RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Potential impact of autoimmune diseases family history in IgG4-related disease: a retrospective cohort study

Ruijie Sun,[1,2] Zheng Liu,[1,2] Hui Lu,[1,2] Yu Peng,[1,2] Jieqiong Li,[1,2] Yuxue Nie,[1,2] Jingna Li,[1,2] Linyi Peng,[1,2] Jiaxin Zhou ,[1,2] Yunyun Fei,[1,2] Xiaofeng Zeng,[1,2] Wen Zhang [1,2]

To cite: Sun R, Liu Z, Lu H, *et al*. Potential impact of autoimmune diseases family history in IgG4-related disease: a retrospective cohort study. *RMD Open* 2023;**9**:e002865. doi:10.1136/rmdopen-2022-002865

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002865).

RS and ZL contributed equally.

Received 14 November 2022
Accepted 26 January 2023

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China
[2]National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), The Ministry of Education Key Laboratory, Beijing, China

Correspondence to
Dr Jiaxin Zhou;
pumczhou@sina.com

Dr Wen Zhang;
zhangwen91@sina.com

ABSTRACT

Objective Autoimmune comorbidities may be associated with IgG4-related disease (IgG4-RD), here we aimed to determine the correlation of autoimmune diseases (AID) family history and IgG4-RD in a Chinese cohort.

Methods This retrospective cohort study identified 628 cases of IgG4-RD in Peking Union Medical College Hospital. Patients were classified into two groups, with AID family history group (AID-positive) and without AID family history group (AID-negative). We viewed the potential value of AID family history on IgG4-RD by comparing the differences between the two groups. In addition, Cox regression analysis estimated CIs and HR for IgG4-RD risk.

Results 93 (14.8%) IgG4-RD patients had AID family history. Compared with AID-negative group, baseline data analysis revealed that AID-positive group patients had an earlier age of IgG4-RD onset (50.4±14.8 vs 54.2±12.6, p=0.014*), a higher percentage of antinuclear antibody (ANA) positivity (38.9% vs 22.7%, p=0.0277*) and Riedel thyroiditis (10.9% vs 2.4%, p=0.001*), were prone to comorbid with other AID (16.1% vs 6.2%, p=0.0238*). Cox analysis found that younger age (HR 0.97 (95% CI 0.94 to 0.99), p=0.0384*) and higher proportions of baseline peripheral eosinophils (HR 1.1 (95% CI 1.02 to 1.2), p=0.0199*) increased the risk of unfavourable prognosis for AID-positive IgG4-RD patients.

Conclusions 14.8% of IgG4-RD patients had AID family history, with younger age of disease onset age and higher frequency of ANA positivity in AID-positive group, indicating that IgG4-RD may share genetic background with other AID.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Family history of autoimmune diseases (AID) is a proxy for an individual's genetic risk of AID, and even regarded as a well-recognised predictor of AID onset.

WHAT THIS STUDY ADDS

⇒ Clinical characteristics of IgG4-related disease (IgG4-RD) differ among AID-positive group and AID-negative group patients.

⇒ Compared with AID-negative group, AID-positive group patients had younger onset age and higher rate of ANA positivity, indicating IgG4-RD may share genetic background with other AID.

⇒ Younger age and higher proportions of baseline peripheral eosinophils increased the risk of unfavourable prognosis for AID-positive group patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies on the role of genetic background and environmental factors in the pathogenesis of IgG-RD might be interesting and of importance.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a systemic immune-mediated chronic inflammatory and fibrotic disease that is characterised by elevation of serum IgG4 concentrations and organ lesions infiltrated by IgG4-positive plasma cells.[1 2] Although IgG4-RD is an immune-mediated disease, whether it is an autoimmune disease (AID) is still on debate, due to low positive rate as well as uncertain role of autoantibodies in the pathogenesis of the disease. However, it has been shown that IgG4-RD could share common risk factors with other AID, and there are possible associations between IgG4-RD and other AID.[3] To date, no study has identified the relationship between IgG4-RD and patients' family history of AID. Whether AID family history of IgG4-RD patients is of any value for clinical features and predicting prognosis of IgG4-RD is also unclear yet. Therefore, identifying the relationship between AID family history and characteristics of IgG4-RD may provide valuable insights of correlations between IgG4-RD and other AID.

