Table 1 The number of participated renal centers and registered renal biopsies or other cases without renal biopsies in J-RBR/J-KDR 2009 and 2010

	2009 J-KDR			2010 J-KDR		
	J-RBR	Other cases[a]	Total	J-RBR	Other cases[a]	Total
Renal centers (*n*)[b]	57[c]	–	59	83	–	94
Total biopsies or cases (*n*)	3,336[d] (83.1 %)	680 (16.9 %)	4,016 (100.0 %)	4,106 (87.7 %)	575 (12.3 %)	4,681 (100.0 %)
Average age (years)	46.7 ± 19.9	58.1 ± 17.8	48.7 ± 20.0	46.7 ± 20.6	56.8 ± 21.1	47.9 ± 20.9
Male (*n*)	1,787 (53.6 %)	418 (61.5 %)	2,205 (54.9 %)	2,183 (53.2 %)	335[e] (58.3 %)	2,518[e] (53.8 %)
Female (*n*)	1,549 (46.4 %)	262 (38.5 %)	1,811 (45.1 %)	1,923 (46.8 %)	238[e] (41.4 %)	2,161[e] (46.2 %)

J-RBR Japan Renal Biopsy Registry, *J-KDR* Japan Kidney Disease Registry

Note that J-RBR started in 2007 and J-KDR started in 2009

[a] Other cases include patients diagnosed by clinical findings without renal biopsies

[b] The number represents principal institutions having affiliate hospitals. All of the participated institutions and hospitals in the J-RBR and J-KDR in 2009 and 2010 are shown in the "Appendix". The number of renal centers in total is based on the registration of cases without renal biopsies but diagnosed by clinical findings in addition to that of data with renal biopsy in J-RBR

[c] Increase of 34 when compared to the number in J-RBR 2008

[d] Increase of 1,754 when compared to the number in J-RBR 2008

[e] No registered data for gender in 2 cases

The frequency of clinical diagnoses in the J-RBR

Three classifications, the clinical diagnosis, histological diagnosis based on the pathogenesis, and the histological diagnosis based on a histopathological examination, were included in the J-RBR database, while the clinical diagnosis alone was registered for the other cases. In the J-RBR, a clinical diagnosis of chronic nephritic syndrome was the most common, followed by nephrotic syndrome, in both total biopsies and native kidneys in 2009 and 2010, which was similar to the findings in 2007 and 2008 (Table 4) [1]. In native kidneys, more than half of the cases that were registered had chronic nephritic syndrome. The age distribution according to the classification of clinical diagnoses in native kidneys in the J-RBR in 2009 and 2010 was analyzed, and cases with rapidly progressive nephritic syndrome exhibited the highest mean age while cases with inherited renal diseases showed the youngest mean age (Table 5).

Table 2 The number of registered renal biopsies in J-RBR 2009 and 2010

Years	2009	2010	Total
Native kidneys, *n* (%)	3,165[a] (94.9)	3,869 (94.2)	7,034 (94.5)
Average age (years)	47.0 ± 20.1	47.1 ± 20.8	47.1 ± 20.5
Median age (years)	50 (30–64)	49 (31–65)	49 (30–64)
Male, *n* (%)	1,671 (52.8)	2,035 (52.6)	3,706 (52.7)
Female, *n* (%)	1,494 (47.2)	1,834 (47.4)	3,328 (47.3)
Renal grafts, *n* (%)	171[b] (5.1)	237 (5.8)	408 (5.5)
Average age (years)	40.9 ± 15.0	41.3 ± 15.4	41.1 ± 15.2
Median age (years)	43 (31–52)	41 (33–54)	42 (32–53)
Male, *n* (%)	116 (67.8)	148 (62.4)	264 (64.7)
Female, *n* (%)	55 (32.2)	89 (37.6)	144 (35.3)

[a] Increase of 1,765 when compared to the number in J-RBR 2008

[b] Decrease of 11 when compared to the number in J-RBR 2008

The frequency of pathological diagnoses in the J-RBR

The pathological diagnoses were classified based on the pathogenesis (Table 6) and histopathology (Table 7). In the classification of the pathogenesis, IgAN was diagnosed most frequently (31.6 %), followed by primary glomerular disease other than IgAN (27.2 %) in native kidneys in both 2009 and 2010 (Table 6). Similar frequencies of IgAN, primary glomerular disease other than IgAN and diabetic nephropathy were observed in the combined data for 2007 and 2008 [1]. In the pathological diagnosis classified based on the histopathology in native kidney biopsies, mesangial proliferative glomerulonephritis was the most frequently observed disease, representing 42.5 % and 35.8 % of the cases in 2009 and 2010 (Table 7).

Primary glomerular disease (except IgAN) and nephrotic syndrome in the J-RBR

In the cohort of primary glomerular diseases (except IgA nephropathy) as classified based on the pathogenesis, membranous nephropathy (MN) was predominant in 2009, followed by minor glomerular abnormalities, while minor glomerular abnormalities were the most common diagnosis in 2010, followed by MN (Table 8).

Table 3 Distribution of age ranges and gender in J-RBR 2009 and 2010

	2009									2010								
	Total biopsies (n = 3,336)			Native kidneys (n = 3,165)			Renal grafts (n = 171)			Total biopsies (n = 4,106)			Native kidneys (n = 3,869)			Renal grafts (n = 237)		
Age (years)	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
0–9	60	33	27	57	32	25	3	1	2	121	94	27	136	87	49	7	7	0
10–19	318	169	149	304	160	144	14	9	5	352	203	149	354	193	161	18	10	8
20–29	413	194	219	392	180	212	21	14	7	406	187	219	429	167	262	22	20	2
30–39	476	221	255	438	193	245	38	28	10	533	278	255	549	248	301	62	30	32
40–49	434	222	212	391	197	194	43	25	18	489	277	212	489	251	238	50	26	24
50–59	545	317	228	509	291	218	36	26	10	575	347	228	541	311	230	49	36	13
60–69	645	382	263	631	371	260	14	11	3	733	470	263	756	452	304	28	18	10
70–79	372	213	159	370	211	159	2	2	0	437	278	159	515	277	238	1	1	0
80+	73	36	37	73	36	37	0	0	0	86	49	37	100	49	51	0	0	0
Total	3,336	1,787	1,549	3,165	1,671	1,494	171	116	55	3,732	2,183	1,549	3,869	2,035	1,834	237	148	89
Under 20 (%)	11.3	11.3	11.4	11.4	11.5	11.3	9.9	8.6	12.7	12.5	13.6	11.4	12.7	13.8	11.5	10.5	11.5	9.0
65 and over (%)	22.4	23.9	20.1	23.4	25.3	21.3	4.7	4.3	5.5	24.2	25.4	20.7	25.4	26.9	23.7	4.6	5.4	3.4

Age (years)	Total								
	Total biopsies (n = 7,442)			Native kidneys (n = 7,034)			Renal grafts (n = 408)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
0–9	203	127	76	193	119	74	10	8	2
10–19	690	372	318	658	353	305	32	19	13
20–29	864	381	483	821	347	474	43	34	9
30–39	1,087	499	588	987	441	546	100	58	42
40–49	973	499	474	880	448	432	93	51	42
50–59	1,135	664	471	1,050	602	448	85	62	23
60–69	1,429	852	577	1,387	823	564	42	29	13
70–79	888	491	397	885	488	397	3	3	0
80+	173	85	88	173	85	88	0	0	0
Total	7,442	3,970	3,472	7,034	3,706	3,328	408	264	144
Under 20 (%)	12.0	12.6	11.3	12.1	12.7	11.4	10.3	10.2	10.4
65 and over (%)	23.4	24.7	21.8	24.5	26.1	22.6	4.7	4.9	4.2

