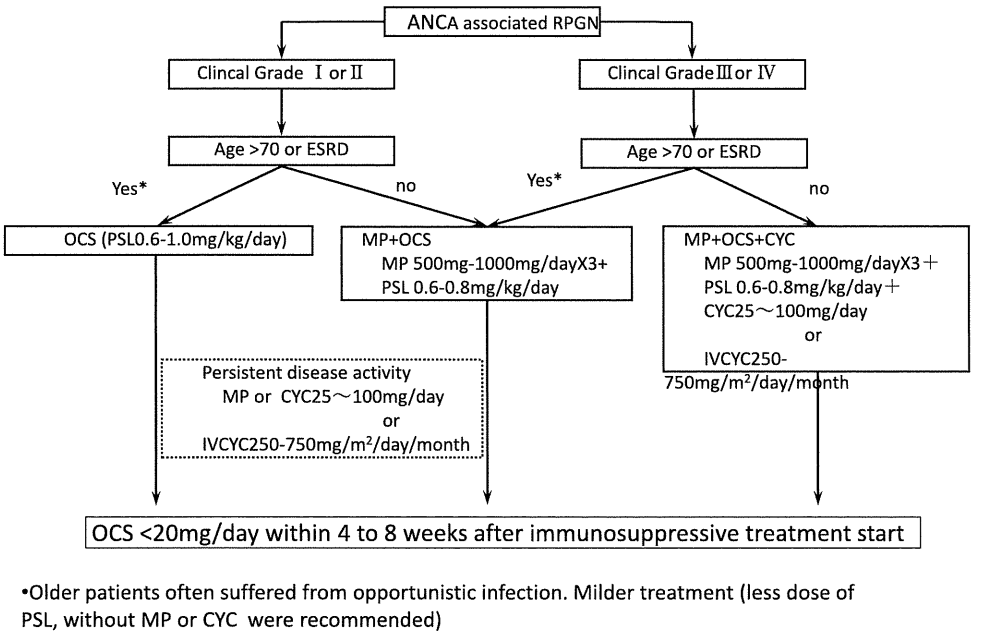


**Fig. 5** Treatment algorithm for ANCA-associated RPGN in Japan. We made three treatment patterns depending on clinical grade and patient age or if the patient had already reached ESRD. The clinical grading system for RPGN was suitable for predicting patient survival. We selected age, serum creatinine level, CRP, and presence of lung involvement, because these were the strongest independent prognostic factors ($p < 0.01$) by Cox regression analysis in group A. We determined the RPGN grading system based on these four factors. All subjects were categorized into four clinical grades by the sum of the scores of the four prognostic factors [6]. After disease activity is remitted with this initial treatment method, appropriate immunosuppressant should be added for maintenance treatment

the results of this trial, we hope to identify the most suitable maintenance treatment for Japanese MPO-ANCA-positive AAV/RPGN patients.

In summary, the outcome of Japanese AAV/RPGN patients was improved after publication of the treatment guidelines in 2002 [7]; however, renal outcome of these

patients varied. To improve renal outcome, more effective maintenance treatment should be established for MPO-ANCA-positive AAV/RPGN patients.

**Acknowledgments** We express our thanks to the doctors who participated in this observational study. We also express our gratitude to Ms. Yuko Sudo, Ms. Keiko Fujioka, and Ms. Michiko Yokoyama for manuscript preparation, as well as to the members of the RPGN Study Group of Progressive Renal Disease from the Ministry of Health, Labor, and Welfare of Japan as follows; Dr. Y Taguma, Dr. S Kaname, Dr. S Horikoshi, Dr. T Hosoya, Dr. T Kawamura, Dr. Y Yuzawa, Dr. T Watanabe, Dr. T Saitoh, Dr. S Fujimoto, Dr. S Hirawa, Dr. K Kimura, Dr. W Yumura, Dr. T Itoh, Dr. K Tabei, Dr. O Inaguma, Dr. M Ogura, Dr. S Yasunaga, Dr. K Tsuruya, Dr. N Nakagawa, Dr. M Yoshida, Dr. S Maruyama, and Dr. K Sada. This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, Research on intractable disease, from the Ministry of Health, Labor, and Welfare of Japan.

