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Improved Renal Function in Initial Treatment Improves Patient Survival, Renal Outcomes, and Glucocorticoid-Related Complications in IgG4-Related Kidney Disease in Japan

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Introduction: We aimed to clarify long-term renal prognosis, complications of malignancy, glucocorticoid (GC) toxicity, and mortality in immunoglobulin G4 (IgG4)-related kidney disease (IgG4-RKD).

Methods: Reviewing the medical records of 95 patients with IgG4-RKD, we investigated clinical and pathologic features at baseline, the course of renal function, complications of malignancy, GC toxicity, and mortality during follow-up (median 71 months). The standardized incidence ratio (SIR) of malignancy and standardized mortality ratio were calculated using national statistics. Factors related to outcomes were assessed by Cox regression analyses.

Results: At diagnosis, the median estimated glomerular infiltration rate (eGFR) was 46 ml/min per 1.73 m^2. GC achieved initial improvement. Additional renal function recovery within 3-months of initial treatment occurred in patients with highly elevated serum IgG and IgG4 levels and hypocomplementemia. During follow-up, 68%, 17%, and 3% of the patients had chronic kidney disease (CKD), >30% eGFR decline, and end-stage renal disease (ESRD), respectively. Age-adjusted and sex-adjusted Cox regression analyses indicated that eGFR (hazard ratio [HR], 0.71) and extensive fibrosis (HR, 2.58) at treatment initiation had a significant impact on the time to CKD. Ten patients died, and the standardized mortality ratio was 0.94. The SIR of malignancy was 1.52. The incidence rate (IR) of severe infection was 1.80/100 person-years. Cox regression analyses showed that the best eGFR within 3 months after treatment initiation were associated with lower mortality (HR 0.67) and fewer severe infections (HR 0.63).

Conclusion: This study suggests that more renal function recovery through early treatment initiation may improve patient survival, renal outcomes, and some GC-related complications in IgG4-RKD.

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IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory condition that can affect almost all organs.[1,2] Renal lesions include tubulointerstitial nephritis, renal pyelitis, and membranous glomerulonephritis, collectively known as IgG4-RKD.[3] The

clinical, radiographic, and histopathologic features have been clarified by many studies.[4–7]

In IgG4-RKD, persistent renal damage may occur despite good initial response to GCs especially if treatment initiation is delayed.[8–12] More progressed kidney diseases such as ESRD has been rarely reported likely due to relatively small participant numbers and short observation periods.

Some recent studies have focused on mortality in IgG4-RD. In type 1 autoimmune pancreatitis (AIP)/ IgG4-related sclerosing cholangitis, mortality was reported to be significantly higher than in the general population, with an estimated odds ratio (OR) of 2.07.[13] In contrast, our recent study of patients with various affected organs in addition to AIP/ IgG4-related sclerosing cholangitis found that, in the rheumatology department, IgG4-RD did not significantly affect long-term patient survival, although multiorgan involvement, renal dysfunction, and malignancy may be associated with higher mortality.[14] However, mortality and its related factors in patients with IgG4-RKD are not well known.

GC toxicities during long-term treatments have not been well evaluated in IgG4-RD. In AIP, a randomized controlled trial found no serious GC-related complications in a 3-year follow-up.[15] Saeki *et al*.[9] reported development or worsening of diabetes mellitus, avascular necrosis, infection, psychosis, and vertebral fracture as GC-related complications in their observation study. We think GC toxicity and its incidence in IgG4-RKD should be evaluated in large populations over long follow-up periods.

These prompted us to conduct the present nationwide study to investigate long-term renal prognosis, malignancy complications, cardiovascular events, GC toxicity, mortality, and outcome related factors in IgG4-RKD.

METHODS

We conducted a long-term nationwide multicenter retrospective observation study in Japan. Due to lack of epidemiologic data, including prevalence, incidence, and mortality of patients with IgG4-RKD, it was quite difficult to determine an appropriate sample size. Therefore, in the present exploratory study, we collected data on as many patients with this disease as possible from 10 institutions with a wealth of experience in treating the disease (Supplementary Table S1).

Patients and Materials

We enrolled 95 consecutive patients diagnosed with IgG4-RKD according to the published diagnostic criteria for IgG4-RKD[16] (Supplementary Table S2) and/ or the 2019 American College of Rheumatology/ European League Against Rheumatism classification criteria for IgG4-RD[17] among patients seen at the 10 collaborating institutions (Supplementary Table S1) between January 1, 2004, and December 31, 2021. Of the 95 patients, 92 patients had IgG4-related involvement of >1 extrarenal organ. Renal biopsy was performed in 72 patients; and biopsy of affected extrarenal organs in 65 patients all showed characteristic histologic and immunohistochemical findings consistent with the diagnosis. No biopsy was performed in 2 patients, who had typical renal multiple low-density lesions on enhanced computed tomography and fulfilled the clinical diagnostic criteria for type 1 AIP.

Reviewing the medical records, we retrospectively evaluated parameters, including laboratory data, imaging, and pathologic findings at baseline, course of renal function, relapse of renal lesions, malignancy complications, cardiovascular events, GC toxicity, and mortality during the long-term observation periods (median 71 months, interquartile range [IQR] 39–102) in 95 patients. The following clinical factors at the time of diagnosis were retrospectively determined: age; sex; allergy history; serum levels of IgG, IgG4, IgE, C3, C4, CH50, C-reactive protein, and creatinine; eGFR calculated on the basis of Chronic Kidney Disease Epidemiology Collaboration equations[18]; peripheral blood eosinophil count; presence or absence of rheumatoid factor, antinuclear antibody, and various disease-specific autoantibodies, including SSA/Ro antibody, antineutrophil cytoplasmic antibody, and double-stranded DNA antibody; and involvement of pancreas, salivary glands, lacrimal glands, kidney, aorta/artery, retroperitoneum, and lung. We also determined GC use, initial GC dose, and other immunosuppressant use during the observation periods. Furthermore, eGFR significantly improved within the first 3 months of initial treatment, and the best value of eGFR during that period is henceforth referred to as the "best" eGFR in the present study.

