

# Malignancy Risk of Immunoglobulin G4-related Disease: Evidence From a Large Cohort Multicenter Study

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## Research article

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# Abstract

**Objective:** To evaluate the prevalence of malignancies in a multicenter cohort of Chinese patients with immunoglobulin G4-related disease (IgG4-RD) and to identify the related risk factors of malignancy in IgG4-RD patients.

**Methods:** We retrospectively analyzed 602 IgG4-RD patients who were recruited in 5 medical centers from 2009 to 2020. Standardized prevalence ratios (SPRs) against general Chinese population were calculated along with 95% confidence intervals (CIs). We identified the risk factors of malignancy in IgG4-RD and calculated the odds ratios (ORs) of different factors. Then, we developed and validated a prediction model for malignancy risk of IgG4-RD based on our cohort.

**Results:** We observed a significantly increased prevalence of total malignancies in this cohort compared to general Chinese population (SPR 8.66 [95%CI 5.84, 12.31]). Logistic regression analysis indicated that eosinophil percentage (OR 1.096 [95%CI 1.019-1.179],  $P=0.016$ ), serum albumin to globulin ratio (AGR) (OR 0.185 [95%CI 0.061-0.567],  $P=0.002$ ) and autoimmune pancreatitis (OR 2.400 [95%CI 1.038-5.549],  $P=0.041$ ) were three independent risk factors of malignancy in IgG4-RD patients. Four predictors were included in our final prediction model: age at IgG4-RD diagnosis, eosinophil percentage, AGR and autoimmune pancreatitis. The nomogram performed well in the internal validation cohort, with a concordance index (C-index) of 0.738.

**Conclusion:** A significantly increased prevalence of total malignancies were observed in our multicenter cohort. Eosinophil percentage and autoimmune pancreatitis are risk factors, whereas AGR is negatively associated with malignancy in IgG4-RD. A prediction model for malignancy risk of IgG4-RD was first developed and validated in our study.

## Introduction

IgG4-related disease (IgG4-RD) is a systemic autoimmune disease characterized by clinicopathological evidence of single or multiple tumefactive lesions, frequent elevation of serum IgG4 concentration and pathological findings such as fibrosis arranged in a storiform pattern, obliterative phlebitis and IgG4-positive plasma cell infiltration in tissue [1-3]. As a recently recognized fibroinflammatory condition, IgG4-RD is manifested as sialadenitis, dacryoadenitis, autoimmune pancreatitis (AIP), sclerosing cholangitis (SC)[4], tubulointerstitial nephritis (TIN), membranous glomerulonephropathy (MGN)[5] and retroperitoneal fibrosis, etc.

Whether patients with IgG4-RD have a higher risk of malignancy than general population is still controversial. Several studies reported an increased risk for malignancies among patients with IgG4-RD [6-10]. However, other studies observed no significant increase in the incidence of malignancies compared with general population [11-13]. It is still too early to draw a definitive conclusion based on limited samples in a single center cohort.

In this study, we evaluated the prevalence of malignancy in a multicenter large cohort of Chinese IgG4-RD patients and compared clinical characteristics between patients with and without malignancies. Risk factors of malignancy in IgG4-RD patients were identified. A prediction model capable of assessing malignancy risk of patients with IgG4-RD were developed and validated.

## Patients And Methods

### Patients

For this multicenter study, we included 602 patients who were referred to as IgG4-RD by the 2019 ACR/EULAR IgG4-RD classification criteria from 5 medical centers in China between April 2009 and January 2020 [14]. Malignant tumors were diagnosed according to available medical records and reliable pathological evidence, fulfilling International Classification of Diseases (ICD-11) criteria. Malignancy diagnosed within one year before or after the diagnosis of IgG4-RD was defined as on the diagnosis of IgG4-RD. Patients with malignancy diagnosed more than one year before or after the diagnosis of IgG4-RD were defined as before or after the diagnosis of IgG4-RD, respectively. The study has been approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China).

### Variables of interest

During the follow-up period, we retrospectively collected baseline data pertaining to demographic characteristics, personal history, past medical history, laboratory results and organ involvement. As possible risk factors of malignancy in IgG4-RD patients, we included the following variables for univariate and multivariate analysis: personal history such as smoke and alcohol, past medical history including allergic diseases, laboratory predictors such as complement, ESR, CRP, serum globulin level, serum albumin to globulin ratio (AGR), serum immunoglobulin level (IgA, IgM, IgE and IgG), serum IgG4 level, eosinophil, ANA and RF, as well as organ involvement. We selected predictors from variables above for our final prediction model.

