

Twenty-eight patients with newly-diagnosed juvenile SLE were treated with a combination of corticosteroid and MZB (4–5 mg/kg/day), while 29 patients were treated with corticosteroid alone. At the end of a 1-year study period, there were no differences in the severity of proteinuria and renal function impairment between the two groups [34].

A single center open trial for 6 months on Tac therapy in 23 adult Japanese was also conducted, in which proteinuria and serum albumin levels were significantly improved after 3 months and 1 month of treatment, respectively. The improvement persisted until the end of the 6-month trial [35]. From 2007 through 2020, an observation study of Tac (TRUST study) is being undertaken on more than 1,139 Japanese patients, which may provide important clinical data for the therapy of lupus nephritis in Japan.

Overall, combination therapies based on glucocorticoids with antimetabolites (MMF) and/or calcineurin inhibitors (Tac), or alkylating agents (IVCY), are similarly effective for proliferative LGN in adult Asians and Japanese.

#### Membranous LGN (ISN/RPS 2003 classification class V)

As mentioned in a recent review by Mok, the optimal treatment of MLN remains enigmatic, as a result of a lack of controlled trials with adequate sample sizes. However, in a recent report from an NIH trial for MLN, three therapeutic modalities were examined in a randomized controlled trial: (1) corticosteroid alone, (2) adjunctive regimens that included either cyclosporine (CsA) for 11 months, or (3) alternate-month IVCY for 6 doses in 42 patients with MLN. In this study, the cumulative probability of remission at 1 year was 27% with prednisone, 60% with IVCY, and 83% with CsA. Although both IVCY and CsA were more effective than prednisone in inducing remission of proteinuria, relapse of nephrotic syndrome occurred significantly more often after completion of CsA than after IVCY. By multivariate survival analysis, treatment with prednisone and high-grade proteinuria (>5 g/day) but not ethnicity were independently associated with a decreased probability of remission [36].

A sub-analysis of 84 patients with pure MLN in the ALMS study and a US study revealed that 52 cases (62.4%) were complicated with nephrotic syndrome, and 40 cases underwent 24 weeks of a therapeutic regimen with either MMF or IVCY; however, only one (2.5%) improved to reach complete remission, with 24 cases (60%) in partial remission [37].

Considering these reports, the indications for immunosuppressive therapy in MLN are serious renal disease, as shown by nephrotic-range proteinuria and/or impaired renal

function; worsening of proteinuria and renal function despite non-immunosuppressive or supportive treatment; mixed membranous and proliferative lupus nephritis; and the presence of concomitant extrarenal major organ manifestations of SLE. The optimal regimen and duration of immunosuppressive treatment for MLN are unclear because of the lack of controlled treatment trials; however, patients with mixed membranous and proliferative lupus nephritis should be treated in the same way as those with proliferative lupus nephritis. Pure MLN associated with renal insufficiency, substantial proteinuria, or failure to respond to supportive therapies is an indication for intensive immunosuppressive therapy. Treatment options include glucocorticoids combined with antimetabolites (MZB, MMF), calcineurin inhibitors (CsA, Tac), or alkylating agents (IVCY) in selected cases. After remission induction therapy, maintenance immunosuppressive therapy seems to be necessary in MLN.

Experimental modalities warrant further study in MLN, particularly in refractory pure MLN cases of Japanese and other Asians.

#### B-cell depletion therapy in LGN

B-cell depletion therapy is becoming a popular treatment for SLE. A few clinical studies have shown that rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, is beneficial in refractory lupus nephritis including class IV, IV + V, and V. The effect of anti-CD20 antibodies was associated with B-cell disappearance within 1 month [38]. Retrospective data from the French AutoImmunity and Rituximab (AIR) registry including a previous report showed a satisfactory tolerance profile and clinical efficacy of RTX in 136 SLE patients [39]. However, the placebo-controlled trial of the Lupus Nephritis Assessment with Rituximab (LUNAR) study could not show the benefit of anti-CD20 antibody compared with corticosteroid plus MMF (controls) in SLE patients [40, 41]. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial tested the efficacy and safety of RTX versus placebo in patients with moderately to severely active extrarenal SLE. No differences were noted between placebo and RTX in the primary endpoint judged by British Isles Lupus Assessment Group (BILAG) A score, except for the beneficial effect of RTX observed in African-American and Hispanic subgroups. [42]. The contrasting results from these 2 recent randomized controlled trials of cases with or without lupus nephritis leave unresolved the issue of the therapeutic use of anti-CD20 antibodies in SLE. Future studies with new designs are needed to define the effect of B-cell depletion in Japanese and other Asian patients with severe lupus nephritis of class IV-S, IV-G, or V.

## Conclusion

The ISN/RPS 2003 classification provides a standardized interpretation of renal biopsy and a pathological diagnosis to compare outcome data across centers in Japan and other countries. J-RBR/J-KDR registration by the Japanese Society of Nephrology can offer nationwide cohort data in epidemiological studies. On the basis of these findings, further studies with high-grade evidence should resolve the therapeutic problems of LGN in Japanese and other Asians.

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## Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan

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### Abstract

**Background** The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database of the Japanese Society of Nephrology started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record the pathological, clinical, and laboratory data of renal biopsies in 2007.

**Methods** The patient data including age, gender, laboratory data, and clinical and pathological diagnoses were recorded

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on the web page of the J-RBR, which utilizes the system of the Internet Data and Information Center for Medical Research in the University Hospital Medical Information Network. We analyzed the clinical and pathological diagnoses registered on the J-RBR in 2007 and 2008.

**Results** Data were collected from 818 patients from 18 centers in 2007 and 1582 patients from 23 centers in 2008, including the affiliated hospitals. Renal biopsies were obtained from 726 native kidneys (88.8%) and 92 renal grafts (11.2%) in 2007, and 1400 native kidneys (88.5%) and 182 renal grafts (11.5%) in 2008. The most common clinical diagnosis was chronic nephritic syndrome (47.4%), followed by nephrotic syndrome (16.8%) and renal

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transplantation (11.2%) in 2007. A similar frequency of the clinical diagnoses was recognized in 2008. Of the native kidneys, the most frequent pathological diagnosis as classified by pathogenesis was immunoglobulin (Ig) A nephropathy (IgAN) both in 2007 (32.9%) and 2008 (30.2%). Among the primary glomerular diseases (except IgAN), membranous nephropathy (MN) was the most common disease both in 2007 (31.4%) and 2008 (25.7%).

**Conclusions** In a cross-sectional study, the J-RBR has shown IgAN to be the most common disease in renal biopsies in 2007 and 2008, consistent with previous Japanese studies. MN predominated in the primary glomerular diseases (except for IgAN). The frequency of the disease and the clinical and demographic correlations should be investigated in further analyses by the J-RBR.

**Keywords** Glomerulonephritis · Tubulointerstitial disorder · Renal vascular disease · Renal grafts · National registry

## Introduction

There has been no national registry of renal biopsies in Japan. The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database in the Japanese Society of Nephrology established the first

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nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data regarding all renal biopsies performed in 2007.

To date, the epidemiological and clinical data of renal diseases are available from nationwide registries of renal biopsies from the United Kingdom [1], Italy [2], Denmark [3], Spain [4], the Czech Republic [5], and Australia [6]. The role of a renal biopsy registry has been recently encouraged [7]. In Japan, several surveys were temporarily conducted for patients with restricted renal diseases, including primary glomerulonephritis [8], idiopathic membranous nephropathy (MN) [9], and immunoglobulin (Ig) A nephropathy (IgAN) [10]. However, there has been no web-based, nationwide, or prospective registry system of overall renal biopsies in Japan. The aim of the current study was to provide data to investigate the epidemiology and frequency of renal diseases with a histological diagnosis for patients registered in 2007 and 2008 on the J-RBR.

