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 UMIN000000618) 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 hypercholesteremia.

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 ± 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,

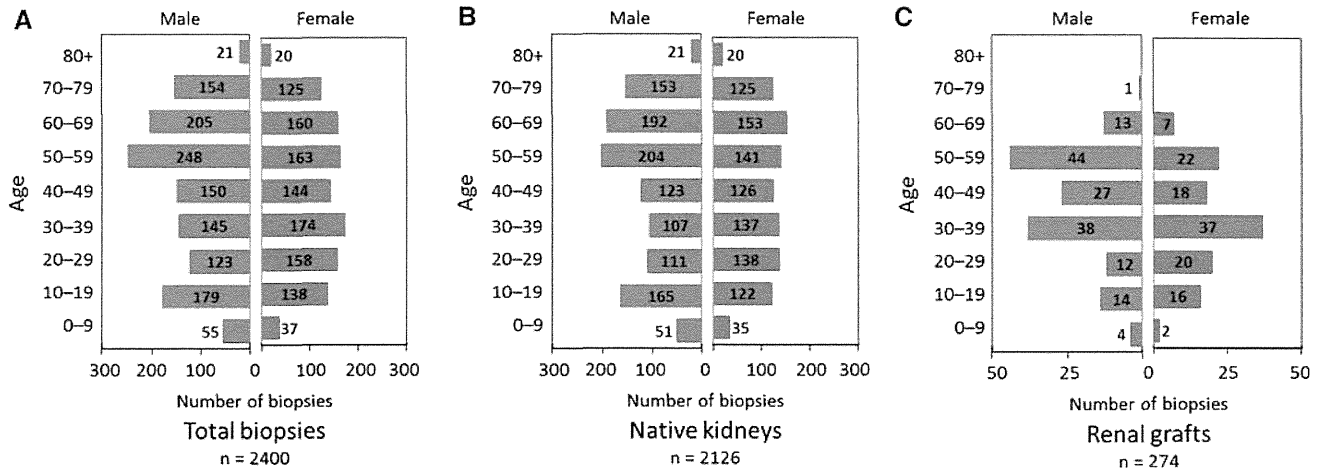


**Fig. 1** Distribution of age ranges and gender in total renal biopsies (**a**), native kidneys (**b**), and renal grafts (**c**) in the combined data of 2007 and 2008

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

| Classification | 2007 | | 2008 | | Total | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 (*n*) | 239 | 421 | 660 |
| Average age (y) | 36.5 ± 19.0 | 36.4 ± 18.2 | 36.4 ± 18.5 |
| Male (*n*) | 112 (46.9%)[a] | 219 (52.0%)[a] | 331 (50.2%)[a] |
| Average age (y) | 37.1 ± 18.9[b] | 37.2 ± 19.3[b] | 37.2 ± 19.1[b] |
| Female (*n*) | 127 (53.1%) | 202 (48.0%) | 329 (49.8%) |
| Average age (y) | 36.1 ± 19.2 | 35.4 ± 17.0 | 35.7 ± 17.8 |

[a] Ratio indicates percentage of each gender in each biopsy category

[b] 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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-INDICE. 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. Therafter 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 | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| 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 enroled 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.

**Acknowledgments** The authors greatly acknowledge the help and assistance of many colleagues in centers and affiliated hospitals with collecting the data. We also sincerely thank Ms. Mayumi Irie in the UNIN-INDICE for establishing and supporting the registration system of J-RBR. This study was supported by the committee grant from the Japanese Society of Nephrology and by a grant-in-aid from the Research Group on Progressive Renal Disease from the Ministry of Health, Labor and Welfare, Japan.

## Appendix

The following investigators participated in the project for developing the J-RBR:

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Clin Exp Nephrol (2011) 15:321–330
DOI 10.1007/s10157-011-0434-0

REVIEW ARTICLE

# Clinicopathological insights into lupus glomerulonephritis in Japanese and Asians

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Received: 4 December 2010 / Accepted: 28 February 2011 / Published online: 25 March 2011


**Abstract** Lupus nephritis comprises a spectrum of glomerular, vascular, and tubulointerstitial lesions, which has significant racial variation in severity and manifestations. The current classification (ISN/RPS 2003) has been improved successfully for the categorization of lupus glomerulonephritis (LGN). On the basis of this classification, 480 Japanese cases revealed the following distribution: class I 3%, class II 16%, class III 13%, class IV-S 11%, class IV-G 41%, class V 16%, and class VI 1%. Class IV-G with chronicity tended to have the worst renal outcome. Nephrotic syndrome was a more frequent complication in class IV-S (50%), class IV-G (72%), and class V (56%), with poor renal and actuarial outcomes. With regard to therapy, treatment options including glucocorticoids alone or combined with antimetabolites (azathioprine, mizoribine, mycophenolate mofetil), calcineurin inhibitors (cyclosporine A, tacrolimus), or alkylating agents (intravenous cyclophosphamide injection) improved the outcome of LGN; however, there is no high-grade clinical evidence from Japan. Further studies are needed to resolve the clinicopathological problems of LGN, especially IV-S, IV-G, and pure membranous lupus nephritis in Japanese patients.

