Evaluating and predicting disease damage accumulation of IgG4-RD over ten years: utility of the IgG4-related Disease Damage Index

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Abstract

Objective

To describe the cumulative degree of disease-induced damage in patients with immunoglobulin G4-related disease (IgG4-RD) during long-term follow-up.

Methods

A total of 334 patients who were diagnosed with IgG4-RD and followed for over 5 years were included from a prospective cohort, with 99 followed for 10 years. The Chinese IgG4-RD Consortium IgG4-RD Damage Index (DI) was scored at baseline (6 months), 5 years, and 10 years. The total DI scores and the frequencies of damage domains and items were described. The characteristics and treatment regimens of patients in increased damage and stable damage subgroups were compared. The risk factors for damage accrual at 5 years and 10 years were explored.

Results

The DI score increased from 0.89 at baseline to 1.29 at 10 years. The 'pancreatic' (13.4%), 'liver/biliary tree' (7.2%), and 'other' (28.9%) domains presented the greatest degree of damage across the assessments. In the 'other' domain, malignancy and diabetes mellitus were crucial items and increased from 0.3% to 5.1% and from 3.6% to 14.4% within 5 years, respectively. Glucocorticoid side effects were also important damage factors. The risk factors for damage accrual at 5 years were baseline pancreatic involvement (OR 2.11, 95% CI: 1.27–3.50; p=0.004) and relapse frequency (OR 1.40, 95% CI: 1.04–1.89; p=0.028). The risk factor for damage accrual at 10 years was baseline pancreatic involvement (OR 2.89, 95% CI: 1.02–8.16; p=0.045).

Conclusion

The long-term damage caused by IgG4-RD includes organ damage and treatment-related damage. The damage caused by IgG4-RD accumulates over time. Pancreatic damage, malignancy, and diabetes are highlighted. Baseline pancreatic involvement and relapse frequency might predict damage accrual within 5 years. The long-term management of IgG4-RD should aim to preserve organ function while minimising treatment-related damage.

Key words

immunoglobulin G4-related disease, damage index, prognosis, glucocorticoid toxicity

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibroinflammatory disease characterised by multiple tumefactive lesions and elevated serum IgG4 levels (1). There has been much progress in the diagnosis, treatment, and assessment of disease activity since its recognition just two decades ago. The diagnostic criteria have been updated since 2010 (2, 3), and the IgG4-RD Responder Index (RI) was established to evaluate disease activity and treatment response (4). Recently, Della-Torre *et al*. made efforts to provide readily implementable red flags for the early recognition of IgG4-RD in primary health care settings (5). There have also been extensive descriptions of damage caused by IgG4-RD. However, insufficient research has evaluated and quantified the damage caused by IgG4-RD.

Currently, the most widely used assessment instrument is the IgG4-RD responder index (RI) (4). Nevertheless, the IgG4-RD RI mainly focuses on disease activity and requires recording irreversible organ dysfunction. However, it does not score treatment-related damage or complications associated with IgG4-RD. Moreover, it does not incorporate a weighted scoring system. In contrast, many indices for quantitative damage evaluation in other autoimmune diseases, such as the Systemic Lupus International Collaborating Clinics Systemic Lupus Erythematosus Damage Index (SLICC SLE-DI) (6), the Sjgren's Syndrome Damage Index (SSDI) (7), and the Vasculitis Damage Index (VDI) (8), have been developed and validated. In these damage indices, scoring items (some weighted) include all three facets of disease-related damage: irreversible dysfunction or abnormality of involved organs, adverse events related to treatment, and complications. In particular, treatment-related adverse events are universally incorporated, as high-dose and/or long-term glucocorticoid (GC) administration and immunosuppressant (IM) usage are recommended for these diseases (9, 10). Clinicians have underscored GC side effects, namely, GC toxicity, and a glucocorticoid toxicity index (GTI) has been developed (11). Another important damage item is the onset of malignancy. Many studies have revealed increased risks of malignancy in patients with IgG4-RD and other autoimmune diseases, often predicting a poor prognosis (12–14). In IgG4-RD, it is still difficult to quantify disease- and treatment-related damage, monitor damage accrual, and identify the exact aspects of damage during long-term follow-up. Hence, an independent and comprehensive damage index for IgG4-RD is needed.

In our previous study, we developed and validated an IgG4-RD damage index (DI) comprising 14 domains and 39 items (Appendix 1) with a glossary for reference (15). Disease damage was defined as irreversible damage for more than 6 months, including organ dysfunction, persistent imaging abnormalities, complications, and treatment-related adverse events. The IgG4-RD DI can differentiate well between disease activity and damage accumulation and has been validated to have good content validity, criterion validity, and interrater reliability. It is a promising tool for assessing damage in IgG4-RD patients under research and clinical circumstances. In this study, we first applied the IgG4-RD DI to patients from a real-world IgG4-RD prospective cohort. We aimed to describe disease-related damage based on the IgG4-RD DI and reveal the degree of damage accrual during a follow-up period of over 10 years. Furthermore, we aimed to explore the risk factors for damage accrual over time.

Patients and methods

Patient enrolment

This study was based on a prospective IgG4-RD cohort from Peking Union Medical College Hospital (PUMCH) beginning in 2012 (registered on ClinicalTrials.gov NCT01670695). We retrospectively recruited patients from the cohort. The inclusion criteria were as follows: 1. patients who fulfilled the 2019 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) IgG4-RD classification criteria (3) and/or the 2020 revised comprehensive diagnostic criteria for IgG4-RD (2) and 2, patients who had a consecutive follow-up period of at least 5 years. The follow-

ing patients were excluded: 1. patients with IgG4-RD mimicry diseases, such as Castleman disease, Rosai-Dorfman disease, inflammatory myofibroblastic tumours and malignancies; 2. patients who lacked clinical data (laboratory and/or imaging tests) for DI scoring at the baseline and 5-year follow-up visits; and 3. patients who were followed up for less than 5 years.