In this study, we first aimed to determine the prevalence of family history of AID in IgG4-RD patients. Then, we compared the discrepancies between IgG4-RD patients

with and without AID family history, including clinical manifestations and prognosis. We further assessed the association between family history of AID and the risk of developing IgG4-RD, using a large retrospective cohort study nested in two cohorts of IgG4-RD patients with positive AID family history and IgG4-RD patients with negative AID family history.

PATIENTS AND METHODS

Patients

In the retrospective study from a prospective cohort of IgG4-RD patients (registered on ClinicalTrails.gov NCT01670695) conducted in Peking Union Medical College Hospital (PUMCH), all IgG4-RD patients were recorded for whether they had a family history of AID during registration into the cohort. A total of 1070 patients, who fulfilled the 2019 American College of Rheumatology/EULAR classification criteria for IgG4-RD,[4] were enrolled between January 2012 and March 2022. The patients with AID-positive were further filled in with the specific information, including the degree of their relatives and disease type, which was reviewed by the specialist. Some patients with ambiguous information were followed-up by telephone to confirm. Among them, detailed AID family history was recorded in 628 patients and were recruited in this study. IgG4-RD patients were divided into two groups, AID family history positive group (AID-pos, n=93) and AID family history negative group (AID-neg, n=535) according to whether their family members (from first-degree to third-degree relatives) had AID or not. In the AID-pos group, the AID history of first-degree to third-degree relative(s), the number of relatives and the type of AID were recorded. A diagram of the research procedure of enrolled patients was shown in figure 1.

Figure 1 Diagram of the research procedure of enrolled patients. *AID family history including but not limited to the following diseases: Rheumatoid arthritis, IgG4-RD, systemic lupus erythematosus, psoriasis and PsA (psoriatic arthritis), JCA (juvenile chronic arthritis), ReA (reactive arthritis), Grave's disease, Sjögren syndrome, undifferentiated connective tissue disease, Hashimoto thyroiditis, vitiligo, IIM (idiopathic inflammatory myopathy), AOSD (Adult-Onset Still's Disease), RPC (relapsing polychondritis), myasthenia gravis, Takayasu arteritis, BD (Behcet's disease), GPA (granulomatosis with polyangiitis), ANCA (antineutrophil cytoplasmic antibody) -associated vasculitis, IBD (inflammatory bowel disease), immune thrombocytopenia, autoimmune haemolytic anaemia, AGAE (anti-GAD associated encephalitis), AS (ankylosing spondylitis), PAN (polyarteritis nodosa), autoinflammatory syndrome, panniculitis. #Relative degree of AID family history: First-degree relatives include an individuals' parents, siblings and offspring. Second-degree relatives include an individuals' grandparents and grandchild, half-siblings, niece/nephew and aunt/uncle. Third-degree relatives include an individuals' first cousins, great grandparents and great grandchildren. AID, autoimmune disease; IgG4-RD, IgG4-related disease.

Clinical and laboratory assessment

For each subject, investigators recorded detail clinical parameters including age (at disease onset/symptom and diagnosis), gender, smoking and drinking history, atopic background (such as asthma, rhinosinusitis, atropic rhinoconjunctivitis or atopic dermatitis), comorbidity of other AID, as well as organ involvement of IgG4-RD and IgG4-RD responder index (RI).[5] We categorised the drinking variable into four categories: non-alcohol drinker (never drink any alcoholic beverage), former alcohol drinker (abstinence alcohol intake at least 1 year at baseline evaluation), occasional alcohol drinker (drank less than once per week or only on special occasions) and continuous alcohol intake (drank at least once per week).[6 7]

Disease duration was calculated by subtracting the time at symptom onset from diagnosis time, reported in months. The involvement organs were divided into superficial organs (including salivary glands, nasal sinus, lacrimal glands, parotid gland and skin) and internal organs (including pancreas, lung, bile duct, aorta, kidney, large arteries, mediastinum, pituitary gland, liver and gastrointestinal tract).[8 9] Lymph nodes were not considered when assessing the involvement of superficial and internal organs in IgG4-RD patients.

We have also invited specialists to assist in the differential diagnosis of certain diseases, such as Riedel thyroiditis or other autoimmune thyroid disease (AITD, predominantly hypothyroidism and Graves's disease), autoimmune pancreatitis (AIP) or other chronic pancreatitis.

The following laboratory variables were recorded for each patient at baseline: erythrocyte sedimentation rate, high-sensitivity C reactive protein levels, eosinophil (Eos), platelet and white blood cells count, serum IgA, IgM, total IgE (T-IgE), IgG subclasses (IgG, IgG2, IgG3, IgG4), C3 and C4 concentrations, antinuclear antibody (ANA), rheumatoid factor. Imaging examinations were performed as well. Part of the patients also underwent pathological biopsy for diagnosis. Patients with malignancy were excluded from the study.