**Conflict of interest** The authors declare no conflicts of interest.

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Clin Exp Nephrol
DOI 10.1007/s10157-012-0740-1

REVIEW ARTICLE

The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012

# Clinical findings on ANCA-associated renal vasculitis from the Japan RPGN registry obtained via a questionnaire survey

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Received: 18 September 2012 / Accepted: 11 November 2012


**Abstract** Renal involvement with significant organ damage is common in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). As a result, it is independently referred to ANCA-associated renal vasculitis. Clinically, ANCA-associated renal vasculitis is characterized by rapidly progressive glomerulonephritis. Pathologically, it is defined by pauci-immune type necrotizing and crescentic glomerulonephritis. According to previous reports from all over the world, the etiology, prevalence, and prognosis of RPGN including ANCA-associated renal vasculitis varies among races and periods. To elucidate the clinical characteristics of Japanese RPGN patients, a registry derived from a questionnaire survey was established in 1999 and maintained until 2006. As a result, 1,772 cases were collected, analyzed, and reported previously. In this mini-review, we outline the characteristic clinical findings of Japanese patients (Asian) with ANCA-associated renal vasculitis, based on the registry data.

**Keywords** ANCA-associated renal vasculitis · RPGN · Japan · Registry · Questionnaire survey

## Clinical findings of ANCA-associated renal vasculitis and RPGN in Japan

The frequency of renal involvement and rapidly progressive glomerulonephritis (RPGN) in Japanese patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is still unclear. A Japan RPGN registry derived from a questionnaire survey was established in

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Published online: 14 December 2012

**Table 1** Number of patients with RPGN. This table was prepared with partial modification [1]

| Diagnosis | Classification | Total RPGN cases | |
|---|---|---|---|
| | | *n* | % |
| Primary | | | |
| Crescentic GN | Anti-GBM antibody-associated crescentic GN | 81 | 4.6 |
| | Immune-complex-associated crescentic GN | 35 | 2.0 |
| | Renal-limited vasculitis | 745 | 42.0 |
| | Overlapped crescentic GN | 31 | 1.7 |
| | Undifferentiated primary crescentic GN | 28 | 1.6 |
| Primary GN with crescents | Mesangioproliferative glomerulonephritis | 15 | 0.8 |
| | Membranous nephropathy | 5 | 0.3 |
| | IgA nephropathy | 43 | 2.4 |
| | Non-IgA mesangial proliferative GN | 8 | 0.5 |
| | Other primary GN | 3 | 0.2 |
| Systemic disease-associated | | | |
| | Goodpasture's syndrome | 27 | 1.5 |
| | Systemic lupus erythematosus | 66 | 3.7 |
| | Granulomatosis with polyangiitis (Wegener's) | 46 | 2.6 |
| | Microscopic polyangiitis | 344 | 19.4 |
| | Other necrotizing vasculitis | 15 | 0.8 |
| | Purpura nephritis | 36 | 2.0 |
| | Cryoglobulinemia | 12 | 0.7 |
| | Rheumatoid arthritis | 24 | 1.4 |
| | Malignant neoplasm | 3 | 0.2 |
| | Other systemic diseases | 40 | 2.3 |
| Infection-associated | | | |
| | Poststreptococcal acute glomerulonephritis | 10 | 0.6 |
| | Abscess | 6 | 0.3 |
| | Hepatitis C virus | 2 | 0.1 |
| | Other infectious diseases | 20 | 1.1 |
| Drug-associated | | 10 | 0.6 |
| Others | | 17 | 1.0 |
| Unknown | | 100 | 5.6 |
| Total | | 1772 | 100.0 |

