

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 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

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.

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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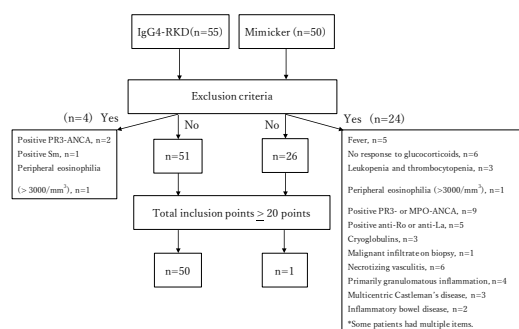


Figure 1 Performance of the American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease in a Japanese kidney cohort. ANCA, antineutrophil cytoplasmic antibody; IgG4-RKD, IgG4-related kidney disease; MPO, myeloperoxidase; PR-3, proteinase 3.

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