Table 4 The frequency of classification of clinical diagnoses in J-RBR 2009 and 2010

Classification	2009			2010			Total		
	Total biopsies (n = 3,336)		Native kidneys (n = 3,165)	Total biopsies (n = 4,106)		Native kidneys (n = 3,869)	Total biopsies (n = 7,442)		Native kidneys (n = 7,034)
	n	%	%[a]	n	%	%[a]	n	%	%[a]
Chronic nephritic syndrome	1,759	52.7	55.4	1,944	47.3	50.0	3,703	49.8	52.5
Nephrotic syndrome	711	21.3	22.4	1,044	25.4	27.0	1,755	23.6	24.9
Rapidly progressive nephritic syndrome	200	6.0	6.3	292	7.1	7.5	492	6.6	7.0
Renal transplantation	160	4.8	–	227	5.5	–	387	5.2	–
Renal disorder with collagen disease or vasculitis	116	3.5	3.7	144	3.5	3.7	260	3.5	3.7
Recurrent or persistent hematuria	97	2.9	3.0	111	2.7	2.9	208	2.8	2.9
Renal disorder with metabolic disease	63	1.9	2.0	61	1.5	1.6	124	1.7	1.8
Acute nephritic syndrome	54	1.6	1.6	58	1.4	1.5	112	1.5	1.6
Hypertensive nephropathy	39	1.2	1.2	54	1.3	1.4	93	1.3	1.3
Acute renal failure	36	1.1	1.1	35	0.9	0.9	71	1.0	1.0
Drug-induced nephropathy	13	0.4	0.4	26	0.6	0.6	39	0.5	0.5
Inherited renal disease	6	0.2	0.2	15	0.4	0.4	21	0.3	0.3
HUS/TTP	–	–	–	3	0.1	0.1	3	0.0	0.0
Others	82	2.5	2.6	92	2.2	2.4	174	2.4	2.5
Total	3,336	100.0	100.0	4,106	100.0	100.0	7,442	100.0	100.0

[a] Patients classified as either "Renal graft" or "Renal transplantation" in other categories were also excluded

In the patients with nephrotic syndrome as classified by the clinical diagnosis, primary glomerular disease other than IgAN was the predominant diagnosis in both 2009 and 2010, followed by diabetic nephropathy, which was the same order as in 2007 and 2008 (Table 9). Among the patients with primary glomerular diseases (except IgA nephropathy) who had nephrotic syndrome, MN was dominant, followed by minor glomerular abnormalities, viz., minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), and membranoproliferative glomerulonephritis (MPGN) (types I and III) in 2009. In 2010, minor glomerular abnormalities were the leading diagnosis, followed by MN, FSGS, and MPGN (types I and III) (Table 10).

Clinical diagnosis of membranous nephropathy, minor glomerular abnormalities, and focal segmental glomerulosclerosis in patients with primary glomerular diseases (except IgA nephropathy) in the J-RBR

A subanalysis of the subjects with a clinical diagnosis of MN, minor glomerular abnormalities, and FSGS who had primary glomerular diseases (except IgA nephropathy) was also performed, since these were the most common forms of such diseases. Nephrotic syndrome was the most common clinical diagnosis in cases with primary MN and primary minor glomerular abnormalities (MCNS) (Tables 11, 12), whereas chronic nephritic syndrome and nephrotic syndrome were the most common in cases with primary FSGS in 2009 and 2010, respectively (Table 13).

Subanalysis of cases of IgA nephropathy in the J-RBR

The profile, distribution of age ranges, classification of the clinical diagnosis, and the pathological diagnosis of IgAN, the most common glomerulonephritis reported in the J-RBR, were further analyzed (Tables 14, 15, 16, 17, 18, S2, S3). The average age of the overall subjects was in the fourth decade. There were no differences in the proportion of patients based on gender, but the age was significantly higher in males than in females in 2009 (Table 14). In terms of the distribution of age ranges, the peak distribution was in the twenties individually in both genders and in the overall cases in 2009, while it was in the thirties in both genders and overall in 2010, as well as in the combined data from 2009 and 2010 (Table 15). Patients younger than 20 years of age comprised 14.4 % of the cases and those 65 years and over comprised 7.9 % of the cases in the combined data from 2009 and 2010 (Table 15). The majority of the clinical and pathological diagnoses were chronic nephritic syndrome (Table 16) and mesangial proliferative glomerulonephritis (Table 17), respectively,

Table 5 The age distribution of classification of clinical diagnoses in native kidneys in J-RBR 2009 and 2010

Classification	2009			2010			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Chronic nephritic syndrome	44.4 ± 18.8	41.2 ± 17.8	42.8 ± 18.4	43.5 ± 19.3	41.0 ± 18.2	42.2 ± 18.8	43.9 ± 19.1	41.0 ± 18.0	42.5 ± 18.6
Nephrotic syndrome	52.6 ± 21.6	54.7 ± 21.1	53.5 ± 21.4	49.5 ± 23.4	50.9 ± 22.6	50.1 ± 23.0	50.8 ± 22.7	52.5 ± 22.0	51.5 ± 22.4
Rapidly progressive nephritic syndrome	64.5 ± 13.0	61.2 ± 17.4	63.0 ± 15.1	65.4 ± 11.5	65.3 ± 15.3	65.4 ± 13.3	65.1 ± 12.1	63.6 ± 16.3	64.4 ± 14.1
Renal disorder with collagen disease or vasculitis	48.0 ± 21.5	46.2 ± 20.1	46.7 ± 20.4	54.3 ± 19.5	46.3 ± 19.6	48.7 ± 19.9	51.6 ± 20.5	46.2 ± 19.8	47.8 ± 20.1
Recurrent or persistent hematuria	33.4 ± 17.4	33.8 ± 16.9	33.6 ± 17.0	49.5 ± 19.0	38.0 ± 17.1	42.6 ± 18.6	41.8 ± 19.9	36.1 ± 17.0	38.4 ± 18.4
Renal disorder with metabolic disease	56.9 ± 12.3	57.9 ± 8.9	57.2 ± 11.5	56.8 ± 14.8	54.8 ± 14.1	56.2 ± 14.5	56.9 ± 13.5	56.2 ± 11.9	56.7 ± 13.0
Acute nephritic syndrome	42.8 ± 19.2	36.0 ± 22.5	39.9 ± 20.7	49.6 ± 17.5	46.6 ± 21.1	48.1 ± 19.3	46.1 ± 18.5	42.0 ± 22.1	44.2 ± 20.3
Hypertensive nephropathy	56.2 ± 13.5	51.0 ± 15.3	55.2 ± 13.8	54.5 ± 15.9	54.7 ± 17.0	54.6 ± 16.0	55.3 ± 14.8	53.3 ± 16.1	54.8 ± 15.1
Acute renal failure	56.0 ± 19.3	56.4 ± 26.2	56.1 ± 21.2	55.2 ± 17.6	58.0 ± 20.6	56.0 ± 18.2	55.6 ± 18.3	57.1 ± 23.1	56.0 ± 19.7
Drug-induced nephropathy	53.6 ± 11.9	35.2 ± 21.6	45.1 ± 18.9	47.3 ± 20.0	60.4 ± 17.6	51.5 ± 19.9	49.1 ± 18.0	49.6 ± 22.7	49.3 ± 19.5
Inherited renal disease	25.0 ± 23.8	40.7 ± 24.1	32.8 ± 23.1	15.0 ± 17.1	24.3 ± 25.3	19.3 ± 21.1	17.7 ± 18.5	29.2 ± 24.9	23.2 ± 22.0
HUS/TTP	–	–	–	10, 69	49	42.6 ± 30.0	10, 69	49	42.6 ± 30.0
Others	50.6 ± 18.2	48.4 ± 19.5	49.6 ± 18.7	48.6 ± 20.9	53.3 ± 18.1	50.5 ± 19.8	49.4 ± 19.6	50.9 ± 18.9	50.0 ± 19.2
Total	48.4 ± 20.0	45.5 ± 20.0	47.0 ± 20.1	48.2 ± 21.0	46.0 ± 20.5	47.1 ± 20.8	48.3 ± 20.6	45.8 ± 20.3	47.1 ± 20.5

in 2009 and 2010. The distribution of chronic kidney disease (CKD) stages, degree of proteinuria and clinical parameters in IgAN were analyzed in the combined data from 2009 and 2010 (Tables 18, S2, S3).

