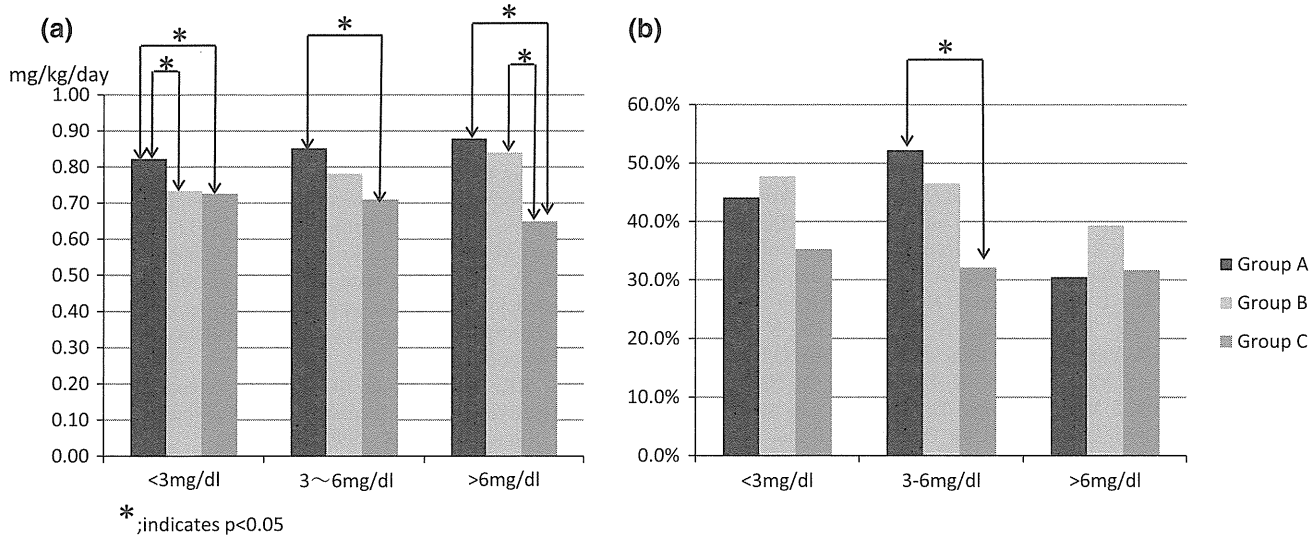

Fig. 4 Initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. The initial prednisolone dosage in groups B and C was significantly lower than that in group A in patients with serum creatinine levels <3 mg/dl. The initial prednisolone dosage in group 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**)

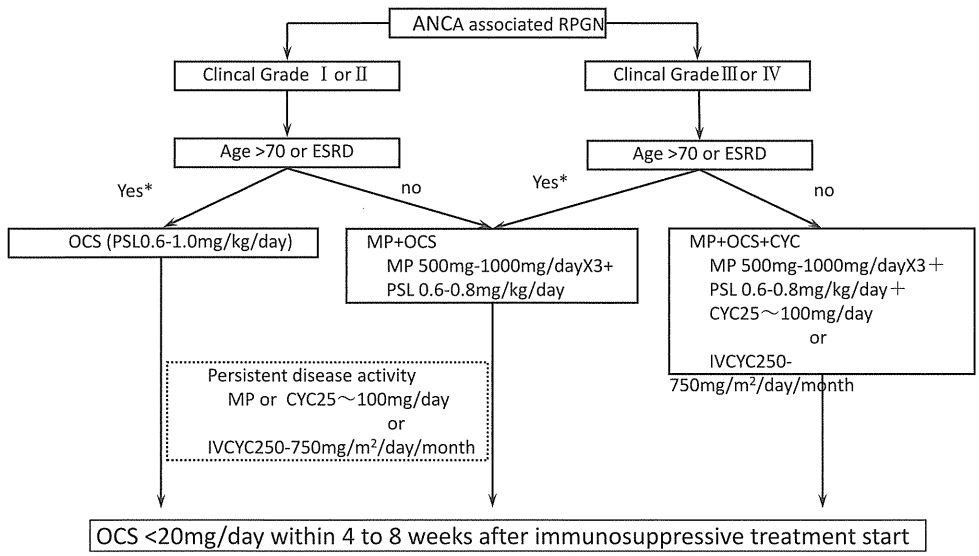

Fig. 5 Treatment algorithm for ANCA-associated RPGN in Japan. We made three treatment patterns depending on clinical grade and patient age or if the patient had already reached ESRD. The clinical grading system for RPGN was suitable for predicting patient survival. We selected age, serum creatinine level, 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.

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Conflict of interest The authors declare no conflicts of interest.

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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

Kunihiro Yamagata · Joichi Usui · Hitoshi Sugiyama · Kosaku Nitta · Takashi Wada · Eri Muso · Yoshihiro Arimura · Akio Koyama · Hirofumi Makino · Seiichi Matsuo

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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

The members of The Japanese RPGN Study Group of Progressive Renal Disease are Kunihiro Yamagata, Hitoshi Sugiyama, Kosaku Nitta, Takashi Wada, Eri Muso, Yoshihiro Arimura, Akio Koyama, Hirofumi Makino, and Seiichi Matsuo.

K. Yamagata (✉) · J. Usui
Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: kidney@md.tsukuba.ac.jp

J. Usui
e-mail: j-usui@md.tsukuba.ac.jp

H. Sugiyama · H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

K. Nitta
Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

T. Wada
Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan

E. Muso
Department of Nephrology and Dialysis, The Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan

Y. Arimura
First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

A. Koyama
Department of Nephrology, Tsukuba Memorial Hospital, Tsukuba, Ibaraki, Japan

S. Matsuo
Department of Nephrology, Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

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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

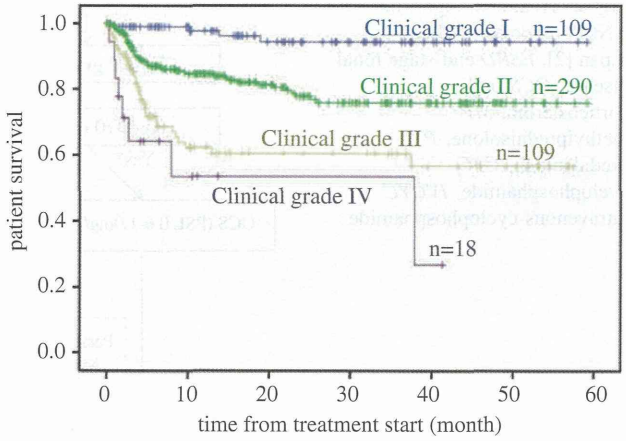

Fig. 1 Clinical grading system for predicting patient prognosis. A clinical grading system was applied to all RPGN patients. This figure was prepared with partial modification [1]

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.

