s-suPAR in FSGS, even for patients showing favorable responses to treatments. On the other hand, s-suPAR rapidly decreased within the 2-month period in MCNS, suggesting that the 2-month s-suPAR reduction rate serves as an index to differentiate MCNS.

We also investigated u-suPAR as a clinical marker in primary NS. Pretreatment u-suPAR was significantly higher in the primary NS and ANCA-GN groups. In contrast to recent findings [5], no significant differences were noted between the primary NS and ANCA-GN groups, or among the disease types of primary NS (FSGS, MCNS, and MN). Since pretreatment u-suPAR positively correlated with UP in all primary NS, similar to previous findings [6], we suspected that u-suPAR may be the only initial indication of UP. However, u-suPAR only decreased after treatments were received by non-intractable NS and MCNS patients, but not by FSGS or MN patients. Thus, we assessed whether changes in u-suPAR could be used to differentiate non-intractable NS from intractable NS or MCNS from FSGS. A ROC analysis revealed that Δ2M u-suPAR was a useful marker for differentiating non-intractable NS from intractable NS or MCNS from FSGS. Huang et al. [5] also reported higher u-suPAR levels in the cellular variant and significant decreases in u-suPAR, even in primary FSGS patients with complete remission. In our study, tip lesions were detected in the majority of FSGS patients. Hence, further investigations are needed to resolve the issue of u-suPAR in MCNS and the different pathological lesions of FSGS such as tip lesions and the cellular variant.

In conclusion, s- or u-suPAR may be useful as an index of treatment responses by patients with primary NS for the differentiation of MCNS from FSGS, but not in pretreatment patients. In addition, our study revealed that s- and u-suPAR were associated with the long-term therapeutic responses of all primary NS patients including those with MCNS, FSGS, MN and MPGN. S- and u-suPAR were significantly decreased in MCNS after therapy and could be used to differentiate MCNS from FSGS. In addition, s-, but not u-suPAR levels before therapy may be useful for judging the clinical severity of and crescent formation in ANCA-GN. The ELISA system used in this study only measured the complete form of suPAR; however, several splicing forms and different glycosylation forms are known to exist. Thus, it is also possible that the molecular size or glycosylation of suPAR differs among these diseases, and differences in physiological activity due to these variations in suPAR may lead to differences in the renal histological phenotype. These issues need to be investigated in future studies.

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ORIGINAL ARTICLE

Clinical manifestations of Henoch–Schönlein purpura nephritis and IgA nephropathy: comparative analysis of data from the Japan Renal Biopsy Registry (J-RBR)

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Abstract
Background The clinical presentation of Henoch–Schönlein purpura nephritis (HSPN) has not been thoroughly investigated among patients of different ages. We therefore compared the features of HSPN and IgA nephropathy (IgAN) based on data from the Japan Renal Biopsy Registry (J-RBR).
Methods This cross-sectional study analyzed data from patients who were registered in the J-RBR between 2007 and 2012. Clinico-pathological findings at diagnosis were compared among children (aged ≤18 years), adult (aged 19–64 years) and elderly (aged ≥65 years) patients with HSPN ($n = 513$) and IgAN ($n = 5679$).
Results The age at diagnosis considerably differed between HSPN and IgAN; HSPN peaked at 1–19 and at 60–69 years, whereas IgAN peaked at 30–39 years. The clinical features were significantly more severe for HSPN than IgAN, especially proteinuria (children, 1.28 vs. 0.57; adult, 1.95 vs. 1.05; elderly patients, 2.71 vs. 1.64 g/day), and low albumin levels (children, 3.72 vs. 4.13; adults, 3.62 vs. 3.99; elderly patients, 3.07 vs. 3.57 g/dL). The rate (%) of histologically classified endocapillary proliferative or crescentic glomerulonephritis was higher in patients with HSPN than with IgAN. Multiple regression analysis revealed that low albumin level and high BP were independent factors associated with decreased estimated glomerular filtration rates in adult and elderly patients with HSPN.
Conclusions Age at HSPN diagnosis was bimodally distributed, and the clinical features of HSPN were more severe than those of IgAN across all age groups.

Keywords Henoch–Schönlein purpura nephritis · IgA nephropathy · Renal biopsy · Registry · Glomerulonephritis · Age distribution

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Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most prevalent types of glomerulonephritis, especially in East Asia, Europe, and North America [1–3]. In contrast, Henoch–Schönlein purpura (HSP) is a type of vasculitis that frequently arises in children. About 30–60 % of patients with HSP also develop nephritis (HSPN) with urinary abnormalities and/or renal impairment [4].

Whether or not IgAN and HSPN are related has been controversial [5], but several progressive studies have shown that aberrantly glycosylated IgA1 is responsible for the onset of both diseases [6–9]. Consequently, the eponym "HSP" was replaced with "IgA vasculitis" in the revised

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International Chapel Hill Consensus Conference nomenclature of vasculitis [10, 11].

Renal function and histological damage at diagnosis, hypertension and heavy proteinuria at diagnosis and during disease progression are established prognostic factors for both HSPN and IgAN [3, 12–17]. Some studies have compared the clinical and pathological findings between IgAN and HSPN [18, 19]. However, these studies included relatively few participants with age restrictions, and thus the clinical presentation of HSPN has not been thoroughly assessed in an adequate sample of patients at different ages.

A nationwide, web-based, prospective registry of renal biopsies (Japan Renal Biopsy Registry; J-RBR) was established during 2007 in Japan, and data from about 20,000 patients have been registered [20, 21]. Hence, the purpose of this study is to clarify the differences and relationship of clinico-pathological findings between IgAN and HSPN by using this nationwide and large database.

Materials and methods

Outline of J-RBR system and selection of patients

The J-RBR was established by the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology in 2007. Patients' data were registered on the J-RBR website using the Internet Data and Information Center for Medical Research (INDICE) system of the University Hospital Medical Information System (UMIN). The J-RBR is registered under the Clinical Trial Registry of UMIN (Registration Number, UMIN000000618), and the Ethics Review Board of the Japanese Society of Nephrology approved the present study in accordance with the Declaration of Helsinki.

The main registration system comprised basic information of the patients, date and number of renal biopsy, pathological information based on pathogenesis and histopathology, urinary and blood findings, and coexisting of hypertension and diabetes. Among 18,967 patients with biopsy-proven disease who were registered in this system between July 2007 and December 2012, we selected 513 with HSPN and 5679 with IgAN, which were registered in IgAN or HSPN as the pathogenesis. The two groups of patients were classified as children, adults, and elderly according to ages $\leq$18, 19–64. and $\geq$65 years, respectively.

Clinical and pathological diagnoses

Primary glomerular diseases were mainly clinically diagnosed as chronic nephritic syndrome, acute nephritic syndrome, recurrent or persistent hematuria, rapidly progressive nephritic syndrome and nephrotic syndrome, according to the modified classification of World Health Organization [20, 21]. Secondary and tubulo-interstitial diseases were categorized as renal disorders with collagen disease or vasculitis, renal disease with metabolic syndrome, hypertensive nephropathy, acute kidney injury, drug-induced nephropathy, thrombotic microangiopathy, and others (including acute/chronic interstitial injury, acute tubular necrosis).

The J-RBR requires classification based on pathogenesis and histopathology. The histopathology of HSPN and IgAN, which comprised the pathogenesis of all our patients, was evaluated as mesangial proliferative glomerulonephritis, endocapillary proliferative glomerulonephritis, minor glomerular abnormalities, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis (types I and III), dense deposit disease (type II), crescentic and necrotizing glomerulonephritis, sclerotic glomerulonephritis, nephrosclerosis, acute/chronic interstitial nephritis, renal transplantation, and others.

Evaluation of other clinical findings

The registered basic information (age, sex, height, and weight), as well as urinary findings (urinalysis, daily proteinuria), blood findings [serum creatinine (sCr), total protein, serum albumin, total cholesterol], and blood pressure (BP) were assessed in the present study. Estimated glomerular filtration rates (eGFR) were calculated using the modified equation for Japanese [22]. Information about prescribed anti-hypertensive agents, the presence of diabetes mellitus and HbA1c that was arbitrarily registered was insufficient and could not be assessed.

Statistical analysis

Continuous variables, except age, are presented as mean $\pm$ standard deviation (SD). Age is expressed as median and interquartile range. Clinical parameters were compared between the groups with HSPN and IgAN using the unpaired t test for normally distributed continuous variables or the Mann–Whitney U test for non-normally distributed continuous variables. Clinical parameters were compared among the three age groups using a single-factor analysis of variance (ANOVA) for normally distributed continuous variables or the Kruskal–Wallis test for non-normally distributed continuous variables. The normality of the variances for each continuous variable was analyzed by the Levene test. Differences in proportions were evaluated using the Chi-square independent test or Fisher's exact test, depending on the number of categories. Independent factors affecting renal function at diagnosis were evaluated using stepwise multiple regression analyses. Quantitative

variables such as body mass index (BMI) calculated by height and weight, proteinuria, systolic BP, serum albumin, and serum total cholesterol were selected as independent variables in the analyses. Age, sex, and the value of sCr were excluded, because these variables were used in the equation of eGFR. All data were statistically analyzed using IBM SPSS Advance Statistical version 22.0 and $p < 0.05$ was considered to indicate a significant difference.