**Keywords** Lupus nephritis · ISN/RPS2003 classification · Race · Japanese · Asian

**Abbreviations**

| | |
|---|---|
| AZP | Azathioprine |
| CsA | Cyclosporine A |
| IVCY | Intravenous cyclophosphamide injection |
| LGN | Lupus glomerulonephritis |
| MLN | Membranous lupus nephritis |
| MZB | Mizoribine |
| MMF | Mycophenolate mofetil |
| Tac | Tacrolimus |

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## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with the characteristic development of autoantibodies to double-strand DNA and other nuclear antigens, as well as to membrane molecules such as phospholipids. About 20–50% of patients with lupus are reported to have abnormal urine test results in their early disease courses, and up to 60% of adults may go on to develop overt renal abnormalities [1]. Renal injuries in lupus nephritis comprise a spectrum of glomerular, vascular, and tubulointerstitial lesions, which may mainly result from circulating or in situ immune complex formation. Although lupus nephritis is strongly associated with substantial morbidity and early mortality, there is significant racial variation in the severity and manifestations of renal pathological lesions and clinical response to therapies [2–5]. The current classification (ISN/RPS 2003) has been improved successfully in terms of categorization and terminology for glomerular lesions in order to standardize the interpretation and reports of renal biopsies [6, 7].

In this review article, the current epidemiology, renal pathological diagnoses according to the ISN/RPS 2003 classification, clinical outcomes, and therapy of lupus nephritis in Japanese and other Asians are summarized.

## Epidemiology of lupus nephritis in Japan

The incidence rate of SLE in Okinawa (Japan) was 0.9 (1.6 for females, 0.4 for males) per 100,000 persons, and the prevalence of SLE from 1972 to 1991 increased from approximately 3.7 to 37.7 [8]. The number of SLE patients registered for a nationwide medical care study of intractable diseases in Japan reached 56,272 in 2008 (Fig. 1a).

With regard to lupus nephritis, nephritis has been reported in 31–65% of lupus cases in the USA and European countries, and in 45–86% of lupus cases in Japan. In the USA, Asian Americans, predominantly Chinese, were more likely to develop lupus nephritis than European Americans (hazard ratio 1.8, 95% confidence interval 1.6–1.9). The risk of lupus nephritis was greatest during the first few years after SLE diagnosis; however, the plateau in risk of lupus nephritis may occur up to 8 years following lupus diagnosis, and the nephritis-free survival of Asian Americans was only 33% [2]. In the cohort study of the Euro-Lupus Project, a cohort composed of 1,000 patients with SLE has been followed prospectively since 1991. Within the first 5 years (1990–1995), 222 cases (22.2%) had the complication of lupus nephritis; however, only 57 of 840 cases (6.8%) had nephritis in the next 5 years (1995–2000) [9]. From the registration data (J-RBR/J-KDR) of the Japanese Society of Nephrology for 2007–2009, 222 out of 5,703 renal biopsied cases, except for those with transplanted kidneys (3.5%), and 54 of 1,294 nephrotic cases (4.5%) were diagnosed with lupus nephritis. Even in the cohort of renal biopsied cases in the twenty first century, 54 of 222 (24.3%) Japanese patients with SLE had severe lupus nephritis.

From 1950 to 1980, lupus nephritis was strongly associated with early mortality, including in Japan; however, from 1980 to 2010, the outcome for SLE greatly improved to over 96% in terms of 5-year renal survival. The registered cases of end-stage renal failure (ESRF) due to lupus nephritis in The Annual Report of Regular Dialysis Treatment in Japan by the Patient Registration Committee, Japanese Society for Dialysis Therapy, numbered consistently around 300 per year (0.8–1.0% of total ESRF cases) in the most recent decade. On the other hand, the average age of ESRF patients who needed hemodialysis owing to lupus nephritis changed from 40 to 61 years old in the past 2 decades. Similarly,the prevalence of patients on hemodialysis due to lupus nephritis has increased from 285 with a mean age of 42 years old to 2,280 with a mean age of 58 years old in Japan since 1988 (Fig. 1b) [10].