The initial therapy for IgG4-RD patients were described in four categories: glucocorticoids (GCs) monotherapy,

immunosuppressants (IMs) monotherapy, GC in combination with IMs (GCs+IMs) and watchful waiting.

Definitions of remission and unfavourable prognosis

Remission was defined as a decline in IgG4-RD RI ≥2 compared with baseline and IgG4-RD RI of every single organ ≤1, along with improvement of signs or symptoms imaging examinations and GC tapered to maintenance dosage (prednisone ≤10 mg per day or equivalent dose) without relapse.[10] Relapse was defined as a recurrence of signs and symptoms and/or worsening of imaging findings, with or without re-elevation of serum IgG4 level. Unfavourable prognosis was defined as the disease relapse or the need of a stronger treatment (some patients need a stronger treatment, such as higher doses of GC or stronger IM therapy, due to disease fluctuation. The long-term effects of these drugs have the potential adverse effect to the patient's long-term prognosis, so these patients were also included in the part of unfavourable prognosis.).

Statistical analysis

Categorical variables were compared using the χ^2 test or two-tailed Fisher's exact test. Continuous parametric variables were compared using the Student's t-test and continuous non-parametric variables were compared using the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. Continuous variables are reported as mean±SD or median (IQR). Dunn's test was used for correcting for multiple comparisons. A two-sided $p<0.05$ was assumed to be statistically significant.

Cox regression analysis was performed to estimate HRs and their 95% CIs. Variables showing a p value≤0.1 in univariable analysis were considered as candidates for the multivariate Cox regression model, and a forward stepwise method was used to determine the final multivariable model. Statistical analysis was performed using Prism software V.9.0 (GraphPad Software, La Jolla, California, USA) and SPSS Statistics V.26 (IBM, Armonk, New York, USA).

RESULTS

Characteristic of 628 IgG4-RD patients in this cohort

A total of 628 IgG4-RD patients were enrolled in this cohort study, including 376 male and 252 female patients (M:F=1.5:1). The mean age at IgG4-RD diagnosis was 53.7±12.9 years, and the median disease duration was 12 (4–36) months. In this cohort, the mean number of involved organs was 2.8±1.4. The most common affected organs were submandibular gland (325, 51.8%) and lacrimal gland (295, 47.0%), followed by pancreas (236, 37.6%), nasal sinus (178, 28.3%), lung (161, 25.6%), bile duct (125, 20.0%), parotid gland (110, 17.5%), aorta (91, 14.5%), kidney (69, 11.0%), thyroid glands (23, 3.7%) and skin (20, 3.2%). Rare involved organs consisted of mediastinum (19, 3.0%), pituitary gland (17, 2.7%), liver (16, 2.6%) and gastrointestinal tract (12, 1.9%).

Table 1 Types of autoimmune diseases in relatives of IgG4-RD patients

Family history of AID	Number of IgG4-RD patients (n=93)	Percentage (%)
RA	34	36.6
IgG4-RD	16	17.2
SLE	8	8.6
Psoriasis	8	8.6
GD	8	8.6
HT	7	7.5
SS	6	6.4
Spondyloarthritis	6	6.4
Vitiligo	3	3.2
PBC	3	3.2
DM	2	2.2
Autoimmune nephritis	2	2.2
ITP	2	2.2
UCTD	1	1.1
Type1 diabetes	1	1.1
AIH	1	1.1
TA	1	1.1
AIHA	1	1.1

AIH, autoimmune hepatitis; AIHA, autoimmune haemolytic anaemia; DM, dermatomyositis; GD, Grave's disease; HT, Hashimoto thyroiditis; IgG4-RD, IgG4-related disease; ITP, immune thrombocytopenia; PBC, primary biliary cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; TA, Takayasu arteritis; UCTD, undifferentiated connective tissue disease.

Characteristics of AID family history in AID-pos IgG4-RD patients

Family history of AID was seen in 93 cases with a prevalence of 14.8% in this cohort. Rheumatoid arthritis (RA) was the most common AID (34, 36.6%), followed by IgG4-RD (16, 17.2%), others including systemic lupus erythematosus (SLE), psoriasis, Grave's disease, Hashimoto's thyroiditis, Sjögren syndrome (SS), etc (table 1). Among the relatives of 93 AID-pos IgG4-RD patients, 85 (91.4%) were first-degree relatives (FDRs), 27 (29.0%) were second-degree relatives and 3 (3.2%) were third-degree relatives. Sixteen IgG4-RD patients have multiple (≥2) relatives with AID. Most of AID relatives of IgG4-RD patients are women (table 2).