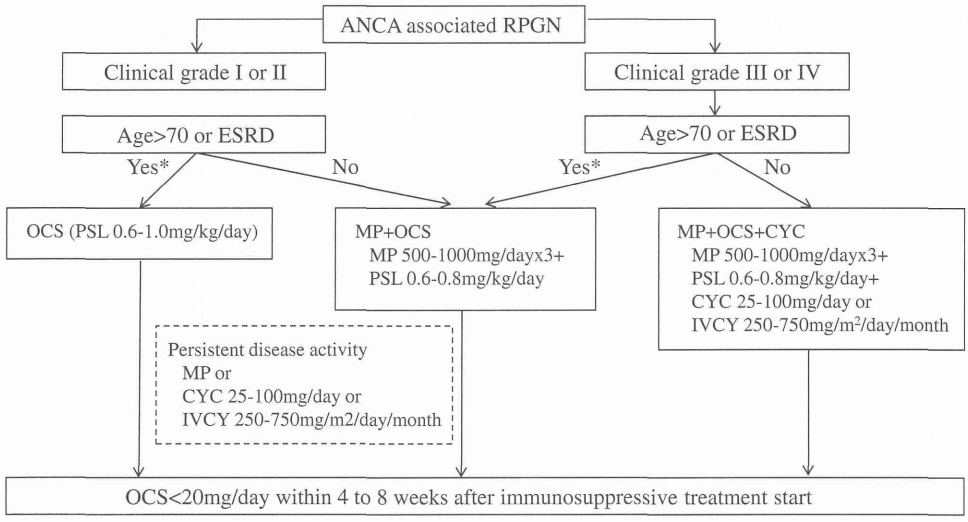

Fig. 2 Treatment algorithm for ANCA-associated RPGN in Japan [2]. *ESRD* end-stage renal disease, *OCS* oral corticosteroid, *MP* methylprednisolone, *PSL* prednisolone, *CYC* cyclophosphamide, *IVCYC* intravenous cyclophosphamide

*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.

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

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ORIGINAL ARTICLE

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

Tetsuya Kawamura · Joichi Usui · Koji Kaseda · Kenji Takada · Itaru Ebihara · Takashi Ishizu · Tadashi Iitsuka · Kentaro Sakai · Katsumi Takemura · Masaki Kobayashi · Akio Koyama · Katsuyoshi Kanemoto · Ryo Sumazaki · Noriko Uesugi · Masayuki Noguchi · Michio Nagata · Machi Suka · Kunihiro Yamagata

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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.

T. Kawamura · J. Usui (✉) · K. Kaseda · K. Yamagata
Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, Japan
e-mail: kidney@md.tsukuba.ac.jp

K. Takada
Department of Nephrology, Tsukuba Gakuen Hospital, Tsukuba, Ibaraki, Japan

I. Ebihara
Department of Nephrology, Mito Saiseikai General Hospital, Mito, Ibaraki, Japan

T. Ishizu
Department of Nephrology, Tsukuba Central Hospital, Ushiku, Ibaraki, Japan

T. Iitsuka · K. Sakai
Department of Nephrology, Ibaraki Seinan Medical Center Hospital, Sakai, Ibaraki, Japan

K. Takemura
Takemura Nephrology Clinic, Kanuma, Tochigi, Japan

M. Kobayashi
Department of Nephrology, Tokyo Medical University Ibaraki Medical Center, Ami, Ibaraki, Japan

A. Koyama
Department of Nephrology, Tsukuba Memorial Hospital, Tsukuba, Ibaraki, Japan

K. Kanemoto
Department of Pediatrics, National Hospital Organization Chiba-East-Hospital, Chiba, Chiba, Japan

R. Sumazaki
Department of Pediatrics, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

N. Uesugi · M. Noguchi · M. Nagata
Department of Pathology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

M. Suka
Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, Tokyo, Japan

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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

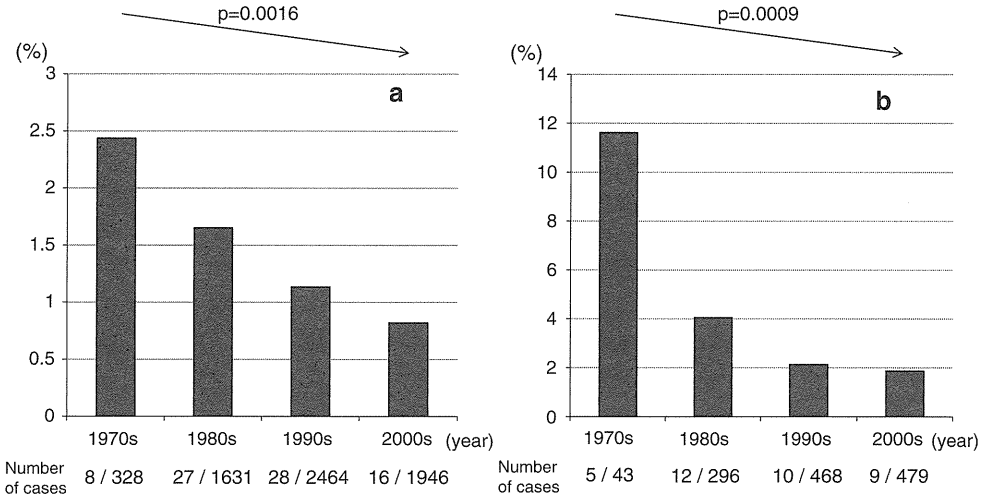

Fig. 1 Distribution of primary MPGN in total biopsies (**a**) and in biopsies with nephrotic syndrome (**b**) over four decades. Both trend tests were statistically significant

the renal biopsy], but the trends in both periods were not statistically significant ($p = 0.2384$).

Discussion

Long-term studies of the rate of primary GN involving over four decades of data are limited throughout the world as well as in Japan. In the present report, we demonstrated that the rate of primary MPGN showed a downward trend over time. Moreover, we statistically revealed a decline in pediatric cases; in particular, the disappearance of pediatric cases with nephrotic syndrome in the 1990s and 2000s was characteristic. By contrast, although the rate of primary MPGN in adults was one-third or one-fourth of that in children, the decrease in adult patients with primary MPGN was not established in the present study.