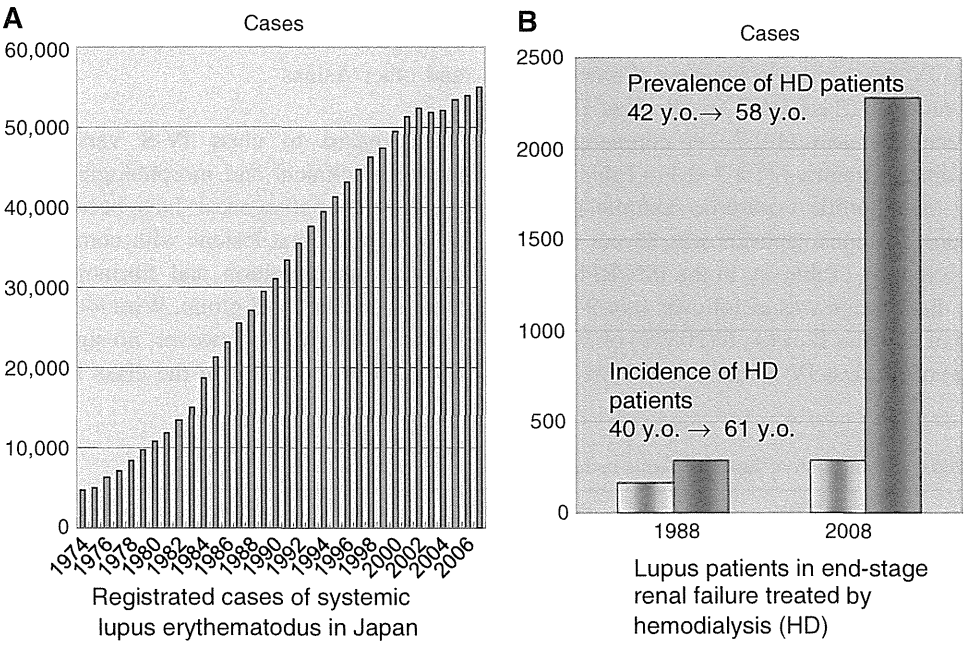


**Fig. 1** The prevalence of patients with systemic lupus erythematosus (SLE) and the incidence and prevalence of end-stage renal failure due to lupus nephritis from 1974 to 2008. **a** The SLE patients registered for a nationwide medical care study of intractable diseases in Japan numbered 56,272 by 2008. **b** Lupus patients with end-stage renal failure (ESRF) treated by hemodialysis (HD). The registered cases of ESRF by lupus nephritis numbered about 300 cases per year (0.8–1.0% of total ESRF cases) in the last decade. On the other hand, the average age of ESRF patients who needed HD owing to lupus nephritis changed from 40 to 61 years old in the past 2 decades. Similarly, the prevalence of patients who needed HD due to lupus nephritis increased from 285 with a mean age of 42 years old to 2,280 with a mean age of 58 years old in Japan from 1988 to 2008

## Assessments for the ISN/RPS 2003 classification of lupus glomerulonephritis (LGN) in Japan and Asia

The ISN/RPS 2003 classification has achieved its goal of improved inter-observer reproducibility. As it gains widespread acceptance, the ISN/RPS 2003 classification is already providing a standardized approach to renal biopsy interpretation needed to compare outcome data across centers [6, 7, 44, 45].

### Clinicopathology of LGN in Japan and Asia

The prevalence of each pathological class as summarized in Tables 1 and 2 is based on reports from Japan, China, South Korea, USA, European countries, and the database of J-RBR/J-KDR.

In renal biopsied cases at Kanazawa University Hospital (60 cases) and Kanazawa Medical University Hospital (31 cases), the populations of each class were similar in the two cohorts, except for the 9 cases of class I (15%) at Kanazawa University (class II 16%, III 16%, IV-S/IV-G 45–50%, V 20%) [11, 12]. Reports from Gunma University [13] and Okayama University [14] also showed similar distributions of pathological diagnoses in ISN/RPS 2003 classification. In addition to these data, 480 Japanese cases including 198 cases in the J-RBR database revealed the following distribution: ISN/RPS 2003 class I 3.1%, class II 16.0%, class III 12.9%, class IV-S 10.6%, class IV-G 40.6%, class V 15.6%, and class VI 1.0% [15] (Table 1). In addition, the population of class IV was similar in Japanese, Chinese and other races. The ratio of Class IV-G in all class IV was much higher in Asian countries (1:2.7–7.6) compared with the USA and European countries (1:1.3–2.1) (Table 2).

The frequency of nephrotic syndrome complication in Japanese biopsy-proven lupus nephritis was 83 out of 183 cases (45.4%) in 3 reports (Table 3). In the ISN/RPS 2003 classification, the distribution was as follows: 0 of 9 class I cases, one (3.7%) of 27 class II cases, 6 (20.7%) of 29 class III cases, 11 (50%) of 22 class IV-S cases, 51 (71.8%) of 71 class IV-G cases, and 14 (56%) of 25 class V cases. The frequency of nephrotic syndrome in class IV-G was similar in China (84 out of 119 cases, 70.6%) [20]. The outcome for patients with nephrotic syndrome ($n = 30$) was significantly poorer than that for patients without nephrotic syndrome ($n = 56$) (Fig. 2) [15]. Nephrotic syndrome was a significant risk factor regarding patient survival (hazard ratio 3.85, $p = 0.0418$) with a mean 50% renal survival time of $200 \pm 29$ months in the cohort of Kanazawa University [11].

As for therapeutic response, Class IV-S and IV-G had relatively lower response rates compared to other classes. Japanese patients with class IV-G or IV-S and those treated by intravenous cyclophosphamide (IVCY) in China and South Korea had a better remission rate compared to that of the USA (Table 4).

Finally, the proportion of Kanazawa University patients with the final outcome judged as ESRF were 82% at 10 years and 80% at 20 years. Finally, 10 patients (17%) progressed to ESRF from 24 to 278 months after the first renal biopsy [11]. These findings were supported by other reports: renal dysfunction was found in one (6%) of 16 class III cases, one (7%) of 14 class IV-S cases, and five (12%) of 41 class IV-G cases, especially IV-G (A/C), at Gunma University [13], and in one (11%) of 9 class III, one (5%) of 20 class IV-S, nine (20%) of 45 class IV-G, and two (25%) of class V patients at Okayama University [14].