### Statistical analysis

**Baseline characteristics.** Categorical variables were presented as the ratio or percentage of subjects, and continuous variables as mean±standard deviation (SD) (for normally distributed data) or median (interquartile range, IQR) (for non-normally distributed data). The statistical significance of differences in frequencies between groups was determined using the Chi square test or the Fisher's exact test as appropriate, while continuous variables were compared by the Mann-Whitney U test.

**Calculation of SPRs.** Standardized prevalence ratios (SPRs) against general Chinese population were calculated along with 95% confidence intervals (CIs). The SPR was calculated by comparing the observed to the expected number of cases. And the 95% CI was calculated based on the Poisson's distribution model.

**Logistic regression analysis.** Univariate and multivariate analysis were performed to identify the risk factors of malignancy in IgG4-RD and calculate the odds ratios (ORs) of different factors based on a logistic regression model. In the multivariate analysis, we applied those variables with  $P \leq 0.1$  in univariate analysis and possible risk factors of malignancy in previous studies [1, 3, 7] and used the backward elimination method.

**Development and validation of a prediction model.** We developed a nomogram for predicting malignancy risk of IgG4-RD based on backward stepwise logistic regression and used the bootstrap method with 1000 repetitions for internal validation, Harrell's C statistic was calculated as well.

The prediction model was developed and validated using R software. All other statistical analyses were performed by SPSS version 25.0.

## Results

### Baseline characteristics of IgG4-RD patients in the cohort

A total of 602 patients with IgG4-RD meeting the inclusion criteria in *Figure 1* were enrolled in this study. The baseline characteristics are presented in *Table 1*. According to the 2019 ACR/EULAR IgG4-RD classification criteria [14], 59.63% patients in our cohort were male. The mean age at IgG4-RD diagnosis was  $54.6 \pm 13.4$  years. The median follow-up time of the patients was 47.0 (27.0-65.0) months. The most frequently involved organs were the submandibular glands (56.81%), followed by the lymph nodes (48.01%) and the lacrimal glands (41.36%). 29 patients (18 males and 11 females) were identified as IgG4-RD accompanied by malignancy. Of all cases with malignancy, the mean age was  $58.9 \pm 12.1$  years at IgG4-RD diagnosis and  $56.8 \pm 13.7$  years at malignancy diagnosis, respectively.

### Clinical characteristics of IgG4-RD patients with malignancies

Baseline clinical characteristics in patients with and without malignancies were compared as shown in *Table 1*. There were no significant differences in demographic data, personal history and past medical history between IgG4-RD patients with and without malignancies. However, we observed statistical differences in laboratory results. The laboratory results revealed that IgG4-RD patients with malignancies had lower serum AGR (1.15 vs. 1.49,  $P = 0.001$ ), higher serum IgG level (21.94 vs. 17.36 g/L,  $P = 0.015$ ) and higher eosinophil percentage (6.10% vs. 2.30%,  $P = 0.001$ ) than those without malignancies. In terms of the distribution of organ involvement, submandibular glands, lymph nodes and lacrimal glands were the most frequently affected organs whether the patients developed malignancies or not.

### Types of malignancy in Chinese IgG4-RD patients and SPRs

Clinical characteristics of the IgG4-RD patients with malignancies are shown in *Table S1*. 14 (48.3%), 3 (10.3%) and 12 (41.4%) patients developed malignancies before, on and after the diagnosis of IgG4-RD, respectively. 25 out of 29 (86.2%) IgG4-RD patients were diagnosed with solid tumours, which consisted of lung cancer, stomach cancer, cervical cancer, thyroid cancer, bladder cancer, testicular cancer, kidney

cancer, intra-abdominal soft tissue sarcoma, colon cancer, prostate cancer, pancreatic cancer and esophageal squamous cell carcinoma (ESCC). Another 4 (13.8%) patients developed haematological malignancy, including 2 non-Hodgkin's lymphoma (NHL) cases, 1 Hodgkin's lymphoma (HL) case and 1 multiple myeloma (MM) case. Among IgG4-RD patients with malignancy in this study, lung cancer (8 cases) was the most common malignancy. Patients were treated for malignancies with a variety of approaches (*Table S1*), including surgery, chemotherapy, radiation, traditional Chinese medicine (TCM) and supporting treatment.