Clinical data collection

Data collection included sex, age at diagnosis, organ involvement, laboratory test results, and objective imaging results. The remission induction and maintenance regimens, duration of GC treatment, frequency and time of relapse, and complications (including malignancy and medication side effects) during follow-up were also recorded.

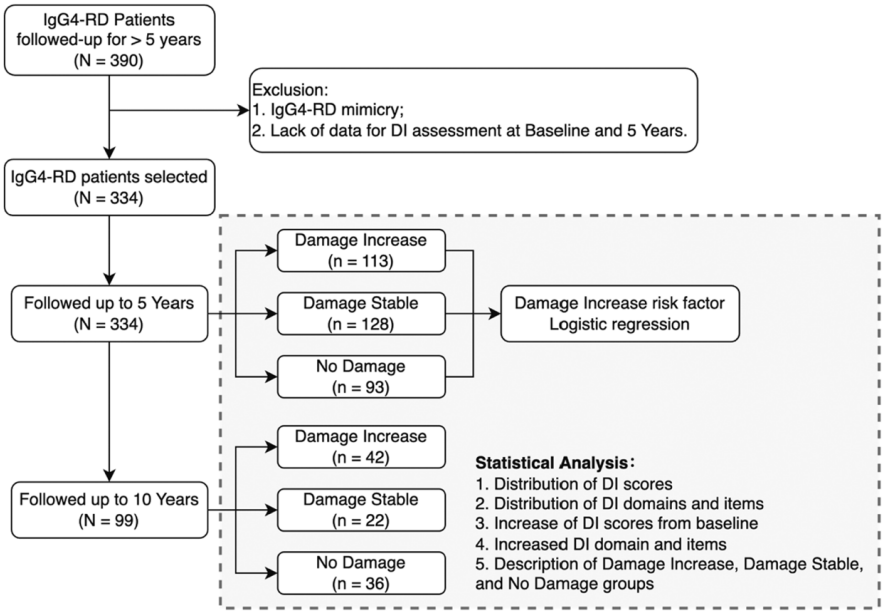

Fig. 1. Flowchart of the study.

Treatment and outcomes

The duration of GC usage was defined as the duration from the initiation of GC prescription to the completion of GC cessation, calculated in months. The IM was graded by intensity as follows: 'strong' was defined as a dosage of cyclophosphamide (CYC) ≥50 mg per day, mycophenolate mofetil (MMF) ≥1.5 g per day, tacrolimus (FK506) ≥3 mg per day or cyclosporin A (CsA) ≥150 mg per day; 'moderate' was defined as CYC <50 mg per day, MMF <1.5 g per day, CsA <150 mg per day or FK506 <3 mg per day; and 'mild' was defined as the use of mild IMs, including methotrexate, leflunomide, iguratimod and hydroxychloroquine (16). Biological agents were not included in the analysis of IM intensity, since only two patients used biological agents at baseline in this study.

Relapse was defined as a recurrence of symptoms and signs and/or worsening of imaging features or the onset of new organ involvement, with any item of the IgG4-RD RI scoring ≥2 in untreated or treatment-discontinued patients or ≥3 in those receiving sustained therapy, with or without re-elevation of the serum IgG4 level (17, 18).

Chinese IgG4-RD Consortium IgG4-RD DI scoring

This study designated three assessment points for the evaluation of damage: at baseline (a follow-up of 6 months), 5 years, and 10 years. Damage to the enrolled patients was evaluated and scored using the CIC IgG4-RD DI at these assessment points. DI scoring was performed by three independent assessors trained in advance, and discrepancies were determined by an expert group. All DI scores were verified to form the final version. The study flowchart is shown in Figure 1.

Ethics approval

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of PUMCH (approval no. S-442). Informed consent was obtained from all the participants at baseline.

Statistical analysis

Normally distributed variables are described as the mean ± standard deviation (SD), and non-normally distributed variables are described as the median and interquartile range (IQR). Wilcoxon's test and Student's t-test were performed to compare continuous variables. The Kruskal-Wallis rank-sum test, chi-square test, or Fisher's exact test was used to compare categorical variables and proportions, where appropriate. *p*-values were adjusted using the Bonferroni method, where appropriate. Missing values were imputed using the multiple imputation method for further analyses (19). Multivariate logistic regression was used to identify the risk factors for damage accrual at the 5-year follow-up. Variables of clinical importance were selected and included in the regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of the associations. Two-tailed *p*-values <0.050 were considered statistically significant. Statistical analysis and visualisation were conducted with R (v. 4.4.2).

Results

Clinical and serological profiles of IgG4-RD patients at baseline

Damage was evaluated in a total of 334 patients with the CIC IgG4-RD DI. The included patients were predominantly male (63.8%). The median age at diagnosis was 55 years, and the mean follow-up period was 88.1±22.6 months. All patients were followed for 5 years, with 99 patients subsequently followed for over 10 years. The major organs involved at baseline included the submandibular gland (51.8%), lacrimal gland (51.5%), lymph node (46.1%), pancreas (37.4%), lung (25.4%), nasal sinus (33.2%), and bile duct (21.6%) (Supplementary Table S1).

Landscape of CIC IgG4-RD DI scores in patients with IgG4-RD

We first examined the distribution of DI scores across assessment points. The majority of patients scored 0 and 1 on the IgG4-RD DI at baseline and at the 5-year and 10-year assessments. The number of patients with DI scores over 2 points increased with prolonged follow-up (Fig. 2A and C). In all included patients, the mean DI score was 0.89±0.96 at baseline and 1.28±1.16 at 5 years (Fig. 2B). Among the 99 patients who were followed for 10 years, the mean DI score was 0.71±0.86 at baseline, 0.91±0.98 at 5 years, and 1.29±1.28 at 10 years (Fig. 2E). Overall, the mean DI score increased over time, with a steeper increase from the 5-year to the 10-year assessment point among the 99 patients followed for 10 years (Figure 2E). Furthermore, we analysed the change in the total DI score over time. Many patients showed no change in their DI score at 5 or 10 years, suggesting stable disease or no damage. However, a few patients had a DI score increase of over 2 points, indicating the onset of new damage or the progression of existing damage (Fig. 2C and F). To summarise, the disease damage accumulated over long-term follow-up in patients with IgG4-RD, as quantified by the CIC IgG4-RD DI.