### Pathogenesis of class IV-S and IV-G in Japanese and other Asians

With regard to class IV-S versus class IV-G lupus nephritis, clinical and morphological differences suggesting different pathogenesis have been discussed. Mittal et al. [16] reported that lesions with combined segmental endocapillary proliferation and fibrinoid necrosis were more frequent in the IV-S group. Wire loops were more common in the IV-G group. However, no significant difference was detected in outcomes in the class IV-S and IV-G groups.

**Table 1** ISN/RPS 2003 classification of lupus nephritis in Japanese

| | Total/Class | I | II | III[a] | IV-S[a] | IV-G[a] | V[a] | VI | References |
|---|---|---|---|---|---|---|---|---|---|
| Kanazawa Univ. | 60 | 9 | 10 | 8 | 6 | 17 | 10 | 0 | [11] |
| Kanazawa Med Univ. | 31 | 0 | 5 | 5 | 2 | 13 | 6 | 0 | [12] |
| Gunma Univ. | 92 | 0 | 12 | 16 | 14 | 41 | 9 | 0 | [13] |
| Okayama Univ. | 99 | 3 | 13 | 9 | 20 | 45 | 8 | 1 | [14] |
| J-RBR | 198 | 3 | 37 | 24 | 9 | 79 | 42 | 4 | [15] |
| Total | 480 | 15 | 77 | 62 | 51 | 195 | 75 | 5 | |
| Percentage | | 3.1 | 16.0 | 12.9 | 10.6 | 40.6 | 15.6 | 1.0 | |

[a] Most of combined cases III + V and cases IV + V are included in the class III and class IV, respectively

**Table 2** ISN/RPS 2003 classification of lupus nephritis in Japanese, Asians and other races

| Countries | Racial background | Total | I | II | III | IV (S:G ratio) | IV-S | IV-G | V | VI | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Japan | Japanese | 480 | 15 | 77 | 62 | 246 | 51 | 195 | 75 | 5 | [15] |
| | | (%) | 3.1 | 16.0 | 12.9 | 51.3 (1:3.8) | 10.6 | 40.6 | 15.6 | 1.0 | |
| China | Chinese | 327 | ND | ND | ND | 172 | 20 | 152 | ND | ND | [19, 20] |
| | | (%) | ND | ND | ND | 52.6 (1:7.6) | 6.1 | 46.5 | ND | ND | |
| South Korea | Korean | ND | ND | ND | ND | 42 | 12 | 32 | ND | ND | [42] |
| | | (%) | ND | ND | ND | ND (1:2.7) | ND | ND | ND | ND | |
| France | #1 | 71 | ND | ND | ND | 46 | 15 | 31 | ND | ND | [17] |
| | | (%) | ND | ND | ND | 64.8 (1:2.1) | 21.1 | 43.7 | ND | ND | |
| USA | #2 | 70 | ND | ND | ND | 33 | 11 | 22 | ND | ND | [16] |
| | | (%) | ND | ND | ND | 47.1 (1:2) | 15.7 | 31.4 | ND | ND | |
| United Kingdom | ND | 507 | 52 | 64 | 62 | 233 | ND | ND | 96 | 3 | [43] |
| | | (%) | 10.3 | 12.6 | 12.2 | 46.0 (ND) | ND | ND | 18.9 | 0.6 | |
| USA | ND | 541 | 5 | 54 | 107 | 198 | 87 | 111 | 159 | 18 | [45] |
| | | (%) | 0.9 | 10.0 | 19.8 | 36.6 (1:1.3) | 16.1 | 20.5 | 29.4 | 3.3 | |

*ND* not described

#1: White 63.3%, North African 17.4%, Black 10.9%, Asian 8.7%

#2: White 40.0%, Black 30.3%, Hispanic 24.2%, Asian 9.1%

**Table 3** Nephrotic cases in ISN/RPS 2003 classes of Japanese lupus nephritis

| Cases | Total | Class | | | | | | References |
|---|---|---|---|---|---|---|---|---|
| | | I | II | III | IV-S | IV-G | V | |
| Kanazawa Univ. | 60 | 9 | 10 | 8 | 6 | 17 | 10 | [11] |
| Nephrotic cases (%) | 21 (35) | 0 | 0 | 1 (13) | 4 (67) | 10 (59) | 6 (60) | |
| Kanazawa Med Univ. | 31 | 0 | 5 | 5 | 2 | 13 | 6 | [12] |
| Nephrotic cases (%) | 11 (35) | 0 | 0 | 0 | 1 (50) | 8 (62) | 2 (33) | |
| Gunma Univ. | 92 | 0 | 12 | 16 | 14 | 41 | 9 | [13] |
| Nephrotic cases (%) | 51 (55) | 0 | 1 (8) | 5 (31) | 6 (43) | 33 (80) | 6 (67) | |
| Total in Japanese | 183 | 9 | 27 | 29 | 22 | 71 | 25 | |
| Nephrotic cases (%) | 83 (45) | 0 (0) | 1 (4) | 6 (21) | 11 (50) | 51 (72) | 14 (56) | |

Alternatively, Hill et al. [17] suggested that class IV-G lesions behave as an immune complex disease. However, in class IV-S lesions, the presence of a greater proportion of glomerular fibrinoid necroses and lack of correlation with the extent of immune deposits suggest that these lesions may have a different pathogenesis. On this issue, Behara et al. [18] reported that a paucity of peripheral immune aggregates is seen in severe segmental lupus nephritis (SSGN), which suggests a mechanism of glomerular injury in SSGN that is separate from the generally accepted unitary concept of immune complex deposition in lupus nephritis.