Some examinations of the change in the rate of MPGN in industrialized countries have been previously reported (Table 1). Major reports from Italy and Spain dealing with patients of all age groups showed that the rate of MPGN statistically decreased from the 1970s to the 1980s [3, 5]. Meanwhile, Swaminathan et al. [6] reported that the rate of MPGN in the USA remained statistically unchanged according to a comparison among the 1970s, 1980s, and 1990s; however, this result and conclusion may have been limited because of the small sample size. The following discussion focuses on an age-based analysis. The decrease of adult patients in industrialized countries is unclear. Jungers et al. [7] reported on a comparative examination of French patients >15 years; the rate of MPGN in France statistically decreased between the 1970s and 1980s. Chang et al. [8] reported on a comparative examination of Korean patients >15 years; the rate of MPGN in Korea statistically decreased between the 1980s and 2000s. By contrast, Braden et al. [9] reported a change in the rate of MPGN in adults with >2 g of daily urinary protein. The rate of MPGN in the USA remained statistically unchanged

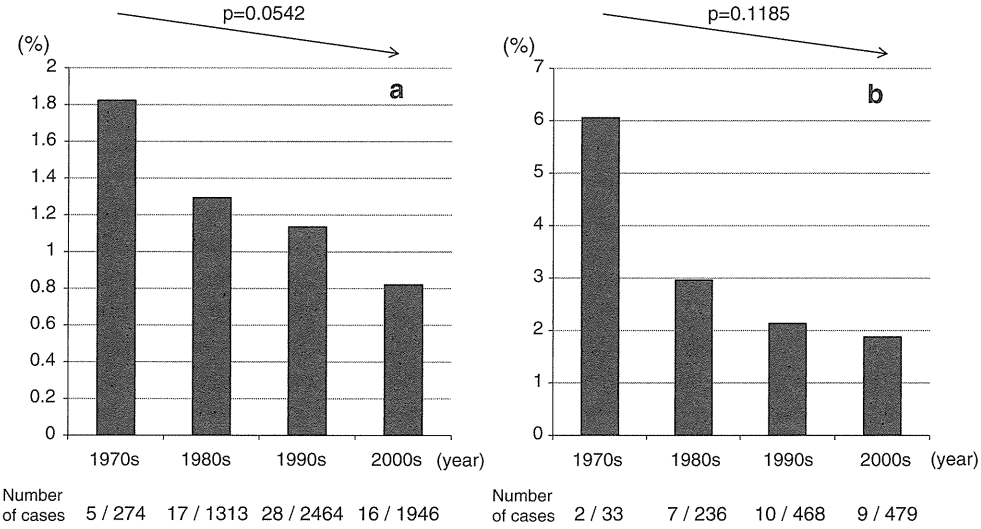

Fig. 2 Distribution of primary MPGN in adult patients (**a**) and patients with nephrotic syndrome (**b**) over four decades. The differences between the groups were not statistically significant

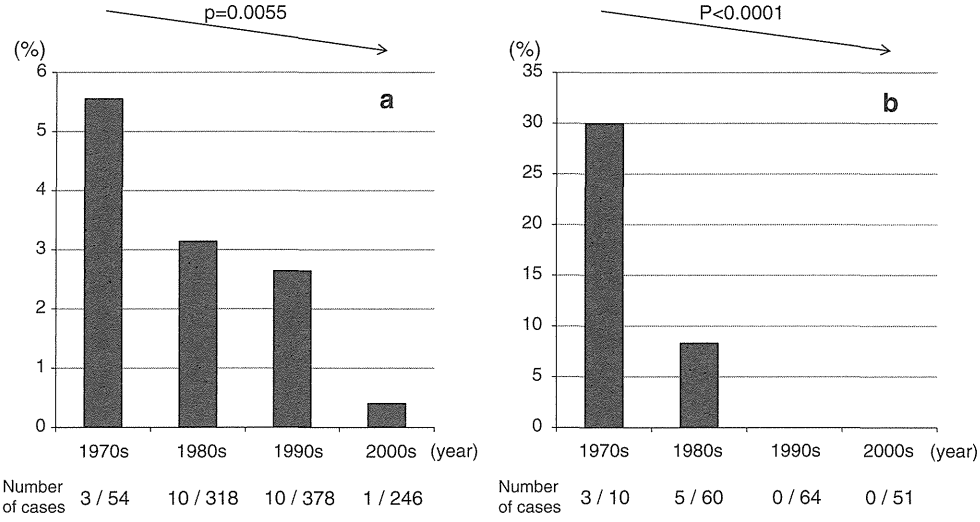

Fig. 3 Distribution of primary MPGN in child patients (**a**) and patients with nephrotic syndrome (**b**) over four decades. Both trend tests were statistically significant

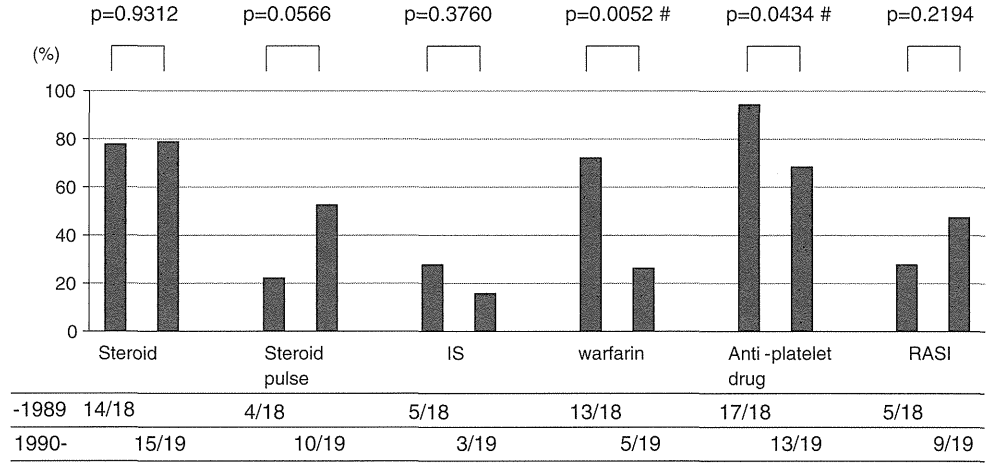

Fig. 4 The secular change in the treatment of primary MPGN. Use of steroid pulse therapy was higher in the more recent group (1990s and 2000s). By contrast, the administration of warfarin and anti-platelet drugs was statistically decreased in the more recent group (*hash symbols*). *IS* immunosuppressive drug, *RASI* renin–angiotensin system inhibitor