1999 and maintained until 2006. As a result, 1772 cases were collected, analyzed and reported [1, 2]. The clinical entity of RPGN is shown in Table 1 [1, 2]. Pauci-immune-type renal-limited vasculitis was the most frequently observed clinical entity of RPGN (42.0 %). Among patients with renal-limited vasculitis (RLV), myeloperoxidase (MPO)-ANCA-associated cases made up 88.1 % and proteinase 3 (PR3)-ANCA-associated cases made up 7.4 %. Among cases of microscopic polyangiitis (MPA), which was the second most common clinical entity of RPGN (19.4 %), MPO-ANCA-associated cases made up 91.8 % and PR3-ANCA-associated cases made up 6.1 %. By contrast, in cases of granulomatosis with polyangiitis (Wegener's) occurring among Japanese individuals with RPGN (2.6 %), MPO-ANCA-associated cases made up 22.7 % and PR3-ANCA-associated cases made up 71.1 %. That is, most Japanese patients with AAV and RPGN were estimated to be positive for MPO-ANCA. Additionally, the age distribution of Japanese RPGN was a characteristic finding [1]. Among all RPGN subjects, the mean age at presentation significantly increased during the observation period. The main reason for this secular change was a significant increase in the mean age of subjects with RLV (61.85–67.28 years), MPA (64.60–68.77 years), and anti-GBM antibody-mediated RPGN (52.05–61.59 years) in recent years. This increase in the age of the onset of RPGN seems to reflect the longevity of the Japanese population and the aging of Japanese society.

Next, the speed of renal deterioration in this RPGN survey was also examined. Because RPGN is a loosely-defined term

**Table 2** The clinical grading system for predicting RPGN patient prognosis [1]

| Clinical score | Serum creatinine (mg/dl) | Age (years) | Lung involvement | Serum CRP (mg/dl) |
|---|---|---|---|---|
| 0 | <3 | ≤59 | Negative | <2.6 |
| 1 | 3–6 | 60–69 | | 2.6–10.0 |
| 2 | ≥6 | ≥70 | Positive | >10.0 |
| 3 | Dialysis | | | |
| Clinical grade | | | | |
| I | | | | 0–2 |
| II | | | | 3–5 |
| III | | | | 6–7 |
| IV | | | | 8–9 |

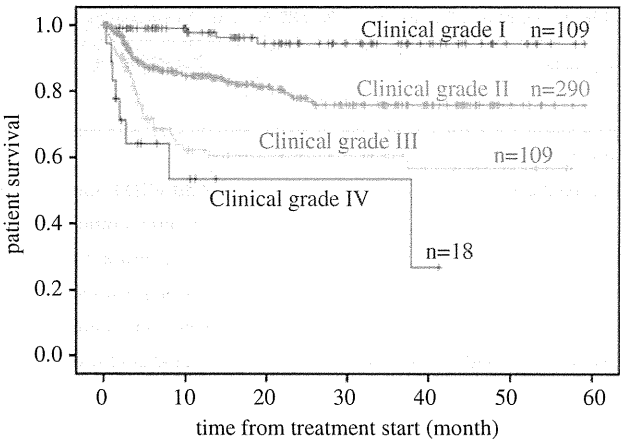


**Fig. 1** Clinical grading system for predicting patient prognosis. A clinical grading system was applied to all RPGN patients. This figure was prepared with partial modification [1]

and is challenging to define, we need to provide specific data for an established definition. Seventy-eight cases in which diffuse crescentic glomerulonephritis was confirmed on renal biopsy were selected and analyzed. In cases with RPGN, the average speed of the increase in the serum creatinine level was 1.03 mg/dl per week and the decrease in the estimated glomerular filtration rate (GFR) was 4.6 ml/min/1.73 $m^2$ (18.5 %) per week. Moreover, in 52 cases with MPO-ANCA-associated RPGN, the average speed of the increase in the serum creatinine level was 0.80 mg/dl per week, and the decrease in the estimated GFR was 3.6 ml/min/1.73 $m^2$ (16.6 %) per week. The Birmingham Vasculitis Activity Score (BVAS), a popular vasculitis activity score, has adopted the following assessment criteria of renal impairment, as specified by professional opinion: an increase in serum creatinine of more than 30 % or a decrease in creatinine clearance of more than 25 % within 4 weeks (personal communication with Professor RA Luqmani) [3]. The definition of RPGN varies among different countries of the world, and a universal standard definition of RPGN should be established in the future.