Results

Age distribution differs between HSPN and IgAN

Figure 1 shows the age distribution of the patients with HSPN and IgAN. The median ages of the HSPN and IgAN groups were almost equivalent (36 years in HSPN and 37 years in IgAN) but the distribution differed between the two groups, as HSPN peaked at 1–19 and at 60–69 years, whereas IgAN peaked at 30–39 years. There were no remarkable differences of the age distribution by gender in both the diseases.

Comparison of clinico-pathological diagnoses and parameters between HSPN and IgAN

Table 1 compares the clinico-pathological diagnoses and clinical findings between the two diseases. The ratio of chronic nephritic syndrome was significantly higher in patients with IgAN than in those with HSPN (88.5 vs. 61.6 %), whereas those of rapidly progressive nephritic syndrome and nephrotic syndrome were significantly higher in patients with HSPN than in those with IgAN (4.5 vs. 1.4 % and 10.5 vs. 3.0 %, respectively). Mesangial proliferative glomerulonephritis was pathologically evident in 90 % of patients with IgAN. The ratios of endocapillary proliferative glomerulonephritis or crescentic and necrotizing glomerulonephritis were significantly higher, and the clinical findings were far worse in the group with HSPN than in that with IgAN [proteinuria, 1.93 ± 2.53 vs. 1.05 ± 1.40 g/day; ratio of overt hematuria (sediment RBC >30/HPF), 50.3 vs. 36.8 %; serum albumin levels, 3.55 ± 0.75 vs. 3.97 ± 0.56 g/dL). The ratio of patients with more advanced chronic kidney disease stages (grade 3–5) was also higher in HSPN, as compared to IgAN.

Comparison of clinico-pathological parameters of HSPN and IgAN according to age

Table 2 compares the clinico-pathological findings among children, adult, and elderly patients with HSPN and IgAN. As for HSPN, the ratios of rapidly progressive nephritic syndrome and nephrotic syndrome (0.6 vs. 3.4 vs. 13.5 % and 5.1 vs. 10 vs. 18.8 %, respectively), and of histopathological endocapillary proliferative glomerulonephritis and crescentic/necrotizing glomerulonephritis (4.5 vs. 5.0 vs. 13.5 % and 1.9 vs. 7.3 vs. 12.5 %, respectively) were significantly higher in elderly patients than in adult and children. The number of patients with hypertension, large amounts of proteinuria, overt hematuria, reduced renal function, and hypoalbuminemia distinctly differed among the age groups, and disease severity was worse in elderly patients with HSPN.

The clinical findings such as hypertension, proteinuria, and renal function were similarly worse in elderly patients with IgAN. In contrast, the ratio of endocapillary proliferative glomerulonephritis (0.7 vs. 0.9 vs. 0.6 %) in IgAN did not differ among the age groups (Table 2).

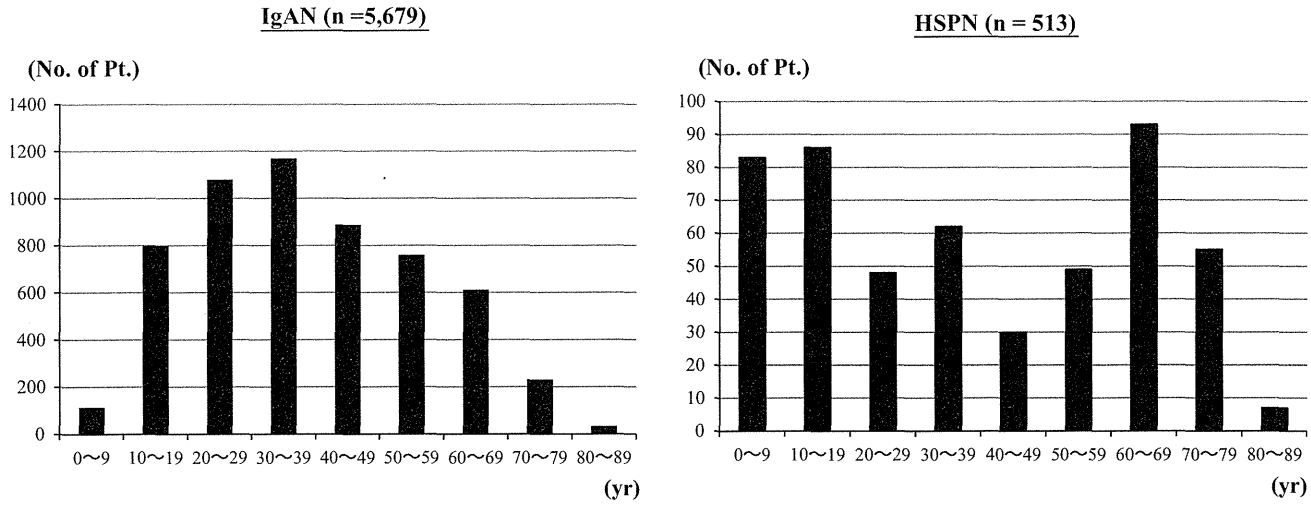

Fig. 1 Age distribution of IgA nephropathy ($n = 5679$) and Henoch–Schönlein purpura nephritis ($n = 513$). Each *histogram* shows 10-year intervals. Frequency of HSPN diagnosis is bimodal with peaks at 1–19 and 60–69 years; frequency of IgAN diagnosis peaks at 30–39 years

Table 1 Comparison of clinico-pathological diagnoses and parameters between HSPN and IgAN ($n = 6192$)

	IgAN ($n = 5679$)	HSPN ($n = 513$)	p
Age [median, (interquartile range)]	37 (24–52)	36 (14–62)	0.41
Gender (male/female)	2887/2792	244/269	0.16
Clinical diagnosis			
Chronic nephritic syndrome	5028 (88.5 %)	316 (61.6 %)	<0.001*
Acute nephritic syndrome	74 (1.3 %)	29 (5.7 %)	<0.001*
Recurrent or persistent hematuria	269 (4.7 %)	17 (3.3 %)	0.14
Rapidly progressive nephritic syndrome	79 (1.4 %)	23 (4.5 %)	<0.001*
Nephrotic syndrome	169 (3.0 %)	54 (10.5 %)	<0.001*
Renal disorder with collagen disease or vasculitis	10 (0.2 %)	63 (12.3 %)	<0.001*
Hypertensive nephropathy	5 (0.1 %)	0 (0.0 %)	0.50
Acute renal failure	8 (0.1 %)	0 (0.0 %)	0.40
Renal transplantation	7 (0.1 %)	0 (0.0 %)	0.43
Others (including metabolic and drug-induced)	30 (0.5 %)	11 (2.1 %)	<0.001*
Pathological diagnosis			
Mesangial proliferative GN	5259 (92.6 %)	397 (77.4 %)	<0.001*
Endocapillary proliferative GN	49 (0.9 %)	33 (6.4 %)	<0.001*
Minor glomerular abnormality	115 (2.0 %)	22 (4.3 %)	0.001*
Focal segmental glomerulosclerosis	39 (0.7 %)	1 (0.2 %)	0.18
Membranous nephropathy	14 (0.2 %)	1 (0.2 %)	0.82
Membranoproliferative GN (type I and III)	21 (0.4 %)	5 (1.0 %)	0.04*
Dense deposit disease	3 (0.1 %)	0 (0.0 %)	0.60
Crescentic and necrotizing GN	46 (0.8 %)	34 (6.6 %)	<0.001*
Sclerosing GN	28 (0.5 %)	0 (0.0 %)	0.11
Nephrosclerosis	25 (0.4 %)	0 (0.0 %)	0.13
Acute/chronic interstitial nephritis	6 (0.1 %)	1 (0.2 %)	0.56
Renal transplantation	3 (0.1 %)	0 (0.0 %)	0.60
Others	71 (1.3 %)	19 (3.7 %)	<0.001*
Clinical findings			
Body mass index	22.5 ± 3.92	21.8 ± 4.95	0.004*
Systolic BP (mmHg)	123.3 ± 18.0	122.6 ± 19.8	0.48
Diastolic BP (mmHg)	74.1 ± 13.1	71.8 ± 13.0	<0.001*
Pt. with hypertension at diagnosis	1982 (34.9 %)	186 (36.3 %)	0.43
Sediment RBC (>30/HPF, %)	2090 (36.8 %)	258 (50.3 %)	<0.001*
Proteinuria (g/day)	1.05 ± 1.40	1.93 ± 2.53	<0.001*
Proteinuria (g/gCr)	1.44 ± 1.93	3.04 ± 3.39	<0.001*
Serum creatinine (mg/dL)	0.98 ± 0.72	0.91 ± 0.88	0.12
Estimated GFR (>20 years old, $n = 5098$)	69.0 ± 26.3	66.2 ± 30.1	0.10
CKD stage (>20 years old, $n = 5098$)			0.008*
Grade 1 (eGFR >90/mL/min/1.73 m^2)	1028 (21.6 %)	72 (21.0 %)	
Grade 2 (eGFR 60–89/mL/min/1.73 m^2)	1945 (40.9 %)	115 (33.5 %)	
Grade 3 (eGFR 30–59/mL/min/1.73 m^2)	1434 (30.2 %)	117 (34.1 %)	
Grade 4 (eGFR 15–29/mL/min/1.73 m^2)	270 (5.7 %)	28 (8.2 %)	
Grade 5 (eGFR <15/mL/min/1.73 m^2)	78 (1.6 %)	11 (3.2 %)	
Serum albumin (g/dL)	3.97 ± 0.56	3.55 ± 0.75	<0.001*
Serum total cholesterol (mg/dL)	199.5 ± 46.5	212.4 ± 60.4	<0.001*