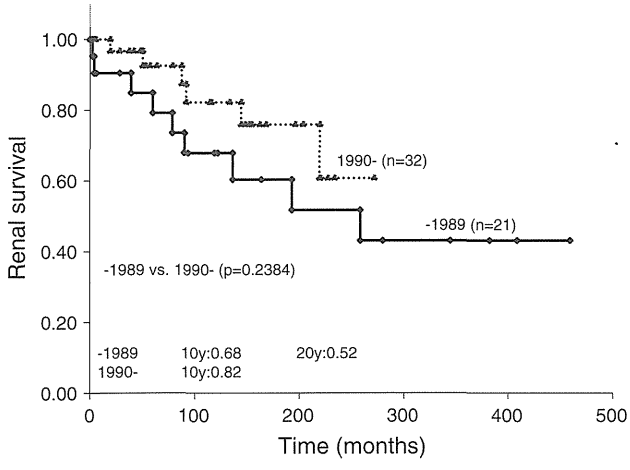

Fig. 5 The secular change in clinical outcomes of primary MPGN. Renal survival was analyzed by Kaplan–Meier method. The difference in renal survival between both periods was not statistically significant

according to a comparison among the 1970s, 1980s, and 1990s. Thus, the decline in adult patients with MPGN in industrialized countries remains statistically unconfirmed. On the other hand, the decrease in child patients with MPGN in industrialized countries (Spain and Japan) was statistically significant [10, 11]. The Study Group of the Spanish Society of Nephrology reported a comparative examination of Spanish patients <15 years of age in the 1970s and 1980s [10]. Iitaka et al. [11] reported on a comparative examination of Japanese patients <15 years of age in the 1970s, 1980s, and 1990s. Moreover, West reported on a comparative examination of child patients in the USA [12]. The rate of MPGN onset was seen to be on a declining trend from the 1970s to the 1980s without statistical analysis. Important differences in the above-mentioned results include the difference in the samples, differences in the race of the individuals sampled or the surrounding environment, the rarity of the disease, and the

possibility of including secondary MPGN. Additionally, the data for the 1990s and 2000s remain insufficient compared with the data for the 1970s and 1980s.

By contrast, the decrease in MPGN in developing countries has never been confirmed. In the Middle East (Saudi Arabia), South America (Peru), and Africa (Nigeria), MPGN remains one of the most common causes of nephrotic syndrome and may account for 30–40 % of all cases [1]. Moreover, the decrease of child patients with primary MPGN in Turkey and of adult patients with primary MPGN in Brazil were not statistically significant (Table 1) [13, 14]. The epidemiological pattern of glomerular diseases in developing countries is distinct from that in industrialized countries [15]. MPGN is the most common primary GN in developing countries, whereas IgA nephropathy is uncommon. The reason for the difference in the epidemiological patterns may be a key to elucidating the mechanism of MPGN onset. Some external factors associated with the hygienic environment and socioeconomic problems, e.g., infection control (especially the control of chronic bacterial, viral, and parasitic infections), have been discussed [1, 2, 15]. Japan is currently one of the most developed countries in the world. After World War II, Japan achieved outstanding economic growth; there was a period of high economic growth from 1956–1973, and a period of stable economic growth from 1974–1990 (reference web page in Japanese: Cabinet Office, Government of Japan. http://www.cao.go.jp/). Therefore, the socio-economic status of Japan developed very quickly in the 1970s and maintained slow progress after the 1970s. The average income in a particular area can be used as an index of the area's socio-economic status. According to the government data for 2009, the average income in Ibaraki Prefecture (2,653,000 yen per resident) was almost the same as the national average (2,791,000 yen per resident) (reference web page: Cabinet Office, Government of Japan.). Therefore, the present results for Ibaraki Prefecture reflect those for Japan as a whole. Additionally, the nation's sanitation and public health developed rapidly after World War II. A number of Schools of Hygiene and Public Health were concurrently established on the basis of a proposal made by the government of the United States. Moreover, laws related to hygiene and public health were established, e.g., the School Health Act was established in 1956 and the Water Supply Act in 1957. Therefore, disease control, immunization, school health, environmental pollution control, the deployment of water supply and sewage systems, and food sanitation progressively improved. All of these developments led to decreases in a variety of infections. Previous reports from Japan mentioned that some infections such as tuberculosis (since the 1980s), hepatitis A virus (since the 1990s), and parasites (*Schistosomiasis japonica*, since the 1980s) were decreasing [16–18]. Johnson et al. [15] suggested that the overall hygiene and socioeconomic status of a country may predispose its citizens to either a Th1- or Th2-dominant phenotype that will increase the susceptibility of that population to specific types of glomerular disease. The Th1-dominant glomerular diseases, such as MPGN and non-IgA mesangial proliferative GN, are more common in impoverished countries. By contrast, the Th2-dominant glomerular diseases, such as IgA nephropathy and minimal change nephrotic syndrome, are common in industrialized countries. It is generally thought that early and frequent exposure to bacterial and other antigens, common in developing countries, leads to a normal Th1 response. However, better public hygiene and fewer infections may lead to the persistence of the Th2 response and thereby increase the risk for developing allergies. In Japan, the incidence of atopic disorder also increased from the 1970s to the 1990s [19]. Moreover, Holdsworth et al. [20] reported that most proliferative GNs were driven by the Th1 response. Thus, the hygiene hypothesis may explain the epidemiologic change in glomerular diseases including primary MPGN. Our result regarding the reduction of child cases in Japan, an industrialized country, may help explain the mechanism of the decrease in primary MPGN. For example, some key changes have occurred in sanitary conditions and in the epidemiology of infectious diseases in children in Japan. In the future, worldwide research about epidemiologies is needed.

In the present study, we statistically proved a reduction in the incidence of primary MPGN. It is necessary to elucidate the reasons for the decrease in primary MPGN. Explaining this decrease may lead to a breakthrough in understanding the onset mechanism of primary MPGN.

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

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ORIGINAL ARTICLE

Membranous nephropathy in Japan: analysis of the Japan Renal Biopsy Registry (J-RBR)

Hitoshi Yokoyama · Takashi Taguchi · Hitoshi Sugiyama · Hiroshi Sato · On behalf of the Committee for the Standardization of Renal Pathological Diagnosis and for Renal Biopsy and Disease Registry in the Japanese Society of Nephrology

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Abstract Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. The J-RBR/J-KDR registry developed by the Japanese Society of Nephrology provides nationwide cohort data for epidemiological studies of MN. MN was present in 36.8% of 1,203 primary nephrotic syndrome patients in Japan. In addition, 633 (77.9%) out of 813 MN patients were referred to as "idiopathic," whereas 22.1% were classified as "secondary" and involved conditions such as systemic lupus erythematosus, drug exposure, infections, cancer, and various collagen diseases. The mean age of the MN patients was 62.2 (2–88) years old, their mean eGFR was 76.7 (7.6–154.6) ml/min/1.73 m^2, and 63.3% had hypertension at the time of renal biopsy. On the basis of these findings, half of Japanese idiopathic MN patients have risk factors (age >60, male, or lower eGFR) for end-stage renal failure, and 10% belong to the high-risk group (daily proteinuria of over 8.0 g). Further studies with high-grade evidence should resolve the natural history and therapeutic problems of idiopathic MN in elderly Japanese.