With regard to the stages of CKD in patients with IgAN, stage 2 was predominant in the combined data from 2009 and 2010 (Table 18) and in both genders (Tables S2 and S3). The degree of proteinuria in the 24-h urine or spot urine samples increased with the progression of CKD stages in the combined data from 2009 and 2010 (Table 18) and in both genders (Tables S2 and S3). The systolic and diastolic blood pressure also increased with the progression of the CKD stage (Tables 18, S2, S3). Overall, 37.0 % of IgAN cases were being treated with antihypertensive agents and 4.6 % had diabetes mellitus (Table 18).

Cases in the J-KDR not reported in the J-RBR

In cases in the J-KDR not reported in the J-RBR, a clinical diagnosis of chronic nephritic syndrome was predominant in 2009, followed by hypertensive nephropathy, and a clinical diagnosis of renal disorder with metabolic disease (diabetic nephropathy) was predominant in 2010, followed by nephrotic syndrome (Table 19). Polycystic kidney disease was detected in 2010 as a result of the secondary research studies performed on the basis of the J-KDR as described in the "Subjects and methods" section.

Secondary and longitudinal research by the J-RBR/J-KDR

Five of the secondary and longitudinal research studies, viz., the JNSCS, J-IDCS, J-IGACS, JRPGN-CS, and JDNCS, were started in 2009, and the J-PKD was started in 2010 in association with the J-RBR/J-KDR.

Discussion and comments

In 2009, the J-KDR started to register clinically-diagnosed cases without renal biopsies, in addition to cases with renal biopsies included in the J-RBR, which had been started in 2007. More than 80 % of the registered cases were in the J-RBR in 2009 and 2010, and thus the detailed data from the J-RBR and the clinical diagnosis alone for the J-KDR are described in this report.

Table 6 The frequency of pathological diagnoses as classified by pathogenesis in J-RBR 2009 and 2010

Classification	2009			2010			Total		
	Total biopsies (n = 3,336)		Native kidneys (n = 3,165)	Total biopsies (n = 4,106)		Native kidneys (n = 3,869)	Total biopsies (n = 7,442)		Native kidneys (n = 7,034)
	n	%	%[a]	n	%	%[a]	n	%	%[a]
IgA nephropathy	1,003	30.1	31.6	1,177	28.7	30.4	2,180	29.3	31.0
Primary glomerular disease (except IgA nephropathy)	862	25.8	27.2	1,090	26.5	28.1	1,952	26.2	27.7
Diabetic nephropathy	184	5.5	5.8	192	4.7	5.0	376	5.1	5.3
Renal graft	161	4.8	–	235	5.7	–	396	5.3	–
Lupus nephritis	137	4.1	4.3	220	5.4	5.7	357	4.8	5.1
MPO-ANCA positive nephritis	129	3.9	4.1	191	4.7	4.9	320	4.3	4.5
Hypertensive nephrosclerosis	123	3.7	3.9	157	3.8	4.1	280	3.8	4.0
Purpura nephritis	64	1.9	2.0	108	2.6	2.8	172	2.3	2.4
Amyloid nephropathy	45	1.3	1.4	58	1.4	1.5	103	1.4	1.5
Infection-related nephropathy	27	0.8	0.9	31	0.8	0.8	58	0.8	0.8
Thin basement membrane disease	26	0.8	0.8	39	1.0	1.0	65	0.9	0.9
PR3-ANCA positive nephritis	13	0.4	0.4	11	0.3	0.3	24	0.3	0.3
Alport syndrome	10	0.3	0.3	16	0.4	0.4	26	0.3	0.4
Thrombotic microangiopathy	9	0.3	0.3	8	0.2	0.2	17	0.2	0.2
Anti-GBM antibody-type nephritis	8	0.2	0.3	16	0.4	0.4	24	0.3	0.3
Others	535	16.0	16.7	557	13.6	13.6	1,092	14.7	15.4
Total	3,336	100.0	100.0	4,106	100.0	100.0	7,442	100.0	100.0

MPO myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *PR3* proteinase 3, *GBM* glomerular basement membrane

[a] Patients classified as either "Renal graft" or "Renal transplantation" in other categories were also excluded

The rates of primary glomerular disease (except IgAN) combined with that of IgAN in native renal biopsies were 59.3 %, 56.5 %, 58.8 %, and 58.5 % in 2007, 2008, 2009, and 2010 in the J-RBR. A recent report from a single center in Japan gave the rates as 77.8 % and 75.9 % between 1979 and 2008 and between 2004 and 2008, respectively [5]. In the present report for the J-RBR, the peak distribution of age was in the sixties in the combined data for 2009 and 2010. The difference in the rates of primary glomerular disease including IgAN may have been due to the higher mean ages of native biopsy cases in the J-RBR compared to the single center in this period (mean age, 46.7 vs. 40.8 years; age of the peak number, sixties vs. twenties), because the incidence of secondary glomerular disease increases in elderly patients, as reported previously [5].

IgAN is still the most frequently diagnosed disease in native kidney biopsies in Japan (33.0 %, 30.2 %, 31.6 %, and 30.4 % of cases in 2007, 2008, 2009, and 2010 in the J-RBR) [1, 4–6] similar to other Asian countries [7, 8] and some European countries [9, 10]. The peak distribution of age ranges was the twenties in 2009 and thirties in 2010. In patients with IgAN, the majority (68.1 %) of renal biopsies were performed in CKD stages G1 and G2, with median proteinuria less than 1 g per day (Table 18), suggesting that there was a relatively early diagnosis of this biopsy-proven disease.

In the present clinical data, the degree of proteinuria increased with the progression of the CKD stage, and was more than 1 g per day for the median value in patients with CKD stages G4 and G5 (Tables 18, S1, S2). Previously, the best single predictor for renal deterioration was severe proteinuria on urine dipstick testing (≥100 mg/dL), followed by hypoalbuminemia, mild hematuria, serum total protein levels, diastolic blood pressure, and histological grade, in a cohort study with 10 years follow-up from 1995 in Japan, the cohort of which exhibited a younger median age (27.7 years) and a peak distribution of age ranges in the teens [11, 12]. A recent report suggested that IgAN with nephrotic syndrome had a worse renal outcome compared to IgAN with non-nephrotic syndrome unless partial or complete remission was achieved [13]. Further studies are necessary to elucidate the risk factors or predictors for renal deterioration in IgAN in the present era utilizing the J-RBR, possibly as part of a new secondary clinical study.