The first version of the clinical guidelines for Japanese RPGN was published in 2002, and the second version was published in 2011; these were based on the Japan RPGN registry established using a questionnaire survey (articles in Japanese). A clinical degree of severity that was calculated using four items, namely serum creatinine level, age, lung involvement, and serum C-reactive protein level, was defined in these clinical guidelines (Table 2). This was well correlated with the life prognosis of all patients with RPGN and MPO-ANCA-associated RPGN (Fig. 1). Moreover, a therapeutic algorithm for ANCA-associated RPGN based on the clinical degree of severity was suggested (Fig. 2) [2]. This clinical grading system was able to estimate the prognosis in cases of ANCA-associated RPGN and provided an approach to the classification of the treatment choices. In a recent report, the authors named this algorithm the Japanese Vasculitis Activity Score (JVAS), and it was found to be useful as a method of grading activity in cases of AAV in comparison with BVAS [4]. It was positively correlated with BVAS. However, at this time, the clinical degree of severity is consistently used as an index of life prognosis in ANCA-associated RPGN. If this clinical grading system is to be applied to the vasculitis activity score, additional investigations are needed.

Because of the publication of the clinical guidelines for Japanese RPGN in 2002, the prognosis for Japanese RPGN including AAV was markedly improved recently [1]. Standard induction therapy consisted of both corticosteroids and cyclophosphamide in Europe, but the clinical guidelines for Japanese RPGN adopted an independent therapeutic algorithm for ANCA-associated RPGN because of the high prevalence of elderly patients as mentioned above. According to the analysis of the Japan RPGN registry, infection was a major cause of death [1]. During the observation period, 31.8 % of patients died within 0–98.8 months. In recent years, the mortality rate decreased from 38.7 % (between 1989 and 1998) to 18.0 % (between 2002 and 2007). By contrast, the rate of infection as a cause of death was not decreased, from 48.1 % (between 1989 and 1998) to 55.9 % (between 2002 and 2007). Infection as the cause of death was frequent in the early phase of treatment. Therefore, the avoidance of severe adverse effects including infections became a priority in Japan, and milder treatment was chosen in the therapeutic regimen. As a result of this change, the life prognosis and renal survival of all RPGN patients were undoubtedly improved [2]. Additionally, the life prognosis and renal survival of patients with MPO-ANCA-associated RPGN were also improved. In contrast, the reduction in the use of immunosuppressant reagents increased the rate of relapse in patients with MPO-ANCA-associated RPGN.

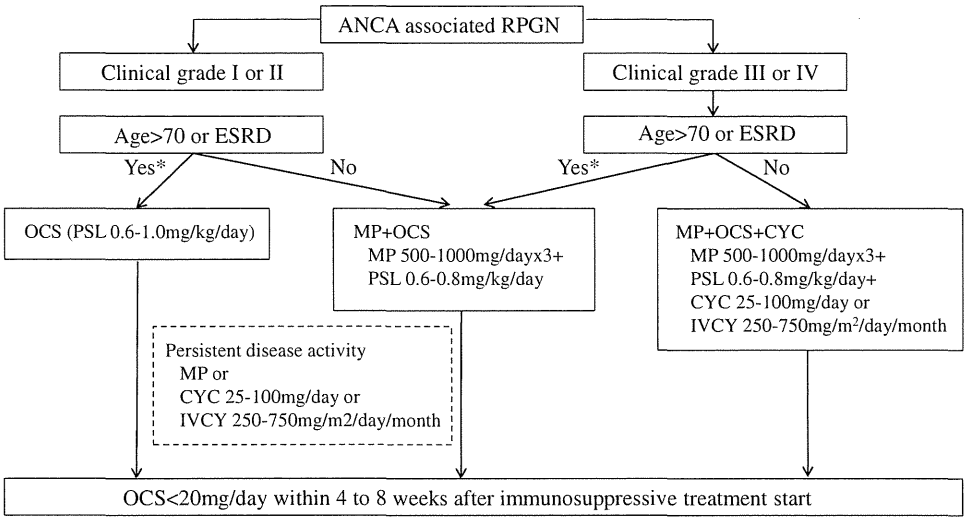


**Fig. 2** Treatment algorithm for ANCA-associated RPGN in Japan [2]. *ESRD* end-stage renal disease, *OCS* oral corticosteroid, *MP* methylprednisolone, *PSL* prednisolone, *CYC* cyclophosphamide, *IVCYC* intravenous cyclophosphamide

*Older patients often suffered from opportunistic infection. Milder treatment (less dose of PSL, without MP or CYC were recommended.