Keywords Membranous nephropathy · Epidemiology · Nephrotic syndrome

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H. Yokoyama (✉)
Division of Nephrology, Kanazawa Medical University School of Medicine, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan
e-mail: h-yoko@kanazawa-med.ac.jp

T. Taguchi
Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

H. Sugiyama
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

H. Sato
Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan

Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. Eighty percent of MN patients are referred to as "idiopathic," whereas approximately 20% of MN patients are classified as "secondary" and are associated with clinical conditions including infections, systemic lupus erythematosus (SLE), cancer, drug exposure, etc. [1–3]. It is generally felt that secondary-type cases involve exogenous antigens such as the hepatitis B virus (HBV) E antigen or tumor antigens. Idiopathic MN is considered to be an autoimmune disease because podocyte-related antigens such as neutral endopeptidase were recently identified in neonatal MN, and the M-type phospholipase A2 receptor (PLA2R) was detected in 70–80% of idiopathic MN patients [4, 5]. Although spontaneous remission of nephrotic syndrome occurs in approximately one-third of patients in Europe and North America, approximately 40% of patients develop end-stage renal failure (ESRF) after 10 years [6]. In Japan, several surveys of patients with certain renal diseases including idiopathic MN have been conducted. In a retrospective cohort study of 949 Japanese idiopathic MN patients performed between 1975 and 1993, renal survival rates judged by a requirement for hemodialysis and/or end-stage renal disease (ESRD) with serum creatinine levels ≥3.0 mg/dL

were 90.3% of patients after 10 years and 60.5% of patients after 20 years [7].

Until recently, there were no web-based, nationwide, or prospective registry systems for renal biopsies in Japan. Thus, in 2007, the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology established the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data about the renal biopsies performed in Japan [8].

The aim of the current review was to investigate the epidemiology of MN using the data registered in the J-RBR between 2007 and 2010.

The Japan Renal Biopsy Registry (J-RBR) system, subjects, and limitations

The researchers of the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology set up the J-RBR [8]. This review includes data obtained from 8,670 patients that were prospectively registered in the J-RBR from July 2007 to September 2010. Patient data including age, gender, laboratory data, and clinical and pathological diagnoses were electronically recorded at each institution and registered on the J-RBR webpage via the Internet Data and Information Center for Medical Research (INDICE) system, which is part of the University Hospital Medical Information Network (UMIN). The ethical committee of the Japanese Society of Nephrology comprehensively approved the study, and the local committees of the participating centers and their affiliate hospitals individually approved the study. The J-RBR was registered to the Clinical Trial Registry of UMIN (UMIN000000618).

It is worth noting that a web-based prospective registry system like the J-RBR can easily increase the number of participating institutions and enlarge the number of patients enrolled. Investigators can then analyze the registered data in real time. Otherwise, we cannot exclude sampling bias and thus ensure that the present sample of patients in the J-RBR is actually representative of the nationwide frequency of renal diseases in Japan. However, an investigation of a larger cohort or a population-based analysis of the rate of each renal disease may reveal the actual frequency of the disease and the distribution of age ranges utilizing this web-based system.

Membranous nephropathy patients in the J-RBR (2007–2010) and in other countries

At the end of September 2010, 813 MN patients (9.4%) had been registered in the J-RBR. As for the frequency of MN in renal biopsied patients, previous Japanese studies reported that MN represented 10.6% of 1,850 cases of primary glomerular disease in 1999 [9] and 12.7% of 1,233 primary glomerular disease cases recorded in the J-RBR between 2007 and 2008 [8]. In other countries, MN accounted for 9.3–23.4% of primary glomerular disease cases recorded in renal biopsy registries (Table 1) [10–15]. IgA nephropathy was the most common primary glomerular disease in Japan. Thus, the frequency of MN in renal biopsied cases might be lower in Japan than in other countries because of racial differences and/or the use of different indication criteria for renal biopsy in each country. Thus, it may not be easy to compare reports across countries. However, studying the changing frequency

Table 1 The frequencies of several primary glomerular diseases in different countries in different years

	Japan [8, 9]		China [10]	Italy [11]	Czech [12]	Romania [13]	Brazil [14, 15]	
Year:	2011	1999	2004	2004	2004	2006	2006	2010
Total cases:	*n* 1223 (%)	*n* 1,850 (%)	*n* 9278 (%)	*n* 6990 (%)	*n* 2333 (%)	*n* 401 (%)	*n* 1131 (%)	*n* 4619 (%)
IgAN	54.2	47.4 (495/1045)	45.3	43.5	34.5	28.9	17.8	20.1
MN	12.7	10.6	9.9	23.4	9.3	11.2	20.7	20.7
MCD	10.5	17.5	0.9	9.2	12.5	8.5	9.1	15.5
FSGS	6.3	4.6	6.0	13.1	10.8	11.5	29.7	24.6
MPGN	2.5	7.5	3.4	6.6	4.6	29.4	7.0	4.2
Cresc GN	0.9	0.9	1.9	2.3	3.2	7.9	4.1	1.7
Non-IgAN mes PGN	10.4	–	25.6	–	11.3	–	3.8	9.9
Other unclassifiable	2.5	–	7.0	1.9	13.8	2.5	7.8	3.3
Total (%)	100	–	100	100	100	99.9	100	100

IgAN IgA nephropathy, *MN* membranous nephropathy, *MCD* minimal change disease, *FSGS* focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis, *mes PGN* mesangial proliferative glomerulonephritis

patterns of renal disease in the same country over a certain time period may be a useful way to judge alterations in disease backgrounds.

In the present analysis, 633 (77.9%) of 813 MN patients were referred to as "idiopathic," whereas 180 MN patients (22.1%) were classified as "secondary," including 74 (9.1%) lupus nephritis patients (ISN/RPS2003 classification class V), 14 patients (1.7%) whose condition had been caused by drug exposure (12 patients treated with bucillamine, a disease-modifying antirheumatic drug, DMARD), 10 patients (1.2%) with infectious disease (hepatitis B virus: 4, hepatitis C virus: 4, syphilis: 1, and human immunodeficiency virus: 1), 8 patients (1.0%) with cancer (prostatic cancer: 1, pancreatic cancer: 1) or hematological disease (post bone-marrow transplantation: 3, IgG4-related disease: 2, and monoclonal gammopathy of undetermined significance: 1), and 7 patients (0.9%) with various collagen diseases (Fig. 1a). As for the age distribution of the MN patients, around 60% of the secondary MN patients were in their second to fourth decade, and lupus nephritis (class V) was the most common primary disease among these patients. In addition, the number of registered patients increased with age and peaked in the seventh decade (Fig. 1b).