Comparison of clinical characteristics between AID-pos group (n=93) and AID-neg group patients (n=535)

AID-pos group patients had an earlier age at IgG4-RD diagnosis compared with AID-neg group patients (50.4±14.8 vs 54.2±12.6, p=0.014*). Furthermore, AID-pos group patients were more likely to complicate with other AID (16.1% vs 6.2%, p=0.0238*), including psoriasis, autoimmune hepatitis, ulcerative colitis, vitiligo, AITD, etc (table 3). And Riedel thyroiditis in AID-pos group

Table 2 The degree of familial relation of IgG4-RD patients with positive AID family history

Degree of relatives	IgG4-RD (n=93)
First degree of relatives	85
Father	9
Mother	29
Son	3
Daughter	8
Sister	28
Brother	8
Second degree of relatives	27
Grandfather	2
Grandmother	3
Uncle	5
Aunt	10
Nephew	2
Niece	4
Grand-daughter	1
Third degree of relatives	3
Cousin*	3

*Cousin included two women and one man.

(10.9% vs 2.4%, p=0.001*) was higher than AID-neg group (table 3 online supplemental table 1). In terms of laboratory parameters, the ratio of ANA positivity (38.9% vs 22.7%, p=0.0277*) was more prominent in the AID-pos group than in AID-neg group (table 4). All patients without interference from disease specific autoantibodies such as anti-dsDNA antibody, anti-SSA antibody, anti-SSB antibody, anti-Smith antibody, anti-RNP antibody, anti-Jo-1 antibody and anti-SCL-70 antibody.

Demographic and clinical characteristic of IgG4-RD patients with single relative and multiple AID relatives in AID-pos group patients

Among AID-pos group patients, 47 (50.5%) were men and 46 (49.5%) were women. A large proportion of patients had multiorgan involvements with a median number of involved organs at 3 (IQR: 2–4). Seventy-three (78.5%) patients had two and more organ involvements, while 20 (21.5%) patients had single organ lesion. The most common clinical manifestations of AID-pos group patients were lacrimal gland (47, 50.5%) and submandibular gland (46, 49.5%) swelling, while pancreas (38, 41.3%) and respiratory system (24, 26.1%) involvement were the most commonly affected internal organs.

Prevalence of multiple (≥2) and single relatives with any AID was 17.2% (n=16) and 82.8% (n=77) among AID-pos groups in IgG4-RD, respectively. There were no significant differences in age of onset, proportion of FDRs, number of involved organs and IgG4-RD RI between patients with multiple AID relatives and those with only one family member of AID. Patients with multiple AID relatives had a relatively higher rates of ANA positivity (53.3% vs 33.9%, p=0.258), Riedel thyroiditis (25% vs 7.9%, p=0.068) and a longer disease duration than the other group but still with no significant difference (online supplemental table 2). Moreover, the male to female ratio of IgG4-RD patients with single AID relative was 1.26:1, however, this condition was reversed in IgG4-RD patients with multiple relatives with AID, showing more females than males (female:male=1:0.33, p=0.049*).

We also tried to explore whether the above information might have value in the IgG4-RD family history and other AID family history but found no significant difference (online supplemental table 3).

Table 3 The demographical and clinical features between IgG4-RD patients with positive and negative AID family history.

Paraments	AID-positive group (n=93)	AID-negative group (n=535)	P value
Age (years)	**50.4±14.8**	**54.2±12.6**	**0.014***
Male/female	1.02:1	1.60:1	0.061
Disease duration (months)	18.0 (4.8, 36)	12.0 (5.0, 36)	0.382
History of allergy, n (%)	49 (92, 53.3)	296 (533, 55.5)	0.771
Combine with other AID, n (%)	**15 (16.1)**	**33 (6.2)**	**0.0238***
IgG4-RD RI	6 (4, 10)	6 (4, 10)	0.343
Riedel thyroiditis, n (%)	**10 (92, 10.9)**	**13 (532, 2.4)**	**0.001***
Numbers of organs involvement	3 (2, 4)	3 (2, 4)	0.613
Cigarette smoking, n (%)	29 (69, 42.0)	192 (389, 49.4)	0.321
Continuous alcohol intake, n (%)	3 (68, 4.4)	19 (377, 5.0)	1

*P<0.05
AID, autoimmune disease ; IgG4-RD, IgG4-related disease ; IgG4-RD RI, IgG4-RD responder index.