As shown in *Table 2*, the expected total malignancies in a cohort of 602 IgG4-RD patients would be 3.347 based on general Chinese population estimates. In our study, 29 (4.82%) patients were identified as IgG4-RD accompanied by malignancy. The SPR for total malignancy compared to the general Chinese population was 8.66 (95%CI 5.84, 12.31). Among male and female IgG4-RD patients, the expected total malignancies according to general Chinese population would be 1.672 and 1.333, respectively. However, we observed 18 males and 11 females in our cohort, corresponding to SPRs of 10.77 (95%CI 6.41, 16.86) and 8.25 (95%CI 4.14, 14.66). Also, we calculated the SPRs for different malignancies. There was a significantly increased SPR for lymphoma (42.86 [95%CI 8.79, 123.88]) as listed in *Table 2*.

### **Predictive factors for malignancy in IgG4-RD patients**

As shown in *Table 3*, odds ratios (ORs) were calculated by univariate analysis and we identified the following four variables as potential risk factors ( $P \leq 0.1$ ): age at IgG4-RD diagnosis, eosinophil percentage, AGR and autoimmune pancreatitis. Among variables above, age at IgG4-RD diagnosis (OR 1.028 [95%CI 0.996-1.062],  $P=0.082$ ), eosinophil percentage (OR 1.101 [95%CI 1.042-1.164],  $P=0.001$ ) and autoimmune pancreatitis (OR 1.904 [95%CI 0.889-4.077],  $P=0.098$ ) were positively correlated to malignancies in IgG4-RD patients, while AGR (OR 0.112 [95%CI 0.040-0.308],  $P \leq 0.001$ ) was negatively correlated to malignancies. Based on univariate analysis and previous studies, we entered the following seven variables into a multivariate logistic regression model: age at IgG4-RD diagnosis, sex, serum IgG level, AGR, eosinophil percentage, serum IgG4 level [7] and autoimmune pancreatitis. Multivariate analysis confirmed that eosinophil percentage (OR 1.096 [95%CI 1.019-1.179],  $P=0.016$ ), AGR (OR 0.185 [95%CI 0.061-0.567],  $P=0.002$ ) and autoimmune pancreatitis (OR 2.400 [95%CI 1.038-5.549],  $P=0.041$ ) were three independent risk factors of malignancy in IgG4-RD patients. Moreover, eosinophil percentage and autoimmune pancreatitis were positive correlation factors, whereas AGR was negatively associated with malignancy risk in IgG4-RD patients.

### **Development of a prediction model for malignancy risk of IgG4-RD**

Based on the analyses above, four predictors were included in our final prediction model: age at IgG4-RD diagnosis, eosinophil percentage, AGR and autoimmune pancreatitis. To visualize the logistic regression model, a nomogram incorporating each of these variables was configured as shown in *Figure 2*. Malignancy risk assessment of a patient with IgG4-RD contains three main steps. First, determine and locate the patient's position on each predictor axis. Second, draw perpendiculars from the corresponding axis of each predictor until the lines intersect with the top line labeled 'Points'. Third, sum up the points for

all predictors and draw a line descending from the axis labeled 'Total points' until it reaches the bottom line labeled 'Malignancy risk' to determine the probability of malignancy.

### **Validation of the nomogram**

An internal validation was performed to test the performance of our nomogram using the bootstrap method with 1000 repetitions. Harrell's C statistic was 0.738 (95%CI 0.635-0.842). Additionally, the calibration curve showed good agreement between the actual probability and the predicted probability by our nomogram (*Figure 3*).

## **Discussion**

In the present study, we first observed a significantly increased prevalence of malignancies based on the largest multicenter cohort of Chinese IgG4-RD patients. We reported higher eosinophil percentage and more frequent AIP presented in IgG4-RD patients with malignancies. However, elevated serum AGR was a possible protective factor for malignancy in IgG4-RD patients.

In this study, we observed a significantly increased prevalence of total malignancies in our cohort compared to general Chinese population (SPR 8.66 [95%CI 5.84, 12.31]). We summarized the types of malignancies in our cohort and compared it between IgG4-RD patients and general Chinese population. Similar to epidemiological studies of general population, lung cancer was the most common malignancy in IgG4-RD patients. However, lymphoma accounted for 10.3% (3 cases) of the malignancies in our cohort, given a standard prevalence ratio of 42.86 (95%CI 8.79, 123.88). Several previous studies suggested discrepancies in the types of malignancies between patients with IgG4-RD and the general population [1, 8-10]. Besides, the distribution of malignant tumours in IgG4-RD observed in previous studies is varied. Wallace et al. [7] reported prostate cancer and lymphoma were the most common malignancies based on a United States cohort, whereas only one prostate cancer case was observed in our study. Additionally, our cohort reported lymphoma, thyroid and stomach cancer were frequent malignancies associated with IgG4-RD, consistent with study by Ahn et al [1]. The disparities may be explained by differences of race, environment and sample capacity.