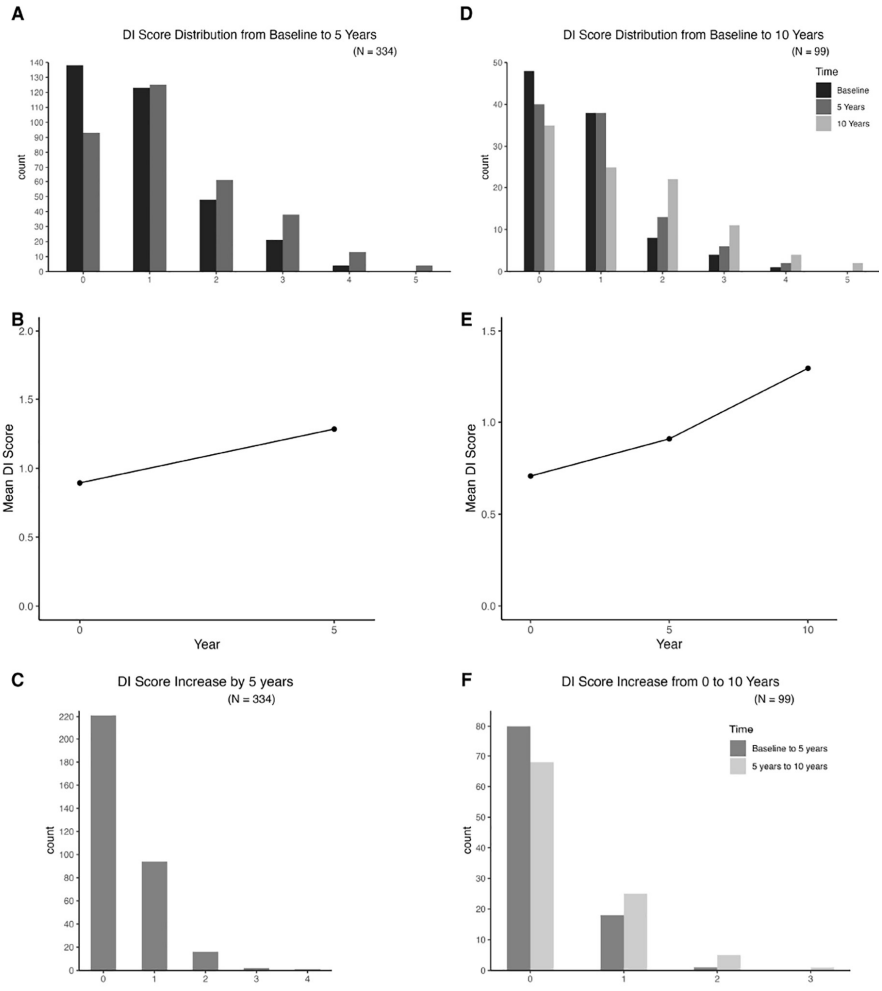

Fig. 2. The distribution and accumulation of DI score across the baseline, 5-year, and 10-year assessment points.
A: the distribution histograms of DI scores at baseline and 5 years in all 334 included patients.
B: the line plots of mean DI scores from baseline to 5 years in all 334 included patients.
C: the distribution histogram of the increased value of DI scores from the Baseline to 5 years in all 334 included patients.
D: the distribution histogram of DI scores at baseline, 5-year, and 10-year assessments in 99 patients who were followed for 10 years.
E: the line plots of mean DI scores from baseline to 10 years in 99 patients who were followed to 10 years.
F: the distribution histogram of the increased value of DI scores from baseline to 5 years and from 5 years to 10 years in 99 patients who were followed up to 10 years.

The 'pancreas', 'liver/biliary tree' and 'other' domains were the most important damage domains during follow-up

Next, we investigated the composition of damage items at the three assessment points. First, the most frequent organ damage domains at baseline were the 'pancreas' (13.4%, 45/334), 'liver/biliary tree' (7.2%, 24/334), 'lung' (14.3%, 48/334), and 'retroperitoneum/mediastinum' (10.8%, 36/334) domains. Additionally, these domains remained prominent at 5 years and 10 years, representing the most important organs involved in IgG4-RD (Fig. 3A-B). Within the 'pancreas domain' and 'liver/biliary tree domain', pancreatic imaging abnormalities and bile duct stricture/stenosis were the dominant damage items. In contrast, pancreatic and liver dysfunctions, such as exocrine pancreatic insufficiency and cirrhosis, were rare. Notably, the 'other' domain also stood out as an essential component at baseline (28.9%, 88/334), showing considerable accumulation from baseline to 5 years (50.0%, 167/334) and 10 years (65.6%, 65/99) (Fig. 3A-B). The 'other' domain consisted of nine items, including other organ damage not previously mentioned, malignancy onset, disease- or treatment-related cardio- or cerebrovascular accidents, drug-related myelosuppression, GC-related femoral necrosis, GC-related osteoporosis with fracture, GC-related cataract, disease- or treatment-related diabetes, and complete or partial excision of involved organs (surgery) (Appendix 1). Within the 'other' domain at baseline, the major component was surgery (72.7%) (Fig. 3C). During follow-up, the incidence of GC toxicity, including diabetes, osteoporosis, and cataracts, gradually increased. The onset of malignancy stood out as a notable component of the 'other' domain at 5 years (10.2%) (Fig. 3D) and 10 years (15.4%) (Fig. 3E). These results highlight the significance of GC toxicity and malignancy onset as damage in IgG4-RD patients, indicating that long-term disease-induced damage is not limited to the involved organs.