GN glomerulonephritis, *CKD* chronic kidney disease

* $p < 0.05$ by un-paired t test or Chi-square test or Fisher's exact test

Table 2 Comparison of clinico-pathological diagnoses and parameters among age group in HSPN and IgAN

	IgAN (n = 5679)				HSPN (n = 513)			
	Child (n = 803)	Adult (n = 4379)	Elderly (n = 497)	p*	Child (n = 158)	Adult (n = 259)	Elderly (n = 96)	p*
Age [median, (interquartile range)]	15 (12–17)	38 (29–50)	70 (67–74)	<0.001*	9 (6–13)	43 (30–59)	72 (68–76)	<0.001*
Gender (male/female)	454/349	2115/2264	318/179	<0.001**	76/82	119/140	49/47	0.69
Clinical diagnosis								
Chronic nephritic syndrome	732 (91.2 %)	3935(89.9 %)	385 (77.5 %)	<0.001**	130 (82.3 %)	151 (58.3 %)	35 (36.5 %)	<0.001**
Acute nephritic syndrome	13 (1.6 %)	29 (0.7 %)	9 (1.8 %)	0.002**	7 (4.4 %)	18 (6.9 %)	4 (4.2 %)	0.44
Recurrent or persistent hematuria	45 (5.6 %)	206 (4.7 %)	18 (3.6 %)	0.26	4 (2.5 %)	8 (3.1 %)	5 (5.2 %)	0.49
Rapidly progressive nephritic syndrome	2 (0.2 %)	52 (1.2 %)	25 (5.0 %)	<0.001**	1 (0.6 %)	9 (3.4 %)	13 (13.5 %)	<0.001**
Nephrotic syndrome	9 (1.1 %)	111 (2.5 %)	49 (9.9 %)	<0.001**	8 (5.1 %)	28 (10.8 %)	18 (18.8 %)	0.002**
Renal disorder with collagen disease or vasculitis	0 (0.0 %)	10 (0.2 %)	0 (0.0 %)	0.23	7 (4.4 %)	38 (14.7 %)	18 (18.8 %)	<0.001**
Pathological diagnosis								
Mesangial proliferative GN	748 (93.2 %)	4070(92.9 %)	441 (88.7 %)	0.003**	129 (81.6 %)	206 (79.5 %)	62 (64.6 %)	0.003**
Endocapillary proliferative GN	6 (0.7 %)	40 (0.9 %)	3 (0.6 %)	0.72	7 (4.5 %)	13 (5.0 %)	13 (13.5 %)	0.007**
Minor glomerular abnormality	34 (4.2 %)	72 (1.6 %)	9 (1.8 %)	<0.001**	15 (9.5 %)	6 (2.3 %)	1 (1.0 %)	<0.001**
Focal segmental glomerulosclerosis	1 (0.1 %)	34 (0.8 %)	4 (0.8 %)	0.11	0 (0.0 %)	1 (0.4 %)	0 (0.0 %)	0.61
Membranous nephropathy	1 (0.1 %)	9 (0.2 %)	4 (0.8 %)	0.03**	0 (0.0 %)	1 (0.4 %)	0 (0.0 %)	0.61
Membranoproliferative GN (type I and III)	0 (0.0 %)	17 (0.4 %)	4 (0.8 %)	0.06	1 (0.6 %)	3 (1.2 %)	1 (1.0 %)	0.87
Crescentic and necrotizing GN	7 (0.9 %)	29 (0.7 %)	10 (2.0 %)	0.006**	3 (1.9 %)	19 (7.3 %)	12 (12.5 %)	0.004**
Sclerosing GN	1 (0.1 %)	22 (0.5 %)	5 (1.0 %)	0.09	0 (0.0 %)	1 (0.4 %)	0 (0.0 %)	0.61
Clinical findings								
Body mass index	19.9 ± 3.83	22.9 ± 3.82	23.4 ± 3.31	<0.001*	18.0 ± 3.89	23.5 ± 4.59	23.5 ± 3.91	<0.001*
Systolic BP (mmHg)	110.5 ± 12.0	123.9 ± 17.5	136.6 ± 18.4	<0.001*	106.4 ± 11.1	125.6 ± 17.5	138.5 ± 19.2	<0.001*
Diastolic BP (mmHg)	64.0 ± 9.48	75.4 ± 13.0	76.8 ± 11.2	<0.001*	62.7 ± 9.97	75.1 ± 12.0	76.6 ± 12.9	<0.001*
Pt. with hypertension at diagnosis	52 (6.5 %)	1619 (37.0 %)	311 (62.6 %)	<0.001**	14 (8.9 %)	107 (41.3 %)	65 (67.7 %)	<0.001**
Sediment RBC (>30/HPF, %)	411 (51.2 %)	1495 (34.1 %)	184 (37.0 %)	<0.001**	73 (46.2 %)	125 (48.3 %)	60 (62.5 %)	0.03**
Proteinuria (g/day)	0.57 ± 1.05	1.05 ± 1.36	1.64 ± 1.86	<0.001*	1.28 ± 2.04	1.95 ± 2.54	2.71 ± 2.88	0.001*
Proteinuria (g/gCr)	0.93 ± 1.51	1.38 ± 1.72	2.74 ± 3.27	<0.001*	3.23 ± 4.03	2.53 ± 2.84	4.08 ± 3.64	<0.001*
Serum creatinine (mg/dL)	0.63 ± 0.41	0.99 ± 0.69	1.39 ± 1.05	<0.001*	0.49 ± 0.72	0.91 ± 0.45	1.62 ± 1.64	<0.001*
Estimated GFR (mL/min/1.73 m^2)	–	71.6 ± 25.7	46.8 ± 19.7	<0.001***	–	74.2 ± 28.6	45.4 ± 24.3	<0.001***
Serum albumin (g/dL)	4.13 ± 0.54	3.99 ± 0.52	3.57 ± 0.67	<0.001*	3.72 ± 0.76	3.62 ± 0.74	3.07 ± 0.59	<0.001*
Serum total cholesterol (mg/dL)	179.6 ± 42.7	202.5 ± 45.7	206.2 ± 50.8	<0.001*	208.1 ± 63.1	215.1 ± 58.4	212.3 ± 61.2	0.53

GN glomerulonephritis

* $p < 0.05$ by one way ANOVA or Kruskal–Wallis test

** $p < 0.05$ by Chi-square test

*** $p < 0.05$ by unpaired t test

Comparison of clinico-pathological parameters between HSPN and IgAN according to age

In all age groups, the patients with HSPN had more proteinuria (children, 1.28 vs. 0.57 g/day; adult, 1.95 vs. 1.05 g/day; elderly patients, 2.71 vs. 1.64 g/day; $p \leq 0.001$), and low albumin level (children, 3.72 vs. 4.13 g/dL; adults, 3.62 vs. 3.99 g/dL; elderly patients, 3.07 vs. 3.57 g/dL; $p \leq 0.001$) than those with IgAN. Moreover, the ratios of histopathological endocapillary proliferative glomerulonephritis (13.5 vs. 0.6 %, $p \leq 0.001$) and crescentic glomerulonephritis (12.5 vs. 2.0 %, $p \leq 0.001$) were distinctly higher in elderly patients with HSPN than in those with IgAN.

Effect of clinico-pathological factors on renal function at the time of diagnosis in adult and elderly patients with HSPN and IgAN

The effects of clinico-pathological factors on renal function at the time of diagnosis were evaluated using multiple regression analysis. The model included important risk factors for IgAN progression as imperative independent variables. Low albumin level and higher value for systolic BP values at diagnosis were significant factors for a decline in renal function in adult and elderly patients with HSPN ($R^2 = 0.190$; $F = 10.54$, $p < 0.05$; Table 3a). Increased proteinuria, lower albumin level, higher value for BMI, and systolic BP were significant factors for a decline in renal function in adult and elderly patients with IgAN ($R^2 = 0.236$; $F = 180.7$; $p < 0.05$; Table 3b).

Discussion

The present study of the J-RBR revealed that the distribution of age at HSPN diagnosis was bimodal with peaks at 1–19 and 60–69 years, whereas that at IgAN diagnosis peaked during the fourth decade. Patients with HSPN had a higher frequency of nephrotic syndrome and rapidly progressive nephritic syndrome at onset, histologically confirmed endocapillary proliferation and crescentic glomerulonephritis, and clinical hypertension, heavy proteinuria and hypoalbuminemia than those with IgAN. Hypoalbuminemia and higher BP level had significant relevance to the decline of renal function at diagnosis in both diseases.