For Japanese, different findings were reported in terms of clinical outcomes in the class IV-S and IV-G groups in 4 reports [11–14]. The mean 50% renal survival time of class IV cases at initial renal biopsy was 189 ± 29 months, and patients in class IV-S tended to have a poorer prognosis (95 ± 22 months for IV-S vs. 214 ± 35 months for IV-G, $p = 0.1495$) at Kanazawa University. However, repeat renal biopsy revealed alteration transition from class IV-S to IV-G in ESRF cases in this cohort [11]. In the class IV group of Okayama University, the class IV-G group tended to exhibit a worse renal outcome than the class IV-S group, but the difference was not significant ($p = 0.433$). In this cohort, independent histological predictors of poor renal outcome were extracapillary proliferation as active lesion, glomerular sclerosis, and fibrous crescents as chronic lesion [14]. Renal function was more likely to deteriorate in class IV-G cases than in class IV-S cases at Gunma University ($p = 0.685$) [13]. In addition, when class IV-G

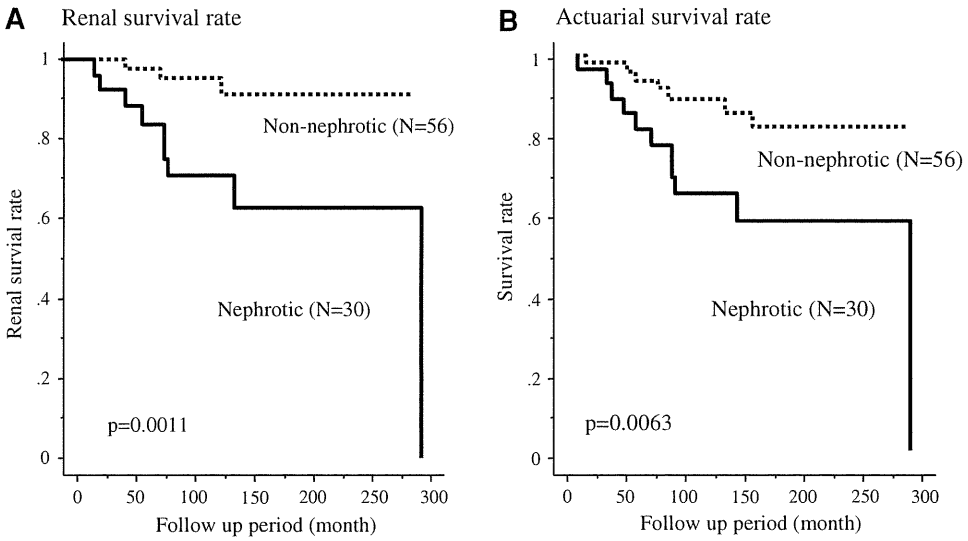


**Fig. 2** The outcome of patients with nephrotic syndrome. The outcome of patients with nephrotic syndrome ($n = 30$) was significantly poorer than that of patients without nephrotic syndrome ($n = 56$). Nephrotic syndrome was a significant risk factor related to patient survival (hazard ratio 3.85, $p = 0.0418$) with a mean 50% renal survival time of 200 ± 29 months at Kanazawa University

**Table 4** Remission rate in ISN/RPS 2003 classes of lupus nephritis in Japan, Asian and USA

| Cases | Total | Class | | | | | | Follow-up mean, months (range) | References |
|---|---|---|---|---|---|---|---|---|---|
| | | I | II | III | IV-S | IV-G | V | | |
| Kanazawa Univ. | 60 | 9 | 10 | 8 | 6 | 17 | 10 | 187 (1–366) | [11] |
| Remission cases (%)[a] | 47 (78) | 9 (100) | 10 (100) | 8 (100) | 2 (33) | 11 (65) | 7 (70) | | |
| Kanazawa Med Univ. | 31 | 0 | 5 | 5 | 2 | 13 | 6 | 117 (1–348) | [12] |
| Remission cases (%)[a] | 29 (94) | ND | 5 (100) | 5 (100) | 1 (50) | 12 (92) | 6 (100) | | |
| Gunma Univ. | 92 | 0 | 12 | 16 | 14 | 41 | 9 | 65 (12–275) | [13] |
| Remission cases (%)[a] | 75 (81) | ND | 11 (92) | 14 (88) | 11 (79) | 30 (73) | 9 (100) | | |
| Subtotal in Japanese | 183 | 9 | 27 | 29 | 22 | 71 | 25 | 114 (1–366) | [11–13] |
| Remission cases (%)[a] | 151 (83) | 9 (100) | 26 (96) | 27 (93) | 14 (64) | 53 (75) | 22 (88) | | |
| China (Peking Univ.) | 172 | ND | ND | ND | 20 | 152 | ND | 53 | [19] |
| Remission cases (%) | 153 (89)[b] | ND | ND | ND | 17 (85)[b] | 136 (89)[b] | ND | ND | |
| South Korea (Univ. Ulsan) | 42 | ND | ND | ND | 12 | 30 | ND | ND | [43] |
| Remission cases (%) | 36 (86)[c] | ND | ND | ND | 11 (92)[c] | 25 (83)[c] | ND | ND | |
| USA | 32 | ND | ND | ND | 10 | 22 | ND | 50 (0.6–149) | [16] |
| Remission cases (%) | 5 (16) | ND | ND | ND | 2 (20) | 3 (14) | ND | | |