To date, the pathogenesis on the association between IgG4-RD and malignancy remains obscure. The chronic inflammatory state of IgG4-RD may play an important role in the development of malignancies. According to previous studies [16-20], mediators produced by activated inflammatory cells promote a variety of damages, including genetic mutations, post-translational modification of proteins involved in apoptosis, DNA repair, cell cycle control and signal transduction, as well as DNA and histone methylation, generating a pathologically conducive microenvironment which may induce the growth and progression of malignancies. Several previous studies suggested that chronic antigenic stimulation, together with oncogenic events such as p53 inactivation and K-ras mutation in IgG4-RD led to an increased risk of malignant transformation compared with the general population [6, 21]. Almost half of our patients developed malignancies after IgG4-RD diagnosis. Inflammation-associated oncogenesis may provide explanations for these cases.

In our study, 3 IgG4-RD patients developed lymphoma, including 2 B cell derived non-Hodgkin's lymphoma (NHL) cases and 1 Hodgkin's lymphoma (HL) case. To our knowledge, a few studies revealed close relationship between IgG4-RD and development of B cell lymphoma [22, 23]. Interestingly, as indicated by previous studies, an increased risk of lymphoma is also observed in patients with other autoimmune and inflammatory diseases [24, 25]. Goldin et al. emphasized the effects of secondary inflammation due to autoimmune stimulation on the processes, such as cytokine and chemokine release and viral reactivation (Epstein-Barr virus, for example). In addition, germline and somatic mutations are likely to induce autoimmunity and lymphomagenesis. Now that activation of B cells by increased Th2 cytokines including interleukin-4, 5, 10 and 13 contributes to the pathogenesis of IgG4-RD [26, 27], the superiority of B cell lymphoma as a secondary condition to IgG4-RD seems explicable. Study by Conde et al. identified the common genetic variants between NHL subtypes and autoimmune diseases, demonstrating a potential shared genetic mechanism [28]. A study reported the reciprocal chromosomal translocation t (14;19) (q32;q13.1) for rearrangements of IgH and BCL3 genes in the DLBCL cells, generating the dysfunction of the protein involved in nuclear factor (NF)- $\kappa$ B family regulation and complex cytogenetic abnormalities [23]. Accumulation of similar events may promote the process of lymphoma development from IgG4-RD. Moreover, the functional disorders of immune system in IgG4-RD may influence the interactions between components in microenvironment and promote lymphomagenesis [29, 30]. The association between IgG4-RD and specific lymphoid malignancies and the potential etiologic mechanisms deserve further discussion.

Several studies have found that AIP is associated with an increased risk of malignancies [3, 31]. In AIP patients, high levels of K-ras mutation have been detected in gastrointestinal tract, associated with persistent IgG4-related fibroinflammation and abundant infiltration of T lymphocytes and Foxp3+ cells, indicating AIP may share the similar molecular pathogenesis with malignancies in IgG4-RD.

It is proved that eosinophils play a pivotal role in several immunological diseases and malignancies [32]. Several previous studies observed eosinophilia in patients with both solid tumours and lymphoma [33-35]. On the one hand, eosinophils exert great influence in tumoricidal response. On the other hand, eosinophils contribute to tumour angiogenesis through the release of proangiogenic molecules such as vascular endothelial growth factor (VEGF) and osteopontin (OPN), and promote endothelial cell proliferation [36, 37]. Accordingly, in this study, we found elevated eosinophil percentage as a risk factor for malignancy in IgG4-RD patients.

In this study, we observed higher serum globulin level in IgG4-RD patients with malignancies. Besides, serum AGR was lower in patients with malignancies than those without, and elevated AGR was identified as a potential protective factor, which is consistent with previous studies [38, 39]. As a pro-inflammatory factor, globulin consists of a variety of components, including acute-phase reactive proteins, immunoglobulins, interleukins and tumour indicators, and participates in the regulation of osmotic pressure and the transportation of various compounds [38]. It is widely known that an increased level of globulin is related to chronic inflammation and various types of malignancies, especially haematological tumours. As serum globulin secreted by tumour-related cells is reported to promote the development,

angiogenesis, immunosuppression and metastasis of malignancies, high serum globulin may indicate the extent of severe chronic inflammation and poor prognosis [39]. As an important component, immunoglobulin G (IgG) expressed by cancer cells is reported to promote growth and survival of malignancies, by interacting with proteins involved in cell growth (RACK1, RAN and PRDX1, etc.) and activating relevant signaling pathway. Downregulation of IgG may arrest the S-phase of the cell cycle.