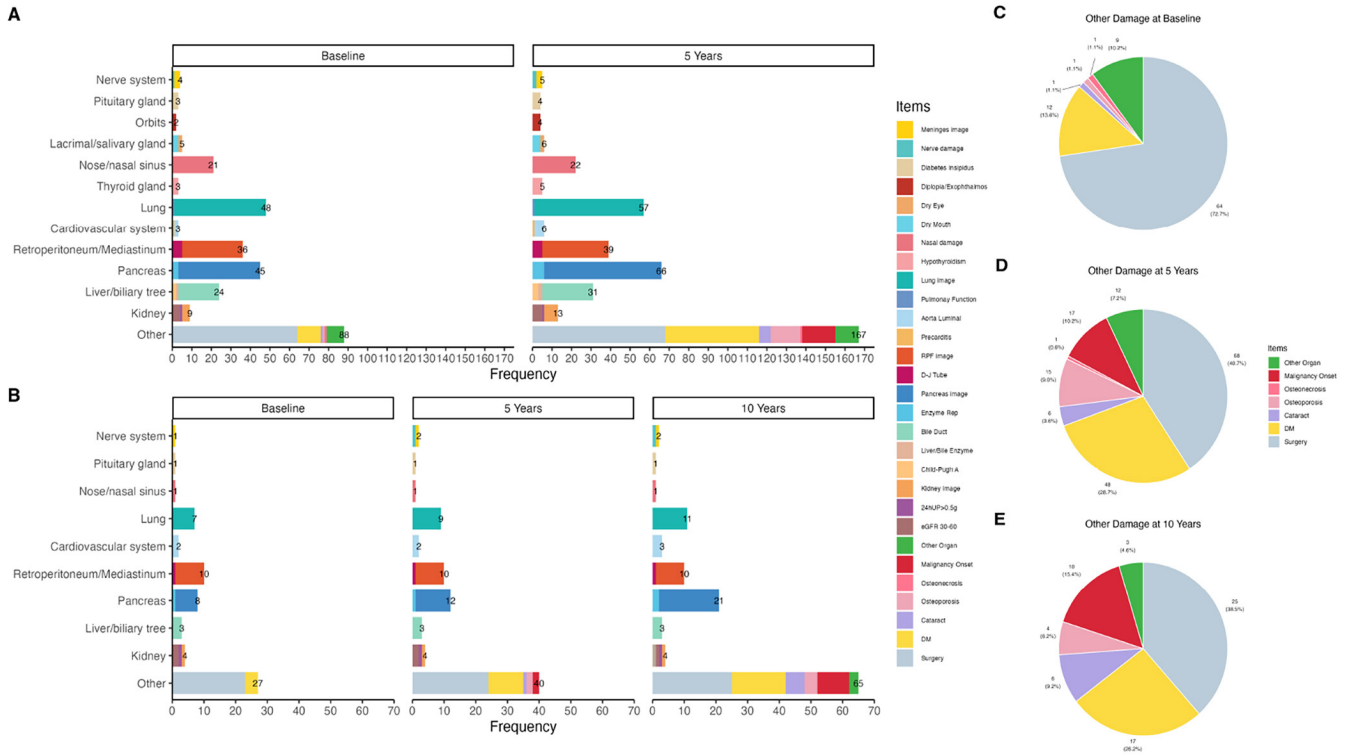

Fig. 3. The landscape of damage items of CIC IgG4-RD DI score across the baseline, 5-year, and 10-year assessment points.
A-**B**: the stack bar plots of DI damage items from the baseline to 5 years in all 334 patients included (A) and from baseline to 10 years in the 99 patients followed up for 10 years (B).
C-**E**: The pie plots of the composition of the 'Other' domain of IgG4-RD DI at baseline (C), 5 years (D) in all 334 patients included, and 10 years in the 99 patients followed to 10 years (E).

Pancreatic damage, malignancy onset, and diabetes represent accumulated damage items by 5 and 10 years

Subsequently, we analysed the newly developed damage in patients during follow-up. Over time, considerable damage accumulated in the 'pancreas' domain. Pancreatic imaging abnormalities developed in 17 patients by 5 years (Fig. 4C) and in another 8 patients by 10 years (Fig. 4D). Notably, by 5 years, only 3 patients had developed pancreatic exocrine insufficiency and required pancreatic enzyme replacement (Fig. 4C). As expected, the 'other' domain was another major domain where damage accumulated (Fig. 4A-B). The most common newly developed damage item by 5 years was diabetes (Fig. 4C). The number of patients with new-onset diabetes dramatically increased [3.6% (12/334) at baseline *vs*. 14.4% (48/334) by 5 years]. The malignancy onset item also stood out. By 5 years, a marked increase was observed in the number of patients newly diagnosed with malignancy [0.3% (1/334) at baseline *vs*. 5.1% (17/334) by 5 years] (Fig. 4C). Another eight patients developed cancer from the 5- to 10-year assessment points (Fig. 4D). By 10 years, 25 patients in our cohort (7.5%) had developed malignancies.

Risk factors for damage accrual by the 5-year assessment

Furthermore, we explored the risk factors for damage accrual by the 5-year assessment point. First, we divided patients into three subgroups according to the baseline DI and increase in DI (ΔDI) over 5 years: the increased damage group (ΔDI >0), stable damage group (baseline DI >0 but remained stable, namely, ΔDI = 0), and no damage group (DI score remained 0 from baseline to 5 years). The demographic data, baseline clinical characteristics and treatment, duration of GC use, and frequency of relapse before the 5-year assessment were compared (Table I). The patients in the increased damage subgroup were older than those in the no damage subgroup at diagnosis [increased damage 58.0 (51.0, 63.0) years vs. no damage 53.0 (45.0, 58.0) years, adjusted p=0.046]. No disparity in the sex distribution was observed. With respect to serological indicators, the serum IgG1 levels were higher in the increased damage subgroup than in the no damage subgroup [increased damage 9070 (7420, 11700) mg/L *vs*. no damage 8935 (6952, 10800) mg/L, adjusted p=0.023]. Surprisingly, however, no significant difference in the serum IgG4 level was observed (p=0.280). In terms of baseline organ involvement, the increased damage subgroup exhibited greater involvement in the pancreas (increased damage 50.4% *vs*. stable damage 34.4% *vs*. no damage 25.8%, p=0.001), bile duct (increased damage 32.7% *vs*. stable damage 17.2% *vs*. no damage 14.0%, p=0.002), and aorta (increased damage 11.5% *vs*. stable damage 14.1% *vs*. no damage 3.2%, p=0.027). The involvement of the retroperitoneum tended to be greater in the increased damage and stable damage subgroups (increased damage 14.2% *vs*. stable damage 21.1% *vs*. no dam-