A Japanese nationwide survey between 1985 and 1993 and a review published in the USA during 2002 showed that the onset of IgAN occurs during the second and third decades of life [23, 24]. The present study confirmed these findings. By contrast, the age distribution of HSPN has not been investigated in detail since the onset of HSP itself is usually during childhood. Coppo et al. reported that the mean age of 57 children and 95 adults with HSPN was 27.5 (3–72) years [12] and Pillebout et al. found that the mean age of 250 adult patients with HSPN was 50 (15–86) years [15]. However, these studies did not include information about the age distribution. The novel findings of the present study are that the frequency of HSPN peaked twice and the clinico-pathological findings were more severe at the peak age of 60–69 years than at the other peak age of 1–18 years.

Whether or not disease severity at diagnosis and prognosis differs between HSPN and IgAN remains controversial. Although the present study found that almost all clinical findings at diagnosis were more severe in all age groups of patients with HSPN than IgAN, we could not investigate the relationship between the severity at diagnosis and prognosis. Oh et al. indicated that clinical outcomes did not vary between adult onset HSPN ($n = 89$) and IgAN ($n = 178$) after clinical severity at presentation was matched [19]. Conversely, Rio et al. found more severe renal involvement in patients with IgAN ($n = 61$) than with HSPN ($n = 142$) after a 10-year follow-up [25].

Table 3 Effect of clinico-pathological factors on renal function at the time of diagnosis in adult and elderly patients with IgAN and HSPN

Parameters at diagnosis	Standard β	t	p value
(a) HSPN			
Serum albumin (g/dL)	0.274	3.428	0.001*
Systolic BP (mmHg)	−0.214	−2.912	0.004*
$R^2 = 0.190$, F value = 10.54 ($p < 0.001$*)			
(b) IgAN			
Serum albumin (g/dL)	0.215	10.82	<0.001*
Systolic BP (mmHg)	−0.303	−17.17	<0.001*
Proteinuria (g/day)	−0.106	−5.081	<0.001*
Body mass index	−0.072	−4.190	<0.001*
$R^2 = 0.236$, F value = 180.7 ($p < 0.001$*)			

* Statistically significant by multiple regression analysis (stepwise method)

Further studies are needed to elucidate relationship between the severity at diagnosis and prognosis.

The histological features of HSPN and IgAN are considered difficult to distinguish without other extra-renal findings, because light microscopic finding shows similar mesangial proliferation and IgA deposition by the immune-fluorescence staining. Therefore, debate about whether or not IgAN and HSPN are related has persisted for several years [4, 5]. Recent findings have indicated that aberrantly glycosylated IgA1 is involved in the onset of both diseases [9, 26]. Novak et al. indicated that circulating IgA1 contains galactose-deficient O-linked glycans in patients with HSPN and in those with IgAN [7]. Kiryluk also found that elevated serum levels of galactose-deficient IgA1 are inherited by pediatric patients with HSPN and IgAN [8]. Moreover, the expression of mRNAs encoding toll-like receptors that play a key role against extrinsic antigens is increased in both diseases [27]. Thus, similar factors contribute to the onset of both diseases, although they are quite different in terms of extra-renal presentation such as gastrointestinal involvement, arthritis and purpuric skin lesions. Furthermore, the present study uncovered differences in the clinical diagnosis and clinico-pathological severity of renal findings between the two diseases. These might be caused by the nature of individual immune responses to circulating immune-complexes of aberrantly glycosylated IgA1. Some other factors might also be involved in elderly patients with HSPN. However, we were unable to investigate this notion. Further studies are needed, because understanding the reasons for the differences might facilitate the development of new disease-specific therapies.

Several studies have indicated that elderly individuals with IgAN are affected not only by continuous immune activity, but also by increases in atherosclerotic changes caused by hypertension, as well as disordered lipid and glucose metabolism, and these factors synergistically affect renal involvement [28, 29]. The present study supports these findings since elderly patients with either IgAN or HSPN had more severe proteinuria and higher BP than adults and children with the same respective diseases. On the other hand, the clinico-pathological findings were more severe in elderly patients with HSPN than with IgAN. This result might suggest that the severity of HSPN in elderly patients cannot explain the known atherosclerotic changes.

The difference between the daily proteinuria (g/day) and urinary protein/creatinine ratio (g/gCr) was evident, especially in elderly and child patients with IgAN and HSPN in this study. The small effect of some missing data (10–15 % of the total) for urinary protein/creatinine ratio could not be denied, although this study had relatively large subjects. Instead, this discrepancy might have more important implication for the assessment of proteinuria in elderly and child. Yokoyama et al. previously suggested that proteinuria was overestimated by the urinary protein/creatinine ratio in the elderly because of the decreased expression of urinary creatinine brought about by the reduction of muscle mass that occurs during aging [30]. This theory might be also applicable to child since muscle mass of them are less than adults.

This study was feasible due to having access to a large database. The J-RBR was the first nationwide, prospective registry of renal biopsies and it was established in 2007; since then, about 5000 patients from 130 institutions in Japan have been registered every year [20]. The registry contributes to not only the standardization of histological diagnosis and classification, but also to nationwide epidemiological studies of conditions such as nephrotic syndrome and glomerulonephritis. In fact, a new perception of the frequency of renal diseases and the outcomes of nephrotic syndrome in elderly patients has emerged based on this system [30, 31]. We also uncovered some useful information about different age groups with HSPN and IgAN using registry data. The formulation and application of the nationwide registry will become even more valuable in the future.

This study has some limitations. Firstly, the registry data might be somewhat inaccurate. IgAN has been accompanied with the other primary glomerular diseases such as minor glomerular abnormality and focal segmental glomerulosclerosis in this study. In fact, there are some difficult cases to distinguish IgAN and other primary glomerular diseases only with pathological findings, because the pathological definition of IgAN is only mesangial proliferation with IgA deposition. Each individual registrant rather than a centralized individual was responsible for the diagnosis of HSPN. Second, the number of items on the registration form was so definitive that we were unable to evaluate the histological findings based on the Oxford classification of IgAN and the International Society of Kidney Disease classification of HSPN. Third, the difference of indication of renal biopsy among child, adult, and elderly should be considered in comparing the clinico-pathological findings at diagnosis. Finally, this cross-sectional study had no reference to the renal outcomes of any of the patients. However, the baseline data of this study have a potential to develop further studies such as a longitudinal cohort study. From this perspective, a large longitudinal cohort study should be planned to clarify and compare actual outcomes between the two diseases.

In conclusion, the clinico-pathological findings were more severe among patients with HSPN than with IgAN across three age groups. The frequency of HSPN diagnosis peaked once in childhood (<18 years of age) and again between the ages of 60 and 69 years, and the clinico-pathological findings were more severe in elderly patients

than in children with HSPN. The clinico-pathological characteristics and actual renal outcomes of elderly patients with HSPN require further investigation.

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Compliance with ethical statements

Conflict of interest The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Drug-induced kidney disease: a study of the Japan Renal Biopsy Registry from 2007 to 2015

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Abstract

Introduction The Japan Renal Biopsy Registry (J-RBR) was started in 2007 by the Committee for the Standardization of Renal Pathological Diagnosis and the Committee for the Kidney Disease Registry of the Japanese Society of Nephrology. The purpose of this report is to clarify drug-induced kidney disease (DIKD) of renal biopsied cases in Japan.

Subjects and methods We analyzed the data of 26,535 cases that were registered in the J-RBR from 2007 to 2015.

Results Based on clinical and pathological diagnoses, 328 cases (176 males and 152 females) of renal biopsy-proven DIKD were registered in the J-RBR from 2007 to 2015 (1.24 % of all cases). The frequency of DIKD increased with age. The number of cases peaked in the 6th–8th decade in all pathological categories, except for the number of chronic tubulointerstitial lesions (CTIL), which peaked in the 4th–5th decade. Overall, the frequency of DIKD was 3 times higher in the 7th decade than in the 2nd decade (1.86 vs. 0.62 %). The main clinical diagnoses were DIKD in 150 cases (45.7 %), nephrotic syndrome in 66 cases (20.1 %), chronic nephritic syndrome in 55 cases (16.8 %), and rapidly progressive glomerulonephritis in 30 cases (9.1 %). DIKD was registered as a secondary diagnosis in 136 cases (41.5 %). The pathological findings of these cases were glomerular lesions in 105 cases (32.0 %), acute tubulointerstitial lesions (ATIL) in 87 cases (26.5 %), CTIL in 72 cases (22.0 %), and sclerotic glomerular lesions and/or nephrosclerosis in 18 cases (5.5 %). ATIL and CTIL were mainly found in cases in which DIKD was

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diagnosed on the basis of the patient's clinical findings. In addition, nephrotic syndrome-related membranous nephropathy (MN) was the major cause of renal damage in 59.4 % of the cases involving glomerular injuries. According to the CGA risk classification, high-risk (red zone) cases accounted for 56.1 % of all cases of DIKD and 75.9, 64.9, and 33.3 % of the cases involving ATIL, CTIL, and glomerular injuries, respectively. The causative drugs were identified in 102 cases, including bucillamine in 38 cases of MN, gemcitabine in 3 cases of thrombotic microangiopathy, and other anticancer drugs in 14 cases (anti-vascular endothelial growth factor drugs in 3 cases and propyl thiouracil in 3 cases of anti-neutrophil cytoplasmic antibody-related nephritis).