As renal outcomes, we defined CKD status as sustained eGFR <60 ml/min per 1.73 m^2 and doubling of serum creatinine levels or ESRD, during the clinical course; eGFR rise >20 ml/min per 1.73 m^2 per year in the first 3 months of initial treatment and eGFR slope < -3.0 ml/min per 1.73 m^2 per year at the last visit; and >30% decline in eGFR at the last visit. Taking the lowest serum creatinine level in the first 3 months of initial treatment as reference, doubling of serum creatinine levels was assessed. Defining the best eGFR values in the first 3 months of initial treatment as reference, eGFR slope and rate of eGFR decline were assessed.

Relapse of IgG4-RKD was determined by the attending physician based on rapid rise in serum

creatinine level after careful exclusion of other renal diseases, and/or recurrence or worsening of the radiologic findings. In IgG4-RD, re-elevation of serologic values such as serum IgG or IgG4 without clinical symptoms or abnormal radiologic findings was not considered as relapse.

The presence of malignancy during the observation periods was defined as malignancy at or after the diagnosis of IgG4-RKD.

Basically, according to Glucocorticoid Toxicity Index,[19] GC toxicity in the present study included major increase in body mass index (increase by at least 5 body mass index units above normal body mass index [24.9 kg/m^2]); moderate steroid myopathy (weakness with functional limitation); moderate skin toxicity; moderate neuropsychiatric symptoms; infection indicating i.v. antibiotic, antifungal, or antiviral intervention, radiologic or operative intervention, hospitalization, or herpes zoster complicated by postherpetic neuralgia or eye involvement; hypertensive emergency or posterior reversible encephalopathy syndrome; fracture; avascular necrosis; tendon rupture; symptomatic adrenal insufficiency; gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) or peptic ulcer disease confirmed by endoscopy (excluding *Helicobacter pylori*); central serous retinopathy, intraocular pressure elevation, or posterior subcapsular cataract.

This study was approved by the Medical Ethics Committee of Kanazawa University and the other 9 collaborating institutions (Supplementary Table S1). All data and samples from patients were collected with their verbal informed consent, or patient approval and/or informed consent were waived with disclosure of the study contents for those with loss of follow-up or death because the study involved a retrospective review of patient records, images, and pathologies. The study adhered to the tenets of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using SPSS V.25. Data are presented as median (IQR1–IQR3]) for continuous variables. Missing data was not imputed. The significance of differences between groups was determined using the Mann-Whitney *U* test, whereas that of differences in frequencies was analyzed with Fisher exact probability test. Using collected data, we calculated the crude IR of various outcomes, including malignancy and death. The SIR of malignancy and standardized mortality ratio were calculated using national Japan statistics. For assessment of factors related to various outcomes, unadjusted and age-adjusted and sex-adjusted logistic regression, or Cox regression analyses and, as appropriately, multivariate analyses were performed. For time-to-event analyses, we considered that the follow-up of the patients started at the time of IgG4-RKD diagnosis (untreated patients) or treatment initiation for IgG4-RKD (treated patients) and was terminated at the time of the end of the observation period (December 31, 2021), loss of follow-up, or death. In our multivariate analyses, we adhered to the guideline suggesting the use of 1 variable for every 10 outcomes.[20–22] We constructed multivariate models by applying significant variables from the univariate regression analyses and comparisons between subjects who did and did not reach an outcome in clinical and demographic variables, along with age and sex as standard variables. However, we excluded serum C4 and CH50 levels from the multivariate analyses because they exhibited a high correlation coefficient (>0.7) and multicollinearity with serum C3 levels among the complement-related variables. Similarly, within the variables related to renal function, we excluded serum creatinine levels from the multivariate analyses because this variable exhibited high correlation coefficients (< -0.7) and multicollinearity with eGFR at the time of diagnosis and the best eGFR in the first 3 months of initial treatment. In the logistic and Cox regression analyses, for continuous variables, units for increments to calculate ORs and HRs were set at 1 year for age; 100 mg/dl for serum IgG4 and IgG levels; 100 IU/ml for serum IgE levels; 1 U/ml for serum CH50 levels; 1 mg/dl for serum C3, C4, C-reactive protein, and creatinine levels; 100 /μl for eosinophil counts; and 10 ml/min per 1.73 m^2 for eGFR. Significant differences were defined as $P < 0.05$.

Considering the issues related to multiple comparisons, we controlled the false discovery rate at 0.05. We calculated *q*-values and used them to determine the significance of the results or describe some as judgment pending, which means a final determination is pending further evaluation.

To mitigate the potential influence of maintenance GC administered at the time of IgG4-RKD diagnosis on the levels of IgG, IgG4, and other parameters, we conducted additional analyses. These analyses involved the exclusion of 4 patients who had received GC treatment at the time of diagnosis. The results of these specific analyses can be found in Supplementary Tables S3 to S7.

RESULTS

Patient Baseline Profiles

In Table 1, we present the baseline (time of diagnosis) profiles of the 95 IgG4-RKD patients (75 men and 20 women), with a median age of 69 years (IQR 60–75). The median follow-up period from the start of

Table 1. Baseline clinical characteristics of 95 patients with IgG4-related kidney disease

Variable	*N* = 95
Age	69 (60–75)
Male sex (%)	79
Allergy (%)	33
Serum IgG4 level (mg/dl)	774 (497–1,324)
Serum IgG level (mg/dl)	2959 (2226–3995)
Serum IgE level (IU/ml)	418 (184–723)
Serum C3 level (mg/dl)	70 (41–92)
Serum C4 level (mg/dl)	9 (2–23)
Serum CH50 level (IU/l)	31 (10–49)
Serum CRP level (mg/dl)	0.17 (0.10–0.50)
Serum creatinine level (mg/dl)	1.14 (0.78–1.75)
eGFR (ml/min per 1.73 m^2)	46.0 (28.6–68.6)
Eosinophil count (/μl)	177 (77–446)
RF positivity (%)	26
ANA positivity (%)	34
Diabetes mellitus (%)	37
Hypertension (%)	46
Dyslipidemia (%)	28
Smoking history (%)	64
History of cardiovascular disease (%)	11
Renal abnormalities in imaging (%)	89
Observation period (mo)	71 (39–102)

ANA, antinuclear antibody; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgG4-RD, immunoglobulin G4-related disease; IgE, immunoglobulin E; PSL, prednisolone; RF, rheumatoid factor.
Conversion factor for Cr: mg/dl to μmol/l, ×88.4. Data are presented as median [interquartile range (IQR1–IQR3)] for continuous variables.

treatment, or the time of diagnosis if not treated, for newly diagnosed IgG4-RKD was 71 months (IQR 39–102).