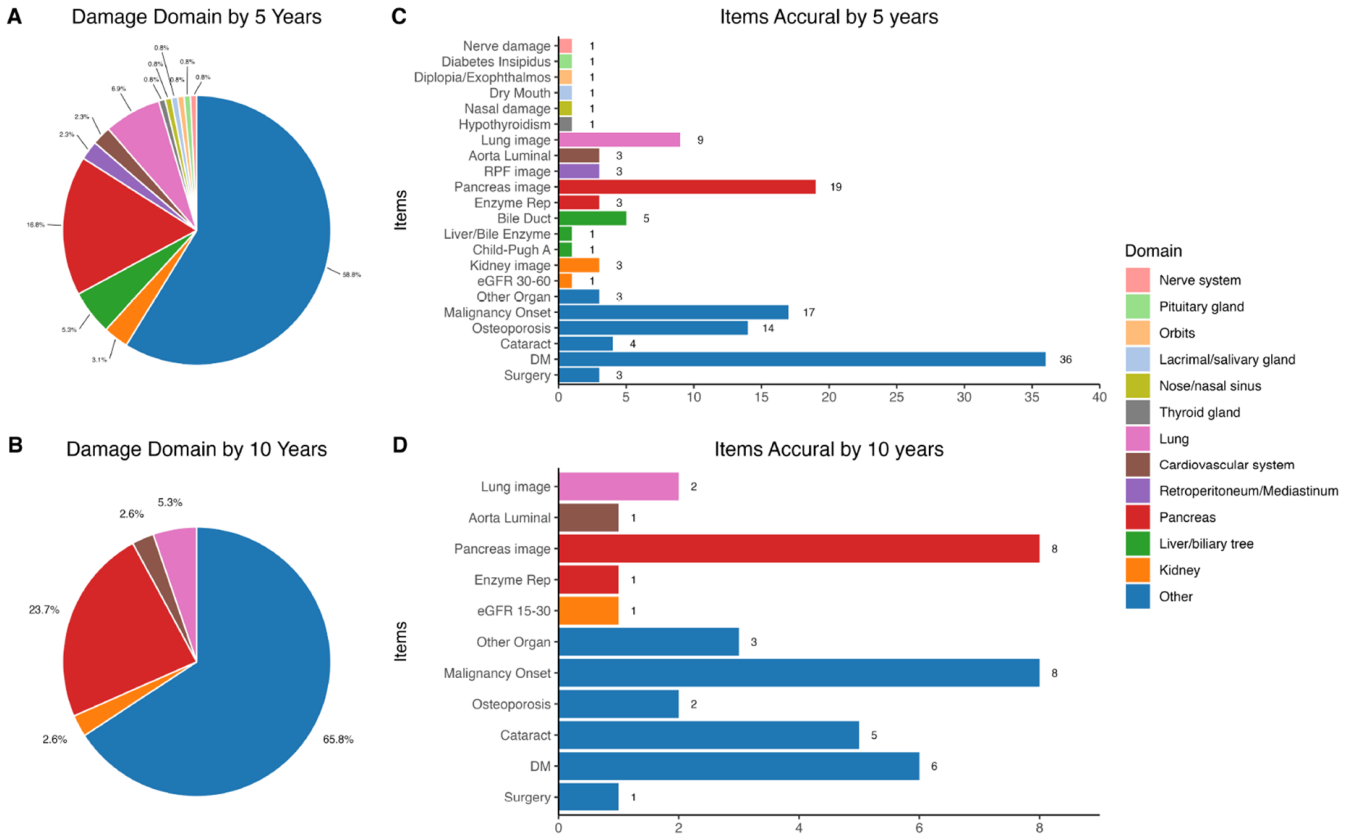

Fig. 4. The landscape of damage items with an increased number of patients of CIC IgG4-RD DI score across the baseline, 5-year, and 10-year assessment points.
A-**B**: the pie plots of DI domains with the most accumulated damage from baseline to 5 years in all 334 patients included (A) and from 5 years to 10 years in the 99 patients followed to 10 years (B).
C-**D**: the bar plots of DI damage items where the number of patients increased from baseline to 5 years in all 334 patients included (C) and from 5 years to 10 years in the 99 patients followed to 10 years (D).

age 9.7%, p=0.061). However, in the no damage subgroup, there was a noticeable prevalence of involvement in the lacrimal gland (increased damage 42.5% *vs*. stable damage 53.9% *vs*. no damage 59.1%, p=0.046). The baseline RI also tended to be greater in the increased damage and stable damage subgroups [increased damage 8.00 (6.00, 10.0) *vs*. stable damage 8.00 (6.00, 10.0) *vs*. no damage 6.00 (4.00, 10.0), p=0.051], as anticipated.

In terms of treatment, the initial GC dosage was also significantly greater in the stable damage subgroup [increased damage 40.0 (20.0, 40.0) mg/d *vs*. stable damage 40.0 (30.0, 50.0) mg/d *vs*. no damage 35.0 (30.0, 40.0) mg/d, p=0.032]. Furthermore, the duration of GC usage within 5 years was longer in the increased damage subgroup [increased damage 61.0 (52.0, 66.0) months *vs*. stable damage 61.0 (52.8, 64.0) months vs. no damage 59.0 (43, 62) months, p=0.018]. The IM intensity was comparable among the three subgroups (p=0.902).