Demographics of idiopathic membranous nephropathy patients in Japan

The demographics of the 633 patients with idiopathic MN are presented in Table 2 and Fig. 2. As for gender, the male to female ratio was 1.3 (358 males and 275 females) and did not differ among the decades (Fig. 2a). In previous reports, the male to female ratio was much higher; i.e., 1.6 in 1,008 Japanese patients [7] and 2.0 in North Americans, Australians, and Asians (1,190 males and 598 females) [5, 6]. The mean age of the patients was 62.2 (2–88) years old, which was 10 years older than that in a report published in 2001 (50.7 years old) [7]. In addition, the mean eGFR of the MN patients was 76.7 (7.6–154.6) ml/min/1.73 m^2. The

Table 2 Patient demographics of idiopathic membranous nephropathy in Japan (J-RBR2007-2010)

	N	Min	Max	Mean	SD
Age (years old, y.o.)	633	2	88	62.2	14.3
Male	358	3	86	61.3	13.9
Female	275	2	88	63.5	14.6
Height (cm)	607	82	184	158.7	10.8
Weight (kg)	607	11.9	112.0	59.9	12.4
Body mass index (BMI)	607	13.7	41.1	23.6	3.7
Proteinuria (g/day)	501	0.00	26.9	3.99	3.3
Urinary protein/creatinine ratio	429	0.00	26.8	5.57	4.36
Serum creatinine (mg/dl)	632	0.17	6.6	0.88	0.49
eGFR (more than 20 y.o.)	592	7.6	154.6	76.7	26.0
Serum total protein (g/dl)	632	3.20	8.4	5.49	0.96
Serum albumin (g/dl)	627	0.70	4.99	2.64	0.83
Serum total cholesterol (mg/dl)	619	125	838	295.4	102.2
Systolic blood pressure (mmHg)	490	77	194	130.8	19.2
Diastolic blood pressure (mmHg)	490	48	156	76.9	12.5
Mean blood pressure (mmHg)	490	64	180	94.9	13. 4
HbA1c (%)	298	4.4	8.6	5.5	0.7

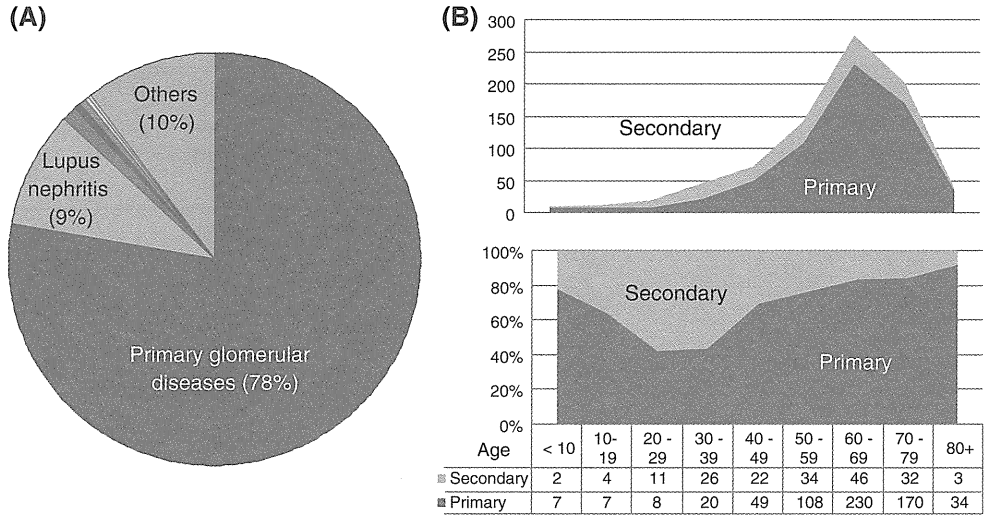

Fig. 1 Primary diseases (**a**) and ages (**b**) of membranous nephropathy patients in Japan. J-RBR 2007–2010 registry: 813 cases in total; 633 cases in which membranous nephropathy was the primary disease (77.9% of all cases)

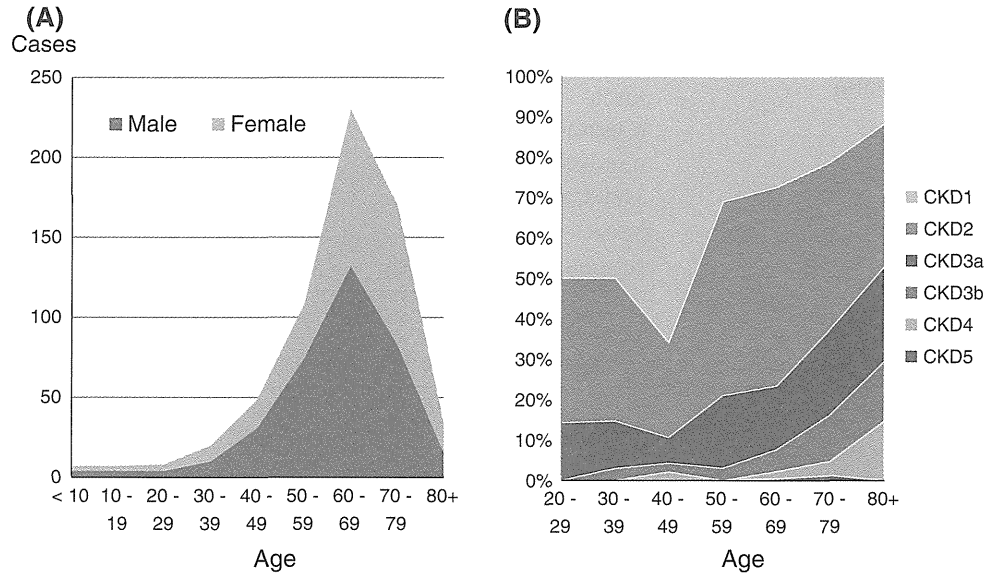

Fig. 2 Ages, genders (**a**), and CKD stages (**b**) of idiopathic membranous nephropathy patients in Japan. J-RBR 2007–2010 registry: 633 cases in total; males: 358 cases (56.6%), females: 278 cases (43.4%)

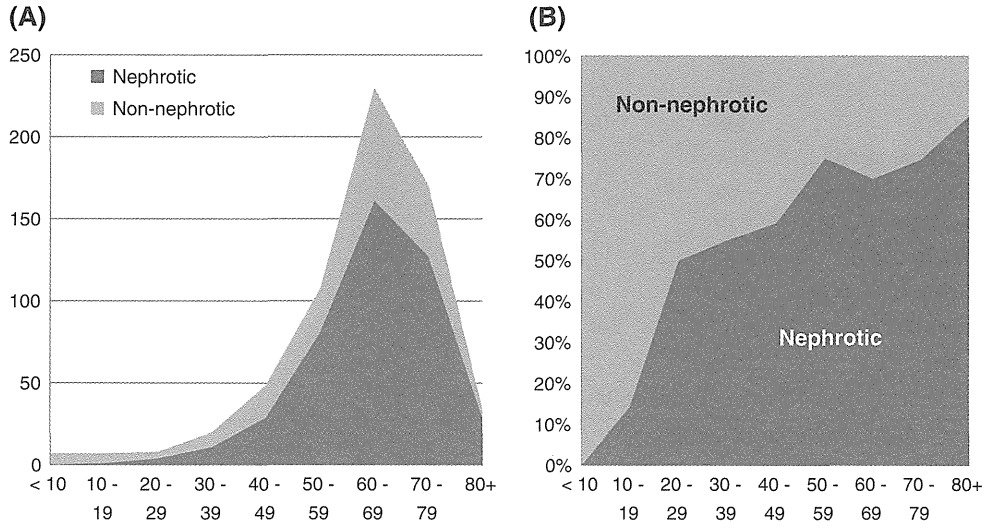

Fig. 3 Nephrotic syndrome in idiopathic membranous nephropathy and age distribution of the population. J-RBR 2007–2010 registry: nephrotic syndrome was present in 444 of 633 cases (70.0%)

number of patients with advanced chronic kidney disease (CKD) (stage 3a, 3b, or 4) [18] increased with age, and more than 20% of them were 60 years old or older. A future analysis using anti-PLA2R antibodies might explain these phenomena, such as the increased number of females and older population.