Table 4 Laboratory indicators between IgG4-RD patients with positive and negative AIDs family history

Paraments	AID-postive group (n=93)	AID-negative group (n=535)	P value
WBC (10^9/L)	6.22 (5.44, 7.59)	6.74 (5.55, 8.27)	0.042*
PLT (10^9/L)	234 (194, 276)	228 (191, 282)	0.815
Eos (10^9/L)	2.55 (1.20, 5.18)	3.20 (1.40, 6.10)	0.316
ESR (mm/hour)	18.5 (7.0, 37.2)	18.0 (8.0, 45.8)	0.484
hsCRP (mg/L)	1.79 (0.72, 7.53)	2.00 (0.79, 6.07)	0.766
ANA positivity, n (%)	**28 (72, 38.9)**	**88 (388, 22.7)**	**0.0277***
RF positivity, n (%)	23 (69, 33.3)	102 (350, 29.1)	0.581
IgG (g/L)	17.1 (13.9, 22.7)	17.8 (13.7, 24.1)	0.500
IgA (g/L)	1.92 (1.18, 2.54)	1.90 (1.35, 2.54)	0.442
IgM (g/L)	0.73 (0.53, 1.23)	0.80 (0.55, 1.18)	0.672
T-IgE (KU/L)	250 (80.7, 603)	278 (102, 706)	0.425
IgG1 (mg/L)	8470 (7130, 10 300)	8640 (7150, 10 700)	0.522
IgG2 (mg/L)	5310 (4455, 6885)	5570 (4090, 7320)	0.676
IgG3 (mg/L)	464 (242, 775)	419 (240, 779)	0.543
IgG4 (mg/L)	5805 (2838, 12 925)	8014 (3190, 15 675)	0.119
C3 (g/L)	0.95 (0.80, 1.11)	0.96 (0.78, 1.15)	0.752
C4 (g/L)	0.18 (0.11, 0.23)	0.17 (0.12, 0.23)	0.928

ANA, antinuclear antibody; Eos, eosinophils; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C reactive protein; IgG4, IgG4-related disease ; PLT, platelet; RF, rheumatoid factor; WBC, white blood cell count.

Unfavourable prognosis of IgG4-RD patients in AID-pos group and AID-neg group

The ratio of unfavourable prognosis in the AID-pos group and the AID-neg group was 44.8% and 52.1%, respectively (p>0.99). However, univariate Cox analysis identified that older age (HR 0.97 (95% CI 0.95 to 0.99), p=0.015*) was a protective factor of unfavourable prognosis in AID-pos group patients. In addition, patients treated with GCs combined with IM (HR 0.42 (95% CI 0.19 to 0.95), p=0.037*) had lower risk of unfavourable prognosis compared with patients treated with GC alone. However, higher proportions of peripheral Eos (HR 1.08 (95% CI 1.01 to 1.16), p=0.021*) and continued alcohol intake (HR 4.64 (95% CI 1.33 to 16.2) (p=0.016*) were risk predictors of unfavourable prognosis (figure 2A; online supplemental table 4). Multivariate Cox analysis identified that younger age (HR 0.97 (95% CI 0.94 to 0.99), p=0.0384*), higher proportions of peripheral Eos (HR 1.1 (95% CI 1.02 to 1.2), p=0.0199*) and continued alcohol intake (HR 5.74 (95% CI 1.44 to 22.88), p=0.0133*) were independent risk factors associated with unfavourable prognosis after