MN was the most common histopathology in terms of primary glomerular disease other than IgAN in 2007

Table 7 The frequency of pathological diagnoses as classified by histopathology in J-RBR 2009 and 2010

Classification	2009			2010			Total		
	Total biopsies (n = 3,336)		Native kidneys (n = 3,165)	Total biopsies (n = 4,106)		Native kidneys (n = 3,869)	Total biopsies (n = 7,442)		Native kidneys (n = 7,034)
	n	%	%[a]	n	%	%[a]	n	%	%[a]
Mesangial proliferative glomerulonephritis	1,346	40.3	42.5	1,388	33.8	35.8	2,734	36.7	38.8
Membranous nephropathy	333	10.0	10.5	418	10.2	10.8	751	10.1	10.7
Minor glomerular abnormality	293	8.8	9.2	559	13.6	14.4	852	11.4	12.1
Crescentic and necrotizing glomerulonephritis	180	5.4	5.7	262	6.4	6.8	442	5.9	6.3
Focal segmental glomerulosclerosis	167	5.0	5.2	211	5.1	5.4	378	5.1	5.3
Nephrosclerosis	163	4.9	5.2	208	5.1	5.4	371	5.0	5.3
Renal graft	151	4.5	–	227	5.5	–	378	5.1	–
Membranoproliferative glomerulonephritis (types I and III)	85	2.5	2.7	97	2.4	2.5	182	2.4	2.6
Chronic interstitial nephritis	71	2.1	2.1	61	1.5	1.6	132	1.7	1.8
Sclerosing glomerulonephritis	63	1.9	2.0	44	1.1	1.1	107	1.4	1.5
Endocapillary proliferative glomerulonephritis	61	1.8	1.9	67	1.6	1.7	128	1.7	1.8
Acute interstitial nephritis	45	1.3	1.4	62	1.5	1.6	107	1.4	1.5
Acute tubular necrosis	9	0.3	0.3	10	0.2	0.2	19	0.3	0.2
Dense deposit disease	3	0.1	0.1	5	0.1	0.1	8	0.1	0.1
Others	366	11.0	11.3	487	11.9	12.5	853	11.5	12.0
Total	3,336	100.0	100.0	4,106	100.0	100.0	7,442	100.0	100.0

[a] Patients classified as either "Renal graft" or "Renal transplantation" in other categories were also excluded

Table 8 The frequency of pathological diagnoses as classified by histopathology in primary glomerular disease except IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	n	%	n	%
Membranous nephropathy	259	30.1	330	30.3	589	30.2
Minor glomerular abnormalities	216	25.1	408	37.5	624	32.0
Mesangial proliferative glomerulonephritis	167	19.4	86	7.9	253	13.0
Focal segmental glomerulosclerosis	113	13.1	149	13.7	262	13.4
Membranoproliferative glomerulonephritis (types I and III)	48	5.6	51	4.7	99	5.1
Crescentic and necrotizing glomerulonephritis	19	2.2	18	1.7	37	1.9
Endocapillary proliferative glomerulonephritis	8	0.9	24	2.2	32	1.6
Chronic interstitial nephritis	7	0.8	3	0.3	10	0.5
Sclerosing glomerulonephritis	7	0.8	3	0.3	10	0.5
Nephrosclerosis	5	0.6	7	0.6	12	0.6
Acute interstitial nephritis	1	0.1	0	–	1	0.1
Acute tubular necrosis	0	–	1	0.1	1	0.1
Others	11	1.3	9	0.8	20	1.0
Total	861	100.0	1,089	100.0	1,950	100.0

Table 9 The frequency of pathological diagnoses as classified by pathogenesis in nephrotic syndrome in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	*n*	%	*n*	%
Primary glomerular disease (except IgA nephropathy)	442	62.3	696	66.7	1,138	64.9
Diabetic nephropathy	85	12.0	78	7.5	163	9.3
IgA nephropathy	30	4.2	36	3.5	66	3.8
Lupus nephritis	30	4.2	58	5.6	88	5.0
Amyloid nephropathy	27	3.8	41	3.9	68	3.9
Infection-related nephropathy	6	0.8	7	0.7	13	0.7
Hypertensive nephrosclerosis	6	0.8	10	0.9	16	0.9
Purpura nephritis	4	0.6	8	0.8	12	0.7
Alport syndrome	3	0.4	0	–	3	0.2
Thrombotic microangiopathy	1	0.1	1	0.1	2	0.1
PR3-ANCA positive nephritis	1	0.1	0	–	1	0.1
MPO-ANCA positive nephritis	1	0.1	2	0.2	3	0.2
Others	74	10.4	106	10.2	180	10.3
Total	710	100.0	1,043	100.0	1,753	100.0

MPO myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *PR3* proteinase 3

Table 10 The frequency of pathological diagnoses as classified by histopathology in primary glomerular disease except IgA nephropathy in nephrotic syndrome in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	*n*	%	*n*	%
Membranous nephropathy	178	40.3	227	32.6	405	35.6
Minor glomerular abnormalities	172	38.9	348	50.0	520	45.7
Focal segmental glomerulosclerosis	47	10.6	82	11.8	129	11.3
Membranoproliferative glomerulonephritis (types I and III)	25	5.7	18	2.6	43	3.8
Mesangial proliferative glomerulonephritis	11	2.5	13	1.9	24	2.1
Crescentic and necrotizing glomerulonephritis	2	0.5	2	0.3	4	0.4
Sclerosing glomerulonephritis	2	0.5	0	–	2	0.2
Endocapillary proliferative glomerulonephritis	1	0.2	5	0.7	6	0.5
Others	4	0.9	1	0.1	5	0.4
Total	442	100.0	696	100.0	1,138	100.0

(31.4 %), 2008 (25.7 %), and 2009 (30.1 %) in the J-RBR and was also the most common type in primary nephrotic syndrome in 2007 (44.0 %) and 2009 (40.3 %) in the J-RBR. MN was also the most common primary cause of nephrotic syndrome in a northern European Caucasian population, with a biopsy rate of 4.5 per million population per year [14]. A total of 68.7 % and 68.8 % of primary MN cases exhibited nephrotic syndrome as the clinical diagnosis at the time of renal biopsy in 2009 and 2010 in the J-RBR. Yokoyama et al. recently reported in their clinical data analysis of 501 cases collected from the combined data of the J-RBR from 2007 to 2010 that nearly half of primary MN (49.1 %) cases showed a daily proteinuria of 3.5 g or higher [15]. The renal survival rate was 60 % at 20 years after diagnosis in patients with primary MN, and the renal survival rate in patients on steroid therapy was significantly higher in patients on supportive therapy alone in Japan [16], while spontaneous remission was reported to be common (32 %) in patients with primary MN with nephrotic syndrome in Spain [17], even in patients exhibiting chronic renal impairment [18]. Whether treatment with renin–angiotensin blockers or immunoglobulins other than steroids has a favorable effect on the renal prognosis of primary MN should be elucidated in future clinical studies.

The minor glomerular abnormalities in primary nephrotic syndrome, which correspond to MCNS, was the most common histopathology reported in 2008 (44.1 %) and 2010 (50.0 %) in the J-RBR. Since MCNS develops in patients at younger ages [5, 15] while primary MN develops in a relatively elderly population [15, 16], the frequency of these diseases may depend on the distribution of

Table 11 The frequency of clinical diagnoses in membranous nephropathy in primary glomerular disease except IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	*n*	%	*n*	%
Nephrotic syndrome	178	68.7	227	68.8	405	68.8
Chronic nephritic syndrome	74	28.6	93	28.2	167	28.4
Recurrent or persistent hematuria	3	1.2	3	0.9	6	1.0
Renal disorder with collagen disease or vasculitis	1	0.4	1	0.3	2	0.3
Hypertensive nephropathy	1	0.4	0	–	1	0.2
Rapidly progressive nephritic syndrome	0	–	1	0.3	1	0.2
Renal disorder with metabolic disease	0	–	1	0.3	1	0.2
Acute nephritic syndrome	0	–	1	0.3	1	0.2
Acute renal failure	0	–	1	0.3	1	0.2
Others	2	0.8	2	0.6	4	0.7
Total	259	100.0	330	100.0	589	100.0

Table 12 The frequency of clinical diagnoses in minor glomerular abnormalities in primary glomerular disease except IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	*n*	%	*n*	%
Nephrotic syndrome	172	79.6	348	85.3	520	83.3
Chronic nephritic syndrome	35	16.2	50	12.3	85	13.6
Recurrent or persistent hematuria	5	2.3	5	1.2	10	1.6
Acute renal failure	1	0.5	0	–	1	0.2
Rapidly progressive nephritic syndrome	1	0.5	1	0.2	2	0.3
Acute nephritic syndrome	1	0.5	1	0.2	2	0.3
Hypertensive nephropathy	0	–	1	0.2	1	0.2
Others	1	0.5	2	0.5	3	0.5
Total	216	100.0	408	100.0	624	100.0

the age ranges of patients registered in each year. Indeed, the rate of native biopsies of subjects younger than 20 years of age slightly increased from 11.4 % in 2009 to 12.7 % in 2010 (Table 3) and the mean age of patients with nephrotic syndrome slightly decreased from 53.5 years in 2009 to 50.1 years in 2010 (Table 5) in the J-RBR.