## Subjects and methods

### Registry system and patients

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for Renal Biopsy Database in the Japanese Society of Nephrology participated in this study. The report includes the data from patients on the J-RBR, registered prospectively from January to December of 2007 and 2008. Patient data including age, gender, laboratory data, and the clinical and pathological diagnoses were electronically recorded at each institution and registered on the web page of the J-RBR utilizing the system of Internet Data and Information Center for Medical Research (INDICE) in the University Hospital Medical Information Network (UMIN). The ethical committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences comprehensively approved the study, and a local committee of participating centers and their affiliated hospitals individually approved the study. Written informed consent was obtained from the patients at the time of biopsy or before participation in the study. The J-RBR is registered to the Clinical Trial Registry of UMIN (registered number UMIN00000618) and is available in Japanese and English.

#### Clinical or renal histopathological diagnosis and laboratory data

Three classifications, clinical diagnosis, histological diagnosis by pathogenesis, and histological diagnosis by histopathology, were selected for each case (Supplementary Table) from the J-RBR. The classification of clinical diagnoses was determined as follows: acute nephritic syndrome, rapidly progressive nephritic syndrome, recurrent or persistent hematuria, chronic nephritic syndrome, nephrotic syndrome, renal disorder with metabolic disease, renal disorder with collagen disease or vasculitis, hypertensive nephropathy, inherited renal disease, acute renal failure, drug-induced nephropathy, renal transplantation, and others. The definitions of the former five clinical diagnoses were based on the clinical syndromes and glomerular histopathology in the classification of glomerular diseases [11]. Acute nephritic syndrome was defined as a syndrome characterized by the abrupt onset of hematuria, proteinuria, hypertension, decreased glomerular filtration,

and edema. Rapidly progressive nephritic syndrome was defined as an abrupt or insidious onset of hematuria, proteinuria, anemia, and rapidly progressing renal failure. Recurrent or persistent hematuria included the insidious or abrupt onset of gross or microscopic hematuria with little or no proteinuria and no evidence of other features of nephritic syndrome. Chronic nephritic syndrome was defined as slowly developing renal failure accompanied by proteinuria, hematuria, with or without hypertension. Nephrotic syndrome was defined as massive proteinuria  $>3.5$  g/day and hypoalbuminemia of  $<3$  g/dL of serum albumin with or without edema or hypercholesterolemia.

The renal histological diagnosis is classified either according to pathogenesis (A) or by histopathology (B) as follows: (A) primary glomerular disease (except IgAN), IgAN, purpura nephritis, lupus nephritis, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-positive nephritis, protein 3 (PR3)-ANCA-positive nephritis, anti-glomerular basement membrane antibody nephritis, hypertensive nephrosclerosis, thrombotic microangiopathy, diabetic nephropathy, amyloid nephropathy, Alport syndrome, thin basement membrane disease, infection-related nephropathy, transplanted kidney, and others; (B) minor glomerular abnormalities, focal and segmental glomerulosclerosis (FSGS), MN, mesangial proliferative glomerulonephritis, endocapillary proliferative glomerulonephritis, membranoproliferative glomerulonephritis (MPGN) (type I, III), dense deposit disease, crescentic and necrotizing glomerulonephritis, sclerosing glomerulonephritis, nephrosclerosis, acute interstitial nephritis, chronic interstitial nephritis, acute tubular necrosis, transplanted kidney, and others. IgAN (Berger disease) was separated from primary glomerular diseases on the basis of basic glomerular alterations in the classification of glomerular diseases [11]. Clinical data, including urinalysis, daily proteinuria, serum creatinine concentrations, total protein, albumin, and total cholesterol values were also recorded, but only the frequency of the disease is described here.

#### Statistics

Data were expressed as mean  $\pm$  SD as appropriate. Statistical analyses were performed using the JMP software program, version 8 (SAS Institute Inc., Cary, NC, USA).

#### Results

##### Baseline characteristics of registered biopsies

Data were collected from 818 patients from 18 centers in 2007 and 1582 patients from 23 centers in 2008, including the affiliated hospitals. Renal biopsies were obtained from

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**Table 1** Number of participating renal centers and registered renal biopsies on the Japan Renal Biopsy Registry (J-RBR) in 2007 and 2008

Year	2007	2008	Total
Renal centers	18	23	23
Total biopsies	818	1582	2400
Average age (y)	44.6 ± 20.7	44.2 ± 21.1	44.4 ± 21.0
Male	430	851	1281
Female	388	731	1119
Native kidneys	726	1400	2126
Average age (y)	45.2 ± 21.4	44.8 ± 22.0	44.9 ± 21.5
Male	378	751	1129
Female	348	649	997
Renal grafts	92	182	274
Average age (y)	40.5 ± 13.5	39.4 ± 16.3	39.8 ± 15.4
Male	52	100	152
Female	40	82	122

726 native kidneys (88.8%) and 92 renal grafts (11.2%) in 2007 and 1400 native kidneys (88.5%) and 182 renal grafts (11.5%) in 2008 (Table 1). The average age of the patients was 44.6 ± 20.7 years of age in 2007 and 44.2 ± 21.1 years of age in 2008. A higher number of male patients than female patients were registered in both years (male patients 52.6% in 2007 and 53.8% in 2008). The distribution of the total number of renal biopsies according to age and gender are presented in Fig. 1, and reveals a different age and gender distribution in native kidneys and renal grafts.

The frequency of clinical diagnoses

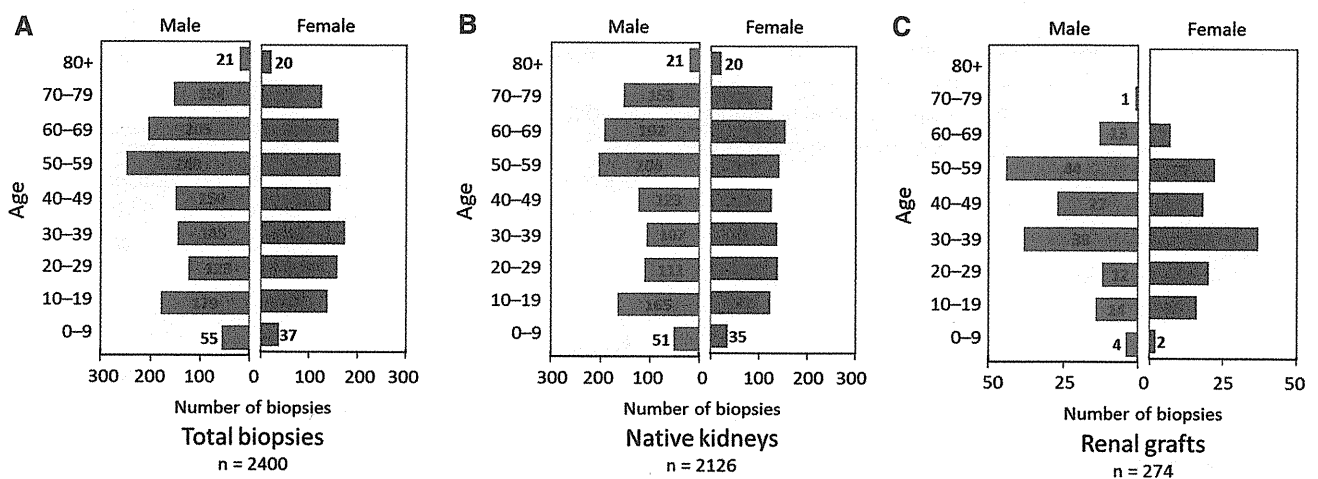
The clinical diagnosis and renal histological diagnosis as classified by pathogenesis and by histopathology were

determined for each biopsy. A clinical diagnosis of chronic nephritic syndrome was the most frequent, followed by nephrotic syndrome and renal transplantation in 2007, which was similar in 2008 (Table 2). In native kidneys, the majority of the cases corresponded to chronic nephritic syndrome, followed by nephrotic syndrome and recurrent or persistent hematuria or renal disorder with collagen disease or vasculitis in 2007 (Table 2). Similar frequencies of chronic nephritic syndrome, nephrotic syndrome and renal disorder with collagen disease or vasculitis were observed in 2008 (Table 2).