We next divided the patients into two subgroups: the increased damage subgroup ($\Delta DI > 0$) and the non-increased damage subgroup ($\Delta DI = 0$, regardless of baseline DI); the latter included patients with stable or no damage, as described above. Multivariate logistic regression identified baseline pancreatic involvement (OR 2.11, 95% CI: 1.27–3.50, p=0.004) and relapse frequency (OR 1.40, 95% CI: 1.04–1.89, p=0.028) as risk factors for damage accrual within 5 years (Table II).

Comparison of the increased damage, stable damage, and no damage subgroups at the 10-year assessment

We further compared the characteristics of the increased damage, stable damage, and no damage subgroups of the 99 patients who were followed for up to 10 years. The increased damage subgroup tended to display greater involvement of the pancreas (increased damage 52.4% *vs*. stable damage 22.7% *vs*. no damage 34.3%, p=0.052). The increased damage group also presented greater involvement of the aorta (increased damage 19.0% *vs*. stable damage 13.6% *vs*. no damage 2.9%, p=0.091). No statistically significant differences were observed in the serological indicators, relapse frequency, or duration of GC usage (Suppl. Table S2). Univariate and multivariate logistic regression were performed. Baseline pancreatic involvement (OR 2.89, 95% CI: 1.02–8.16, p=0.045) was identified as the sole risk factor for 10-year damage accrual (Suppl. Table S3), which was consistent with the results of the 5-year damage accrual analysis.

Deceased patients in the cohort

Three patients died during follow-up, all of whom were diagnosed with IgG4-RD at or over 60 years of age. Two patients had pancreatic involvement,

Table I. Comparison of baseline characteristics and treatment between different damage subgroups of patients with IgG4-RD by 5-year assessment.

	Damage increase (n=113)	Damage stable (n=128)	No damage (n=93)	*p*-value
Gender, Male (n, %)	72 (63.7%)	84 (65.6%)	57 (61.3%)	0.803
Age (yrs, median [IQR])	58.0 [51.0, 63.0]	55.5 [42.0, 61.0]	53.0 [45.0, 58.0]	**0.008**
Baseline laboratory test				
Eos% (median [IQR])	3.25 [1.48, 5.53]	3.30 [1.30, 6.60]	3.40 [1.67, 6.82]	0.705
ESR (mm/h, median [IQR])	21.5 [9.00, 47.5]	28.0 [10.0, 61.0]	16.0 [7.50, 41.5]	0.049
CRP (mg/L, median [IQR])	2.05 [0.92, 7.53]	2.00 [0.78, 6.78]	1.52 [0.54, 4.52]	0.238
C3 (mg/L, mean ± SD)	0.93 ± 0.29	0.90 ± 0.30	1.00 ± 0.33	0.203
C4 (mg/L, median [IQR])	0.16 [0.11, 0.21]	0.15 [0.10, 0.22]	0.16 [0.13, 0.23]	0.661
IgG (mg/L, median [IQR])	19400 [14000, 25900]	18700 [15000, 26500]	17700 [13600, 23800]	0.529
IgA (mg/L, median [IQR])	1920 [1330, 2380]	1900 [1310, 2460]	1960 [1370, 2680]	0.599
IgM (mg/L, median [IQR])	750 [500, 1060]	780 [570, 1180]	780 [570 1220]	0.527
IgG1 (mg/L, median [IQR])	9070 [7420, 11700]	8935 [6952, 10800]	8065 [6825, 9888]	**0.025**
IgG2 (mg/L, median [IQR])	5550 [4560, 7410]	5455 [4122, 7130]	5295 [3662, 7022]	0.392
IgG3 (mg/L, median [IQR])	419 [249, 856]	472 [275, 861]	368 [210, 664]	0.155
IgG4 (mg/L, median [IQR])	11500 [4270, 18400]	7160 [3210, 17500]	8590 [2800, 17100]	0.280
T-IgE (KU/L, median [IQR])	290 [126, 628]	256 [90.6, 581]	399 [136, 859]	0.335
Baseline involved organs				
Pancreas (n, %)	57 (50.4%)	44 (34.4%)	24 (25.8%)	**0.001**
Bile duct (n, %)	37 (32.7%)	22 (17.2%)	13 (14.0%)	**0.002**
Submandibular gland (n, %)	57 (50.4%)	61 (47.7%)	55 (59.1%)	0.226
Lacrimal gland (n, %)	48 (42.5%)	69 (53.9%)	55 (59.1%)	**0.046**
Parotid gland (n, %)	18 (15.9%)	26 (20.3%)	20 (21.5%)	0.548
Retroperitoneum (n, %)	16 (14.2%)	27 (21.1%)	9 (9.7%)	0.061
Lung (n, %)	28 (24.8%)	40 (31.2%)	17 (18.3%)	0.09
Kidney (n, %)	17 (15.0%)	16 (12.5%)	9 (9.7%)	0.512
Aorta (n, %)	13 (11.5%)	18 (14.1%)	3 (3.2%)	**0.027**
Mediastinum (n, %)	3 (2.6%)	4 (3.1%)	1 (1.1%)	0.672
Prostate (n, %)	12 (10.6%)	16 (12.5%)	7 (7.5%)	0.491
Lymph node (n, %)	50 (44.2%)	59 (46.1%)	45 (48.4%)	0.839
Inflammatory pseudotumour (n, %)	1 (0.9%)	0 (0.0%)	4 (4.3%)	**0.023**
Nasal sinus (n, %)	34 (30.1%)	43 (33.6%)	34 (36.6%)	0.614
Total organ (median [IQR])	3.00 [3.00, 5.00]	4.00 [2.75, 5.00]	3.00 [2.00, 4.00]	0.172
Baseline RI (median [IQR])	8.00 [6.00, 10.0]	8.00 [6.00, 10.0]	6.00 [4.00, 10.0]	0.051
Remission induction therapy GCs* (mg/d, median [IQR])	40.0 [20.0, 40.0]	40.0 [30.0, 50.0]	35.0 [30.0, 40.0]	**0.032**
IM Intensity				0.902
Biological agents	0 (0.0%)	1 (0.8%)	1 (1.1%)	
Mild	27 (23.9%)	34 (26.6%)	26 (28.0%)	
Moderate	27 (23.9%)	20 (15.6%)	12 (12.9%)	
Strong	29 (25.7%)	37 (28.9%)	22 (23.7%)	
None	30 (26.5%)	36 (28.1%)	32 (34.4%)	
Relapse frequency in 5 yrs (median [IQR])	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.126
Duration of GC treatment in 5 yrs (mths, median [IQR])	61.0 [52.0, 66.0]	61.0 [52.8, 64.0]	59.0 [43, 62]	**0.018**