Regarding proteinuria, 70.0–91.6% of idiopathic MN patients had nephrotic syndrome in previous reports. On the other hand, about 5% of the MN patients displayed mild proteinuria of less than 1.0 g/day.

In this study, the mean daily proteinuria value was 3.99 g, and the mean urinary protein to creatinine ratio was 5.57 g/gCr. When we judged the patients' nephrotic state based on the new criteria for nephrotic syndrome used in Japan [19]; i.e., daily proteinuria (or a urinary protein to creatinine ratio if daily proteinuria was not measured) of more than 3.5 g (or g/gCr) and serum albumin levels of less than 3.0 g/dL or serum total protein levels of less than 6.0 g/dL, 444 (70%) of 633 idiopathic MN patients were considered to be nephrotic (Fig. 3a). The frequency of a nephrotic state increased with age from 0% in the first decade to 80% in the ninth decade (Fig. 3b). The high-risk group; i.e., the patients with daily proteinuria values of over 8.0 g based on a previous report on North Americans [1], included 53 (10.6%) patients out of 501 patients (12.2% of 279 males and 8.6% of 222 females, Table 3).

As for hypertension, blood pressure and/or the intake of anti-hypertensive drugs were registered in 455 idiopathic MN patients. Hypertension, as judged by a systolic blood pressure of more than 140 mmHg, a diastolic blood pressure of more than 90 mmHg, or drug intake, was observed in 308 (67.7%) patients with idiopathic MN. In addition, only 31.7% patients (153 out of 482 patients) were considered to have well-controlled blood pressure, as judged by the recommended levels outlined in the Japanese CKD guidelines [20]; i.e., a systolic blood pressure of less than

Table 3 Proteinuria of idiopathic membranous nephropathy in Japan (J-RBR2007-2010)

Proteinuria (g/day)	Total *n* 501	Percentage	Male *n* 279	Percentage	Female *n* 222	Percentage
<0.30	15	3.0	11	3.9	4	1.8
0.30–0.49	18	3.6	10	3.6	8	3.6
0.50–0.99	37	7.4	16	5.7	21	9.5
1.00–3.49	185	36.9	98	35.1	87	39.2
3.50+	246	49.1	144	51.6	102	45.9
High-risk group (≥8.0 g/day)	53	10.6	34	12.2	19	8.6

Table 4 Pathology in primary nephrotic syndrome including IgA nephropathy

	Japan		Korea [16]		Brazil [15]		USA [17]		
Year:	2011		2009		2010		1966		
Observed period:	2007–2010		1987–2006		1993–2007		1975–1994		
Biopsied cases:	8,670		1,818		9,617		1,056		
Nephrotic cases:	*n* 1,307	%	*n* 611	%	*n* 2,754	%	Total *n* 340 (%)	Black *n* 121 (%)	White *n* 170 (%)
MCNS	490	37.5	235	38.5	776	28.2	16	14	20
MN	443	*33.9*	157	*25.7*	698	*25.3*	*33*	*24*	*36*
FSGS	138	10.6	58	9.5	1013	36.8	34	57	23
IgA nephropathy	104	8.0	68	11.1	158	5.7	7	2	8
MPGN type (I/III)	66	5.0	51	8.3	71	2.6	6	2	6
Mes PGN	30	2.3	–	–	38	1.4	–	–	–
Crescentic GN	13	1.0	–	–	–	–	–	–	–
Endocapillary PGN	12	0.9	–	–	–	–	–	–	–
Sclerotic GN	2	0.2	–	–	–	–	–	–	–
Others	9	0.7	42	6.9	–	–	4	1	6
		100.0		100.0		100.0	100	100	100

Italic values are statistically significant ($p = 0.0002$)

MCNS minimal change nephrotic syndrome, *MN* membranous nephropathy, *FSGS* focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis, *Mes* mesangial, *PGN* proliferative glomerulonephritis, *GN* glomerulonephritis

125 mmHg and a diastolic blood pressure of less than 75 mmHg in patients displaying daily proteinuria of more than 1.0 g or a urinary protein to creatinine ratio of more than 1.0 g/gCr, or a systolic blood pressure of less than 130 mmHg and a diastolic blood pressure of less than 80 mmHg in patients displaying daily proteinuria of less than 1.0 g or a urinary protein to creatinine ratio of less than 1.0 g/gCr, at the time of renal biopsy. These findings revealed that Japanese patients with idiopathic MN often have insufficiently controlled hypertension at the initial presentation.

Idiopathic membranous nephropathy in nephrotic syndrome in Japan and other countries

Two thousand sixty-six patients with nephrotic syndrome were selected from the J-RBR using the previously described criteria [19]. In this population, primary glomerular disease including IgA nephropathy accounted for 63.2% of the patients, and their secondary glomerular diseases included diabetic nephropathy (9.9%), lupus nephritis (6.1%), and amyloidosis (4.2%) (Fig. 4, left). Idiopathic MN was found in 36.8% of 1,203 primary nephrotic syndrome patients without IgA nephropathy, and about 25% of all nephrotic syndrome patients (Fig. 4, right). Compared to other countries (South Korea, Brazil, and USA), the frequency of MN (33.9% of patients with nephrotic syndrome due to primary glomerular disease including IgA nephropathy) was similar to that found for Caucasians in the USA (36%), but much higher than those obtained for South Koreans (25.7%), Brazilians (25.3%), and African blacks in the USA (24%) (Table 4). These differences might reflect the age distributions of the renal biopsied patients in each area, because Japanese MN patients tend to be much older, as described below.