Conclusion Our analysis of the J-RBR revealed that DIKD mainly affects elderly people in Japan. ATIL or CTIL were found in approximately half of the biopsied cases of DIKD, and one-third involved glomerular lesions, mainly MN or clinical nephrotic syndrome.

Keywords Drug · Kidney injury · Japanese · Nephrotic syndrome · Tubulointerstitial nephritis

Introduction

The Japanese Society of Nephrology (JSN) established the Japan Renal Biopsy Registry (J-RBR) in 2007, and in 2011 it conducted the first analysis of the registry, which examined the data for 2007 and 2008 [1]. In 2009, the JSN started the Japan Kidney Disease Registry (J-KDR) to record clinically diagnosed cases of kidney disease. The clinical training hospitals of the JSN were requested to add data to this nationwide registry. Based on these data, annual reports [1, 2], epidemiological and cross-sectional studies of membranous nephropathy (MN) [3], elderly patients with renal disease [4], diabetic nephropathy [5], and renal disease combined with obesity [6], and a retrospective study of the outcomes of elderly patients with nephrotic syndrome [7] have been reported, which have helped to clarify the epidemiology of biopsied and unbiopsied renal disease in Japan.

Drug-induced kidney disease (DIKD) accounts for 19–26 % of cases of acute kidney injury (AKI) among hospitalized patients [8]. Recently, Mehta et al. have developed consensus definitions for DIKD based on the patient's clinical presentation, which take into account the wide spectrum of the condition and the need to balance practicality with reliability. They proposed 4 phenotypes of DIKD: AKI, glomerular disorders, tubular dysfunction, and nephrolithiasis [9]; however, there are no biopsy-proven nationwide epidemiological data about DIKD, even in Japan. Thus, we should develop methods of identifying DIKD and produce preventive plans to protect patients from developing the condition.

In this report, the data about renal biopsy-proven DIKD that were registered in the J-RBR between July 2007 and June 2015 are summarized, and the frequency of the condition is analyzed according to clinicopathological diagnosis and age.

Subjects and methods

Registry system and patients

This report includes data for the patients that were prospectively registered in the J-RBR between July 2007 and June 2015. The patients' data, including their age, gender, laboratory findings, and clinical and pathological diagnoses were recorded at each institution and registered on the webpage of the J-RBR via the Internet Data and Information Center for Medical Research (INDICE) system of the University Hospital Medical Information Network (UMIN), as described previously [1]. The ethics committee of the JSN approved the study protocol, as did the local committees of the participating centers and their affiliated hospitals. Written informed consent was obtained from the patients at the time of biopsy or at the time they were registered to participate in the study. The J-RBR is registered in the UMIN Clinical Trials Registry (registered number: UMIN000000618).

Clinical or renal histopathological diagnosis and laboratory data

The clinical diagnosis, the histological diagnosis based on the pathogenesis of the disease, and the histological diagnosis based on a histopathological examination were recorded for each case included in the J-RBR, as described previously [1]. Each diagnosis was based on the patients' clinical symptoms and renal histopathology, as described previously [10]. IgA nephropathy (Berger's disease) was differentiated from primary glomerular disease on the basis of the glomerular alterations it causes, as described in the classification of glomerular diseases produced by the World Health Organization [10].

Clinical data, including urinalysis results and daily proteinuria, serum creatinine (Cr), total protein, albumin, and total cholesterol levels were recorded in all cases, while recording data regarding systolic and diastolic blood pressure, the use of anti-hypertensive agents, hemoglobin A1c values, and the presence/absence of diabetes mellitus

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were considered to be optional. The estimated glomerular filtration rate (eGFR) was calculated based on the patients' serum Cr levels, as described previously [11].

Analyses of the frequency of DIKD according to age and risk category (the heat map method)

We analyzed the frequency of DIKD according to age. In addition, the frequency of high-risk (red zone) cases was assessed in various arbitrary pathological categories, such as glomerular lesions, acute tubulointerstitial lesions (ATIL), chronic tubulointerstitial lesions (CTIL), and sclerotic glomerular lesions and/or nephrosclerosis (sclerotic lesions), based on the CGA risk classification for chronic kidney disease (the heat map method) [12].

Statistical analyses

Data are expressed as the mean ± SD for continuous parametric data, the median and interquartile range for continuous non-parametric data, and as frequencies for categorical data.

Comparisons of categorical variables among groups of different indications or diagnoses were performed using Fisher's exact test. Continuous variables were compared using ANOVA for parametric data and the Kruskal–Wallis test for non-parametric data. All statistical analyses were performed using SPSS version 18.0 (SPSS, Tokyo, Japan).

Results

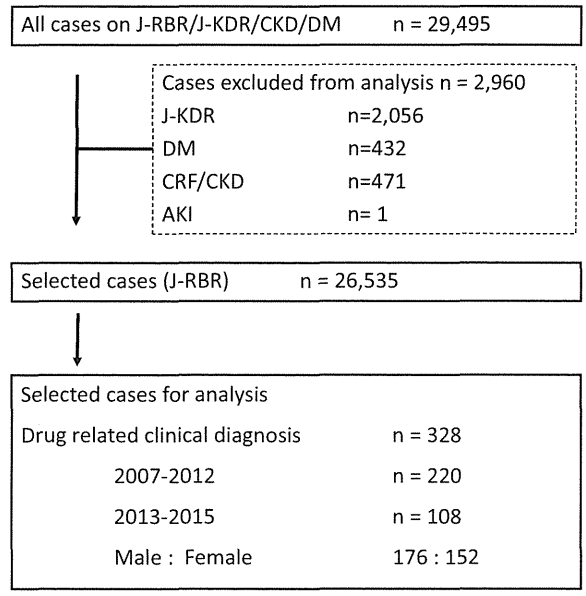
Baseline characteristics of the patients included in the J-RBR and the DIKD patients

Among the cases included in the registry from July 2007 to June 2015, the numbers of cases in which renal biopsies were and were not performed are shown in Fig. 1. From this cohort, 328 cases (176 males and 152 females) of renal biopsy-proven DIKD were extracted based on their clinical and/or pathological diagnoses (1.24 % of the 26,535 cases registered in the J-RBR from 2007 to 2015).

There was no significant difference in the frequency of DIKD between the first period (July 2007–June 2012) and the second period (July 2012–June 2015) (220 cases out of 17,297 cases, 1.27 % vs. 108 cases out of 9238 cases, 1.17 %; not significant).

The frequency of clinical and pathological diagnoses in DIKD

The main clinical diagnoses were DIKD in 150 cases (45.7 %), nephrotic syndrome in 66 cases (20.1 %), chronic



Baseline characteristics of the J-RBR population and DIKD patients

Fig. 1 Baseline characteristics of the J-RBR population and the drug-induced kidney disease patients. From among the 26,535 cases that were registered in the J-RBR between 2007 and 2015, 328 cases (176 males and 152 females) of renal biopsy-proven DIKD were extracted based on their clinical and/or pathological diagnoses

nephritic syndrome in 55 cases (16.8 %), and rapidly progressive nephritic syndrome in 30 cases (9.1 %). DIKD was registered as a secondary diagnosis in 136 cases (41.5 %); thus, 286 cases (87.2 %) were diagnosed as DIKD based on their clinical symptoms (Table 1). Another 36 cases (12.8 %) were diagnosed as DIKD based on their pathological findings.

The pathological findings of these cases included glomerular lesions in 105 cases (32.0 %), ATIL in 87 cases (26.5 %), CTIL in 72 cases (22.0 %), and sclerotic glomerular lesions and/or nephrosclerosis in 18 cases (5.5 %) (Table 2, Supplemental Table 1). ATIL and CTIL were most commonly associated with a clinical diagnosis of DIKD. In addition, nephrotic syndrome-related MN was the major cause of glomerular lesions in 59.4 % of the cases involving glomerular lesions (Table 2).

The frequencies of the 3 major pathological categories did not differ significantly between the first (July 2007–June 2012) and second periods (July 2012–June 2015) (Supplemental Table 1).