The frequency of pathological diagnoses

Pathological diagnoses were classified by pathogenesis (Table 3) and histopathology (Table 4). In the classification of pathogenesis, IgAN was diagnosed most frequently, followed by primary glomerular disease (except IgAN) and renal grafts both in 2007 and 2008 (Table 3). In the present cohort, except for renal grafts, the frequency of IgAN was 32.9%, followed by primary glomerular disease (except IgAN) (26.3%) and diabetic nephropathy (5.9%) in 2007 (Table 3). A slightly lower frequency of IgAN was present (30.2%), but similar frequencies of primary glomerular disease (except IgAN) (26.3%) and diabetic nephropathy (5.1%) were observed in 2008 (Table 3).

In the pathological diagnoses as classified by histopathology, mesangial proliferative glomerulonephritis was primarily observed in 2007 and 2008 (Table 4). In the present cohort, except for renal grafts, the frequency of mesangial proliferative glomerulonephritis was the highest followed by MN, minor glomerular abnormalities, nephrosclerosis, and crescentic and necrotizing glomerulonephritis in 2007 (Table 4). In 2008, mesangial proliferative glomerulonephritis was the most frequently diagnosed,

**Fig. 1** Distribution of age ranges and gender in total renal biopsies (a), native kidneys (b), and renal grafts (c) in the combined data of 2007 and 2008

**Table 2** Frequency of classification of clinical diagnoses

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Chronic nephritic syndrome	388	47.4	768	48.5	1156	48.2
Nephrotic syndrome	138	16.9	259	16.4	397	16.5
Renal transplantation	92	11.2	182	11.5	274	11.4
Renal disorder with collagen disease or vasculitis	41	5.0	87	5.5	128	5.3
Rapidly progressive nephritic syndrome	33	4.0	80	5.1	113	4.7
Recurrent or persistent hematuria	41	5.0	33	2.1	74	3.1
Renal disorder with metabolic syndrome	29	3.5	46	2.9	75	3.1
Hypertensive nephropathy	14	1.7	30	1.9	44	1.8
Acute nephritic syndrome	15	1.8	20	1.3	35	1.5
Acute renal failure	7	0.9	13	0.8	20	0.8
Drug-induced nephropathy	3	0.4	11	0.7	14	0.6
Inherited renal disease	5	0.6	8	0.5	13	0.5
Others	12	1.6	45	2.8	57	2.4
Total	818	100.0	1582	100.0	2400	100.0

**Table 3** Frequency of pathological diagnoses as classified by pathogenesis

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
IgA nephropathy	239	29.2	424	26.8	663	27.6
Primary glomerular disease (except IgA nephropathy)	191	23.3	369	23.3	560	23.3
Renal graft	93	11.3	179	11.3	272	11.3
Diabetic nephropathy	43	5.2	71	4.5	114	4.8
Hypertensive nephrosclerosis	31	3.7	61	3.9	92	3.8
Lupus nephritis	29	3.5	59	3.7	88	3.7
MPO-ANCA-positive nephritis	25	3.0	58	3.7	83	3.5
Purpura nephritis	18	2.2	39	2.5	57	2.4
Amyloid nephropathy	12	1.4	22	1.4	34	1.4
Infection-related nephropathy	16	1.9	16	1.0	32	1.3
Thin basement membrane disease	11	1.3	5	0.3	16	0.7
Alport syndrome	1	0.1	9	0.6	10	0.4
PR3-ANCA-positive nephritis	1	0.1	7	0.4	8	0.3
Thrombotic microangiopathy	3	0.3	2	0.1	5	0.2
Anti-glomerular basement membrane antibody-type nephritis	0	0.0	4	0.3	4	0.2
Others	105	12.8	257	16.2	362	15.1
Total	818	100.0	1582	100.0	2400	100.0

with minor glomerular abnormalities being the second, and MN being the third (Table 4).

#### Primary glomerular disease (except IgAN) and nephrotic syndrome

In the cohort of primary glomerular disease as classified by pathogenesis, MN was predominant, followed by mesangial proliferative glomerulonephritis, minor glomerular

abnormalities, and FSGS in 2007 (Table 5). In 2008, MN was still the most frequently diagnosed, present at the same frequency as minor glomerular abnormalities (Table 5).

In nephrotic syndrome as classified by clinical diagnosis, primary glomerular disease (except IgAN) was predominant, followed by diabetic nephropathy, amyloid nephropathy, IgAN, and lupus nephritis in 2007 (Table 6). A similar ordering of the disease frequencies was noted in 2008 (Table 6). Among the primary glomerular diseases



**Table 4** Frequency of pathological diagnoses as classified by histopathology

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Mesangial proliferative glomerulonephritis	326	39.8	607	38.4	933	38.9
Renal graft	90	11.0	171	10.8	261	10.9
Membranous nephropathy	74	9.0	128	8.1	202	8.4
Minor glomerular abnormalities	52	6.3	143	9.0	195	8.1
Crescentic and necrotizing glomerulonephritis	32	3.9	87	5.5	119	5.0
Nephrosclerosis	38	4.6	77	4.9	115	4.8
Focal segmental glomerulosclerosis	32	3.9	65	4.1	97	4.0
Membranoproliferative glomerulonephritis (type I and III)	20	2.4	32	2.0	52	2.2
Chronic interstitial nephritis	24	2.9	21	1.3	45	1.9
Endocapillary proliferative glomerulonephritis	18	2.2	27	1.7	45	1.9
Sclerosing glomerulonephritis	10	1.2	33	2.1	43	1.8
Acute interstitial nephritis	7	0.9	18	1.1	25	1.0
Acute tubular necrosis	5	0.6	6	0.4	11	0.5
Dense deposit disease	1	0.1	5	0.3	6	0.3
Others	89	10.8	162	10.2	251	10.5
Total	818	100.0	1582	100.0	2400	100.0

**Table 5** Frequency of pathological diagnoses as classified by histopathology in primary glomerular disease (except IgA nephropathy)

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Membranous nephropathy	60	31.4	95	25.7	155	27.7
Minor glomerular abnormalities	33	17.3	95	25.7	128	22.9
Mesangial proliferative glomerulonephritis	45	23.6	82	22.2	127	22.7
Focal segmental glomerulosclerosis	24	12.6	53	14.4	77	13.8
Membranoproliferative glomerulonephritis (type I and III)	13	6.8	19	5.1	32	5.7
Crescentic and necrotizing glomerulonephritis	5	2.6	6	1.6	11	2.0
Endocapillary proliferative glomerulonephritis	1	0.5	6	1.6	7	1.3
Nephrosclerosis	2	1.0	4	1.1	6	1.1
Dense deposit disease	1	0.5	3	0.8	4	0.7
Sclerosing glomerulonephritis	2	1.0	1	0.3	3	0.5
Others	5	2.6	5	1.4	10	1.8
Total	191	100.0	369	100.0	560	100.0

(except IgAN) in nephrotic syndrome, MN was dominant followed by minor glomerular abnormalities, such as minimal change nephrotic syndrome (MCNS), FSGS, and MPGN (type I and III) in 2007 (Table 7). In 2008, the frequency of minor glomerular abnormalities was predominant, followed by MN (Table 7).