The average age of rapidly progressive nephritic syndrome was the highest (64.4 years) in the age distribution in the classification of clinical diagnosis in the J-RBR (Table 5). Elderly subjects (65 years and over) comprised nearly 25 % of cases, and very elderly subjects (80 years and over) comprised 2.5 % of the cases in the combined data for 2009 and 2010 in the J-RBR. It has been reported that there were statistically significant differences in the renal disease spectrum between elderly and younger subjects [19, 20]. The frequency of rapidly progressive nephritic syndrome in the clinical diagnosis dramatically increased from 4.0 % in the younger group (20–64 years) to 19.6 % in the very elderly in the combined data from 2007 to November 2011 in the J-RBR [20]. A nationwide survey of rapidly progressive glomerulonephritis (RPGN) was conducted between 1989 and 2007 in Japan, and showed that 64.0 % of patients had pauci-immune-type RPGN, including 42.0 % renal-limited vasculitis, 19.4 % microscopic polyangiitis, and 2.6 % Wegener's granulomatosis (currently granulomatosis with polyangiitis) [21]. Since the frequency of myeloperoxidase–anti-neutrophil cytoplasmic antibody (MPO-ANCA)-positive nephritis has increased recently [22], a further subanalysis of rapidly progressive nephritic syndrome in the J-RBR should be performed to validate the recently published Japanese guidelines for RPGN [23].

Five new secondary research studies of the J-KDR were started in 2009, viz., the J-NSCS, J-IDCS, J-IGACS, J-RPGNCS, and J-DNCS, and the J-PKD was started in 2010. The J-RBR and J-KDR initiated two more clinical

Table 13 The frequency of clinical diagnoses in focal segmental glomerulosclerosis in primary glomerular disease except IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Classification	2009		2010		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	62	54.9	55	36.9	117	44.7
Nephrotic syndrome	47	41.6	82	55.0	129	49.2
Rapidly progressive nephritic syndrome	1	0.9	1	0.7	2	0.8
Renal disorder with metabolic disease	1	0.9	3	2.0	4	1.5
Recurrent or persistent hematuria	1	0.9	1	0.7	2	0.8
Hypertensive nephropathy	0	–	2	1.3	2	0.8
Acute nephritic syndrome	0	–	1	0.7	1	0.4
Inherited renal disease	0	–	1	0.7	1	0.4
Others	1	0.9	3	2.0	4	1.5
Total	113	100.0	149	100.0	262	100.0

Table 14 The profile of IgA nephropathy in native kidneys in J-RBR 2009 and 2010

IgA nephropathy	2009	2010	Total
Total native kidney biopsies (*n*)	1,001	1,176	2,177
Average age (years)	38.1 ± 17.2	39.3 ± 17.0	38.7 ± 17.1
Median age (years)	35 (24–52)	38 (26–53)	37 (25–52)
Male, *n* (%)	498 (49.8 %)[a]	585 (49.7 %)	1,083 (49.7 %)
Average age (years)	39.5 ± 18.2[b]	40.5 ± 18.4[b]	40.0 ± 18.3[b]
Median age (years)	38 (24–55)[b]	39 (25–56)	38 (24–56)[b]
Female, *n* (%)	503 (50.2 %)[a]	591 (50.3 %)	1,094 (50.3 %)
Average age	36.6 ± 15.9[b]	38.1 ± 15.4[b]	37.5 ± 15.7[b]
Median age	34 (24–49)[b]	37 (26–49)	36 (25–49)[b]

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

[b] $P < 0.05$ compared to other gender

Table 15 Distribution of age ranges and gender in IgA nephropathy in J-RBR in 2009 and 2010

Age (years)	2009			2010			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0–9	11	5	16	12	9	21	23	14	37
10–19	73	68	141	80	55	135	153	123	276
20–29	91	116	207	91	127	218	182	243	425
30–39	87	115	202	113	153	266	200	268	468
40–49	65	81	146	94	106	200	159	187	346
50–59	87	62	149	84	75	159	171	137	308
60–69	62	45	107	82	48	130	144	93	237
70–79	19	9	28	20	18	38	39	27	66
80+	3	2	5	9	0	9	12	2	14
Total	498	503	1,001	585	591	1,176	1,083	1,094	2,177
Under 20 (%)	16.9	14.5	15.7	15.7	10.8	13.3	16.3	12.5	14.4
65 and over (%)	9.4	5.2	7.3	11.5	5.4	8.4	10.5	5.3	7.9

Table 16 The frequency of classification of clinical diagnoses in IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Clinical diagnosis	2009		2010		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	886	88.5	1,064	90.5	1,950	89.6
Recurrent or persistent hematuria	49	4.9	40	3.4	89	4.1
Nephrotic syndrome	30	3.0	36	3.1	66	3.0
Rapidly progressive nephritic syndrome	14	1.4	20	1.7	34	1.6
Acute nephritic syndrome	8	0.8	9	0.8	17	0.8
Renal disorder with collagen disease or vasculitis	4	0.4	1	0.1	5	0.2
Acute renal failure	2	0.2	2	0.2	4	0.2
Drug-induced nephropathy	2	0.2	1	0.1	3	0.1
Renal disorder with metabolic disease	1	0.1	0	–	1	0.0
Hypertensive nephropathy	0	–	1	0.1	1	0.0
Others	5	0.5	2	0.2	7	0.3
Total	1,001	100.0	1,176	100.0	2,177	100.0

Table 17 The frequency of pathological diagnoses as classified by histopathology in IgAN in native kidneys in J-RBR 2009 and 2010

Pathological diagnosis by histopathology	2009		2010		Total	
	n	%	*n*	%	*n*	%
Mesangial proliferative glomerulonephritis	937	93.6	1,111	94.5	2,048	94.1
Endocapillary proliferative glomerulonephritis	12	1.2	2	0.2	14	0.6
Minor glomerular abnormalities	12	1.2	15	1.3	27	1.2
Focal segmental glomerulosclerosis	9	0.9	6	0.5	15	0.7
Crescentic and necrotizing glomerulonephritis	8	0.8	10	0.9	18	0.8
Nephrosclerosis	6	0.6	4	0.3	10	0.5
Membranous nephropathy	4	0.4	2	0.2	6	0.3
Membranoproliferative glomerulonephritis (types I and III)	4	0.4	5	0.4	9	0.4
Sclerosing glomerulonephritis	3	0.3	2	0.2	5	0.2
Chronic interstitial nephritis	1	0.1	2	0.2	3	0.1
Acute interstitial nephritis	0	–	1	0.1	1	0.0
Others	5	0.5	16	1.4	21	1.0
Total	1,001	100.0	1,176	100.0	2,177	100.0

research studies (J-RBR201001 and J-KDR201001) being performed by members of the JSN who had already participated in the registry and who registered cases under the precise regulations presented on the website of the JSN in 2011.