Six patients had received prednisolone treatment before their IgG4-RKD diagnosis. Among them, 2 patients had discontinued prednisolone treatment at the time of IgG4-RKD diagnosis but resumed it after diagnosis. The remaining 4 patients had been taking 3–10 mg/day prednisolone at the time of IgG4-RKD diagnosis and were prescribed an increased dosage after the diagnosis. The remaining 89 patients received no immunosuppressants before diagnosis.

Out of the 92 patients with involvement of ≥1 extrarenal organs, salivary gland involvement was observed in 69% of cases, lacrimal gland involvement in 44%, pancreas involvement in 31%, aorta/retroperitoneum involvement in 27%, and lung involvement in 22%. In 82 patients, IgG4-RKD and IgG4-RD in extrarenal organ(s) were diagnosed simultaneously. On the other hand, in 10 patients, IgG4-RKD was identified at a median of 12 months (IQR 9–31) following the diagnosis of extrarenal IgG4-RD.

At diagnosis of the 95 patients, the median serum IgG4 level (normal range: <105 mg/dl) measured by nephelometry was 774 mg/dl (IQR 497–1324). Forty-seven patients (49%) had hypocomplementemia defined as abnormal decreased serum C3 and/or CH50 levels. The median eGFR was 46 ml/min per 1.73 m^2 (IQR 29–69), and 56 patients (59%) had eGFR <60 ml/min per 1.73 m^2.

Regarding comorbidities at baseline, diabetes mellitus was present in 35 patients; hypertension in 44; dyslipidemia in 26; and ischemic heart disease, cerebral vascular disease, or peripheral arterial disease in 10. Of the 89 patients whose smoking history was available, 57 were past or current smokers.

In Supplementary Table S3, we show baseline profiles of the 91 patients with IgG4-RKD who were not administered GC at the time of IgG4-RKD diagnosis, indicating no remarkable difference compared with profiles of the 95 patients.

Treatment

The indications and regimens for treatment were decided by respective attending physicians. On the diagnosis of IgG4-RKD, 92 patients were treated with prednisolone at a median initial dose of 30 mg/day (IQR 30–40), which was gradually tapered then maintained at a median dose of 5 mg/day (IQR 3–6) at the last visit. GC discontinuation at the last visit was achieved in only 5 patients. Seventy-four patients were treated with GC alone, and the remaining 18 with a combination of GC and another immunosuppressant such as azathioprine, mizoribine, tacrolimus, or cyclosporine. The immunosuppressants were administered to the patients with concomitant nephrotic syndrome as initial treatment at the time of IgG4-RKD diagnosis; to those with relapse of renal and/or nonrenal lesions; and to those without relapse with the aim to reduce the dose of GC as much as possible.

In accordance with a Japanese guideline,[23] bisphosphonate and/or active type vitamin D agent were administered to the enrolled patients to reduce the risk of osteoporotic fractures.

Course of Renal Function After GC Therapy

The median eGFR of all 95 patients before therapy was 46 ml/min per 1.73 m^2 (IQR 29–69), 51 ml/min per 1.73 m^2 (IQR 38–70) at 1 month after the start of therapy, 58 ml/min per 1.73 m^2 (IQR 41–75) at 3 months, 58 ml/min per 1.73 m^2 (IQR 42–70) at 6 months, 53 ml/min per 1.73 m^2 (IQR 41–66) at 12 months, and 54 ml/min per 1.73 m^2 (IQR 43–66) at the last review (Figure 1), showing significant initial improvement by GC and long-term preserved renal function under maintenance therapy. Among the 95 patients, 14 who followed-up with for ≥10 years showed a similar course of renal function (Figure 2).

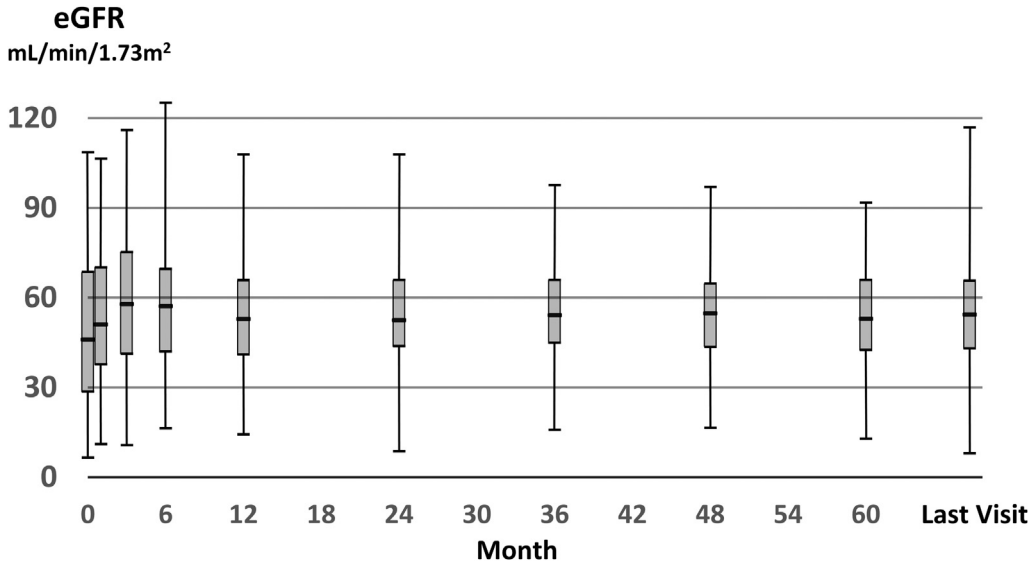

Figure 1. Course of renal function in 95 patients with IgG4-RKD. Boxes and bars represent interquartile and whole ranges, respectively. eGFR, estimated glomerular infiltration rate; IgG4-RKD, immunoglobulin G4-related kidney disease.