Clinical diagnosis of MN, minor glomerular abnormalities, and FSGS

Subanalyses of subjects with a clinical diagnosis of MN, minor glomerular abnormalities, and FSGS were

performed since these were the most common forms of primary glomerular diseases (except IgAN) (Tables 8, 9, 10). Nephrotic syndrome was the most common clinical diagnosis in MN and minor glomerular abnormalities (Tables 8, 9), whereas chronic nephritic syndrome was the most common in FSGS (Table 10). In the pathogenesis of minor glomerular abnormalities (total 195 cases), primary glomerular diseases (except IgAN) comprised 65.6% (128 cases), followed by others 13.8% (27 cases), IgAN 8.2% (16 cases) and thin basement membrane disease 5.1% (10 cases). In the pathogenesis of FSGS (total 97 cases), primary glomerular diseases (except IgAN) comprised 79.4%

**Table 6** Frequency of pathological diagnoses as classified by pathogenesis in nephrotic syndrome

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Primary glomerular disease (except IgA nephropathy)	91	65.9	179	69.1	270	68.0
Diabetic nephropathy	15	10.9	15	5.8	30	7.6
Amyloid nephropathy	9	6.5	13	5.0	22	5.5
IgA nephropathy	8	5.8	9	3.5	17	4.3
Lupus nephritis	4	2.9	8	3.1	12	3.0
Purpura nephritis	1	0.7	4	1.5	5	1.3
Infection-related nephropathy	3	2.2	1	0.4	4	1.0
Thrombotic microangiopathy	1	0.7	0	0.0	1	0.3
MPO-ANCA-positive nephritis	0	0.0	1	0.4	1	0.3
Hypertensive nephrosclerosis	0	0.0	1	0.4	1	0.3
Others	6	4.3	28	10.8	34	8.6
Total	138	100.0	259	100.0	397	100.0

**Table 7** Frequency of pathological diagnoses as classified by histopathology in primary glomerular disease (except IgA nephropathy) in nephrotic syndrome

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Minor glomerular abnormalities	29	31.9	79	44.1	108	40.0
Membranous nephropathy	40	44.0	56	31.3	96	35.6
Focal segmental glomerulosclerosis	10	11.0	25	14.0	35	13.0
Membranoproliferative glomerulonephritis (type I and III)	7	7.7	13	7.3	20	7.4
Mesangial proliferative glomerulonephritis	1	1.1	4	2.2	5	1.9
Crescentic and necrotizing glomerulonephritis	2	2.2	1	0.6	3	1.1
Endocapillary proliferative glomerulonephritis	1	1.1	0	0.0	1	0.4
Others	1	1.1	1	0.6	2	0.7
Total	91	100.0	179	100.0	270	100.0

**Table 8** Frequency of clinical diagnoses in membranous nephropathy

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Nephrotic syndrome	44	59.5	66	51.6	110	54.5
Chronic nephritic syndrome	20	27.0	47	36.7	67	33.2
Renal disorder with collagen disease or vasculitis	7	9.5	9	7.0	16	7.9
Renal disorder with metabolic syndrome	1	1.4	1	0.8	2	1.0
Recurrent or persistent hematuria	1	1.4	0	0.0	1	0.5
Renal transplantation	0	0.0	1	0.8	1	0.5
Rapidly progressive nephritic syndrome	0	0.0	1	0.8	1	0.5
Acute nephritic syndrome	0	0.0	1	0.8	1	0.5
Drug-induced nephropathy	0	0.0	1	0.8	1	0.5
Others	1	1.4	1	0.8	2	1.0
Total	74	100.0	128	100.0	202	100.0

**Table 9** Frequency of clinical diagnoses in minor glomerular abnormalities

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Nephrotic syndrome	29	55.8	82	57.3	111	56.9
Chronic nephritic syndrome	9	17.3	43	30.0	52	26.7
Recurrent or persistent hematuria	6	11.5	10	7.0	16	8.2
Renal disorder with collagen disease or vasculitis	1	1.9	5	3.5	6	3.1
Rapidly progressive nephritic syndrome	1	1.9	0	0.0	1	0.5
Renal disorder with metabolic syndrome	1	1.9	0	0.0	1	0.5
Acute nephritic syndrome	1	1.9	0	0.0	1	0.5
Drug-induced nephropathy	1	1.9	0	0.0	1	0.5
Inherited renal disease	0	0.0	1	0.7	1	0.5
Others	3	5.8	2	1.4	5	2.6
Total	52	100.0	143	100.0	195	100.0

**Table 10** Frequency of clinical diagnoses in focal segmental glomerulosclerosis

Classification	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Chronic nephritic syndrome	18	56.3	32	49.2	50	51.5
Nephrotic syndrome	10	31.3	26	40.0	36	37.1
Inherited renal disease	2	6.3	0	0.0	2	2.1
Renal disorder with collagen disease or vasculitis	1	3.1	1	1.5	2	2.1
Rapidly progressive nephritic syndrome	1	3.1	1	1.5	2	2.1
Renal transplantation	0	0.0	1	1.5	1	1.0
Recurrent or persistent hematuria	0	0.0	1	1.5	1	1.0
Renal disorder with metabolic syndrome	0	0.0	1	1.5	1	1.0
Others	0	0.0	2	3.1	2	2.1
Total	32	100.0	65	100.0	97	100.0

**Table 11** Profile of IgA nephropathy

IgA nephropathy	2007	2008	Total
Total native kidney biopsies ( <i>n</i> )	239	421	660
Average age (y)	36.5 ± 19.0	36.4 ± 18.2	36.4 ± 18.5
Male ( <i>n</i> )	112 (46.9%) <sup>a</sup>	219 (52.0%) <sup>a</sup>	331 (50.2%) <sup>a</sup>
Average age (y)	37.1 ± 18.9 <sup>b</sup>	37.2 ± 19.3 <sup>b</sup>	37.2 ± 19.1 <sup>b</sup>
Female ( <i>n</i> )	127 (53.1%)	202 (48.0%)	329 (49.8%)
Average age (y)	36.1 ± 19.2	35.4 ± 17.0	35.7 ± 17.8

<sup>a</sup> Ratio indicates percentage of each gender in each biopsy category

<sup>b</sup> Not significant as compared to another gender

(77 cases), followed by others 11.3% (11 cases) and hypertensive nephrosclerosis 4.1% (4 cases).