The numbers of cases and frequency of DIKD according to age and pathological category

The total number of cases of DIKD is shown in Fig. 2 and Supplemental Table 2, and the frequency of DIKD increased with age until the 7th decade (Fig. 2a). The number of cases of DIKD peaked in the 6th–8th decade in

Table 1 Clinical diagnoses of the cases of drug-induced kidney disease in the J-RBR (2007–2015)

Clinical diagnosis	Cases	%
DIKD[a]	150	45.7
Chronic nephritic syndrome + DIKD[a]	46	14.0
Nephrotic syndrome + DIKD[a]	45	13.7
RPGN[b] + DIKD[a]	29	8.8
Nephrotic syndrome	17	5.2
Acute nephritic syndrome + DIKD[a]	11	3.4
Acute kidney injury	5	1.5
Chronic nephritic syndrome	5	1.5
Recurrent hematuria + DIKD[a]	4	1.2
Chronic nephritic syndrome + others	4	1.2
Others	3	0.9
Nephrotic syndrome + others	2	0.6
Nephrotic syndrome + collagen disease/vasculitis	2	0.6
HUS/TTP[c]	1	0.3
Acute nephritic syndrome + acute kidney injury	1	0.3
Acute kidney injury + DIKD[a]	1	0.3
RPGN[b]	1	0.3
Collagen disease/vasculitis	1	0.3
Total	328	100

Based on their clinical symptoms, 136 patients (41.5 %) were given a secondary diagnosis of DIKD, and a total of 286 patients (87.2 %) were diagnosed with DIKD

J-RBR, Japan Renal Biopsy Registry; [a]DIKD, drug-induced kidney disease; [b]RPGN, rapidly progressive glomerulonephritis; [c]HUS/TTP, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura

Table 2 Pathological categories of the cases of drug-induced kidney disease in the J-RBR (2007–2015)

Pathological diagnosis	Cases	%
Acute kidney injuries	87	26.5
Acute tubulointerstitial nephritis	76	23.2
Acute tubular necrosis	11	3.4
Chronic tubulointerstitial lesions	72	22.0
Glomerular disorders	105	32.0
Membranous nephropathy	63	19.2
Minor glomerular abnormalities	14	4.3
Mesangial proliferative glomerulonephritis	12	3.7
Crescentic glomerulonephritis	8	2.4
Membranoproliferative glomerulonephritis Type I or III	3	0.9
Focal segmental glomerulosclerosis	3	0.9
Endocapillary proliferative glomerulonephritis	2	0.6
Sclerotic lesions	18	5.5
Nephrosclerosis	14	4.3
Sclerosing glomerulonephritis	4	1.2
Others	45	13.7
Transplanted kidney	1	0.3
Total	328	100

J-RBR, Japan Renal Biopsy Registry

both genders, and in males a particularly marked peak was seen in the 7th decade (Fig. 2b).

As for the frequency of DIKD among the renal biopsied cases in each decade, the frequency of DIKD was 3 times higher in the 7th decade than in the 2nd decade (1.86 vs. 0.62 %) (Fig. 3, Supplemental Table 3). The number of cases of DIKD also peaked in the 6th–8th decade in all pathological categories, except for in the cases involving CTIL, in which it peaked in the 4th–5th decade (Fig. 4a, b, Supplemental Fig. 2).

Baseline clinical and laboratory characteristics of the DIKD patients

The patients' urinary findings are shown in Table 3. In dipstick tests, 104 cases (31.7 %) were classified as (−) or (±), and 83 cases (25.3 %) were classified as ≥3+. Similarly, 77 cases (32.5 %) and 58 cases (24.2 %) involved patients that exhibited daily proteinuria values of <0.3 g/day ($n = 237$) or urinary protein/creatinine ratios (UPCR) of <0.3 g/gCr (during spot urine tests) ($n = 240$). In addition, 86 cases (36.3 %) and 128 cases (51.7 %) involved patients that demonstrated daily proteinuria values of ≥0.3 g/day and UPCR of ≥0.3 g/gCr (in spot urine tests), respectively (Table 3). As for the results obtained in each pathological category, in the ATIL and CTIL categories 30 cases (32.6 %) and 35 cases (48.6 %), respectively, were classified as (−) or (±) during dipstick tests (Table 4).

As for hematuria, 195 cases (59.4 %) were found to be (−) or (±) for occult blood in dipstick tests, and 235 cases (70.6 %) were considered to be red blood cell (RBC)-negative or to have <5 RBC/high-powered field (hpf) in their urinary sediments (Table 3). In addition, 52 cases (56.5 %) of ATIL and 54 cases (77.0 %) of CTIL were classified as (−) or (±) for hematuria in dipstick tests (Table 4).

The baseline clinical and laboratory findings of the cases in each of the 3 major pathological categories are shown in Table 4. As mentioned above, the patients with ATIL and CTIL exhibited milder urinary abnormalities than those with glomerular lesions. However, more marked changes in the serum creatinine level and the eGFR were seen in the patients with ATIL or CTIL (ATIL, CTIL, and glomerular lesions: mean serum creatinine levels: 3.42, 2.34, and 1.12 mg/dl, respectively; mean eGFR: 24.2, 33.6, and 66.6 ml/min/1.73 m^2, respectively; $p < 0.001$). On the other hand, the patients with glomerular lesions exhibited lower serum albumin levels (2.82 ± 0.95 g/dl, $p < 0.001$), higher serum cholesterol levels (274.4 ± 122 mg/dl, $p < 0.001$), and nephrotic range proteinuria (daily proteinuria: 3.11 ± 3.28 g; UPCR: 5.48 ± 5.69 g/gCr, $p < 0.001$).

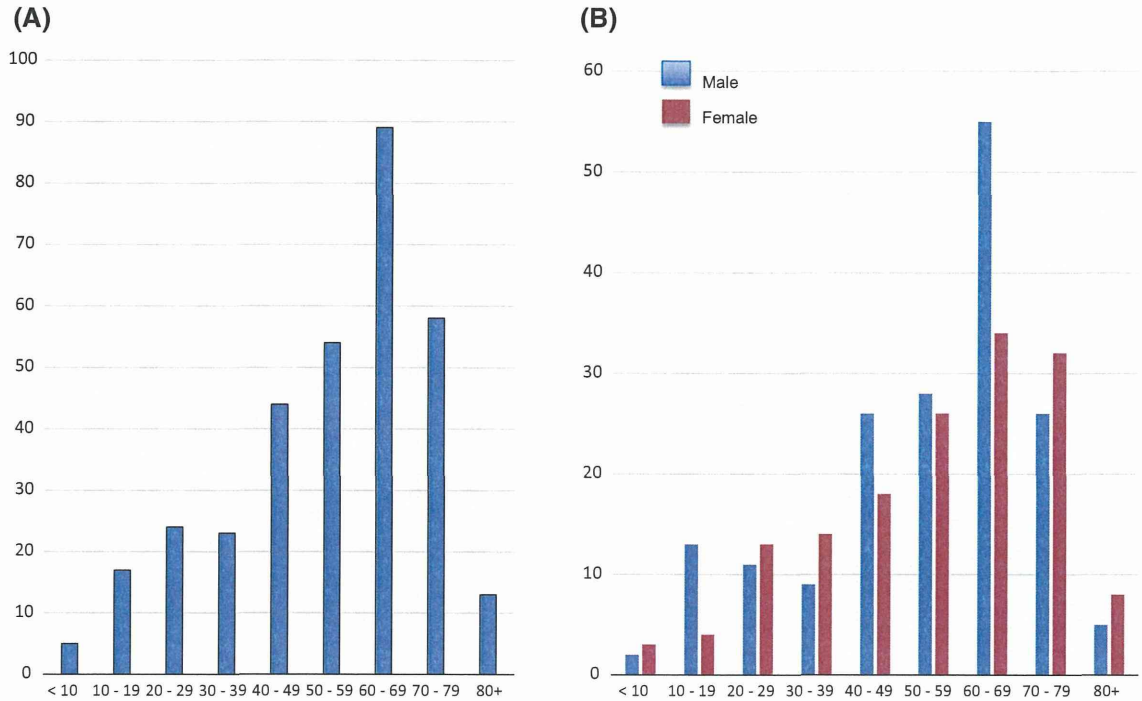


Fig. 2 Number of cases of drug-induced kidney disease in the J-RBR. **a** The number of cases of drug-induced kidney disease increased with age, peaking in the 7th decade*. **b** The number of cases peaked in the 6th–8th decade in both genders, and the males exhibited an especially marked peak in the 7th decade (*data for each decade are shown in Supplemental Table 2)

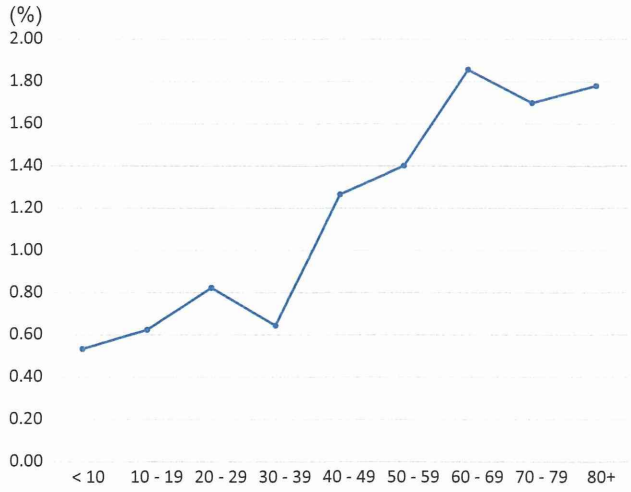


Fig. 3 The frequency of drug-induced kidney disease among renal biopsied cases according to age. The frequency of drug-induced kidney disease increased with age and peaked in the 7th decade*. The frequency of drug-induced kidney disease was elderly 3 times higher in the 7th decade than in the 2nd decade (1.86 vs. 0.62 %) (*data for each decade are shown in Supplemental Table 3)

The CGA risk classification (heat map) in each pathological category of DIKD

The CGA classification results for each pathological category are shown in Fig. 5 and Supplemental Tables 4 and 5.