Renal Outcomes

Only 3 patients (3%) showed doubling of serum creatinine levels or ESRD during the clinical course, with an IR of 0.5/100 person-years. In 82 patients followed-up for >2 years, median eGFR rise in the first 3 months of initial treatment was 26.6 ml/min per 1.73 m^2 per year (IQR 3.9–54.2), with 41 (50%) showing eGFR rise >20 ml/min per 1.73 m^2 per year. Logistic regression analysis revealed that lower serum C3 levels (OR 0.97, 95% confidence interval [CI] 0.95–0.99) and higher serum IgG4 (per 100 mg/dl, OR 1.10, 95% CI 1.01–1.20) and IgG levels (per 100 mg/dl, OR 1.06, 95% CI 1.01–1.10) were associated with such eGFR rise. Among them, based on a *q*-value, serum C3 levels were confirmed to be significant, whereas serum IgG4 and IgG levels were regarded as judgment pending. Multivariate analysis revealed that lower serum C3 levels and higher serum IgG4 levels were independently associated with eGFR rise (Table 2). In an additional analysis including 91 patients without GC administration at diagnosis, male sex, lower serum C3 levels, higher serum IgG4 and IgG levels, and higher peripheral eosinophil counts were associated with such eGFR rise. Based on a *q*-value, serum C3 levels were confirmed to be significant (Supplementary Table S4). In contrast, the median eGFR slope from initial treatment to the last visit was −1.21 ml/min per 1.73 m^2 per year (IQR −2.44 to −0.39), with 15 (18%) showing eGFR slope < −3.0 ml/min per 1.73 m^2 per year at the last visit.

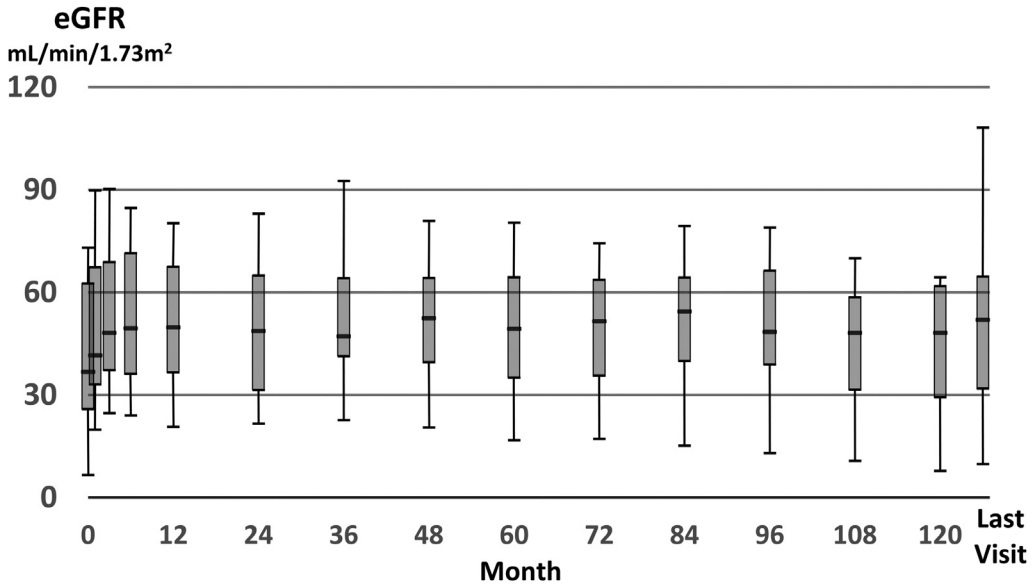

Figure 2. Course of renal function in 14 patients with IgG4-RKD with >10-years follow-up. Boxes and bars represent interquartile and whole ranges, respectively. eGFR, estimated glomerular infiltration rate; IgG4-RKD, immunoglobulin G4-related kidney disease.

Table 2. Odds ratio for risk of eGFR rise >20 ml/min per 1.73 m^2 per year in the first 3 months of initial treatment: unadjusted and age-adjusted and sex-adjusted logistic regressions

	Unadjusted				Age-adjusted and sex-adjusted				Multivariate		
Variable	OR	95% CI	*P*-value	*q*-value	OR	95% CI	*P*-value	*q*-value	OR	95% CI	*P*-value
Age (yr)	0.995	0.955–1.038	0.823	0.920	0.987	0.944–1.032	0.562	0.763	0.921	0.857–0.989	**0.024**
Male sex	2.979	0.941–9.430	0.063	0.171	3.177	0.977–10.331	0.055	0.149	2.492	0.521–11.909	0.253
Allergy	1.573	0.615–4.023	0.344	0.545	1.495	0.551–4.057	0.430	0.681	-	-	-
Serum IgG4 level (100 mg/dl)	1.101	1.015–1.194	**0.021**	0.067	1.100	1.011–1.197	**0.027**	0.086	1.194	1.029–1.386	**0.019**
Serum IgG level (100 mg/dl)	1.053	1.013–1.095	**0.009**	0.057	1.056	1.014–1.101	**0.009**	0.057	0.952	0.880–1.030	0.225
Serum IgE level (100 IU/ml)	0.929	0.859–1.004	0.063	0.150	0.927	0.854–1.006	0.071	0.150	-	-	-
Serum C3 level (mg/dl)	0.977	0.961–0.993	**0.005**	**0.048**	0.972	0.954–0.990	**0.002**	**0.019**	0.963	0.933–0.995	**0.022**
Serum C4 level (mg/dl)	0.967	0.932–1.004	0.079	0.150	0.963	0.925–1.002	0.063	0.150	-	-	-
Serum CH50 level (IU/l)	0.970	0.948–0.993	**0.012**	0.057	0.967	0.944–0.992	**0.009**	**0.043**	-	-	-
Serum CRP level (mg/dl)	0.701	0.400–1.277	0.214	0.370	0.674	0.372–1.220	0.193	0.333	-	-	-
Serum Cr level (mg/dl)	2.074	1.119–3.843	**0.020**	0.076	2.189	1.115–4.298	**0.023**	0.087	-	-	-
eGFR (10 ml/min per 1.73 m^2)	0.697	0.565–0.859	**0.001**	**0.019**	0.611	0.470–0.796	**<0.001**	**0.019**	0.569	0.412–0.785	**<0.001**
Eosinophil counts (100/μl)	1.116	0.991–1.255	0.069	0.146	1.111	0.984–1.256	0.089	0.169	1.055	0.913–1.219	0.465
Diabetes mellitus	1.378	0.555–3.421	0.489	0.664	1.235	0.477–3.198	0.664	0.742	-	-	-
Hypertension	1.217	0.510–2.902	0.658	0.833	1.285	0.508–3.252	0.597	0.756	-	-	-
Dyslipidemia	1.033	0.376–2.837	0.949	0.949	0.898	0.317–2.540	0.839	0.839	-	-	-
Smoking	0.863	0.349–2.129	0.748	0.888	0.715	0.272–1.885	0.498	0.728	-	-	-
Cardiovascular disease	1.759	0.392–7.902	0.461	0.674	1.510	0.323–7.056	0.600	0.713	-	-	-
Initial dose of PSL (mg/kg/d)	1.308	0.082–20.767	0.849	0.896	1.712	0.092–31.936	0.719	0.759	-	-	-