#### Subanalysis of IgAN

The profile, classification of clinical diagnosis, and the pathological diagnosis of IgAN, the most frequent

glomerulonephritis on the J-RBR, were further analyzed (Tables 11, 12, 13). The percentage of IgAN detected in total biopsies and native kidneys was 27.5 and 31.0% in 2007 and 2008, respectively. The average age was the fourth decade in both genders. There was no difference in the proportion based on gender (Table 11). The majority of the clinical and pathological diagnoses were chronic

**Table 12** Frequency of classification of clinical diagnoses in IgA nephropathy

Clinical diagnosis	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Chronic nephritic syndrome	197	82.4	387	91.9	584	88.5
Recurrent or persistent hematuria	23	9.6	17	4.0	40	6.1
Nephrotic syndrome	8	3.3	9	2.1	17	2.6
Rapidly progressive nephritic syndrome	8	3.3	1	0.2	9	1.4
Acute nephritic syndrome	2	0.8	4	0.9	6	0.9
Hypertensive nephropathy	0	0.0	2	0.5	2	0.3
Renal disorder with metabolic disease	1	0.4	0	0.0	1	0.2
Acute renal failure	0	0.0	1	0.2	1	0.2
Total	239	100.0	421	100.0	660	100.0

nephritic syndrome (Table 12) and mesangial proliferative glomerulonephritis (Table 13), respectively.

#### Other diseases

Rare diseases such as Alport syndrome, Fabry disease, lipoprotein glomerulopathy, and dense deposit disease (one case each) were registered in 2007, and one subject was diagnosed with POEMS syndrome in 2008.

#### Discussion

The J-RBR obtained data from 818 and 1582 patients with kidney disease and renal transplantation who submitted renal biopsies in 2007 and 2008, respectively. The main objectives of the registry were, based on the histopathological findings, to establish the frequency of glomerulopathies, tubulointerstitial diseases, renal vascular disorders,

and renal grafts in renal biopsies in Japan. Data for all patients with histopathological evidence of renal disease at the participating centers were collected on standard forms and registered on the J-RBR program in the UMIN-IN-DICE. Chronic nephritic syndrome was the most frequent clinical diagnosis in both years of the registry. IgAN was the most frequently diagnosed disease in renal biopsies in 2007 and 2008, consistent with previous reports [8]. In patients with nephrotic syndrome, primary glomerular diseases (except IgAN) were predominant in both years.

Regarding the classification of clinical diagnosis in native kidney biopsies, more than half were diagnosed with chronic nephritic syndrome, which was usually accompanied by urinary abnormalities, as shown in Table 2. The frequency of clinical diagnosis may reflect the prevalence of renal biopsy in Japan. Indications of renal biopsy in Japan included urinary abnormalities such as mild-to-moderate proteinuria with or without hematuria, massive proteinuria such as nephrotic syndrome, rapidly progressive glomerulonephritis, and renal allografts (a protocol or episode biopsy). Solitary hematuria may be indicated after urological examinations. In Japan, all students in primary and junior high schools routinely undergo an annual urinalysis by the dip-stick test as one of the national health programs. Thereafter students in high schools and universities and employees of companies submit to a urinalysis as part of a nationwide screening program. This social system promotes the early referral to nephrologists and may thus influence the frequency of chronic nephritic syndrome according to the clinical diagnoses of the J-RBR.

In the present study, IgAN was the most frequently diagnosed by pathological findings, which is consistent with a previous report [8]. The frequency of IgAN was 32.9% in 2007 and 30.2% in 2008 in native kidneys of patients registered on the J-RBR, which was less than that in the previous nationwide survey [8]. IgAN is the most common biopsy-proven renal disease among primary glomerulopathies in Asia as described in reports from

**Table 13** Frequency of pathological diagnoses as classified by histopathology

Pathological diagnosis by histopathology	2007		2008		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Mesangial proliferative glomerulonephritis	228	95.4	398	94.5	626	94.8
Minor glomerular abnormalities	0	0.0	16	3.8	16	2.4
Crescentic and necrotizing glomerulonephritis	2	0.8	3	0.7	5	0.8
Sclerosing glomerulonephritis	3	1.3	0	0.0	3	0.5
Nephrosclerosis	1	0.4	1	0.2	2	0.3
Membranous nephropathy	1	0.4	1	0.2	2	0.3
Membranoproliferative glomerulonephritis (type I and III)	1	0.4	0	0.0	1	0.2
Others	3	1.3	2	0.5	5	0.8
Total	239	100.0	421	100.0	660	100.0

Korea [12] and China [13]. In the United States, IgAN is the most common primary glomerulopathy in young adult Caucasians and the most common cause of end-stage renal disease, while it was found to be rare in African Americans in whom FSGS remained more common [14]. In Australia, IgAN, FSGS, lupus nephritis, and vasculitis are the most common renal diseases in adults with a male predominance, excepting lupus nephritis [6]. In Europe, IgAN is the most frequent primary glomerulonephritis in several countries [2, 4, 5, 15], while MN is the most frequent in Macedonia [16], MPGN in Romania [17], and non-IgA mesangial proliferative glomerulonephritis in Serbia [18]. FSGS is the most frequent renal disease in a recent report from Brazil [19]. Because there is a different policy of renal biopsy practice in each country, it may not be easy to compare the different databases across countries. Instead, the changing frequency patterns of renal disease in the same country over a certain time period are useful to treat disease and reduce chronic kidney disease burden [20].

The frequency of nephrotic syndrome was 19.0% in 2007 and 18.5% in 2008 for patients registered on the J-RBR. Primary renal diseases were present in approximately two-thirds of all patients with nephrotic syndrome. MN was the most common primary nephrotic syndrome in 2007 (44.0%) and MCNS was the most common in 2008 (44.1%). The reason for this difference may depend on the cohort of registered biopsies in both years, since the number of patients registered was not as large as other registries [2, 4, 13, 19].

For the registry of patients with end-stage renal disease in Japan, there has been a nationwide and yearly statistical survey of chronic dialysis patients since 1968, conducted by the Japanese Society for Dialysis Therapy in Japan [21]. The combined data of the J-RBR with this dialysis registry will allow us to evaluate the long-term outcome of patients with various renal diseases in the near future. Similarly, the combined renal transplant registry data allows the evaluation of patient outcome. A sizeable frequency of renal grafts was registered on the J-RBR. Consequently, the future analysis of renal grafts, including the frequency of the protocol and episode biopsies and the precise histological diagnosis, will be necessary.

There is no overall registry of renal biopsies in Japan at the moment. It is noteworthy that the J-RBR is web-based, and a prospective registry system that can easily increase the number of participating centers and enlarge the number of patients enrolled in the future. We cannot conclude that the present sample of patients on the J-RBR in 2007 and in 2008 is actually representative of the nationwide frequency of glomerular, tubulointerstitial, or renal vascular diseases or renal grafts in Japan. However, in the near future, 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 by utilizing the J-RBR system.