With regard to estimating the number of yearly native renal biopsies in Japan, the Research Group on Progressive Renal Disease from the Ministry of Health, Labor and Welfare of Japan recently reported by a questionnaire method that it was between 18,000 and 21,000 in 2010. The J-RBR may cover nearly one fourth to one fifth of the number of yearly native renal biopsies in Japan in 2010. Since 128,057,352 people resided in Japan in 2010, the estimated rate of renal biopsy was 140.6 to 164.0 per million population. This rate was higher than that in Romania [24], Spain [25], the Czech Republic [10], Denmark [26], and Scotland [27], was similar to that in France [28], and was lower than that in USA, Finland [29], and Australia [30].

There are some limitations in the J-RBR and J-KDR. The J-RBR records three diagnoses for each case, viz., the clinical diagnosis, diagnosis based on the pathogenesis, and the diagnosis based on a histopathological examination, so there may be still some inconsistency in the case records. The terms hypertensive nephropathy, hypertensive nephrosclerosis, nephrosclerosis, and diabetic nephropathy may need to be defined more precisely to improve the accuracy of the report by the J-RBR. The incidence of renal biopsy

Table 18 Distribution of CKD stages and clinical parameters in total in IgA nephropathy in J-RBR: Combined data of 2009 and 2010

	CKD stage					Total	*P* value*
	G1	G2	G3a/b	G4	G5		
Total	663	814	551	111	30	2,169	–
n (%)	30.6	37.5	25.4	5.1	1.4	100.0	–
Age (years), average	23.5 ± 10.9	40.3 ± 13.5	50.9 ± 13.0	55.7 ± 16.2	46.3 ± 20.4	38.7 ± 17.1	<0.0001
Median	22 (17–29)	38 (30–50)	52 (42–61)	59 (44–68)	46 (29–62)	37 (25–52)	<0.0001
Body mass index	21.0 ± 4.0	22.9 ± 3.8	23.6 ± 3.7	23.0 ± 4.5	23.4 ± 5.9	22.5 ± 4.0	<0.0001
Estimated GFR (mL/min/1.73 m^2)	108.2 (96.9–128.0)	75.2 (67.8–82.7)	49.1 (42.0–54.6)	23.6 (20.9–27.6)	8.5 (6.1–12.0)	74.6 (53.8–95.0)	<0.0001
Proteinuria (g/day)	0.30 (0.10–0.81)	0.50 (0.21–1.00)	0.92 (0.40–2.00)	1.60 (0.71–2.84)	2.81 (1.17–4.58)	0.59 (0.22–1.29)	<0.0001
Proteinuria (g/gCr)	0.39 (0.14–0.91)	0.63 (0.28–1.23)	1.03 (0.51–2.01)	1.69 (0.77–4.21)	2.91 (1.30–4.58)	0.70 (0.27–1.47)	<0.0001
Sediment RBC ≥5/hpf (%)	82.4	81.3	74.6	82.0	86.7	80.0	0.0075
Serum creatinine (mg/dL)	0.60 (0.53–0.70)	0.79 (0.70–0.91)	1.16 (1.00–1.36)	2.10 (1.86–2.47)	5.34 (4.06–7.66)	0.81 (0.65–1.07)	<0.0001
Serum albumin (g/dL)	4.15 ± 0.46	4.02 ± 0.49	3.79 ± 0.59	3.45 ± 0.63	3.22 ± 0.59	3.96 ± 0.56	<0.0001
Serum total cholesterol (mg/dL)	184.6 ± 37.4	204.3 ± 46.2	209.9 ± 51.1	211.6 ± 52.3	221.0 ± 58.6	200.2 ± 46.8	<0.0001
Systolic BP (mmHg)	113.9 ± 14.0	123.3 ± 16.2	130.3 ± 17.5	137.6 ± 22.5	147.5 ± 27.9	123.2 ± 18.1	<0.0001
Diastolic BP (mmHg)	67.6 ± 11.4	75.1 ± 12.3	78.9 ± 12.5	81.0 ± 15.6	87.8 ± 18.0	74.2 ± 13.3	<0.0001
Anti-hypertensive agents (%)	13.8	33.3	59.6	75.8	71.4	37.0	<0.0001
Diabetes mellitus (%)	1.5	3.1	7.7	21.1	0.0	4.6	<0.0001

Data are presented as the mean ± SD or the medians (interquartile ranges)

CKD chronic kidney disease, *GFR* glomerular filtration rate, *RBC* red blood cell count, *BP* blood pressure

* ANOVA, Kruskal–Wallis or χ^2-test as appropriate. There are eight (0.4 %) missing values of CKD stage because of inappropriate data for serum creatinine

Table 19 The frequency of classification of clinical diagnoses in other 680 cases than J-RBR in J-KDR 2009 and 2010

Classification	Other cases 2009 (n = 680)		Other cases 2010 (n = 575)		Total (n = 1,255)	
	n	%	n	%	n	%
Chronic nephritic syndrome	165	24.3	72	12.5	237	18.9
Hypertensive nephropathy	142	20.9	43	7.5	185	14.7
Renal disorder with metabolic disease	106	15.6	177	30.8	283	22.5
Nephrotic syndrome	86	12.6	118	20.5	204	16.3
Renal disorder with collagen disease or vasculitis	24	3.5	7	1.2	31	2.5
Rapidly progressive nephritic syndrome	21	3.1	18	3.1	39	3.1
Inherited renal disease	18	2.6	3	0.5	21	1.7
Acute renal failure	9	1.3	10	1.7	19	1.5
Recurrent or persistent hematuria	8	1.2	0	–	8	0.6
Acute nephritic syndrome	5	0.7	4	0.7	9	0.7
Drug-induced nephropathy	5	0.7	0	–	5	0.4
Renal transplantation	2	0.3	9	1.6	11	0.9
Polycystic kidney disease	–	–	82	14.3	82	6.5
Others	89	13.1	32	5.6	121	9.6
Total	680	100.0	575	100.0	1,255	100.0

and the incidence of biopsy-proven renal diseases such as IgAN and primary glomerular disease (except IgAN) could be surveyed in major renal centers in Japan in terms of the epidemiological aspects to work out appropriate countermeasures. In this aspect, the incidence of pediatric IgAN was reported to be 4.5 cases/year per 100,000 children under 15 years of age from 1983 to 1999 in Yonago City, Japan [31], although center variations in the country in terms of the incidence, indications and diagnosis of adult native renal biopsy have been reported [27].

Finally, a committee report of J-KDR including J-RBR in 2009, 2010 and their total was conducted. The J-RBR exhibited the majority of the registry system to elucidate yearly demographic data of renal biopsies in Japan, and J-KDR was utilized to promote advanced clinical research in the field of nephrology in our country.

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Appendix

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Original Article

A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy

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ABSTRACT

Background. The study aim was, for the first time, to conduct a multicenter randomized controlled trial to evaluate the effect of tonsillectomy in patients with IgA nephropathy (IgAN).

Methods. Patients with biopsy-proven IgAN, proteinuria and low serum creatinine were randomly allocated to receive tonsillectomy combined with steroid pulses (Group A; $n = 33$) or steroid pulses alone (Group B; $n = 39$). The primary end points were urinary protein excretion and the disappearance of proteinuria and/or hematuria.

Results. During 12 months from baseline, the percentage decrease in urinary protein excretion was significantly larger in Group A than that in Group B ($P < 0.05$). However, the frequency of the disappearance of proteinuria, hematuria, or both (clinical remission) at 12 months was not statistically different between the groups. Logistic regression analyses revealed the assigned treatment was a significant, independent

factor contributing to the disappearance of proteinuria (odds ratio 2.98, 95% CI 1.01–8.83, P = 0.049), but did not identify an independent factor in achieving the disappearance of hematuria or clinical remission.