With regard to the G and A stages of the DIKD patients, stages G4 and A3 were the most common from 2007 and 2015. Furthermore, 123 cases (39.7 %) were considered to involve advanced G stages (G4 or 5), and 175 cases (58.5 %) were classified as stage A3.

The degree of proteinuria detected in the patients' 24-h urine or spot urine samples increased with the G stage, even among the cases involving AKII and CTIL. According to the CGA risk classification, high-risk (red zone) cases accounted for 56.1 % of all cases of DIKD and 75.9, 64.9, and 33.3 % of cases involving ATIL, CTIL, and glomerular lesions, respectively (Fig. 5a–d).

The causative drugs in 102 cases

The causative drugs were identified in 102 cases. Of these, bucillamine was the causative drug in 38 cases of MN; calcineurin inhibitors (CNI), such as cyclosporine or tacrolimus, were found to be the causative drug in 27 cases of CTIL or sclerotic lesions; and anticancer drugs were demonstrated to be the causative drugs in 17 cases (including gemcitabine in 3 cases of thrombotic microangiopathy and anti-vascular endothelial growth factor (VEGF) drugs in 3 cases with various pathologies). Anti-neutrophil cytoplasmic antibody (ANCA)-related nephritis, a representative glomerular lesion, was caused by propyl thiouracil (PTU) in 3 cases (Table 5, Supplemental Fig. 3).

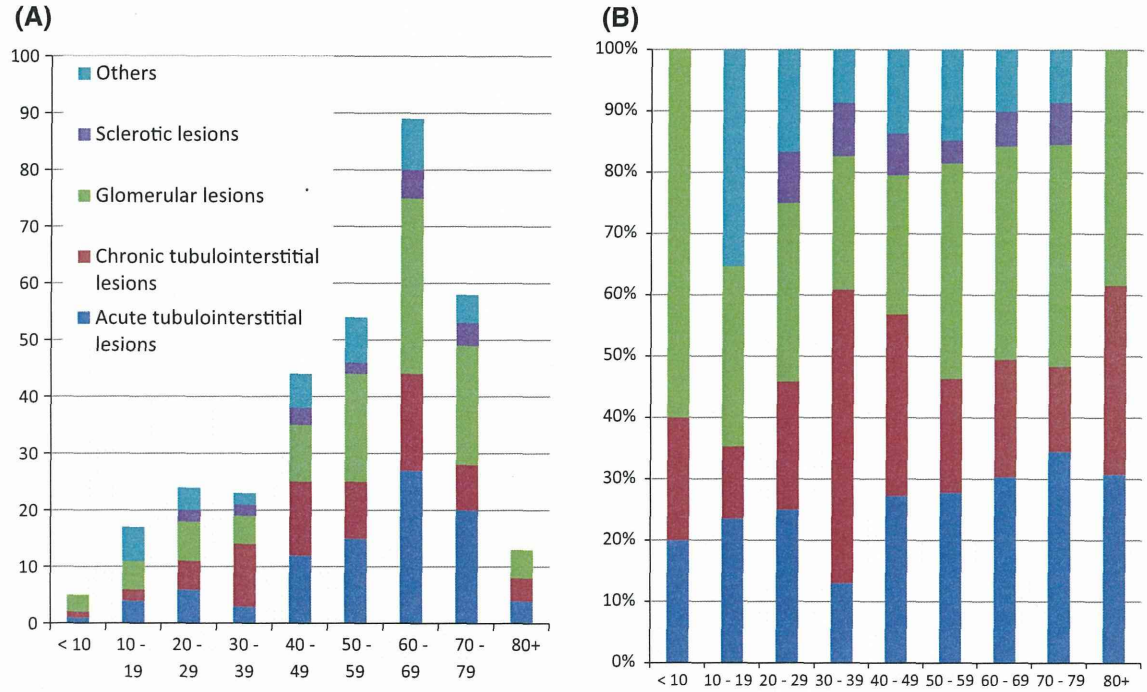


Fig. 4 The frequency of each pathological category of drug-induced kidney disease according to age. **a** Total number of cases in each pathological category, **b** the frequency of each pathological category in each decade. The number of cases peaked in the 6th–8th decade in all pathological categories, except for the number of cases involving chronic tubulointerstitial lesions, which peaked in the 4th–5th decade

Discussion and comments

J-RBR/J-KDR and DIKD

In Japan, renal biopsies have been recorded in the J-RBR since 2007, and clinically diagnosed cases of kidney disease in which renal biopsies were not performed have been registered in the J-KDR since 2009 [1, 2]. More than 18 % of cases of DIKD were registered in the J-RBR in 2009 and 2010 [2]; however, only 7 out of 231 cases (3.0 %) of the condition were registered in the J-KDR from 2007 to 2013 (data not shown); thus, the data from the J-RBR are described in this report. It was speculated that the J-RBR contains data about 20–25 % of the renal biopsies performed in Japan. Thus, reports based on the J-RBR are considered to provide representative data of renal biopsied cases for Japan.

Clinical presentation of DIKD

Among drug-induced kidney injuries, DIKD accounts for 19–26 % of cases of AKI involving hospitalized patients [8]. However, DIKD is often unrecognized because there are no standard clinical definitions for the condition. Our data showed that 12.8 % of DIKD cases were diagnosed based on their pathological findings. Recently, the International Serious Adverse Event Consortium [13] and the working group of Mehta et al. [9] initiated a phenotype standardization project to develop consensus definitions for drug-induced organ toxicities, including DIKD, based on patients' clinical symptoms. As a result, Mehta et al. proposed 4 phenotypes of DIKD: AKI, glomerular disorders, tubular dysfunction, and nephrolithiasis, and suggested that they are useful for evaluating drug toxicities across various settings [9]. Previous reports (published in 2007–2009) from the study group of the Japanese Ministry of Welfare and Labor showed that among the hospitals at which 47 representative nephrologists worked (the hospitals were located throughout Japan) DIKD accounted for 0.935 % of all admissions [14]. The major causative drugs responsible for the patients' renal injuries were non-steroidal anti-inflammatory drugs (NSAID) in 25.1 % of cases, anticancer drugs in 18.0 % of cases, antibiotics in 17.5 % of cases, and radiocontrast agents in 5.7 % of cases. In these cases, 54.6 % of the renal injuries were direct renal injuries. Moreover, 36.5 % of the patients did not recover. In the current study, we dealt more severe and complex cases of DIKD, in which the clinicians decided to perform renal biopsies to obtain more accurate pathological diagnoses. Therefore, it is not surprising that there were discrepancies in the patients' background data between our study population and those of previous studies in which DIKD was diagnosed based on the patients' clinical symptoms. Thus, we need to obtain up-to-date information about non-renal

Table 3 Urinalysis results of all cases of drug-induced kidney disease

Urinary protein (dipstick test)	Cases	%
(−)	67	20.4
(±)	37	11.3
1+	75	22.9
2+	66	20.1
3+	55	16.8
4+	28	8.5
Total	328	100.0

Daily proteinuria levels and urinary protein levels according to spot urine tests

g/day	Cases	%	g/gCr	Cases	%
<0.30	77	32.5	<0.30	58	24.2
0.30–0.49	22	9.3	0.30–0.49	19	7.9
0.50–0.99	52	21.9	0.50–0.99	39	16.3
1.00–3.49	45	19.0	1.00–3.49	64	26.7
3.50+	41	17.3	3.50+	60	25.0
Total	237	100.0	Total	240	100.0

Hematuria (occult blood grade and red blood cell grade of urinary sediment)

OB	Cases	%	/hpf	Cases	%
(−)	144	43.9	(−)	91	27.7
(±)	51	15.5	<5	144	43.9
1+	41	12.5	5–10	28	8.5
2+	46	14.0	<10–30	26	7.9
3+	46	14.0	Many	39	11.9
Total	328	100.0	Total	328	100.0

OB, occult blood levels according to the dipstick test; hpf, high-powered field

biopsied DIKD patients based on standardized clinical criteria in future.

