

Validation of the 2019 ACR/EULAR criteria for IgG4-related disease in a Japanese kidney disease cohort: a multicentre retrospective study by the IgG4-related kidney disease working group of the Japanese Society of Nephrology

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that can affect various organs. The kidney is one of the organs most frequently affected and IgG4-related tubulointerstitial nephritis (TIN) is the most dominant feature.¹ However, several radiologically characteristic lesions within the kidney have also been shown to be diagnostic for IgG4-RD affecting the kidney, in the setting of definitively diagnosed IgG4-related lesions in extrarenal organs.² Therefore the term 'IgG4-related kidney disease (IgG4-RKD)' has been proposed as a comprehensive term for the renal lesions associated with IgG4-RD.^{2,3}

In 2011, the IgG4-RKD working group of the Japanese Society of Nephrology proposed diagnostic criteria for IgG4-RKD.⁴ Recently, we validated those criteria in a Japanese kidney cohort and developed a revised version.⁵ On the other hand, the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD (the ACR/EULAR criteria) were proposed in 2019.⁶ According to the latter criteria, exclusion criteria should be applied first to any potential IgG4-RD case. Then, inclusion criteria consisting of eight weighted domains are applied to any case that does not satisfy any of the exclusion criteria, and if the total inclusion points score is ≥ 20 , the case can be classified as 'IgG4-RD'. We validated the ACR/EULAR criteria in the Japanese kidney cohort used in our validation study for IgG4-RKD 2011.⁵ Briefly, the cohort comprised Japanese patients diagnosed as having renal injury on the basis of urinalysis, radiographic findings and/or function tests between April 2012 and May 2019, in whom serum IgG4 values and/or data for immunohistological staining of IgG4 in renal biopsy samples were known and for whom sufficient clinical information was available. These patients were classified as IgG4-RD or mimickers based on the ACR/EULAR criteria, and the results were evaluated by expert opinion.

Among the 105 patients included, the expert panel diagnosed 55 as true IgG4-RKD and 50 as mimickers. One patient in each group was used for validation of the ACR/EULAR criteria. The clinical and renal pathological features of each group are shown in table 1. In the IgG4-RKD group, renal biopsy was performed in 51 patients and IgG4-TIN was evident in 48 of them (tissue samples being inadequate in 3). Of the 48 patients with biopsy-proven IgG4-RKD, 34 had extrarenal lesions. Among 14 patients who had only renal lesions, 13 had at least one of the following items: storiform fibrosis demonstrated by renal biopsy, hypocomplementaemia or bilateral renal cortex low-density areas demonstrated by radiology. In seven patients for whom renal histology confirmation was not possible (unavailable in four and inadequate in three), diagnosis of IgG4-RKD was based on radiologically evident bilateral renal cortex low-density areas, in the setting of biopsy-proven IgG4-related

Table 1 Data are available on reasonable request

	IgG4-RKD (n=55)	Mimicker (n=50)	P value
Age at diagnosis of the kidney disease, mean \pm SD (years)	69.9 \pm 9.4	56.7 \pm 17.4	<0.001
Male (%)	76.4	44	0.001
Allergy (%)	27.5	36.7	0.393
Serum IgG4 (mg/dL), mean \pm SD	1028 \pm 796	226 \pm 261	<0.001
Elevated serum IgG4 (≥ 135 mg/dL), n/total (%)	54/55 (98.2)	18/50 (36.0)	<0.001
Hypocomplementaemia, n/total (%)	39/55 (70.1%)	7/42 (16.7%)	<0.001
Renal pelvis thickening/soft tissue, n/total (%)	5/55 (9%)	1/50 (2%)	0.20
Bilateral renal cortex low-density areas, n/total (%)	29/55 (52.7%)	7/50 (14.0%)	<0.001
Extrarenal organ(s) involvement, n/total (%)	41/55 (74.5)	20/50 (40.0)	<0.001
Renal biopsy, performed, n/total (%)	51/55 (92.7)	50/50 (100)	0.120
Dense IgG4+PC, n/total (%)	48/51 (94.1)	13/40 (32.5) (not evaluated in 10)	<0.001
Storiform fibrosis in the renal pathology, n/total (%)	28/51 (54.9)	3/50 (6)	<0.001
Renal pathological diagnosis (n)	IgG4-TIN (48) with MN (4) with FSGS (1) with mesPGN (2) Inadequate tissue (3)	AAV (8) MPA (5), EGPA (3) Idiopathic TIN (5) Drug-induced TIN (5) Nephrosclerosis (4) Sjögren's syndrome (4) Sarcoidosis (3) MCD (3) Necrotising GN without ANCA (3) MN (3) Others* (12)	

Dense IgG4+PC: dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells $>10/$ high power field and/or ratio of IgG4-positive plasma cells $>40\%$ in the renal pathology.

Others*: TIN and uveitis syndrome (n=2), TIN associated with inflammatory bowel disease (n=2), TIN with IgM-positive plasma cells (n=2), TIN associated with infection (n=2), IgA nephropathy (n=1), diabetic nephropathy (n=1), malignant lymphoma (n=1) and antibody-mediated rejection after renal transplantation (n=1).

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; EGPA, eosinophilic granulomatosis with polyangiitis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgG4-TIN, IgG4-related tubulointerstitial nephritis; MCD, multicentric Castelman's disease; mesPGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; MPA, microscopic polyangiitis; TIN, tubulointerstitial nephritis.

extrarenal lesions (n=6) or a definite diagnosis of autoimmune pancreatitis (n=1).