Conclusions. The results indicate tonsillectomy combined with steroid pulse therapy has no beneficial effect over steroid pulses alone to attenuate hematuria and to increase the incidence of clinical remission. Although the antiproteinuric effect was significantly greater in combined therapy, the difference was marginal, and its impact on the renal functional outcome remains to be clarified.

Keywords: clinical remission, estimated glomerular filtration rate, hematuria, proteinuria

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide, with primary IgAN characterized by the deposition of IgA antibodies in the glomerulus. The renal outcome of IgAN varies among individual patients [1–4]. Although ~20% of patients remain stable in their renal function [1], 30–40% develop end-stage renal disease (ESRD) within 20 years from its onset [1–4]. The most important determinant of renal outcome in IgAN is the severity and duration of proteinuria, and a decreased severity in proteinuria is distinctly associated with a better renal outcome [1–10].

A number of studies have shown that corticosteroid therapy is effective for progressive IgAN [11–15]. A randomized controlled trial and its 10-year follow-up examined whether steroid pulse therapy is more effective than conventional therapy for long-term preservation of renal function [14, 15]. The risk of a doubling in serum creatinine after 10 years was found to be significantly lower in the group receiving steroid pulses than in the one receiving supportive therapy alone. However, steroid pulse therapy is associated with several problems. For instance, only a small fraction of the treated patients achieved remission of proteinuria after 1 year [15], and severe proteinuria relapsed in a sizable fraction of the patients after the cessation of treatment [15].

Several studies have examined the therapeutic efficacy of tonsillectomy in IgAN. A retrospective study by Rasche *et al.* [16] reported that tonsillectomy had no impact on renal outcome 10 years after biopsy. By contrast, in a retrospective study of 329 IgAN patients, Hotta *et al.* [17] found that tonsillectomy was an independent predictor of the remission of urine abnormalities and a lack of progression in renal injury. Xie *et al.* [18] followed-up 118 patients for an average of 20 years, and found that renal survival was better in the group with prior tonsillectomy than in the one without tonsillectomy at 240 months. More recently, in a non-randomized prospective study, Komatsu *et al.* [19] found that tonsillectomy combined with steroid pulse treatment had a significant impact on the disappearance of both proteinuria and hematuria, when compared with steroid pulse treatment alone. A recent meta-analysis has also reported that tonsillectomy combined with either conventional steroid or steroid pulse treatment resulted in higher remission rates with favorable long-term efficacy [20]. Thus, tonsillectomy combined with steroid pulses has become one of the most widely used therapy protocols in the treatment of active IgAN, and is now being performed in ~50% of the institutions in Japan [21]. However, none of the previous analyses were randomized controlled studies, and there is growing concern that the evidence to date is insufficient for recommending tonsillectomy to IgAN patients [22, 23]. Importantly, the recent Kidney Disease: Improving Global Outcomes clinical guideline for glomerulonephritis suggests that tonsillectomy not be performed for IgAN, because no randomized controlled trial of tonsillectomy has been performed [24].

Here, we report the results of a multicenter, randomized, controlled trial of tonsillectomy combined with steroid pulse therapy in patients with IgAN conducted by the Special IgAN Study Group of the Progressive Glomerular Diseases Study Committee organized by the Ministry of Health, Labour and Welfare of Japan.

MATERIALS AND METHODS

Patients

This multicenter study was conducted between 1 April 2005 and 31 March 2010 in 18 university or community hospitals located in major cities across Japan. The participating institutions routinely performed tonsillectomy combined with steroid pulses to treat IgAN. The study was approved by the local ethics committees and was regulated by an independent data safety and monitoring board.

The inclusion criteria were established primarily according to the previous trial by Pozzi *et al.* [14, 15], and were biopsy-proven IgAN, an age ranging from 10 to 69 years, urinary protein excretion ranging from 1.0 to 3.5 g/day, serum creatinine of ≤1.5 mg/dL, a histological grade diagnosed as a relatively good prognosis, a relatively poor prognosis, or a poor prognosis in the classification proposed in 2004 [25], and systolic and diastolic blood pressures of <140 and <90 mmHg, respectively, regardless of the use or non-use of antihypertensive drugs. Exclusion criteria were nephrotic syndrome, serum creatinine of >1.5 mg/dL, recent treatment with corticosteroids and/or immunosuppressive agents, and contraindications for general anesthesia and/or tonsillectomy as assessed by otolaryngologists. Informed consent was obtained from individual patients following the confirmation of eligibility.

We estimated the frequency of the disappearance of proteinuria at 12 months after the initiation of the treatment would be 40% in patients treated with tonsillectomy plus steroid pulses [21, 26] and 10% in those with steroid pulses alone [14, 15]. Based on the power of 80% for detecting a significant difference (P < 0.05, two-sided), 38 patients were required for each study group. To compensate for non-evaluable patients, we planned to enroll 40 patients per group.

Randomization and masking

The profiles of patients with informed consent were sent to the registration center located at Jikei University School of Medicine. Randomization was done by a technical assistant in

the registration center using a computer-based allocation program with a minimization method, which was developed by an outside company (East Asia Trading Corporation, Hyogo) independent of this study. Immediately after the input of patient information, including the date of enrollment, gender, histological grade, the severity of proteinuria (<2.0 g/day or ≥2.0 g/day), serum creatinine (male, <1.2 mg/dL or ≥1.2 mg/dL; female, <0.9 mg/dL or ≥0.9 mg/dL) and the use or non-use of renin-angiotensin system (RAS) inhibitors, the participants were randomly assigned to receiving tonsillectomy combined with steroid pulses (Group A) or steroid pulses alone (Group B). Since the allocation was based on the presence or absence of tonsillectomy, neither the patients nor the physicians were blinded to the group assignment. Although those assessing the outcomes were not blinded, they assessed the data regarding the pre-defined outcomes using pre-specified statistical analyses.

Study protocol

After the random allocation to Group A or Group B, the center sent the enrollment certificate with the results of randomization to the participating institutions. The patients assigned to Group A underwent tonsillectomy and subsequently received 0.5 g/day of methylprednisolone intravenously for 3 consecutive days at 1–3 weeks later and then at 2 and 4 months later. The patients were also given oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months. The patients assigned to Group B received only the steroid pulse therapy, and were also given oral prednisolone in a manner identical to that in Group A. The protocol of steroid pulse therapy was essentially the same as the one in the trial by Pozzi *et al.* [14, 15], with the exception that a half dose of intravenous methylprednisolone was provided in the current study. The entire trial period (treatment + follow-up) was 12 months. If needed, the patients in both groups were given antihypertensive drugs to control blood pressure to <125/75 mmHg during the trial period. RAS inhibitors were the primary antihypertensive drugs recommended during the study.

Data collection

During the trial, the patients were examined every other month for blood pressure, urinary protein excretion, serum creatinine and urinary sediment with red blood cells. Other data including the incidence of adverse effects and the prescription of additional drugs were also obtained. Urinary protein was measured primarily by the Pyrogaroll Red method. Urinary protein at baseline was represented by a mean value from three consecutive data points prior to the treatment (i.e. tonsillectomy in Group A, first steroid pulses in Group B). The disappearance of proteinuria was defined as urinary protein excretion of <0.3 g/g creatinine in a 24-h urine collection or in urine samples at visits as described previously [15, 27], although the distinct value for disappearance of proteinuria had not been specified at pre-registration. Urinary creatinine concentration was not available in three patients (one patient, Group A; two, Group B). In these patients, the disappearance of proteinuria was defined as levels of <0.3 g/day. Disappearance of hematuria was defined as a number of red blood cells in urinary sediments of <5 per high power field. Clinical remission was defined as the disappearance of both proteinuria and hematuria. eGFR was computed using the following equation [28] developed as a modification of the modified MDRD equation [29]: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine in mg/dL)$^{-1.094}$ × (age in years)$^{-0.287}$ (×0.739 if female).