*ND* not determined

[a] Remission was defined by complete remission (CR) or incomplete remission with daily proteinuria below 1.0 g

[b] CR 5 (25) cases (%) + partial remission 12 (60) cases (%) in class IV-S and CR 34 (22) cases (%) + partial remission 80 (53) cases (%) in class IV-G

[c] CR 8 (67) cases (%) + partial remission 3 (25) cases (%) in class IV-S and CR 10 (33) cases (%) + partial remission 15 (50) cases (%) in class IV-G

was subdivided into cases involving active lesion alone (IV-G (A)) and/or chronic lesion (IV-G (A/C)), the majority of cases of IV-G (A) were nephrotic, but responded well to therapy. In contrast, renal function declined only in class IV-G (A/C) cases. Patients in class IV-G (A/C) had persistent proteinuria in spite of intensified therapies. Moreover, the higher proportion of chronic lesions was related to the deterioration of renal function. Overall, the class IV-G group, especially those with chronicity, tended to have a worse renal outcome than the class IV-S group in Japan.

With regard to class IV-G and IV-S lupus nephritis in other Asians, Yu et al. [19] reported that, in 172 Chinese patients including 152 cases with class IV-G and 20 cases with class IV-S, the level of proteinuria was milder, serum creatinine was lower, and serum C3 was higher in class

IV-S patients. On pathological evaluation, the proportion of glomerular fibrinoid necrosis and the frequency of serum anti-neutrophil cytoplasmic antibody (ANCA) were higher in class IV-S cases (20% of class IV-S vs. 4.6% of class IV-G).

In addition, the same study group analyzed 152 Chinese class IV-G cases including 109 patients (71.7%) with nephrotic syndrome and 33 patients (21.7%) with crescentic glomerulonephritis. In patients with crescentic lupus nephritis, activity scores, chronicity indexes, relapse rates, and the frequency of positive serum ANCA (10 cases out of 33 cases, 30%) were each significantly higher, whereas complete remission rates and renal outcomes, over a mean follow-up of 4 years, were significantly poorer [20]. This suggested the key role of ANCA in the pathological course of crescentic formation and/or fibrinoid necrosis, even in class IV-G lupus nephritis.

On the other hand, with regard to ANCA involvement in Japanese lupus nephritis, there were only a few case reports of lupus nephritis with extracapillary lesions and positive serum myeloperoxidase (MPO)-ANCA [46, 47]. Suzuki et al. [48] analyzed the epitopic specificity of MPO-ANCA, and found that MPO-ANCA recognizing specific regions of the N-terminus of the MPO H-chain confer an increased risk of vasculitis, while SLE sera (4 cases) reacted to all epitopes. These results suggest that the epitopic specificity of MPO-ANCA differentiates vasculitic syndromes associated with kidney involvement from non-vasculitic syndromes associated with MPO-ANCA positivity.

There are some differences in clinical and pathological manifestations between class IV-S and IV-G lupus nephritis even in Asians, which warrant further investigation of pathogenesis, especially between ANCA-positive class IV (with fibrinoid degeneration and/or crescents) and ANCA-negative class IV cases (mainly with endocapillary proliferation and/or wire loop lesion) among Japanese and other Asian patients.

## Membranous LGN (membranous lupus nephritis (MLN), ISN/RPS2003 class V)in Japanese and other Asians

Few published studies have specifically reported on the long-term outcomes in terms of actuarial survival of patients with ESRF and renal survival without dialysis in MLN and MLN subgroups [21]. We studied 22 Japanese class V cases (20 females and 2 males, 17 de novo cases and 5 relapsed cases), among which 5 cases (22.7%) were combined with proliferative lesions of class IV-G or class IV-S and 14 cases (64%) involved nephrotic syndrome. In the clinical course, 8 cases (36%) showed prolonged massive proteinuria, and only 12 cases (55%) were improved in terms of daily proteinuria below 1.0 g (incomplete remission type I) by immunosuppressive therapy. Three cases (14%) with clinical relapse of nephrotic syndrome and superimposed class IV-G progressed to ESRF (unpublished data).

A recent retrospective analysis of 100 adult Chinese patients (90 females and 10 males) with biopsy-proven MLN revealed that renal survival rates at 5 and 10 years were 96.1 and 92.7%, respectively. Severe tubulointerstitial lesion, nephrotic range proteinuria, and refractoriness to treatments were independent risk factors for developing ESRF. Twenty-one patients underwent a repeat biopsy after a 33-month follow-up; 8 (38.1%) of these patients had been transformed (5 to class V + IV, 2 to class V + III, and 1 to class VI), while 3 patients had progressed to ESRF [22].