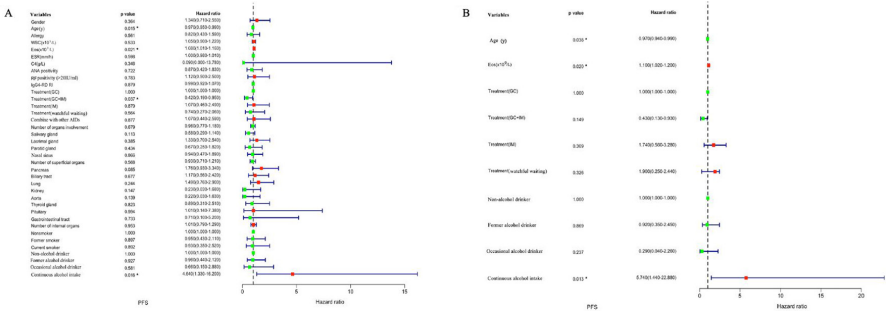

Figure 2 Univariate and multivariate Cox regression analysis and forest plot of potential factors associated with unfavourable prognosis in AID-pos group. Cox regression analysis was performed to estimate risk factors between different prognosis (remission and unfavourable prognosis) in AID-pos IgG4-RD patients with more than 1-year follow-up period. Forest plot of univariate (figure 2A) and multivariate (figure 2B) Cox regression analysis of the baseline clinical parameters and demographical characteristic of AID-pos IgG4-RD. Univariate variables with p<0.1 were included in multivariate Cox regression analysis. *P value<0.05. ANA, antinuclear antibody; AID, autoimmune disease; AID-pos, AID family history positive group; Eos, eosinophils; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; GC+IM, glucocorticoid combined with immunosuppressant; IgG4-RD, IgG4-related disease; PFS, progression-free survival; PLT, platelet; RF, rheumatoid factor; RI, responder index; WBC, white blood cell count.

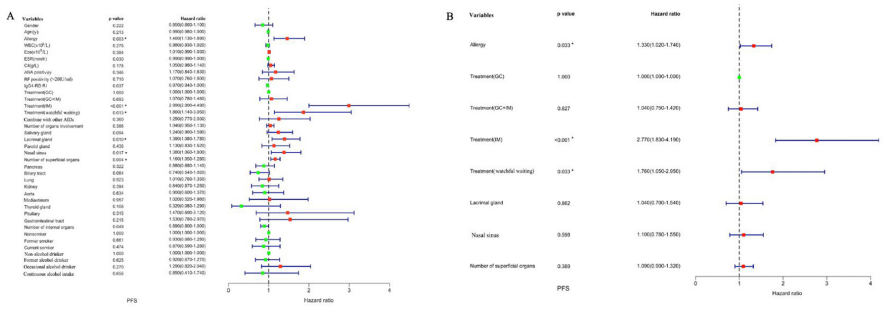

Figure 3 Univariate and multivariate Cox regression analysis and forest plot of potential factors associated with unfavourable prognosis in AID-neg group. The cohort of AID-neg IgG4-RD patients with more than 12-month follow-up period were divided into two groups bases on different prognostic outcomes (remission and unfavourable prognosis). Forest plot of univariate (3A) and multivariate (3B) Cox regression analysis of the baseline clinical parameter and demographical characteristic of AID-neg IgG4-RD. Univariate variables with p<0.1 were included in multivariate Cox regression analysis. *P value<0.05. ANA, antinuclear antibody; AID, autoimmune disease; AID-neg, AID family history negative group; Eos, eosinophils; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; GC+IM, glucocorticoid combined with immunosuppressant; IgG4-RD, IgG4-related disease; PFS, progression-free survival; PLT, platelet; RF, rheumatoid factor; RI, responder index; WBC, white blood cell count.

in AID-pos group patients (figure 2B; online supplemental table 4).

Prior to adjustment for matched pairs, the risk of unfavourable prognosis of AID-neg group patients with history of allergy was 1.46-fold (95% CI 1.13 to 1.85, p=0.003*) compared with those not having a history of allergy. After adjustment for univariate factors, the relationship between unfavourable prognosis and allergy remained significant among those with AID-neg IgG4-RD patients (HR 1.33 (95% CI 1.02 to 1.74), p=0.0332*). Compared with patients treated with GCs monotherapy, the patients treated with IMs monotherapy (HR 2.77 (95% CI 1.83 to 4.19), p<0.001*) and watchful waiting (HR 1.76 (95% CI 1.05 to 2.95), p=0.0329*) was significantly more common among IgG4-RD patients with unfavourable prognosis (figure 3A,B; online supplemental table 5). In addition, more superficial organ involvements (HR 1.16 (95% CI 1.05 to 1.28), p=0.004*), especially lacrimal gland involvement (HR 1.39 (95% CI 1.08 to 1.78), p=0.01*) and nasal sinus involvement (HR 1.38 (95% CI 1.06 to 1.18), p=0.0017*) were risk factors for unfavourable prognosis in AID-neg IgG4-RD patients, but the predictive role of this risk factor disappeared after adjustment for other factors such as treatment.

Moreover, multivariate Cox analysis of all IgG4-RD patients in this study showed that patients treated with IMs monotherapy (HR 2.12 (95% CI 1.36 to 3.31), p<0.001*) had a significant association with unfavourable prognosis compared with patients treated with GCs monotherapy (online supplemental table 6).