Therefore, it became important to establish maintenance therapy for MPO-ANCA-associated RPGN as quickly as possible. In Japan, a randomized controlled trial of a maintenance therapy using a milder immunosuppressant drug, mizoribine, for MPO-ANCA-associated RPGN is currently underway [Mizoribine for ANCA RPGN Relapse-Prevention Study (MARPGN study)]. A total of 44 cases had been enrolled as of December, 2011, at which point the entry of new patients into the study was ended. The rate of relapse and the effectiveness of mizoribine for maintenance therapy are expected to be determined in this study.

In the present article, we reviewed the clinical findings of ANCA-associated renal vasculitis in Japan. The Japan RPGN registry, based on a questionnaire survey, and the establishment of independent clinical guidelines have definitely improved the medical practice involved in the treatment of Japanese patients with AAV. A comparative discussion regarding the Japanese clinical guidelines and global guidelines is now needed.

**Acknowledgments** This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, Research on Intractable Disease, from the Ministry of Health, Labour and Welfare of Japan.

**Conflict of interest** We declare that we have no conflicts of interest.

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Clin Exp Nephrol
DOI 10.1007/s10157-012-0690-7

ORIGINAL ARTICLE

# Primary membranoproliferative glomerulonephritis on the decline: decreased rate from the 1970s to the 2000s in Japan

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Received: 17 April 2012 / Accepted: 21 August 2012


**Abstract**
*Background* A prolonged change in the rate of primary membranoproliferative glomerulonephritis (MPGN) was identified using a Japanese database of renal biopsies.
*Methods* We retrospectively investigated 6,369 renal biopsies that were performed between 1976 and 2009. Primary MPGN patients were selected, and the clinical and pathological findings were examined. We also statistically analyzed the changing rate of the onset of primary MPGN according to each decade.
*Results* Seventy-nine cases with primary MPGN (1.2 % of total biopsies) were diagnosed. The age of the patients ranged from 6–79 years (average 34.6 years). There were 24 children and 55 adults, including 37 male and 42 female patients. Thirty-six cases of primary MPGN (45.6 %) showed nephrotic syndrome—8 childhood and 28 adult cases. In the pathological classification of 44 samples using electron microscopy, 29 cases were MPGN type I, 1 case was MPGN type II, and 14 cases were MPGN type III. The secular change of the rate of primary MPGN onset showed a statistically significant reduction from the 1970s to the 2000s. The rate of primary MPGN onset in the child population also significantly decreased, but not in the adult population. Among the clinical parameters, disease severity and prognosis remained unchanged. Regarding treatment in recent years, steroid pulse therapy became more available but the administration of warfarin and antiplatelet drugs significantly decreased.

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Published online: 13 September 2012

*Conclusion* We concluded that the rate of total primary MPGN and that of pediatric patients with primary MPGN decreased.

**Keywords** Membranoproliferative glomerulonephritis · Primary glomerular disease · Nephrotic syndrome · Pediatrics

## Introduction

Primary membranoproliferative glomerulonephritis (MPGN), also termed mesangiocapillary glomerulonephritis, typically shows steroid-resistant nephritic syndrome in childhood [1]. The term 'MPGN' is a pathological diagnostic name that was determined by renal histology. In recent medical care, nephrologists in industrialized countries including countries in Europe have observed a decrease in primary MPGN and an increase in secondary MPGN including hepatitis C virus (HCV)-related glomerular disease [1, 2]. However, because this is a rare disease, only a few statistical examinations of the accurate yearly change in primary MPGN have been performed for the period between the 1970s and 1980s. Di Belgiojoso et al. [3] first reported a decline of MPGN onset in primary glomerular diseases (Table 1), noting that the rate of primary MPGN statistically decreased between the 1970s and 1980s in Italy. Very few previous reports have focused on the rate of primary MPGN over the long term, i.e., from the 1970s to the 2000s. Furthermore, no studies have examined why the rate of primary MPGN has decreased.