Mixed proliferative and MLN adult patients had a poor prognosis compared with those with pure MLN; however, there was no predictor of unresponsiveness to therapy and/or persistent heavy proteinuria in pure MLN. Thus, further studies are needed to resolve the clinical problems of pure MLN in Japanese and other Asians.

## Additional glomerular lesions in lupus nephritis

The ISN/RPS2003 classification of LGN including glomerular lesions was: (1) endocapillary proliferative lesions composed of cellular infiltration and glomerular cell proliferation combined with wire loop lesions and/or hyaline thrombi caused by circulating immune-complexes, (2) extracapillary lesions with or without fibrinoid necrosis (sometimes accompanied by ANCA), and (3) in situ formed immune-complex deposition on subepithelial and/or intramembranous regions. In addition to these well-known pathological lesions, there is thrombotic microangiopathy (TMA) or lupus podocytopathy without any immune-complex deposition (Fig. 3). TMA was found in cases with anti-phospholipid antibody or cases treated with drugs such as calcineurin inhibitors. Podocytopathy that resembled minimal change nephritic syndrome or collapsing glomerulopathy has been reported in SLE or SLE-like disease, especially in African Americans [23–25]. With regard to podocytopathy, bisphosphonates that induced collapsing glomerulopathy or focal segmental glomerulosclerosis were found in Caucasians and also in Japanese [25, 26]. Recently, we also encountered a nephrotic Japanese patient with class V lupus nephritis superimposed with collapsing glomerulopathy caused by oral pamidronate intake (unpublished data).

In future, we should define the clinicopathological impacts of these atypical pathological lesions— TMA and podocytopathy in Japanese and Asians.

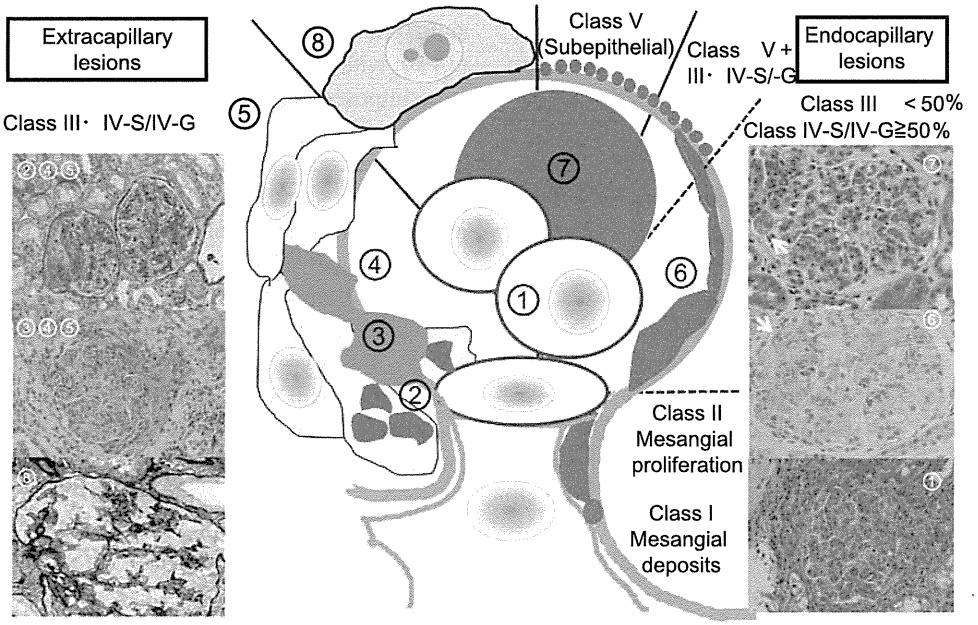


**Fig. 3** The schema of pathological lesions of lupus glomerulonephritis. The ISN/RPS2003 classification of lupus glomerulonephritis that includes glomerular lesions was (1) endocapillary proliferative lesions composed of cellular infiltration and glomerular cell proliferation combined with wire loop lesions and/or hyaline thrombi caused by circulating immune-complexes, (2) extracapillary lesions with or without fibrinoid necrosis (sometimes accompanied by ANCA), and (3) in situ formed immune-complex deposition on subepithelial and/or intramembranous regions. In addition to these well-known pathological lesions, there is thrombotic microangiopathy (TMA) or lupus podocytopathy without any immune-complex depositions. **1**: Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction. **2**: Karyorrhexis. **3**: Fibrinoid necrosis. **4**: Rupture of glomerular basement membranes. **5**: Crescents, cellular or fibrocellular. **6**: Subendothelial deposit identifiable by LM (wireloops). **7**: Intraluminal immune aggregates (hyaline thrombi). **8**: Podocytopathy

## Recent advances in therapy of LGN

There are also significant racial differences in the clinical response to therapies for LGN.

### Proliferative LGN (ISN/RPS 2003 classification class IV-G/IV-S and III)

As a standard therapeutic regimen for proliferative LGN, IVCY or combination therapy with methylprednisolone (MPSL) pulse therapy has been widely accepted since the 1980s on the basis of data from the National Institutes of Health (NIH) [27, 28]. However, there were considerable risks for adverse effects, including gonadal toxicity for females of child-bearing age and malignancies, especially bladder cancer [28].