AID family history on the unfavourable prognosis of AID-pos IgG4-RD patients

Cox analysis was also used to analyse AID family history on the unfavourable prognosis of AID-pos IgG4-RD patients. There was no significant statistical difference between the number and degree of AID relatives and unfavourable prognosis in the pos-group. Similarly, the types of AID also provided limited clues to the unfavourable prognosis of IgG4-RD, except Takayasu arteritis (n=1) and autoimmune haemolytic anaemia (n=1), indicating that either IgG4-RD family history or other AID family history may have less significance in AID-pos patients with disease prognosis (online supplemental table 7).

DISCUSSION

Autoimmune diseases, such as SLE, SS, RA and dermatomyositis, are generally associated with genetic factors.[11] Genetic predisposing factors that increase the threshold of antigen receptor signalling, may render an individual more susceptible to the development of AID.[12] Familial clustering is always caused by genetic backgrounds and environmental factors shared within families, and, therefore, its magnitude and pattern of distribution may provide information on the aetiology of AID.[13 14] Family history is known to be an important predictor of AID, even after genetic and environment factors are considered.[15] A case cohort study has shown that family history of several AID such as hyper/hypothyroidism and inflammatory bowel disease were associated with elevated risk of RA.[16] In addition, family history of lupus was also clearly associated with an elevated risk of SLE onset.[17 18]

Aberrant innate and adaptive immune responses are both involved in the pathogenesis of IgG4-RD.[19] However, due to the low positive rate and uncertain role of autoantibodies, whether IgG4-RD is an AID remains in debate. IgG4-RD might share common risk factors with other immune disorders, previous studies have evaluated the similar signatures in gut microbiomes association between IgG4-RD and systemic sclerosis.[3] It is interesting to note that, based on our clinical observations, many family members of IgG4-RD patients had AID and even some IgG4-RD patients also had complications with other AID. To our knowledge, this is the first study to analyse the association between IgG4-RD patients and AID family history in a large cohort. The findings of the present study may support the hypotheses that there may be relationships between AID family history and subsequent development of IgG4-RD.

In recent years, researchers have found that autoantigens play an important role in the pathogenesis of autoimmunity diseases. However, only limited autoantigens have been found in IgG4-RD. Jarrell *et al* reported that anti-interleuukin-1RA autoantibodies, which promote pro-inflammatory and pro-fibrotic, in part of patients with IgG4-RD.[20] The presence of these autoantibodies in RA and SLE suggest an underappreciated mechanism for the crosstalk pathogenesis of multiple autoimmune diseases. In addition, a study has proposed that 51% AIP (26/51) patients present anti-laminin 511-E8 IgG antibody, but only in 1.6% controls (2/122). Histological studies with patient pancreatic tissues showed colocalisation of patient IgG and laminin 511. Mice with human laminin 511-E8 induced pancreatic injury.[21] In this study, we found a higher percentage of ANA positivity was found in AID-pos IgG4-RD patients compared with AID-neg group, and the majority of these patients had low-titre ANA levels. Considering these IgG4-RD patients may have a family history of AID, as well as the occurrence of serum ANA in certain patients. Longer-term follow-up should be performed to further clarify the role of ANA positivity in IgG4-RD patients in future studies.

The onset-age at diagnosis in IgG4-RD subjects with an AID-family was significantly earlier than those without AID family, which was consistent with other AID reports. According to a large-scale cross-sectional study of 803 cases of RA, the onset age of patients with family history was 6.04 years earlier than that in patients without family history of rheumatic diseases.[22] Further Cox analysis showed that older age (HR 0.97 (95% CI 0.94 to 0.99), p=0.0384*) was a protective factor with unfavourable prognosis among AID-pos IgG4-RD patients, suggesting the early onset is a risk element of IgG4-RD with AID-pos. Consistent with our previous findings which reported that younger age (≤56 years) at diagnosis was an independent risk factor of relapse in IgG4-RD.[23]

IgG4-RD patients have long been considered to accompany clinical history of allergy and atopy.[24–27] Of note, our previous study found peripheral Eos levels were elevated in 33.7% of cases, and the serum IgE levels were increased in 83.6% of IgG4-RD patients.[8] In this study, we found the higher peripheral Eos proportions (HR 1.1 (95% CI 1.02 to 1.2), p=0.02*) and allergic condition (HR 1.33 (95% CI 1.02 to 1.74), p=0.0332*) were deterioration risk factors in AID-pos and AID-neg cohort, respectively. Consistent with our previous study result is that higher proportions of Eos were a risk predictor association with relapse in IgG4-RD.[28]