ANA, antinuclear antibody; CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgE, immunoglobulin E; OR, odds ratio; PSL, prednisolone.
Conversion factor for Cr: mg/dl to μmol/l, ×88.4.
The boldface was used when $P < 0.05$ or $q < 0.05$.

Sixteen (17%) showed >30% decline in eGFR at the last visit. Logistic regression analysis revealed that the best eGFR in the first 3 months of initial treatment was negatively associated with >30% decline in eGFR (per 10 ml/min per 1.73 m^2, OR 0.77, 95% CI 0.59–1.00), whereas eGFR at the time of diagnosis (per 10 ml/min per 1.73 m^2, OR 0.89, 95% CI 0.71–1.11) and the changes in eGFR before and after the initial 3-month treatment (OR 0.97, 95% CI 0.92–1.03) were unassociated.

The IR of CKD status was 30.6/100 person-years, with 68% of the patients showing CKD during their clinical course. Age-adjusted and sex-adjusted Cox regression analyses indicated that several factors had a significant impact on the time to CKD status: eGFR (per 10 ml/min per 1.73 m^2, HR 0.71, 95% CI 0.63–0.80), hypertension (HR 1.81, 95% CI 1.08–3.04), and extensive fibrosis (>50% vs. <5%, HR 2.58, 95% CI 1.10–6.02) in biopsied renal specimens at treatment initiation. Among these factors, eGFR was confirmed to be significant based on a *q*-value, whereas hypertension and extensive fibrosis were regarded as judgment pending. In a multivariate analysis, only eGFR was found to independently have a significant impact on the time to CKD status (Table 3). In an additional analysis that included 91 patients who did not receive GC administration at the time of diagnosis, the same 3 factors were associated with CKD status. Based on a *q*-value, eGFR was confirmed to be significant (Supplementary Table S5). Relapse of renal lesions was diagnosed in 15 patients (16%), with an IR of 2.89/100 person-years.

Malignancy Complications

Sixteen patients (17%) were diagnosed as having malignancies during follow-up. The median period from start of therapy or observation without therapy to the diagnosis of malignancies was 68 months (IQR 8–83), with malignancy diagnosed within 12 months in 5 patients (31%). Malignancies involved colon in 4 patients, stomach in 4, lung in 3, bladder in 3, pancreas, esophagogastric junction, prostate, and myelodysplastic syndrome in 1 each. The IR of malignancy was 2.93/100 person-years, and the SIR was 1.52 (95% CI 0.88–2.43) based on Japan national statistics.

Cardiovascular Events and GC Toxicities

During the observation periods, 9 patients suffered cardiovascular complications, including myocardial infarction in 3, aortic dissection in 2, angina attack, aortic arch aneurysm, high-grade atrioventricular block, and deep vein thrombosis in 1 each. The median period from start of therapy or observation without therapy to these events was 65 months (IQR 40–116), with an IR of 1.61/100 person-year.

Ten patients suffered 13 severe infections, including pneumonia, enterocolitis, pyelonephritis, iliopsoas muscle abscess, intervertebral discitis, infectious foot gangrene, sepsis, and herpes zoster of the trigeminal

Table 3. Hazard ratio for risk of persistent renal insufficiency: unadjusted and age- and sex-adjusted Cox regressions

	Unadjusted				Age-adjusted and sex-adjusted				Multivariate		
Variable	HR	95% CI	*P*-value	*q*-value	HR	95% CI	*P*-value	*q*-value	HR	95% CI	*P*-value
Age (yr)	1.023	0.999–1.047	0.059	0.212	1.021	0.996–1.046	0.094	0.255	1.015	0.976–1.054	0.463
Male sex	1.907	0.970–3.749	0.061	0.183	1.794	0.909–3.541	0.092	0.276	1.377	0.553–3.429	0.492
Allergy	0.799	0.466–1.371	0.415	0.534	0.886	0.506–1.554	0.674	0.758	-	-	-
Serum IgG4 level (100 mg/dl)	0.981	0.940–1.023	0.364	0.546	0.978	0.936–1.022	0.321	0.578	-	-	-
Serum IgG level (100 mg/dl)	1.007	0.988–1.027	0.466	0.559	1.003	0.982–1.024	0.792	0.839	-	-	-
Serum IgE level (100 IU/ml)	1.007	0.993–1.022	0.333	0.545	1.004	0.989–1.018	0.615	0.791	-	-	-
Serum CH50 level (IU/l)	0.994	0.983–1.006	0.331	0.596	0.997	0.986–1.009	0.661	0.793	-	-	-
Serum CRP level (mg/dl)	0.966	0.807–1.158	0.711	0.711	0.923	0.765–1.114	0.405	0.608	-	-	-
Serum creatinine level (mg/dl)	1.450	1.246–1.687	**<0.001**	**0.009**	1.402	1.193–1.647	**<0.001**	**0.009**	-	-	-
eGFR (10 ml/min per 1.73 m^2)	0.717	0.644–0.797	**<0.001**	**0.018**	0.709	0.631–0.798	**<0.001**	**0.018**	0.723	0.620–0.844	**<0.001**
Eosinophil counts (100/μl)	1.016	0.972–1.062	0.470	0.529	1.025	0.980–1.073	0.284	0.568	-	-	-
Diabetes mellitus	1.234	0.749–2.034	0.409	0.566	1.070	0.644–1.777	0.795	0.795	-	-	-
Hypertension	1.955	1.187–3.220	**0.008**	**0.048**	1.810	1.077–3.042	**0.025**	0.150	1.830	0.916–3.655	0.087
Dyslipidemia	0.710	0.398–1.268	0.247	0.494	0.648	0.361–1.160	0.144	0.324	-	-	-
Smoking	1.201	0.704–2.048	0.502	0.532	1.209	0.691–2.118	0.506	0.701	-	-	-
Cardiovascular disease	1.660	0.788–3.499	0.183	0.412	1.419	0.665–3.028	0.366	0.599	-	-	-
Inflammatory areas (>50% vs. <10%)	1.987	0.890–4.438	0.094	0.242	2.080	0.922–4.693	0.078	0.281	-	-	-
Fibrotic areas (>50% vs. <5%)	2.371	1.027–5.471	**0.043**	0.194	2.575	1.103–6.015	**0.029**	0.131	1.585	0.655–3.830	0.307

CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgE, immunoglobulin E.
Conversion factor for Cr: mg/dl to μmol/l, ×88.4.
The boldface was used when $P < 0.05$ or $q < 0.05$.

nerve, with pneumonia being the most common. The IR of severe infection was 1.80/100 person-years. Univariate Cox regression analysis revealed the best eGFR within 3 months of initial treatment (HR 0.63, 95% CI 0.46–0.88) was associated with a lower risk of severe infections, whereas changes in eGFR before and after the initial 3-month treatment (OR 0.97, 95% CI 0.92–1.03) showed no significant association. Based on a *q*-value, all the extracted factors were regarded as judgment pending (Table 4). In an additional analysis that included 91 patients who did not receive GC administration at the time of diagnosis, the same factors except for serum creatinine levels were associated with severe infections. Based on a *q*-value, none of the extracted factors were confirmed to be significant (Supplementary Table S6).

Associations between cumulative amounts of prednisolone given to the patients and the development of complications such as cardiovascular diseases, severe infections, and diabetes mellitus were also investigated. Cox regression analyses revealed no association between cumulative amounts of prednisolone and cardiovascular events (per 1000 mg, HR 1.03, 95% CI 0.95–1.11) or severe infections (per 1000 mg, HR 0.94, 95% CI 0.86–1.03). Logistic regression analysis showed that cumulative amounts of prednisolone were not associated with new development of diabetes mellitus (per 1000 mg, OR 1.03, 95% CI 0.97–1.09) during the observation periods. These findings might be influenced by the fact that the patients with a good clinical course had long-term observation periods and therefore received a greater cumulative dose of GC.

The IRs of other GC toxicities included: vertebral fracture, 0.88/100 person-years; avascular necrosis, 0.35; moderate GC myopathy, 0.53; intraocular pressure elevation, 0.68; posterior subcapsular cataract, 0.62; and 0.17 for each of moderate neuropsychiatric

Table 4. Hazard ratio for risk of severe infection: univariate Cox regressions

	Univariate			
Variable	HR	95% CI	*P*-value	*q*-value
Age (yr)	1.052	0.980–1.128	0.163	0.344
Male sex	29.721	0.034–26,254	0.327	0.518
Allergy	0.989	0.247–3.955	0.987	0.987
Serum IgG4 level (100 mg/dl)	0.939	0.827–1.066	0.331	0.484
Serum IgG level (100 mg/dl)	0.980	0.930–1.033	0.457	0.543
Serum IgE level (100 IU/ml)	1.029	1.003–1.054	**0.026**	0.247
Serum CH50 level (IU/l)	1.016	0.984–1.048	0.344	0.467
Serum CRP level (mg/dl)	1.174	0.913–1.510	0.212	0.366
Serum creatinine level (mg/dl)	1.366	1.002–1.863	**0.049**	0.233
eGFR (10 ml/min per 1.73 m^2)	0.755	0.564–1.012	0.060	0.228
Best eGFR (10 ml/min per 1.73 m^2)	0.634	0.455–0.883	**0.007**	0.133
ΔeGFR during initial treatment	0.973	0.916–1.034	0.377	0.478
Eosinophil counts (100/μl)	0.953	0.807–1.126	0.574	0.642
Diabetes mellitus	2.514	0.673–9.385	0.170	0.323
Hypertension	5.160	1.068–24.935	**0.041**	0.260
Dyslipidemia	1.385	0.346–5.541	0.645	0.681
Smoking	3.379	0.650–17.563	0.148	0.352
Cardiovascular disease	4.282	0.865–21.205	0.075	0.238
Initial dose of PSL (mg/kg/d)	0.028	0.001–1.604	0.084	0.228

Best eGFR, the best estimated glomerular filtration rate in the first 3 months of initial treatment; CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgE, immunoglobulin E; PSL, prednisolone.
Conversion factor for Cr: mg/dl to μmol/l, ×88.4.
The boldface was used when $P < 0.05$ or $q < 0.05$.

Table 5. Cause of death in 10 patients

No.	Age	Sex	IgG4 (mg/dl)	Best eGFR within 3 mo (ml/min per 1.73 m^2)	Cause of death	Time since diagnosis of IgG4-RD (mo)
1	81	M	548	44.5	Recurrent gastric cancer	4
2	60	M	886	38.1	Lung cancer	72
3	76	M	1,030	74.1	Severe pneumonia	72
4	84	M	329	37.0	Sudden death	85
5	76	F	984	71.8	Myocardial infarction	88
6	83	M	924	40.6	Cerebral hemorrhage	99
7	74	M	798	72.6	Pancreatic cancer	114
8	85	M	232	25.6	Sigmoid colon perforation	125
9	60	M	730	74.2	Colon cancer	235
10	60	M	305	39.9	Sepsis, iliopsoas abscess	253

eGFR, estimated glomerular filtration rate; F, female; IgG4, serum immunoglobulin G4 level; IgG4-RD, immunoglobulin G4-related disease; M, male.

symptoms, gastrointestinal perforation, and peptic ulcer disease.