In the present study, we analyzed the trend of primary MPGN onset over four decades—from the 1970s to the 2000s. As a result, we found that primary MPGN has decreased over this period in Japan.

## Patients and methods

Based on 6,369 renal biopsies, including necropsies, performed from 1976–2009 at the University of Tsukuba and local affiliated hospitals (mainly in Ibaraki Prefecture but also including parts of Tochigi and Chiba Prefectures), approximately 200 cases per year were examined. All the institutes obtained informed consent before renal biopsy. We searched among these biopsies for primary MPGN and investigated these cases. First, we excluded MPGN-like lesions due to other primary glomerulonephritis (GN) including acute GN, immunoglobulin A (IgA) nephropathy, etc. Second, we excluded secondary MPGNs, such as infection-associated GN (hepatitis B virus, HCV, infectious endocarditis, deep-seated abscess, etc.), hepatitis-associated GN (including blood transfusion-associated hepatitis before HCV was discovered), malignancy-associated GN, collagen diseases including lupus nephritis, cryoglobulinemia, purpura nephritis, and hematologic disorder-associated glomerular diseases (Crow-Fukase syndrome, thrombotic microangiopathy). We examined the clinical and pathological characteristics at the time of renal biopsy. Pathological features were classified by WHO classification [4]. Moreover, we analyzed the rate changes of primary MPGN over four decades—1970s, 1980s, 1990s, and 2000s. The analysis was performed using the grouped data, total biopsies, age [<20 years, ≥20 years], and nephrotic syndrome. The Cochran–Armitage trend test was also used to determine the secular change of the MPGN rate. The secular changes of disease severity (serum creatinine value and hypocomplementemia), treatment, and clinical outcome were evaluated. The data were statistically compared between two periods—before 1989 and after 1990. The unpaired Student's $t$ test and the chi-squared test were used for data analysis. Renal survival rates were calculated by the Kaplan–Meier method, log rank test. A $p$ value $<0.05$ was defined as statistically significant. This research protocol was approved by the Ethics Committee of the Graduate School of Comprehensive Human Science, University of Tsukuba.

## Results

### Clinical and pathological characteristics of primary MPGN

Of 6,369 total renal biopsies, 79 cases with primary MPGN (incidence rate 1.2 %) were definitely diagnosed. For the pathological material, 79 samples of light microscopy, 64 samples of immunofluorescence, and 44 samples of electron microscopy were available. All patients were Asian in race. We summarized the clinical and pathological characteristics at the time of the biopsies. The age of the primary MPGN patients ranged from 6–79 years, with an average age of 34.6 years. There were 24 children (<20 years) and 55 adults (≥20 years), including 37 males and 42 females. In terms of clinical features, 36 cases of primary MPGN (45.6 %) showed nephrotic syndrome—8 cases were children, and 28 cases were adults. The incidence of primary MPGN was 2.8 % in 1,286 patients who underwent renal biopsy for nephrotic syndrome. In the pathological classification of 44 samples using electron microscopy, 29 cases had MPGN type I, 1 case had MPGN type II, and 14 cases had MPGN type III.

### Secular change of rate of primary MPGN

We compared the rates of primary MPGN over four decades—the 1970s, 1980s, 1990s, and 2000s, using trend