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## Appendix

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## 膜性腎症の疫学—腎臓病総合レジストリーの解析から

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### はじめに

膜性腎症は、腎糸球体係蹄基底膜上皮下の免疫複合体沈着と補体の活性化により惹起される疾患である。その成因として、これまで悪性腫瘍、薬物、膠原病、感染症などに伴って生じる二次性のものが約 10~20%含まれていると考えられてきた<sup>1,2)</sup>。この抗原として、B 型肝炎ウイルスの HBe 抗原などの感染症関連抗原、CEA などの癌関連抗原が報告されている。さらに糸球体係蹄上皮細胞(足細胞, podocyte)に存在する内因性抗原として、新生児膜性腎症における中性エンドペプチダーゼ、あるいは特発性の約 70~80%に抗体が陽性と報告された膜型ホスホリパーゼ A<sub>2</sub>受容体(M-type phospholipase A<sub>2</sub> receptor: PLA<sub>2</sub>R)が注目されている<sup>3,4)</sup>。臨床的にみると、本症の約 30%の症例は発症より 2 年以内に自然寛解するが、残りの症例は持続する蛋白尿を呈し末期腎不全へと進行する重要な疾患である<sup>5,6)</sup>。全国 85 施設アンケート調査における 1975~1993 年に発症した成人膜性腎症 1,008 例の末期腎不全発症率(透析導入率)は 10 年で 89%, 15 年で 80%, 20 年で 59%と長期予後は不良であると報告されている<sup>7)</sup>。

本稿では、日本腎臓学会腎臓病総合レジストリー(Japan Kidney Disease Registry/Japan Renal Biopsy Registry: J-KDR/J-RBR)に登録された症例解析による膜性腎症の現状およびこれまでの報告を比較して、本邦における膜性腎症の疫学的側面を考察する。

### 腎臓病総合レジストリーにおける膜性腎症

#### 1. 膜性腎症の基礎疾患と年齢分布

2007~2010 年に登録された J-RBR 8,670 例から抽出した膜性腎症は 813 例(腎生検登録の 9.4%)であった。そのうち、一次性は 633 例(膜性腎症診断の 77.9%)であり、二次性が 180 例(22.1%)を占めた。二次性の主な疾患は、ループス腎炎(V型)が 74 例(9.1%), 薬剤性 14 例(ブシラミン 12 例, その他 2 例; 1.7%), 感染症 10 例(B 型肝炎ウイルス陽性 4 例, C 型肝炎ウイルス陽性 4 例, 梅毒 1 例, HIV 1 例; 1.2%), 悪性新生物あるいは血液疾患 8 例(前立腺癌・膵臓癌各 1 例, 骨髄移植後 3 例, MGUS(monoclonal gammopathy of undetermined significance) 1 例, IgG4 関連 2 例; 1.0%), その他の膠原病 7 例(0.9%)であった(図 1a)。その生検年齢層別比率をみると、10~30 歳代で二次性が占める割合が約 60%と増加しており、その主体はループス腎炎であった。一方、実数からみると 20 歳以降に年齢層が進むにつれて登録数は増加し、60 歳代でピークを認めた(図 1b)。

#### 2. 一次性膜性腎症の疫学と臨床背景

これまで、一次性膜性腎症の初診時に 70.0~91.6%の症例がネフローゼ状態を伴う一方で、約 5%は尿蛋白が 1.0 g/日以下の軽症例であり、軽症蛋白尿例への腎生検実施が少ない欧米では、本症の発生頻度が実際よりも過小評価されている可能性が指摘されていた。実際、各国の腎生検診断による一次性糸球体疾患をみると、膜性腎症は 9.3~23.4%であり、わが国においても 1999 年の一次性糸球体疾患 1,850 例の報告では 10.6%, J-RBR 2007~2008 年の 1,223 例の集計報告でも 12.7%であった<sup>8~15)</sup>。

今回検討した一次性膜性腎症 633 例の背景を図 2、表 2 に示すが、男女比は 1.3:1(男性 358 例, 女性 275 例)と男性の発症頻度が高く、各年齢層による性別比に差はなかった(図 2a)。一方、これまでの厚生労働省進行性腎障害調査

#### Epidemiology of membranous nephropathy in Japan

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表 1 Frequency of several forms of primary glomerular diseases in different countries

	Japan <sup>8,9)</sup>		China <sup>10)</sup>	Italy <sup>11)</sup>	Czech <sup>12)</sup>	Romania <sup>13)</sup>	Brazil <sup>14,15)</sup>	
Reported year	2011	1999	2004	2004	2004	2006	2006	2010
Total cases	n : 1,223	n : 1,850	n : 9,278	n : 6,990	n : 2,333	n : 401	n : 1,131	n : 4,619
IgAN (%)	54.2	47.4 (495/1,045)	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
Crescentic GN (%)	0.9	0.9	1.9	2.3	3.2	7.9	4.1	1.7
Non-IgAN mesangial 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

MN : membranous nephropathy, MCD : minor glomerular abnormality, FSGS : focal segmental glomerulosclerosis, MPGN : membranoproliferative glomerulonephritis, GN : glomerulonephritis, IgAN : IgA nephropathy

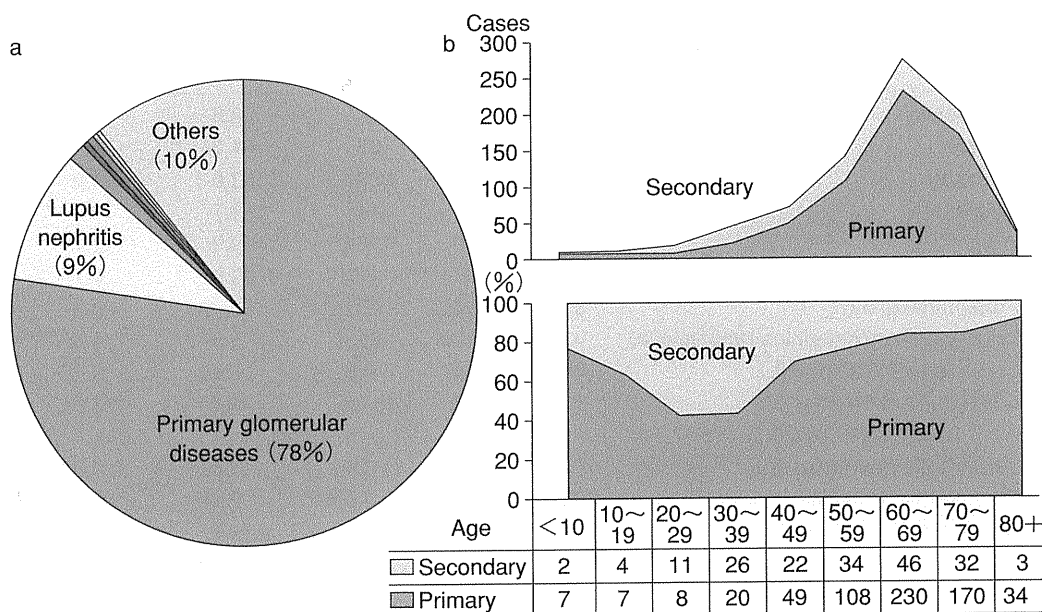


図 1 Basic diseases (a) and age (b) of membranous nephropathy in Japan

J-RBR 2007~2010 registry : 813 cases in total, 633 cases in primary disease (77.9 % in total cases)

研究班報告(1997~2001年)1,008例の成績(1.6:1)を含む北米、オーストラリア、アジア諸国からの報告においては、より男性の比率(男女比2:1;男性1,190例,女性598例)が高いことが報告されている<sup>5~7)</sup>。また、発症は各年齢層に認められ、その平均年齢は62.2歳と先の進行性腎障害調査研究班報告の50.7歳よりさらに高齢化している<sup>7)</sup>。また、

推算糸球体濾過率は76.7(7.6~154.6)mL/min 1.73 m<sup>2</sup>であり、年齢層が進むにつれて慢性腎臓病ステージ(chronic kidney disease: CKD)3a, 3b, 4での腎生検例が増加し、60歳以後では20%以上を占めている(図2b)。この高齢化と女性比率の増加の要因に関しては、本症を自己免疫疾患として捉え直す意義のある抗PLA2R抗体の検討により今後明