Mortality and Mortality-Related Factors

Of the 10 patients (11%) who died during follow-up (Table 5), 4 died of malignancy, 2 of severe infections, 2 of cardiac or cerebral vascular events, 1 of sigmoid colon perforation, and 1 of sudden death of unknown cause, with a median period from start of therapy or observation without therapy to death of 94 months (IQR 72–125). The crude all-cause mortality rate was 1.68/100 person-years, with the standardized mortality ratio of 0.94 (95% CI 0.45–1.72).

Factors related to mortality were assessed using univariate Cox regression analysis, which revealed that age at diagnosis was associated with higher mortality (HR 1.16, 95% CI 1.06–1.28), and malignancy diagnosed during the observation periods tended to be associated with higher mortality (HR 3.27, 95% CI 0.81–13.14). In contrast, the best eGFR within 3 months of initial treatment was associated with lower mortality (HR 0.67, 95% CI 0.45–0.99). Based on a *q*-value, only age at diagnosis was confirmed to be significant (Table 6). In an additional analysis that included 91 patients who did not receive GC administration at the time of diagnosis, age at diagnosis was associated with higher mortality, whereas the best eGFR within 3 months of initial treatment tended to be associated with lower mortality. Based on a *q*-value, age at diagnosis was confirmed to be significant (Supplementary Table S7).

Table 6. Hazard ratio for risk of death: univariate Cox regression

	Univariate			
Variables	HR	95% CI	*P*-value	*q*-value
Age (yr)	1.164	1.057–1.281	**0.002**	**0.040**
Male sex	1.352	0.164–11.142	0.779	0.916
Allergy	0.025	0.000–11.448	0.239	0.598
Serum IgG4 level (100 mg/dl)	0.919	0.808–1.045	0.196	0.784
Serum IgG level (100 mg/dl)	0.968	0.916–1.023	0.252	0.560
Serum IgE level (100 IU/ml)	0.974	0.852–1.114	0.704	>.0.999
Serum CH50 level (IU/l)	0.997	0.960–1.036	0.884	0.931
Serum CRP level (mg/dl)	1.048	0.519–2.117	0.895	0.895
Serum creatinine level (mg/dl)	1.152	0.767–1.730	0.496	0.902
eGFR (10 ml/min per 1.73 m^2)	0.820	0.600–1.119	0.211	0.703
Best eGFR (10 ml/min per 1.73 m^2)	0.670	0.452–0.993	**0.041**	0.410
ΔeGFR during initial treatment	0.989	0.927–1.054	0.730	0.913
Eosinophil counts (100/μl)	0.739	0.450–1.214	0.232	0.663
Diabetes mellitus	1.383	0.367–5.216	0.632	0.972
Hypertension	1.589	0.422–5.985	0.494	0.988
Dyslipidemia	0.853	0.171–4.260	0.847	0.941
Smoking	1.305	0.324–5.264	0.708	0.944
Cardiovascular disease	0.041	0.000–838.43	0.529	0.882
Malignancy at or after diagnosis	3.268	0.813–13.135	0.095	0.633
Initial dose of PSL (mg/kg/d)	0.041	0.001–2.013	0.108	0.540

Best eGFR, the best estimated glomerular filtration rate in the first 3 months of initial treatment; CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgE, immunoglobulin E; PSL, prednisolone.
Conversion factor for Cr: mg/dl to μmol/l, ×88.4.
The boldface was used when $P < 0.05$ or $q < 0.05$.

DISCUSSION

The present study suggested that patients with IgG4-RKD who have typical serologic features, including hypocomplementemia and highly elevated serum IgG and IgG4 levels were more likely to show better recovery of renal function in the first 3 months of initial treatment. Few patients had harsh outcomes such as ESRD, doubling of serum creatinine levels, or eGFR slope < -3.0 ml/min per 1.73 m^2 per year. Median eGFR slope during the observation periods was -1.2 ml/min per 1.73 m^2 per year, suggesting feasible renal function preservation by maintenance therapy. In contrast, our results also revealed that the majority of patients with IgG4-RKD reached a CKD state and confirmed that renal insufficiency and extensive fibrosis at treatment initiation were CKD risk factors. Malignancy may develop long after IgG4-RKD diagnosis to become a major cause of death, albeit the SIR was not significantly high. The mortality of patients with IgG4-RKD was equivalent to age-adjusted and sex-adjusted mortality in Japan national statistics. In addition to patient age at IgG4-RKD diagnosis, the best eGFR in the first 3 months of initial treatment was significantly associated with mortality; therefore, attaining good renal function at an early phase of treatment is important to improve patients' prognosis. These results might provide novel hints to manage IgG4-RKD, leading to significant advances.

The results highlight the importance of renal function recovery early in treatment and long-term preservation of renal function under GC maintenance therapy. Only a few patients had harsh renal outcomes although many reached CKD. Renal function recovery early in treatment is characteristic of IgG4-RKD. This study showed that greater initial improvement of renal function may be expected in those with typical serologic features such as hypocomplementemia and highly elevated serum IgG and IgG4 levels, indicating the need for early treatment of such patients. Moreover, median eGFR slope during long-term observation was -1.21 ml/min per 1.73 m^2 per year in this study, indicating relatively good preservation of renal function. In contrast, smaller population studies reported that patients with IgG4-RKD with renal insufficiency at treatment initiation result in persistent renal dysfunction[9,11] and/or renal atrophy[12] despite effective standard GC treatment. This long-term nationwide survey also found that worse renal function and more extensive renal fibrosis at treatment initiation were significantly associated with reaching CKD, confirming the importance of early treatment. A few patients showed $>30\%$ decline in eGFR at the last observation compared with baseline, and the best eGFR within 3 months of initial treatment was negatively associated with such decline. Further work is necessary to clarify the risk-benefit balance of GC toxicity and renal function preservation by maintenance therapy comparing renal function outcomes with and without maintenance therapy.