Although many AID are more common in young and middle-aged woman, we did not find this phenomenon between AID-pos and AID-neg group IgG4-RD patients. A comparison of laboratory tests of IgG4-RD patients between the gender revealed the male patients had more severe disease than female patients, as evidenced by higher C reactive protein, IgG4, peripheral Eos proportions and trend to a higher proportion of the CD19+CD24–CD38hi plasmablast/plasma cell subset.[29] However, the sex differences of IgG4-RD were more significant after menopause, which suggest that sex hormones might not be the major cause in IgG4-RD.[29] Moreover, several studies have revealed IgG4-RD genetic variations, none of these located on sex chromosomes.[1 30] A genome association study of a large sample size is required to further explore the sex disparity of IgG4-RD is potentially associated with any genes on sex chromosomes.[30]

Finally, our study accounted for other exposure such as smoking and drinking. Patients without AID-family history had a higher ratio of smoking than those with AID-family history. In a 239 RA cohort study, Hutchinson *et al*[31] found heavy cigarette smoking is strongly associated with RA, particularly in patients without a family history of RA. However, the association between smoking and IgG4-RD prognosis was not significant in this study. Whether adverse environmental exposure is a component for the development of AID-neg patients with IgG4-RD still needs to be further explored. Of note, we found that continued alcohol intake is a risk factor of unfavourable prognosis merely in AID-pos cohort of IgG4-RD by adjusting with potential confounder (figure 2A,B; online supplemental table 4). IgG4-RD predominantly occurs in blue-collar workers.[32] The underlying mechanism for the inducting effect of alcohol, however, is unknown. Further investigation of this question may prove valuable, as identifying predictive guide and education interventions for individuals at higher risk for IgG4-RD is important for prognosis.

There was no significant statistical difference in clinical parameters and demographical characteristics between the different AID types of groups, indicating that either IgG4-RD family history or other AID family history may have less significance in AID-pos patients with disease onset (online supplemental table 3). Similarly, the numbers of AID relatives of AID-pos patients also provided limited clues to the pathogenesis of IgG4-RD (online supplemental table 2).

There are several limitations in this study. The number of IgG4-RD patients with unfavourable prognosis and the type of AID in the AID family history positive cohort is small and not sufficient to assess the impact of a specific AID on risk outcomes. Further studies are needed to expand the sample and explore possible susceptibility genes. Due to the limited number of samples from the various kind of AIDs, limited information may be available. However, among the various kinds of family AIDs, the ratio of RA and IgG4-RD was much higher than that of other AIDs and there were significant differences in ANA antibodies between the AID-pos and AID-neg groups, which may predict the further research value of genetics and IgG4-RD. Although there was no statistical difference in the rate of unfavourable prognosis between the AID-pos and AID-neg groups, the respective risk factors for unfavourable prognosis of themselves may provide some clinical guidance. In the future study, we will future expand the sample size, supplement other relevant

clinical information to find out the correlation between IgG4-RD and autoimmune family history information.

In conclusion, in this study, 14.8% of IgG4-RD patients had AID family history. IgG4-RD patients with an AID-family have a younger age at diagnosis, a more pronounced positive rate of ANA positivity and were more likely to have a combination of other AID. The onset age, peripheral Eos proportions and continued alcohol intake of was associated with unfavourable prognosis in AID-pos IgG4-RD patients.

Contributors JZ and WZ conceived and designed the study. RS and ZL were involved in the acquisition of the patients' clinical data, analysed the data and drafted the manuscript. HL, YP, JL, YN and JL also participated in the case and data collection. LP, YF and XZ contributed to the disease diagnosis. JZ and WZ revised the manuscript. The author(s) read and approved the final manuscript. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. WZ is responsible for the overall content as the guarantor.

Funding This work was supported by the National Natural Science Foundation of China (82071839, 82271848), Beijing Municipal Science & Technology Commission (No. Z201100005520023). CAMS Innovation Fund for Medical Sciences (CIFMS 2021–1-I2M-003). National High Level Hospital Clinical Research Funding (2022-PUMCH-C-006).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the ethical committee of the PUMCH (Approve number S-442). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Jiaxin Zhou http://orcid.org/0000-0002-1664-3495
Wen Zhang http://orcid.org/0000-0001-7808-9867

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