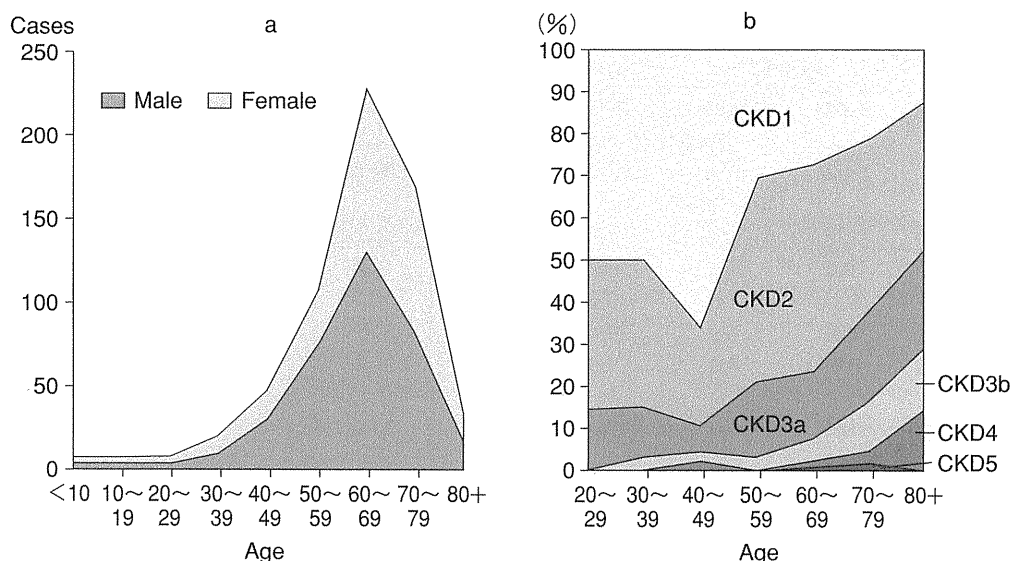


図 2 Age, gender (a) and CKD stages (b) of idiopathic membranous nephropathy in Japan  
J-RBR 2007~2010 registry : 633 cases in total : male 358 cases (56.6 %), female 275 cases (43.4 %)

表 2 Patient demographics of idiopathic membranous nephropathy in Japan (J-RBR 2007~2010)

	n	Min	Max	mean	SD
Age (years)	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
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 (g/gCr)	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.) (mL/min/1.73 m <sup>2</sup> )	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
HbA <sub>1c</sub> (%)	298	4.4	8.6	5.5	0.7

らかになると考えられる。尿蛋白量は、平均 3.99 g/日 (尿蛋白・クレアチニン比 5.57 g/gCr) と高く、「新たなネフローゼ症候群診断基準：尿蛋白排泄量が 3.5 g/日以上 (未測定の場合は、尿蛋白・クレアチニン比 3.5 g/gCr 以上) かつ血清アルブミン値 3.0 g/dL 以下もしくは血清総蛋白 6.0 g/dL 以下」により 444 例 (70.0 %) がネフローゼ状態にあった (図 3a)。一方、1 日尿蛋白定量が実施されていた 501 例

中 70 例 (14 %) が 1.0 g/日未満の軽症例であった。さらに、腎生検の適応の影響も考えられるが、ネフローゼ症候群の占める割合は年齢層が進むにつれて増加した (図 3b)。

なお、1 日尿蛋白定量によるハイリスク群 (8.0 g/日以上) は、501 例中 53 例 (10.6 % ; 男性 12.2 %, 女性 8.6 %) であった (表 3)。

血圧に関してみると、血圧と降圧薬服用が判明している

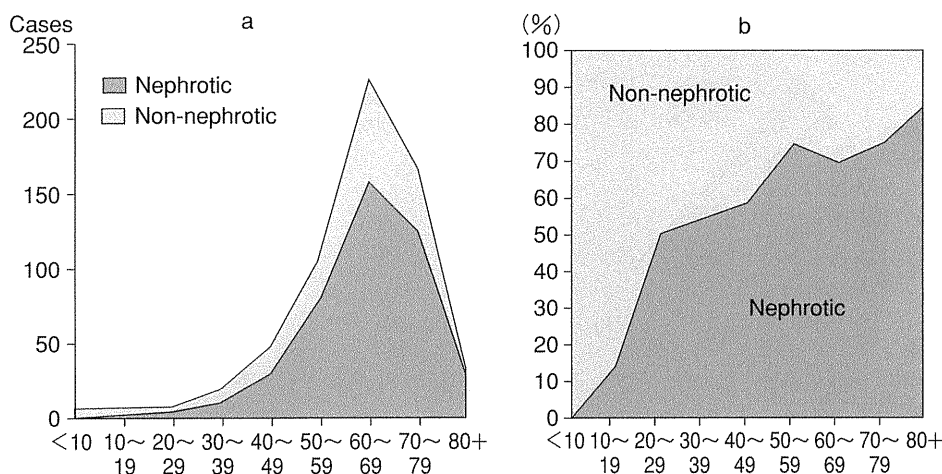


図 3 Nephrotic syndrome in idiopathic membranous nephropathy and age-related population

J-RBR 2007~2010 registry : nephrotic cases in 444 out of 633 cases (70.0 %)

表 3 Proteinuria of idiopathic membranous nephropathy in Japan (J-RBR 2007~2010)

Proteinuria(g/day)	Total		Male		Female	
	n : 501	(%)	n : 279	(%)	n : 222	(%)
<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 ( $\geq 8.0$ g/day)	53	10.6	34	12.2	19	8.6

455 例中で、高血圧(収縮期血圧 140 mmHg 以上あるいは拡張期血圧 90 mmHg 以上)あるいは降圧薬服用は 308 例 (67.7%) に認められた。さらに、降圧薬の有無を問わず CKD 診療ガイドラインにおける 1 日尿蛋白定量 1.0 g/日以上もしくは尿蛋白・クレアチニン比 1.0 g/gCr 以上で収縮期血圧 125 mmHg 以上あるいは拡張期血圧 75 mmHg 以上と、1 日尿蛋白定量 1.0 g/日未満もしくは尿蛋白・クレアチニン比 1.0 g/gCr 未満で収縮期血圧 130 mmHg 以上あるいは拡張期血圧 80 mmHg 以上の降圧コントロールが不十分な症例は、抽出された 482 例中 329 例 (68.3%) であった。一次性膜性腎症例では高率に高血圧を伴い、腎生検の時点ではそのコントロールが十分でない面が明らかとなった。

## ネフローゼ症候群における膜性腎症

### 1. 日本におけるネフローゼ症候群の病因解析

臨床分類登録上のネフローゼ症候群およびその他の臨床診断において「新しいネフローゼ症候群の診断基準」を満たした 2,322 例(うち J-RBR 2,066 例, J-KDR 216 例, その他 40 例; 男 1,326 例, 女 966 例; 年齢 1~94 歳, 平均 51.5 歳)が抽出され、一次性糸球体疾患が J-RBR 2,066 例中 1,203 例 58.2% (IgA 腎症 5.0% を含めると 63.2%) と最も多く、次いで二次性疾患として糖尿病性腎症 9.9%, ループス腎炎 6.1%, アミロイド腎 4.2% であった(図 4a)。一次性・二次性を合わせた病型分類では、微小糸球体変化 31%, 膜性腎症が 30%, メサングウム増殖性 11%, 巣状分節性硬化症 9%, 膜性増殖性 (I 型, III 型) 6%, 半月体形成性壊死性 2.3% であった。ネフローゼ症候群に占める膜性腎症の頻度は、金沢大学で観察された過去 40 年間の比