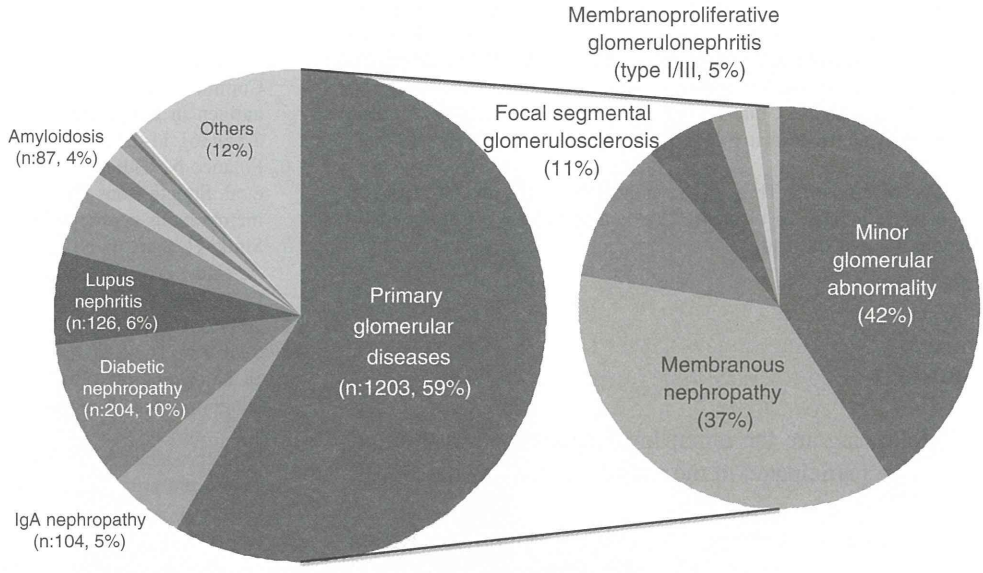

Fig. 4 Glomerular lesions of nephrotic syndrome patients in Japan. J-RBR 2007–2010 registry: 2066 cases in total; 1203 cases of primary glomerular disease. Membranous nephropathy accounted for 37% of the idiopathic nephrotic syndrome cases in Japan

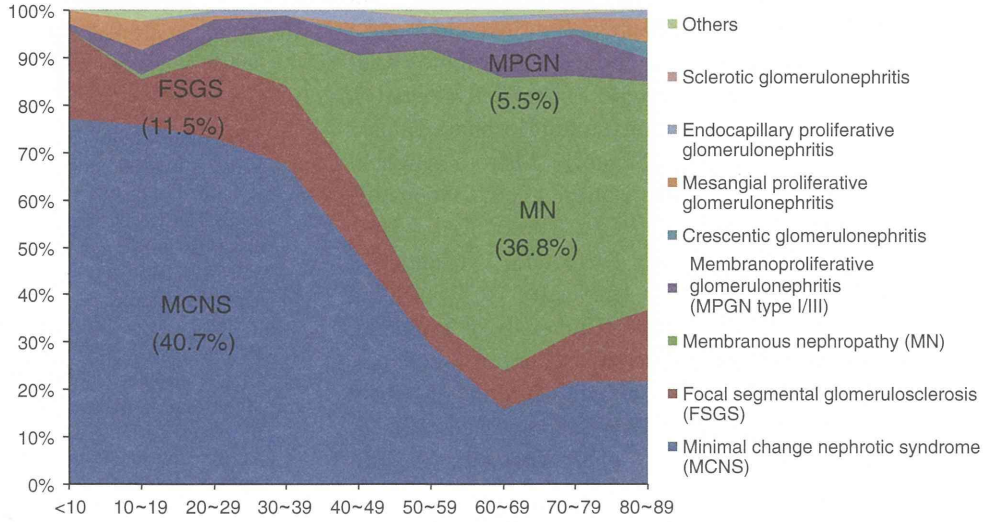

Fig. 5 Glomerular lesions of idiopathic nephrotic syndrome patients in Japan according to age. J-RBR 2007–2010 registry: 1203 cases of primary glomerular disease excluding IgA nephropathy

Age distribution of nephrotic syndrome and idiopathic membranous nephropathy patients in Japan

When we analyzed the 1,203 renal biopsy-proven nephrotic syndrome patients by age, the incidence of idiopathic MN gradually increased from the fourth decade and peaked in the seventh decade. Idiopathic MN was present in 48.3–61.9% of the primary nephrotic syndrome patients who were older than 50, and 57.6% of the 550 patients who were older than 60 (Fig. 5). In other words, 317 (71.6%) out of 443 idiopathic MN patients were aged over 60 years. A previous report found that being aged over 60 years was an independent risk factor for ESRF in Japanese idiopathic MN (hazard ratio 1.98; 95% cumulative interval 1.20–3.28; $p = 0.008$) [7]. In addition, being aged over 50 years, being male, daily proteinuria of more than 8.0 g, and an elevated serum creatinine level were also found to be independent risk factors for ESRF in North American idiopathic MN patients [1]. On the basis of these findings, half of Japanese idiopathic MN patients have risk factors for ESRF.

Conclusion

The J-RBR/J-KDR registry developed by the Japanese Society of Nephrology provides nationwide cohort data for epidemiological studies of MN. On the basis of our findings, half of nephrotic Japanese idiopathic MN patients have risk factors for ESRF, and 10% belong to the high-risk group. Further studies with high-grade evidence should resolve the natural history and therapeutic problems of idiopathic MN in elderly Japanese.

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Conflict of interest Three of the authors (HY, TT, and HS) have no conflicts of interest to disclose. One author (SH) was supported by Daiichi-Sankyo Co. Ltd.

Appendix

The following are the initial investigators and institutions who have participated in the project to develop the J-RBR since 2007:

Takao Saito (Fukuoka University), Yukimasa Kohda (Kumamoto University; present address, Hikarinomori Clinic), Shinichi Nishi (Niigata University; present address: Kobe University), Kazuhiko Tsuruya and Yutaka Kiyohara (Kyushu University), Hideyasu Kiyomoto (Kagawa University; present address: Tohoku University), Hiroyuki Iida (Toyama Prefectural Central Hospital), Tamaki Sasaki (Kawasaki Medical School), Makoto Higuchi (Shinshu University), Motoshi Hattori (Tokyo Women's Medical University), Kazumasa Oka (Osaka Kaisei Hospital; present address: Hyogo Prefectural Nishinomiya Hospital), Shoji Kagami (The University of Tokushima Graduate School), Michio Nagata (University of Tsukuba), Tetsuya Kawamura (Jikei University School of Medicine), Masataka Honda (Tokyo Metropolitan Children's Medical Center), Yuichiro Fukasawa (KKR Sapporo Medical Center; present address: Sapporo City Hospital), Atsushi Fukatsu (Kyoto University Graduate School of Medicine), Kunio Morozumi (Japanese Red Cross Nagoya Daini Hospital), Norishige Yoshikawa (Wakayama Medical University), Yukio Yuzawa (present address: Fujita Health University) and Seiichi Matsuo (Nagoya University Graduate School of Medicine), Kensuke Joh (Chiba-East National Hospital; present address: Sendai Shakai Hoken Hospital), Hirofumi Makino (Okayama University Graduate School of Medicine).

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