* Prednisone or equivalent dose.
GC: glucocorticoids; IM: immunosuppressant; yrs: years; mths: months; RI: Responder Index.
The involved organs with less than 5% prevalance are not shown in the table, including thyroid gland, liver, pituitary gland, meninges, orbit, and other.

while one patient had multiple organ involvement, excluding the pancreas and bile duct. The DI scores of these patients were 0 at baseline and 1 at five years. One female patient passed away 141 months after diagnosis. The other two patients died shortly after the 5-year follow-up. One patient died of an unknown cause, while the others died of complications of Alzheimer's disease and of colorectal cancer (Suppl. Table S4).

Discussion

In this study, we first applied the CIC IgG4-RD DI to real-world patients with IgG4-RD. We revealed that damage accumulated in patients with IgG4-RD throughout the follow-up period. The most common damage items were pancreatic imaging abnormalities, malignancy onset, diabetes, and surgical procedures. Overall, damage accumulated in the patients with IgG4-RD over a mean follow-up period of 88 months. The damage items that most patients developed by the 5- and 10-year assessment points were pancreatic imaging abnormalities, malignancy onset, and diabetes. Additionally, we identified baseline pancreatic involvement and relapse frequency as risk factors for damage accrual by the 5-year assessment.

The CIC IgG4-RD DI is the first instrument focused on damage related to IgG4-RD and treatment (15). The IgG4-RD DI defines damage as per-

Table II. Univariate and multivariate logistic regression analysis for risk factors of damage accrual in patients with IgG4-RD by 5-year assessment.

Variables	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Gender, Male (n, %)	0.99	(0.62, 1.59)	0.970			
Age (yrs, median [IQR])	1.03	(1.01, 1.05)	0.005	1.02	(1.00, 1.04)	0.096
Baseline laboratory test						
Eos% (median [IQR])	0.98	(0.94, 1.02)	0.225			
C3 (mg/L, median [IQR])	0.96	(0.36, 2.58)	0.931			
IgG1 (mg/L, median [IQR])	1.00	(1.00, 1.00)	0.093			
IgG4 (mg/L, median [IQR])	1.00	(1.00, 1.00)	0.588			
Baseline involved organs						
Pancreas (n, %)	2.26	(1.41, 3.61)	0.001	2.11	(1.27, 3.50)	**0.004**
Bile duct (n, %)	2.56	(1.50, 4.37)	0.001			
Submandibular gland (n, %)	0.90	(0.57, 1.43)	0.663			
Lacrimal gland (n, %)	0.58	(0.36, 0.91)	0.019	0.55	(0.32, 0.96)	**0.029**
Retroperitoneum (n, %)	0.84	(0.44, 1.59)	0.589			
Lung (n, %)	0.96	(0.57, 1.62)	0.875			
Kidney (n, %)	1.37	(0.71, 2.67)	0.348			
Aorta (n, %)	1.23	(0.59, 2.56)	0.586			
Mediastinum (n, %)	1.17	(0.27, 5.00)	0.834			
Total organ (median [IQR])	1.04	(0.91, 1.19)	0.600			
Baseline RI (median [IQR])	1.02	(0.96, 1.08)	0.581			
Remission induction therapy						
GCs* (mg/d, median [IQR])	0.99	(0.98, 1.00)	0.080			
IM Intensity†						
Strong	1.11	(0.60, 2.07)	0.732			
Moderate	1.91	(0.98, 3.74)	0.058			
Mild	1.02	(0.54, 1.91)	0.951			
Relapse frequency in 5 yrs (median [IQR])	1.32	(1.00, 1.74)	0.047	1.40	(1.04, 1.89)	**0.028**
Duration of GC treatment in 5 yrs (mths, median [IQR])	1.01	(1.00, 1.02)	0.279			

*Prednisone or equivalent dose.
†Two patients were excluded for their use of biological agents.
GC: glucocorticoids; IM: immunosuppressant; yrs: years; mths: months; RI: Responder Index.

sistent for >6 months and irreversible. When scoring, the assessors were trained to distinguish between disease activity and irreversible damage. Thus, the IgG4-RD DI is a convenient and clear tool for assessors to use in documenting and monitoring damage, setting itself apart from the IgG4-RD RI (4). By applying the DI to real-world patients with IgG4-RD, we revealed the landscape of disease damage at baseline and at the 5-year and 10-year assessment points. A considerable number of patients scored 0 or 1 for the IgG4-RD DI, suggesting that IgG4-RD is generally a benign disease that causes limited damage in many patients. However, the damage gradually accrued during follow-up, as reflected by the increase in mean DI scores from baseline to the 10-year assessment point. According to the 5-year assessment, approximately one-third of the patients presented increased damage. The damage accumulation revealed by the IgG4-RD DI calls for exploration of the risk factors and damage management methods in patients with IgG4-RD.