GC toxicity during maintenance therapy has not been sufficiently elucidated in IgG4-RKD. From a GC toxicity index,[19] we evaluated many GC toxicities. Whereas a multicountry study reported cardiovascular event IR to be 0.41/100 person-years for female and 0.64/100 person-years for male[24] and a Japanese study reported 0.08/100 person-years for female and 0.32/100 person-years for male,[25] the present study found cardiovascular event IR to be 1.61/100 person-years in patients with IgG4-RKD, suggesting a higher risk in this disease. The IR of vertebral fracture was 0.88/100 person-years in our study, whereas that of GC-induced osteoporotic vertebral fracture was reported to be 4.30/100 person-years in a Japanese retrospective cohort study,[26] suggesting lower incidence may be due to prophylaxis strategies. Ten patients suffered from severe infection, which was the most frequent toxicity and an important problem in patients with IgG4-RKD treated with GC. As a risk factor of severe infection, the best eGFR within 3 months of initial treatment was detected, suggesting that early treatment of patients with IgG4-RKD not only improves renal prognosis but also prevents development of severe infection. In Table 3, we indicate that early treatment before renal insufficiency developed prevents persistent renal insufficiency, resulting in improved renal function (eGFR) within 3 months of initial treatment. In Table 4, we demonstrate a significant association between better eGFR within 3 months of initial treatment and a lower risk of severe infections, likely due to reduced influence from renal insufficiency-related immunodeficiency. Therefore, we speculate that early treatment of IgG4-RKD is associated with a lower risk of severe infections.

Although a definitive conclusion on association between IgG4-RD and malignancy is absent, high prevalence and/or incidence of malignancy and its impact on mortality are suggested in IgG4-RD. Some studies reported high malignancy IR in IgG4-RD,[13,27-33] whereas others did not.[34,35] A Japanese single-center study[14] reported that malignancy IR at or after IgG4-RD diagnosis was significantly higher than that in healthy Japanese. In contrast, few studies have evaluated malignancy IR in IgG4-RKD. The present study suggested a high tendency of such IR and its potential impact on death among patients with IgG4-RKD, albeit not significantly. Timing of malignancy onset is another point of interest. Although Shiokawa *et al.*[32]

reported the highest risk of cancer within the first year after AIP diagnosis in 108 patients, subsequent studies and the present one showed that among patients with malignancies at or after IgG4-RD diagnosis, 40% to 74% developed malignancies >1 year after IgG4-RD diagnosis,[29,31,33] suggesting caution of malignancies developing long after IgG4-RD diagnosis. Differences in time of malignancy onset in these studies may reflect differences in the bias of organs involved. Considering that malignancy was the most prevalent cause of death in the present study, continued systemic screening for malignancy in IgG4-RKD patients may improve survival.

To our best knowledge, the present study is the first to focus on mortality among patients with IgG4-RKD. Some recent large cohort studies reported mortality and causes of death in type 1 AIP/ IgG4-related sclerosing cholangitis and the whole IgG4-RD. Huggett *et al.*[13] reported significantly higher mortality in patients with type 1 AIP/ IgG4-related sclerosing cholangitis compared with the British population and the importance of malignancy as cause of death.[13] Kawahara *et al.*[14] reported an equivalent mortality in the whole IgG4-RD consisting mainly of salivary and lacrimal gland lesions as an age-adjusted and sex-adjusted Japanese general population, whereas malignancy complications during the clinical course and renal insufficiency at diagnosis were significantly associated with death.[14] In the present study, mortality of the 95 patients with IgG4-RKD was equivalent to an age-adjusted and sex-adjusted mortality in the Japan population. As reported by Huggett and Kawahara, malignancy was the most common cause of death in this study; however, in IgG4-RKD, the best eGFR within 3 months of initial treatment had a significant impact on the time to death. These results suggested that, in addition to systemic examination for malignancy, achievement of better renal function within 3 months of initial treatment through earlier treatment induction, especially in patients with typical serologic features, improved patient survival.

This study had several limitations. First, the treatment regimen and follow-up protocols were inconsistent among patients due to the multicenter retrospective design, complicating evaluation of the influence of detailed treatment protocol differences on patient outcomes. Second, time-to-event analyses could not be performed for some outcomes of renal function because they were evaluated at fixed observation times. Third, although in its favor our study cohort is one of the largest multicenter nationwide cohorts of patients with IgG4-RKD thus far accumulated, the number of patients was insufficient to observe many harsh outcomes such as death and ESRD and to identify independent factors by multivariate analyses. Fourth, this study was conducted in only Japan although the patients were enrolled from extensive areas in this country. How race, lifestyle, and geography affect the outcomes evaluated needs to be clarified through multinational studies. Therefore, larger-scale prospective studies are needed to confirm our results.

In conclusion, the present study suggests that more recovery of renal function by early treatment initiation, especially in patients with typical serologic abnormalities, may improve patient survival, renal outcomes, and some GC-related complications in IgG4-RKD. Although a larger-scale multicenter prospective study is needed for confirmation, our findings may help to establish optimal management strategies.

DISCLOSURE

The author declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

IM and MK conceived and designed the study. IM and MK contributed to acquisition and interpretation of data, drafted, and revised the manuscript. TS, DK, NS, HH, YT, HN, KY, SM, TN, HT, and MY contributed to acquisition and interpretation of data and revised the manuscript. All authors approved the final version manuscript for publication and agreed to be accountable for the authors' contributions.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Information of each ethical committee and its approval for the present study.

Table S2. The 2020 Japanese diagnostic criteria for IgG4 -related kidney disease.

Table S3. Baseline clinical characteristics of 91 IgG4 -related kidney disease patients without glucocorticoid administration at diagnosis.

Table S4. Odds ratio for risk of eGFR rise >20 mL/min/ 1.73m 2 /year in the first 3 months of initial treatment: unadjusted and age- and sex-adjusted logistic regressions.

Table S5. Hazard ratio for risk of persistent renal insufficiency: unadjusted and age- and sex-adjusted Cox regressions.

Table S6. Hazard ratio for risk of severe infection: univariate Cox regressions.

Table S7. Hazard ratio for risk of death: univariate Cox regression.

STROBE statement.

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