**Table 1** Comparison of incidence of primary MPGN in renal biopsy database

| Author | Nation | Sample characteristic | Sample number | 1970s (%) | | 1980s (%) | | 1990s (%) | | 2000s (%) | Significant difference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All ages | | | | | | | | | | | |
| Di Belgiojoso et al. [3] | Italy | Primary GN | 1,548 | 21 | 14 | 6 | | | | | Significant |
| Gonzalo et al. [5] | Spain | Primary GN | 275 | | 17 | 8 | | | | | Significant |
| Swaminathan et al. [6] | USA | Total RBx | 195 | | 2.9 | | 10.7 | | 5.8 | | Not significant |
| Adults | | | | | | | | | | | |
| Jungers et al. [7] | France | Age ≥15 years, primary GN | 1,231 | 16.1 | | 7.9 | | | | | Significant |
| Chang et al. [8] | Korea | Age ≥15 years | 1,818 | | | | 6.7 | | | 1.7 | Significant |
| Braden eet al. [9] | USA | Adult, primary GN, UP ≥2 g/day | 616 | | 3.7 | 8.3 | 4.8 | 8.6 | | | Not significant |
| Children | | | | | | | | | | | |
| Study group[a] [10] | Spain | Age <15 years | 1,447 | 10.9 | 6.6 | 5.4 | | | | | Significant |
| Iitaka et al. [11] | Japan | Age <15 years, primary GN | 547 | | 9.6 | 18 | 8.6 | 5.3 | | | Significant |
| West [12] | USA | Child | NA | 2 | 4.1 | 2.2 | 1.6 | | | | NA |
| Developing countries | | | | | | | | | | | |
| Yalcinkaya et al. [13] | Turkey | Child, primary GN | 445 | | | 13.6 | 13.8 | 13.1 | | | Not significant |
| Bahiense-Oliveira et al. [14] | Brazil | Age ≥15 years, primary GN | 943 | | | 19 | 8.4 | 9.2 | 11.3 | | Not significant |
| Present report | | | | | | | | | | | |
| Kawamura et al. | Japan | Total RBx | 6,369 | 2.4 | | 1.7 | | 1.1 | | 0.8 | Significant |
| | | NS | 1,286 | 11.6 | | 4.1 | | 2.1 | | 1.9 | Significant |
| | | Age ≥20 years | 5,373 | 1.8 | | 1.3 | | 1.1 | | 0.8 | Not significant |
| | | Age ≥20 years, NS | 1,101 | 6.1 | | 3.0 | | 2.1 | | 1.9 | Not significant |
| | | Age <20 years | 996 | 5.6 | | 3.1 | | 2.6 | | 0.4 | Significant |
| | | Age <20 years, NS | 185 | 30.0 | | 8.3 | | 0 | | 0 | Significant |

Blank or NA means that data were not available

*GN* glomerulonephritis, *RBx* renal biopsy, *NS* nephrotic syndrome, *UP* urinary protein

[a] Study Group of the Spanish Society of Nephrology

tests. The examination was performed using total sample biopsies, age (<20 and ≥20 years), and nephrotic syndrome. In all biopsy cases, the rate of primary MPGN was significantly reduced from the 1970s to the 2000s ($p = 0.0016$) (Fig. 1a). In patients with nephrotic syndrome, the rate of primary MPGN decreased significantly over the four decades ($p = 0.0009$) (Fig. 1b).

We then investigated the changing rate of primary MPGN according to age. In adult patients, the number of cases tended to decrease when compared with the preceding period (Fig. 2a); however, this decrease was not statistically significant. In the adult population with nephrotic syndrome, the proportion of primary MPGN also decreased (Fig. 2b); however, this decrease was not statistically significant.

By contrast, in the analysis of the child population, the rate of primary MPGN was significantly reduced from the 1970s to the 2000s ($p = 0.0055$) (Fig. 3a). In the analysis of the child population with nephrotic syndrome, the rate of primary MPGN decreased significantly from the 1970s to the 2000s ($p < 0.0001$) (Fig. 3b).

## Secular change of clinical severity, treatment, and prognosis of primary MPGN

We compared the changes of some clinical findings between the 1970s and 1980s and the 1990s and 2000s. First, we compared the difference of disease severity observed upon renal biopsy. The serum creatinine value at the renal biopsy was similar between the two respective periods [1.182 ± 0.800 mg/dL ($n = 28$) vs. 1.066 ± 0.843 mg/dL ($n = 41$), $p = 0.5684$]. The rate of hypocomplementemia was not significantly different [66.7 % ($n = 24$) vs. 53.7 % ($n = 41$), $p = 0.3044$]. We then investigated the change in treatment between these two time periods (Fig. 4). The use of steroid pulse therapy tended to be higher in the more recent group (1990s and 2000s). By contrast, the administration of warfarin ($p = 0.0052$) and anti-platelet drugs ($p = 0.0434$) was statistically decreased in the more recent group. Finally, we evaluated the secular change in the clinical outcome of 53 patients with follow-up medical records (Fig. 5). Renal survival seemed to show a trend of improvement [0.68 (−1989, $n = 21$) vs. 0.82 (−1990, $n = 32$) at 10 years after