Pathology of DIKD and newer drugs

Previous studies in which DIKD was diagnosed based on the patients' clinical symptoms obtained quite different findings regarding the frequencies of each clinical category and causative drug among DIKD patients than the present study. However, studies in which DIKD was diagnosed based on the patients' pathological findings reported similar pathological data regarding the patients' categories. Since the 1980s, it has been recognized that drug-induced acute interstitial nephritis associated with methicillin or other penicillins, diuretics, or NSAID commonly presents as acute renal failure [15]. In addition, tubulointerstitial lesions such as acute tubular necrosis can be caused by directly tubulo-toxic drugs (e.g., cisplatin, gentamicin, etc.), which induce minimal glomerular histological changes in the human kidney. In toxicological screening programs for nephrotoxic substances, it was suggested that some types of drug-induced renal injuries are mediated by immune mechanisms; i.e., immune complex glomerular disease and nil disease (a minor glomerular abnormality) [16]. In the past decade, we have identified other glomerular lesions such as collapsing focal segmental glomerulosclerosis, which can be caused by pamidronate [17] and other drugs. Finally, a number of newer therapies such as anti-VEGF therapy have emerged as causative agents of renal toxicity, which produce a variety of pathological changes in the kidney [18, 19]. Some drugs can cause irreversible changes and even end-stage renal disease [20, 21]. The present study included some cases of DIKD involving these new drugs, such as gemcitabine, PTU, and anti-VEGF drugs, and their associated pathological findings. In addition, it was demonstrated that bucillamine is a major cause of DIKD-associated glomerular lesions in Japan. Cases of MN involving a different IgG subclass from idiopathic MN have been described in the literature, and such renal changes are considered to be characteristic bucillamine-induced lesions [22, 23] (Supplemental Table 6). However, the precise mechanisms responsible for bucillamine-induced MN remain unclear.

Aging and DIKD

Our analysis of the J-RBR revealed that in Japan DIKD mainly affects the elderly. There are several possible reasons for this: (1) the elderly are exposed to drugs more frequently than younger individuals, (2) the elderly are administered inappropriate doses of nephrotoxic drugs that have not been adjusted for age-related renal and systemic changes, (3) the use of serum Cr levels for diagnostic purposes might be of limited use in the elderly, and (4) there is a lower chance of renal recovery in older patients. It is well known that the risk of developing AKI is significantly increased in the elderly for various reasons, e.g., they are at greater risk of drug toxicities, such as contrast medium-induced nephropathy [24].

As concern to ATIL in the elderly, Muriithi et al. reported recently that drug-induced acute interstitial nephritis (AIN) (87 vs. 64 %), especially proton pump inhibitor (PPI)-induced AIN (18 vs. 6 %), was observed significantly more in the elderly compared with younger patients. Moreover, the elderly had higher prevalence of baseline CKD, higher peak creatinine, and more need for dialysis. Thus, the vast majority of AIN cases in the elderly are due to drugs, primarily owing to PPI and antibiotics in the United State [25].

Table 4 Demographic characteristics of the patients with the 3 major pathological subtypes of drug-induced kidney disease

Category	ATIL (92 cases)		CTIL (72 cases)		Glomerular lesions (106 cases)		*p* value*
	Mean	SD	Mean	SD	Mean	SD	
Age	56.9	18.49	52.9	18.59	55.79	19.6	0.346
Height (cm)	159.0	11.2	159.6	11.4	156.1	12.3	0.020
Weight (kg)	57.4	14.4	55.0	12.1	55.6	12.5	0.176
BMI	22.5	4.4	21.5	3.8	22.6	3.7	0.390
Systolic BP (mmHg)	126.9	22.5	121.5	17.5	126.3	19.3	0.314
Diastolic BP (mmHg)	73.8	14.4	73.2	14.0	75.8	11.9	0.576
Mean BP (mmHg)	91.5	16.0	89.3	14.0	92.6	13.3	0.455
Daily proteinuria (g)	0.73	1.00	0.82	2.30	3.11	3.28	<0.001
uPCR (g/gCr)	2.12	7.82	1.20	2.70	5.48	5.69	<0.001
Urinary protein levels <1+	30 (32.6 %)		35 (48.6 %)		18 (13.0 %)		ND**
Urinary OB levels <1+	52 (56.5 %)		54 (75.0 %)		49 (46.2 %)		ND**
Serum Cr (mg/dl)	3.42	2.72	2.34	2.24	1.12	1.13	<0.001
eGFR (ml/min/1.73 m^2)	24.2	18.7	33.6	20.3	66.6	30.7	<0.001
Serum TP (g/dl)	6.90	1.07	7.10	0.82	5.94	1.12	<0.001
Serum Alb (g/dl)	3.35	0.72	3.96	0.58	2.82	0.95	<0.001
Serum TC (mg/dl)	177.1	46.0	187.5	43.6	274.4	122.0	<0.001
HbA1c (NGSP) (%)	6.14	0.80	5.93	1.27	5.91	0.78	0.017

ATIL, acute tubulointerstitial lesions; CTIL, chronic tubulointerstitial lesions; BP, blood pressure; OB, occult blood level according to the dipstick test; uPCR, urinary protein to creatinine ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; TP, total protein; Alb, albumin; TC, total cholesterol; HbA1c, glycated hemoglobin

* *p* values were calculated using ANOVA or the Kruskal–Wallis test; ** *ND* not determined

(A) Total cases

Stage	A1	A2	A3	Subtotal	
G1	6	2	21	29	10.2%
G2	8	2	32	42	14.7%
G3a	21	4	21	46	16.1%
G3b	29	3	22	54	18.9%
G4	16	5	39	60	21.1%
G5	12	7	35	54	18.9%
Subtotal	92	23	170	285	160
	32.3%	8.1%	59.6%	High risk	56.1%

(B) Acute tubulo-interstitial lesions

Stage	A1	A2	A3	Subtotal	
G1	0	0	1	1	1.3%
G2	1	1	1	3	3.8%
G3a	5	2	0	7	8.9%
G3b	8	2	2	12	15.2%
G4	3	3	20	26	32.9%
G5	6	3	21	30	38.0%
Subtotal	23	11	45	79	60
	29.1%	13.9%	57.0%	High risk	75.9%

(C) Chronic tubulo-interstitial lesions

Stage	A1	A2	A3	Subtotal	
G1	1	0	0	1	1.8%
G2	3	0	0	3	5.3%
G3a	5	1	2	8	14.0%
G3b	10	0	5	15	26.3%
G4	9	1	7	17	29.8%
G5	3	3	7	13	22.8%
Subtotal	31	5	21	57	37
	54.4%	8.8%	36.8%	High risk	64.9%

(D) Glomerular lesions

Stage	A1	A2	A3	Subtotal	
G1	5	2	16	23	23.2%
G2	2	1	31	34	34.3%
G3a	2	1	14	17	17.2%
G3b	6	1	7	14	14.1%
G4	0	0	5	5	5.1%
G5	1	0	5	6	6.1%
Subtotal	16	5	78	99	33
	16.2%	5.1%	78.8%	High risk	33.3%

Fig. 5 The CGA risk classification of DIKD. According to the CGA risk classification, high-risk (*red* zone) cases accounted for 56.1 % of all cases (**a**), and 75.9 % (**b**), 64.9 % (**c**), and 33.3 % (**d**) of those involving acute tubulointerstitial lesions, chronic tubulointerstitial lesions, and glomerular injuries, respectively (color figure online)

Moreover, the frequencies of nephrotic syndrome-related glomerular diseases caused by immune complex diseases, such as idiopathic MN and rapidly progressive glomerulonephritis caused by ANCA-positive vasculitis are increasing in Japan [4]. Aging might affect the immune responses of the elderly. Thus, the elderly might be more

Table 5 The causative drugs and pathological classifications of 102 cases of drug-induced kidney disease

	Glomerular lesions	ATIL	CTIL	Sclerotic lesions	Others	*n*
Bucillamine	38 (MN)					38
Other DMARD	4					4
CNI	14		2	7	4	27
Anticancer drugs		2	2		7	11
Gemcitabine					3 (TMA)	3
Anti-VEGF drugs	2 (MN, CrGN)				1 (NS)	3[a]
NSAID		4	3			7
PTU	3 (ANCA vasculitis)					3
Antibiotics		2	1			3
Mesalazine		1	1			2
Others					1	1
Subtotal	61	9	9	7	16	102

ATIL, acute tubulointerstitial lesions; CTIL, chronic tubulointerstitial lesions; MN, membranous nephropathy; DMARD, disease modified anti-rheumatic drugs; CNI, calcineurin inhibitor; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor; CrGN, crescentic glomerulonephritis; NS, nephrosclerosis; NSAID, non-steroidal anti-inflammatory drugs; PTU, propyl thiouracil; ANCA, anti-neutrophil cytoplasmic antibody

[a] All cases were registered in the J-RBR after July 2012

sensitive to drugs, e.g., they might be more susceptible to drug-induced nephrotoxicity or exhibit hypersensitive immune responses to drugs.

Limitations of this study

1. We cannot exclude the possibility that the J-RBR is subject to sampling bias; however, the J-RBR represents the largest renal biopsy series of elderly (aged over 65 years) and very elderly (over 75 years old) patients in the world [4]. Thus, it is likely to be reasonably representative of the nationwide situation of renal biopsied cases in Japan.
2. We could not examine the outcomes of the DIKD patients in this study. Further studies of the clinical outcomes of DIKD will be necessary.
3. There are no standard definitions for drug-induced nephrotoxicity based on patients' clinical symptoms. We need to develop clinical strategies for diagnosing and managing DIKD.

Conclusion

Our analysis of the J-RBR revealed that DIKD mainly affects elderly people in Japan. In addition, approximately half of the renal biopsied cases involved ATIL or CTIL, and roughly one-third involved glomerular lesions, mainly MN and clinical nephrotic syndrome. In future studies, we need to examine the outcomes of DIKD and develop clinical strategies for managing the condition.

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