More recent studies have focused on mycophenolate mofetil (MMF) [29, 30] and calcineurin inhibitors (cyclosporine and tacrolimus) to avoid these adverse effects of cytotoxic drugs. In the ALMS study, there was no difference in response rate, adverse events, or infection between MMF and IVCY in Asians (53.2 vs. 63.9%) [5, 31]. With regard to tacrolimus (Tac), a multi-target study in China has shown that tacrolimus in combination with MMF and prednisolone is beneficial in the treatment of proliferative lupus nephritis [32].

As for Japan, there has been no randomized controlled study for IVCY or MMF. However, Matsuyama et al. reported on the long-term prognosis of lupus nephritis patients treated with IVCY (500 mg or 750 mg) every month for 2 to >6 months. This included a total of 67 Japanese patients, who were divided into the following 3 groups: patients with fresh nephritis (Group A), patients with relapse nephritis (Group B), and patients with nephritis as a transition of the main clinical manifestation (Group C). They found that the rate of remission was 78%, and Group A revealed a significantly higher rate of remission than the other groups. The combination of MPSL pulse therapy with IVCY revealed a moderate increase of remission rate in Group A. There was no adverse effect at late onset. They concluded that the long-term prognosis of IVCY differed according to the patient's clinical course, and the result differed from those reported in other countries [33]. Therefore, we should consider the racial specificity in lupus nephritis treatment for Japanese subjects.

With regard to antimetabolites, there has been no randomized, controlled trial, except for on mizoribine (MZB).

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.

**Acknowledgments** The authors greatly acknowledge the help and assistance of many colleagues in centers and affiliated hospitals who helped with the collection of data for J-RBR/J-KDR. This study was supported in part by the committee of the Japanese Society of Nephrology, a Grant-in-Aid for Progressive Renal Disease Research, from the Ministry of Health, Labour and Welfare of Japan, and Grants-in-Aid for Scientific Research (C) 19590967 (HY) and 22590902 (HY).

**Conflict of interest** The authors of this manuscript have no conflicts of interest to disclose.

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Clin Exp Nephrol (2011) 15:539–545
DOI 10.1007/s10157-011-0428-y

ORIGINAL ARTICLE

# The relationship between renal volume and renal function in autosomal dominant polycystic kidney disease

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Received: 10 February 2010 / Accepted: 17 February 2011 / Published online: 24 March 2011


**Abstract**
*Background* In patients with autosomal dominant polycystic kidney disease (ADPKD), renal cysts grow exponentially. Since remaining renal parenchyma has a capacity to compensate for the loss of glomerular filtration, the glomerular filtration rate (GFR) may be sustained until the disease progresses. The purpose of this study was to determine if renal volumetric indices and clinical parameters are associated with renal function in Japanese patients with ADPKD.
*Methods* In 73 ADPKD patients (28 men, 45 women), the associations of mean systolic blood pressure, mean diastolic blood pressure, estimated GFR (eGFR), the amount of proteinuria and albuminuria, body mass index (BMI), brachial-ankle pulse wave velocity (baPWV), ankle-brachial index, and total kidney volume (TKV) were retrospectively analyzed.
*Results* Multivariate linear regression analysis showed that eGFR was significantly and independently inversely correlated with patients' age and BMI. The median change in eGFR per year (ΔeGFR/y) was −2.8 ml/min/1.73 $m^2$/year. Multiple linear regression analysis showed that ΔeGFR/y was significantly and independently inversely correlated with the change in TKV per year (ΔTKV/y). Multiple linear regression analysis showed that ΔTKV/y was significantly related to initial TKV and the change in albuminuria per year.
*Conclusions* This study demonstrated a significant relationship between the change in renal function and the change in renal volume in Japanese ADPKD patients without renal insufficiency. It is possible that the volume measurements can be used as useful markers for disease progression in Japanese ADPKD patients.

**Keywords** Autosomal dominant polycystic kidney disease · Renal function · Renal volume · Marker

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## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common progressive hereditary kidney disease affecting all ethnic groups worldwide, with an incidence of 1:500–1:1000. Typically, only a few renal cysts are detected in most affected individuals before 30 years of age; however, by the fifth decade of life, hundreds to thousands of renal cysts are found in the majority of patients. Renal cysts grow exponentially in ADPKD [1]. This continuous growth and expansion of cysts leads to progressive, grotesque, renal enlargement and subsequent loss of renal function [2]. End-stage renal failure requiring renal replacement therapy occurs in approximately 50% of patients and typically develops in the sixth decade of life [3]. However, renal insufficiency is usually not detected until the fifth or sixth decade of life. Since the remaining kidneys have a capacity to compensate for the loss of glomerular filtration in ADPKD patients, the renal function remains stable for many years, but there is a sharp decline in the glomerular filtration rate (GFR) once a critical expansion of renal cysts is reached [4, 5]. GFR, the usual biomarker of renal disease progression, does not decrease substantially until extensive and irreversible damage to noncystic parenchyma occurs. Therefore, it is necessary to identify some reliable biomarkers to follow the progression of this disease [6]. Modeling experiments using prospective