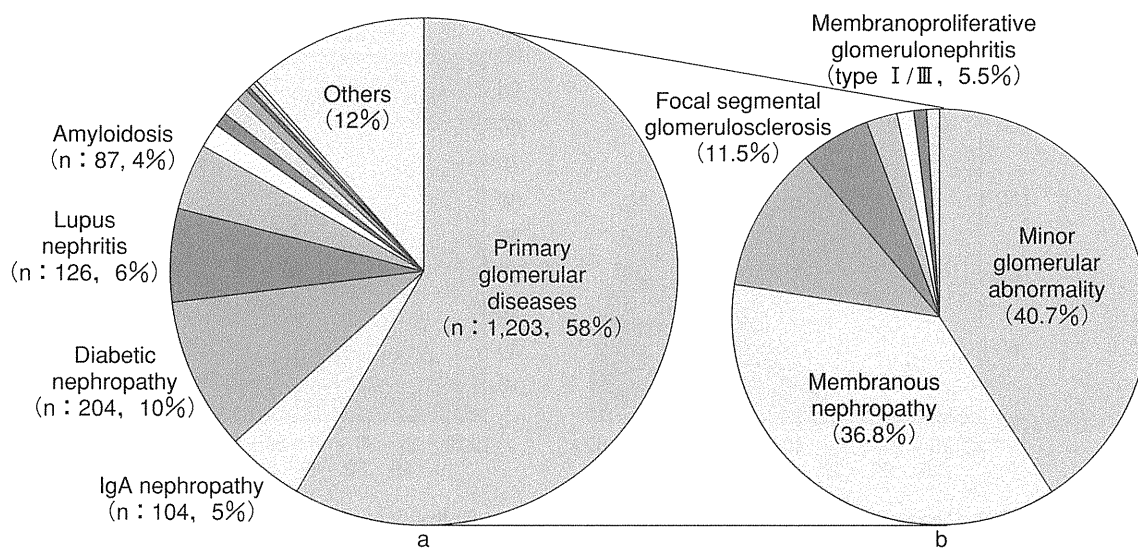


図 4 Glomerular lesions of nephrotic syndrome in Japan

J-RBR 2007~2010 registry : 2,066 cases in total, 1,203 cases in primary glomerular diseases  
 Membranous nephropathy shared in 37 % of idiopathic nephrotic syndrome in Japan.

表 4 Pathology in primary nephrotic syndrome including IgA nephropathy

	Japan		Korea <sup>16)</sup>		Brazil <sup>15)</sup>		USA <sup>17)</sup>		
Reported 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	1,013	36.8	34	57	23
IgAN	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

MCNS : minimal change nephrotic syndrome, PGN : proliferative glomerulonephritis

較においても約 25 % と大きな変化を認めない。

2. 一次性ネフローゼ症候群の病型と年齢層別分布：膜性腎症の臨床疫学

IgA 腎症を含まない一次性糸球体疾患 1,203 例の病型分類 (図 4b) では、微小糸球体変化 (微小変化型ネフローゼ症候群) が 40.7 %、膜性腎症 36.8 %、巣状分節性糸球体硬化

症 11.5 %、膜性増殖性糸球体腎炎 (I 型, III 型) 5.5 % であった。これを IgA 腎症を含むネフローゼ症候群において、韓国、ブラジルおよび米国 (人種別) と比較すると、アジア人 (日本, 韓国) では巣状分節性糸球体硬化症の頻度が低く、微小変化型の頻度が高いことが示される。また、IgA 腎症を含むネフローゼ症候群における膜性腎症の頻度は、わが

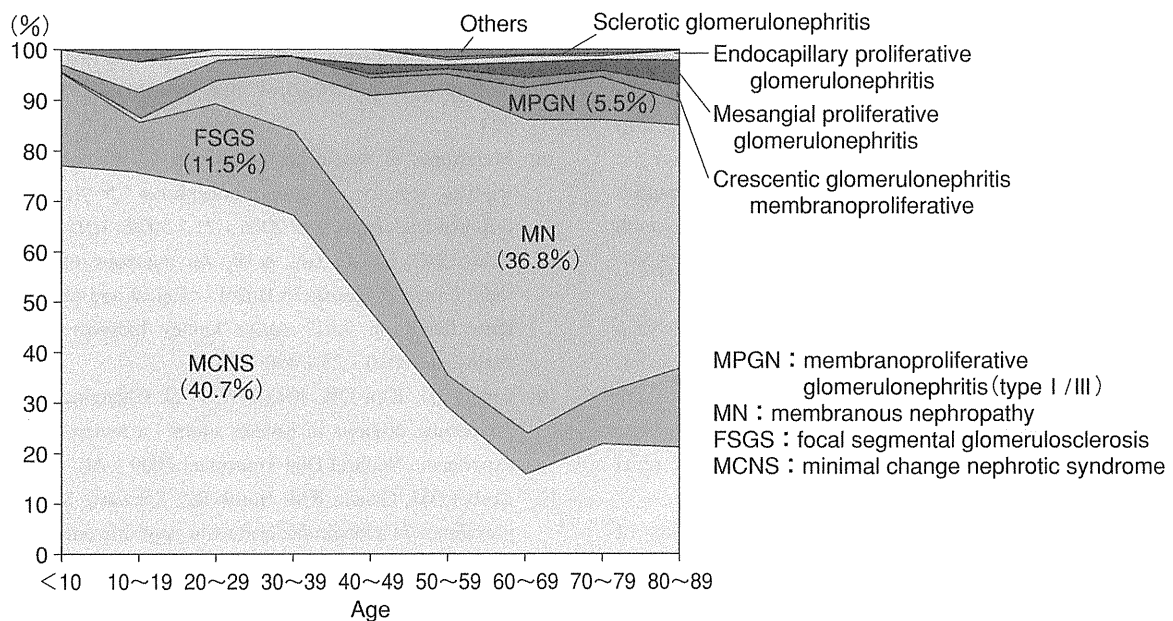


図5 Age related glomerular lesions of idiopathic nephrotic syndrome in Japan

J-RBR 2007~2010 registry : 1,203 cases in primary glomerular diseases except for IgA nephropathy

国において最も高かった(表4)。これは腎生検対象、特に後述する年齢(高齢化)を反映していると推測される。

年齢層別として10歳未満から90歳までの10歳毎に区別して登録された病因分類(図5)をみると、40歳未満では微小糸球体変化が77.0~67.4%を占めていた。一方、膜性腎症は主に20歳以後に登録され、50歳以後では48.3~61.9%の頻度であり、60歳以上の高齢者ネフローゼ症候群550例中317例(57.6%)と高かった。さらに、ネフローゼ症候群を伴う一次性膜性腎症443例における60歳以上の占める割合は317例(71.6%)であった。先の厚生労働省進行性腎障害調査研究班報告(1997~2001年, 1,008例)において、60歳以上(相対危険度1.98, 95%信頼区間1.20~3.28,  $p=0.008$ )が有意な腎不全危険因子であると指摘されており、本症の治療において高齢者の取り扱いが重要である<sup>7)</sup>。同じく、欧米でも予後危険因子として50歳以上、男性、ネフローゼ症候群、特に尿蛋白8~10g/日以上、血清クレアチニン値上昇が報告されており、予後因子としての年齢要素が確認されている<sup>1)</sup>。

以上より、日本人の膜性腎症、特に一次性膜性腎症は、その疫学的・臨床的背景から約半数が腎不全危険因子を持ち、さらに約10%が高リスク群であると考えられる。今後、高齢者を主体とする膜性腎症の治療を行うにあたって、これらの点を十分に考慮する必要がある。

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