Four of the 55 IgG4-RKD patients and 24 of the 50 mimickers had exclusion criteria. Of the remaining cases, 50 of 51 IgG4-RKD patients and 1 of 26 mimickers had an inclusion criterion score of ≥ 20 points (figure 1 and online supplemental table 1). One IgG4-RKD patient, whose autoimmune pancreatitis was the focal swelling type, was misclassified as non-IgG4-RKD. As a result, 50 of the 55 IgG4-RKD patients were classified as IgG4-RKD and 49 of the 50 mimickers were classified as non-IgG4-RKD (sensitivity 90.9%, specificity 98.0%, positive predictive value 98.0% and negative predictive value 90.7%).

Many IgG4-RKD patients had extrarenal lesions and IgG4-positive cell-rich TIN associated with other diseases was effectively excluded on the basis of exclusion criteria. In conclusion, the ACR/EULAR criteria showed an excellent test performance for IgG4-RKD in Japanese patients, although further validation studies of other racial groups will be necessary.

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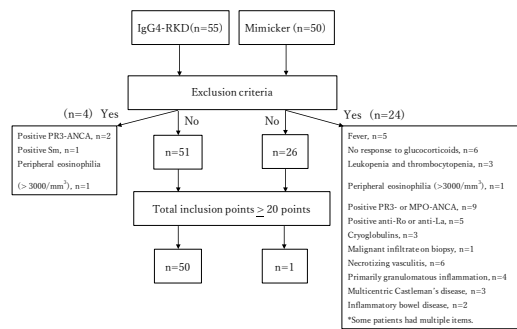


Figure 1 Performance of the American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease in a Japanese kidney cohort. ANCA, antineutrophil cytoplasmic antibody; IgG4-RKD, IgG4-related kidney disease; MPO, myeloperoxidase; PR-3, proteinase 3.

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Handling editor Josef S Smolen

Contributors All authors made contributions to the conception and design of this study. TSAeki, TN and MK performed the data analysis. TSAeki and MK wrote the manuscript. TSAeki, YU, YT, MY, HN and MK collected the data. All authors contributed to reviewing the manuscript and approved the final version for publication.

Funding This work was supported in part by the committee of the Japanese Society of Nephrology and MHLW Research Programme on Rare and Intractable Diseases (grant number JPMH20FC1040).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was initially approved by the ethics committee of Fukuoka University Hospital (reference number 2017M174) and subsequently by the boards of the collaborating institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

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► Prepublication history and additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2020-219510>).



To cite Saeki T, Nagasawa T, Ubara Y, *et al.* *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-219510

Received 12 November 2020

Revised 24 December 2020

Accepted 29 January 2021

Ann Rheum Dis 2021;0:1–2. doi:10.1136/annrheumdis-2020-219510

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Supplementary Table S1. Inclusion criteria in IgG4-related kidney disease and mimickers

Domains and items (number is weight of each item)	IgG4-RKD (n=51)	Mimickers (n=26)
1. Histopathology (including extra-renal organs)		
0; Uninformative biopsy	1	8
+4; Dense lymphocytic infiltrate	23	18
+6; Dense lymphocytic infiltrate and obliterative phlebitis	0	0
+13; Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	27	0
2. Immunostaining (including extra-renal organs)		
0; the IgG4+:IgG+ ratio is 0-40% or indeterminate and the number of IgG4+cells/hpf is 0-9	1	16
+7; 1) the IgG4+:IgG+ ratio is $\geq 41\%$ and the number of IgG4+cells/hpf is 0-9 or indeterminate; or 2) the IgG4+:IgG+ ratio is 0-40% or indeterminate and the number of IgG4+cells/hpf is ≥ 10 or indeterminate	13	8
+14; 1) the IgG4+:IgG+ ratio is 41-70% and the number of IgG4+ cells/hpf is ≥ 10 ; or 2) the IgG4+:IgG+ ratio is $\geq 71\%$ and the number of IgG4+ cells/hpf is 10-50	26	2
+16; the IgG4+:IgG+ ratio is $\geq 71\%$ and the number of IgG4+ cells/hpf is ≥ 51	11	0
3. Serum IgG4 concentration		
0; normal or not checked	1	20
+4; >Normal but < 2x upper limit of normal	4	2
+6; 2-5x upper limit of normal	9	3
+11; >5x upper limit of normal	37	1
4. Bilateral lacrimal, parotid, sublingual and submandibular glands		
0; No set of glands involved	24	26
+6; One set of glands involved	11	0
+14; Two or more sets of glands involved	16	0
5. Chest		
0; Not checked or neither of the items listed is present	43	26
+4; Peribronchovascular and septal thickening	7	0
+10; Paravertebral band-like soft tissue in the thorax	1	0
6. Pancreas and biliary tree		
0; Not checked or none of the items listed is present	41	26

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+8; Diffuse pancreas enlargement (loss of lobulations)	4	0
+11; Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	3	0
+19; Pancreas (either of above) and biliary tree involvement	3	0
7. Kidney		
0; Not checked or none of the items listed is present	3	23
+6; Hypocomplementemia	16	1
+8; Renal pelvis thickening/soft tissue	4	0
+10; Bilateral renal cortex low-density areas	28	2
8. Retroperitoneum		
0; Not checked or neither of the items listed is present	43	26
+4; Diffuse thickening of the abdominal aortic wall	1	0
+8; Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	7	0
Total inclusion points, mean \pm SD	48.4 \pm 14.0	8.4 \pm 5.5
Total inclusion points \geq20, n/total	50/51	1/26

Values are the number.