The landscape of damage items across the assessment points revealed the pancreas as a critical target organ. The major damage item was pancreatic imaging abnormalities, including atrophy, enlargement, and pseudocyst formation. These imaging abnormalities typically persist and progress during follow-up in patients with autoimmune pancreatitis (20, 21). Other crucial parts of damage to the pancreas are endocrine and exocrine insufficiency. Diabetes stood out as a prominent damage item in our study and might be attributed to pancreatic dysfunction in some patients. However, the IgG4-RD DI does not distinguish between disease- and treatment-related diabetes (15). This is due to the difficulty in discerning diabetes caused by GC or pancreatic endocrine insufficiency, particularly in patients who experienced relapse and/or were receiving prolonged GC maintenance therapy. Our study also revealed that a small proportion of patients developed exocrine pancreatic insufficiency (EPI). The gold standard for EPI diagnosis is a faecal elastase level of 100–200 mg/g (22). The reported incidence of EPI in patients with autoimmune pancreatitis ranges from 47% to 73%, as determined by measuring faecal elastase (23–25). A cohort study from South Korea reported only 11.6% prevalence of pancreatic endocrine/exocrine insufficiency when faecal elastase was not measured (26). In the IgG4-RD DI, exocrine insufficiency is defined as the need for pancreatic enzyme replacement therapy, considering that the faecal elastase test is not commonly used in patients with IgG4-RD and is not readily available in most hospitals. This discrepancy in diagnostic practices may lead to an underestimation of the EPI incidence in our cohort.

Damage related to GC usage is another fundamental aspect revealed by our study. GC is the first-line treatment for IgG4-RD (1, 27). Despite a favourable response to GCs, IgG4-RD is a relapsing disease and may require multiple courses of GC-based remission induction. It has also been suggested that extending GC maintenance to 3 years may reduce relapse rates (28). Our previous study further indicated that a GC maintenance dosage ≤6.25 mg/d was associated with relapse. Moreover, the side effects of GC usage should be noted (29). Our study indicated that GC toxicity accounted for a considerable proportion of the damage items. Furthermore, there was an increase in patients who developed GC-related complications during follow-up. The result was anticipated, as the mean duration of GC usage was relatively long (average of 53.8 months by the 5-year assessment and 103.0 months by the 10-year assessment) in our cohort. These findings provide further justification for the concern about GC usage and the necessity of GC tapering and cessation in the management of IgG4-RD. Additionally,

these findings call for the investigation of a threshold for the GC maintenance dose in the definition of the IgG4-RD remission status. In systemic lupus erythematosus (SLE), the lupus low disease activity state (LLDAS) (30) and the definitions of remission in SLE (DORIS) (31) designate the remission maintenance GC dosage as prednisone ≤7.5 mg/d and ≤5 mg/d (or equivalent dosage), respectively. In contrast, IM-related damage was not observed in our cohort, despite the use of strong IMs at baseline in many patients. The use of IMs not only facilitates remission induction and GC tapering (32, 33) but also reduces relapse rates, regardless of whether IMs are used in combination with GCs (17). Considering the incidence and accumulation of GC-related damage revealed by the IgG4-RD DI, combining IMs in remission induction and remission maintenance treatment might be beneficial.

The CIC IgG4-RD DI also included malignancy onset as a damage item under the 'other' domain, as do the SLICC SLE-DI and VDI (6, 8). The association between increased risk for malignancy and IgG4-RD is well recognised (12, 34, 35). Several cohort studies and meta-analyses have indicated that the risk of malignancy is highest within 1 year of IgG4-RD diagnosis (12, 35, 36). One study from Japan reported an increased risk for malignancy in patients with IgG4-RD even after 12 years of follow-up (37). In our study, we documented a noticeable increase in the incidence of malignancy at the 5-year assessment point. Another 6 patients developed cancer between the 5- and 10-year assessment points. One patient died of cancer just after the 5-year follow-up. This finding corroborates the association of increased malignancy risk with IgG4-RD diagnosis reported in previous studies and suggests that malignancy can be considered relatively short-term disease damage. Moreover, this finding highlights the importance of cancer screening within 5 years of follow-up.

We used the IgG4-RD DI to explore the risk factors for damage accumulation. The risk factors identified were pancreatic involvement at baseline and relapse frequency. Since damage to the pancreas stood out throughout the three assessment points, it is expected that the baseline involvement of the pancreas served as a risk factor. The other risk factor was the frequency of relapse. Relapse can contribute to different damage domains in the IgG4-RD DI. Shimizu *et al*. reported relapse as a risk factor for serious side effects of GC therapy, namely, GC toxicity, in type 1 autoimmune pancreatitis (AIP-1) patients (38). Kubota *et al*. reported that relapse was a risk factor for malignancy onset in patients with IgG4-related sclerosing cholangitis (39). Intriguingly, our study revealed that the baseline GC dosage and duration of GC use might have a limited association with damage accrual, despite the accumulation of GC toxicity during follow-up. It has been suggested that high [0.8–1.0 mg/(kg·d)] and medium [0.5–0.6 mg/(kg·d)] initiation GC doses have similar effects on remission induction. However, for patients with a higher baseline RI and more involved organs, a higher initial GC dosage might be beneficial for maintaining remission (40). In turn, refractory and relapsing patients are given higher initial GC doses (41). When administering GC-based therapy, it is important to balance the risk of disease relapse against the potential for GC toxicity. Achieving this delicate balance requires the state-of-the-art use of GCs. Future research on the optimal initiation and maintenance GC dosages is warranted.

There are limitations to our study. First, the CIC IgG4-RD DI is a newly developed index, and further validation of its intrarater and test-retest reliability is needed. Additionally, this index may be further compared with the organ damage index in the IgG4-RD RI. Second, this study is observational and based on a single-centre cohort, and multicentric cohort studies and prospective studies are warranted for a more representative landscape of damage in patients with IgG4-RD. Finally, this study did not investigate the associations between DI scores and outcome events, such as the all-cause mortality rate. More research is needed to explore the potential of the DI as a prognostic predictor.

In summary, the CIC IgG4-RD DI is a useful tool for damage assessment and management in both clinical and research contexts. As a preliminary application of the CIC IgG4-RD DI, we revealed the pancreas and GC toxicity as important damage domains during long-term follow-up of IgG4-RD patients. Baseline pancreatic involvement and relapse frequency were risk factors for damage accumulation, whereas initial GC dose and baseline lacrimal gland involvement were protective factors.

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