Outcome definitions

The primary end points were the percentage decrease in urinary protein excretion from baseline and the frequency of the disappearance of proteinuria and/or hematuria 12 months after the initial treatment. The secondary end points were a change in eGFR from baseline, the frequencies of a 100% increase in serum creatinine from baseline, a 50% decrease in eGFR from baseline, indications for renal replacement therapy and adverse effects.

Statistical analysis

Data were subjected to intention-to-treat analysis. All patients, physicians and those assessing the outcomes were not blinded to group assignment. Stata version 11 for Windows (StataCorp LP, College station, TX, USA) was used for the analysis. The percent reduction of proteinuria from baseline was compared between Groups A and B by analyzing the values from six fixed time points (2, 4, 6, 8, 10 and 12 months after randomization) using a mixed effects model. We included as fixed effects group allocation, time, baseline eGFR, mean arterial pressure and the use of RAS inhibitors at baseline. Time was coded as months after the randomization and was given the values of 0, 2, 4, 6, 8, 10 and 12. The patients were included as a random effect. For comparing the parameters between the two groups, the unpaired *t*-test and non-parametric Wilcoxon rank-sum test were used for normally and non-normally distributed variables, respectively. The difference in frequency between the two groups was evaluated using Pearson's chi-square test. Logistic regression analysis was used to evaluate the impact of tonsillectomy, eGFR, mean arterial pressure, urinary protein excretion and the use of RAS inhibitors at baseline on the disappearance of proteinuria, hematuria or both after adjusting for the other covariates. The results were presented as odds ratios with 95% confidence intervals and P-values; $P < 0.05$ was considered statistically significance in all analyses.

RESULTS

Characteristics of the study subjects

Eighty eligible patients were enrolled and randomly allocated to receive tonsillectomy with steroid pulses (Group A) or steroid pulses alone (Group B) (Figure 1). In Group A, three and four patients failed to meet the inclusion criteria and withdrew consent, respectively. In Group B, one patient withdrew consent. One patient in Group A did not undergo tonsillectomy after randomization but was analyzed within this group according to the policy of intention-to-treat analysis. Likewise, two patients in Group B who underwent tonsillectomy after

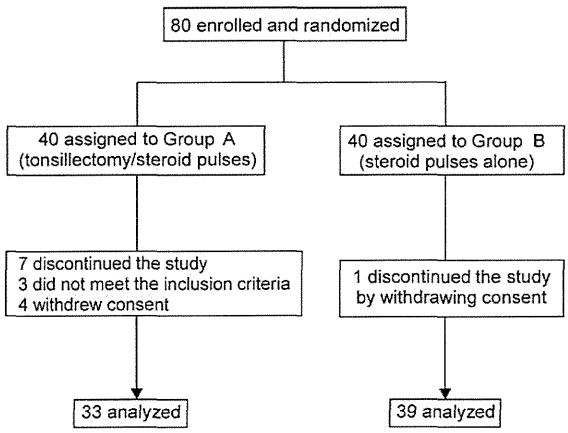

FIGURE 1: Trial profile.

Table 1. Baseline patient characteristics

	Group A Tonsillectomy/steroid pulse therapy ($n = 33$)	Group B Steroid pulse therapy alone ($n = 39$)
Age (years)	36 (13)	40 (13)
Gender		
Male	17* (52)	18* (46)
Female	16* (48)	21* (54)
eGFR (mL/min/1.73 m^2)	75 (24)	69 (22)
Proteinuria (g/day)	1.6 (0.5)	1.6 (0.6)
Proteinuria (g/g creatinine)	1.7 (1.0)	1.7 (1.0)
Systolic blood pressure (mmHg)	117 (12)	121 (10)
Diastolic blood pressure (mmHg)	69 (9)	73 (8)
Mean arterial pressure (mmHg)	85 (9)	89 (8)
Patients receiving RASi (%)	16* (48)	18* (46)
Histological grade		
Good prognosis	0*	0*
Relatively good prognosis	2* (6)	3* (8)
Relatively poor prognosis	20* (61)	23* (59)
Poor prognosis	11* (33)	13* (33)

Data are mean (SD) or *number of patients (%). Histological grade was assessed by the classification proposed by the Special IgAN Study Group in 2004 [30].
eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors.

randomization were analyzed as part of Group B. We therefore analyzed 33 and 39 patients in Groups A and B, respectively. The two groups did not differ in age, gender distribution, estimated glomerular eGFR, urinary protein excretion, blood pressure, the proportion of patients given RAS inhibitors or histological grades (Table 1).

Impact of steroid pulses and tonsillectomy on proteinuria

Figure 2 shows the percent changes in urinary protein excretion from baseline during the trial period. As revealed by a mixed effect model employing six fixed effects (group allocation, eGFR, mean arterial pressure, the use of RAS inhibitors at baseline, time and the interaction of group and time; Supplementary Table S1), the percentage decrease in urinary protein excretion during the 12 months from baseline was significantly larger in Group A than that in Group B (coefficient estimate −1.316, 95% CI −2.617 to −0.015, P = 0.047).

The percentage of patients with the disappearance of proteinuria (<0.3 g/gCr) was significantly higher in Group A than in Group B after 10 months (P = 0.029; Figure 3). However, at 12 months, the difference was not statistically significant (Group A, 63%; Group B, 39%; P = 0.052).

Impact of steroid pulses and tonsillectomy on hematuria

The severity of microscopic hematuria gradually decreased following the initiation of therapy in both groups (Figure 4). However, the proportion of patients with the disappearance of hematuria was not different between the two groups at any time point (e.g. at 12 months, Group A, 68%; Group B, 64%, P = 0.672).

Impact of steroid pulses and tonsillectomy on clinical remission

The disappearance of both proteinuria and hematuria (i.e. clinical remission) did not occur at a higher rate in Group A than in Group B at any time point (P = 0.160 at 10 months, P = 0.103 at 12 months; Figure 5).

Impact of steroid pulse and tonsillectomy on renal functions

eGFR remained stable throughout the trial period and was comparable between the two groups at 12 months (Group A, 75 mL/min/1.73 m^2; Group B, 69 mL/min/1.73 m^2; Figure 6). No patient in either group showed a 100% increase in serum creatinine from baseline or a 50% decrease in eGFR from baseline, or had indications for renal replacement therapy. No adverse effect related to tonsillectomy or general anesthesia was reported. One patient in Group A and three in Group B developed diabetes during the trial period, with one of these Group B patients requiring insulin therapy during the

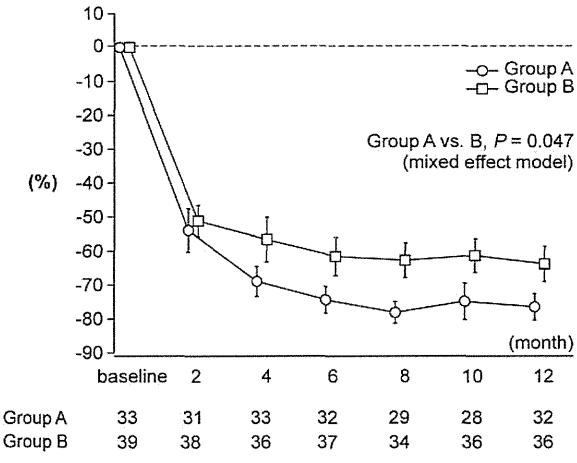

FIGURE 2: Urinary protein excretion during the trial period. Mean values and standard errors are presented. The rate of decrease in urinary protein excretion was significantly higher in Group A than in Group B using a mixed effect model. The numbers of patients analyzed at each time point are shown below the figure for each group.