This study has several limitations. First, a retrospective study could not overcome the defects of the design itself. Second, examinations of the whole body, even the FDG-PET, may lead to the detection bias. Third, as an inevitable issue for a rare condition, low number of malignancies and wide 95% CI ranges were reported in our study. Moreover, the prediction model was validated only internally. Further collection of data based on an independent external cohort is under way. In consideration of the low incidence of both IgG4-RD and malignancy, the nomogram for predicting malignancy risk in IgG4-RD deserves long-term verification and adjustment.

## Conclusions

In conclusion, our study first reported a comparatively large, multicenter cohort of Chinese patients with IgG4-RD and confirmed credibly the necessity of comprehensive examination during the follow-up of IgG4-RD patients. Eosinophil percentage and autoimmune pancreatitis were identified as potential risk factors, whereas AGR was negatively associated with malignancy risk in IgG4-RD. Furthermore, a nomogram for prediction of malignancy risk in IgG4-RD patients was first developed and validated in our study, leading to improved follow-up management and prognosis in IgG4-RD patients.

## Abbreviations

**IgG4-RD:** immunoglobulin G4-related disease

**SPRs:** standardized prevalence ratios

**CIs:** confidence intervals

**ORs:** odds ratios

**AGR:** albumin to globulin ratio

**AIP:** autoimmune pancreatitis

**SC:** sclerosing cholangitis

**TIN:** tubulointerstitial nephritis

**MGN:** membranous glomerulonephropathy

**SD:** standard deviation

**IQR:** interquartile range

**ESR:** erythrocyte sedimentation rate

**CRP:** C-reactive protein

**RF:** rheumatoid factor

**ANA:** anti-nuclear antibodies

**M:** male

**F:** female

**DLBCL:** diffuse large B cell lymphoma

**MM:** multiple myeloma

**HL:** Hodgkin's lymphoma

**FL:** follicular lymphoma

**TCM:** traditional Chinese medicine

**ESCC:** esophageal squamous cell carcinoma

**VEGF:** vascular endothelial growth factor

## **Declarations**

### **Ethical Approval and Consent to participate**

This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China). All patients provided written informed consent for the utilization of their medical materials.

### **Consent for publication**

All authors gave their consent to publication of this manuscript.

### **Availability of supporting data**

Not applicable.

### **Competing interests**

The authors have no conflicts of interest to disclose.

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## **Authors' contributions**

Yanying Liu and Jiangnan Fu contributed equally to this paper. All authors participated in the analyses and interpretation of data, wrote or critically reviewed the manuscript, reviewed and approved the final version.

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## Tables

**Table 1** Characteristics of IgG4-RD patients with and without malignancies (n =602)

Variables	Total (n=602)	IgG4-RD with malignancies (n=29)	IgG4-RD without malignancies (n=573)	P-value
<b>Demographic data</b>				
Age†, years	54.6±13.4	58.9±12.1	54.4±13.4	0.081
Male:Female	359: 243 1.48: 1	18: 11 1.64: 1	341: 232 1.47: 1	0.784
Follow up time, months	47.0(27.0-65.0)	54.0(23.0-73.0)	46.0(27.0-65.0)	0.515
Time from onset to diagnosis, months	12.0(6.0-36.0)	24.0(7.0-60.0)	12.0(6.0-36.0)	0.052
<b>Personal history</b>				
Smoke, n (%)	92(15.28%)	6(20.69%)	86(15.01%)	0.407
Alcohol, n (%)	47(7.81%)	2(6.90%)	45(7.85%)	1.000
<b>Past medical history</b>				
Allergic diseases††	223 (37.04%)	14(48.28%)	209(36.47%)	0.199
Cardiovascular disease, n (%)	64(10.63%)	4(13.79%)	60(10.47%)	0.797
Hypertension, n (%)	150 (24.92%)	11(37.93%)	139(24.26%)	0.097
Diabetes, n (%)	99(16.45%)	8(27.59%)	91(15.88%)	0.097
Hyperlipidemia, n (%)	59(9.80%)	3(10.34%)	56(9.77%)	1.000
<b>Laboratory results</b>				
Complement 3 (C3), g/L	0.897(0.736-1.090)	0.873(0.762-1.100)	0.898(0.731-1.090)	0.965
Complement 4 (C4), g/L	0.210(0.155-0.273)	0.180(0.137-0.233)	0.210(0.159-0.275)	0.135
ESR, mm/h	13.0(7.0-34.0)	15.0(6.5-46.0)	13.0(7.0-34.0)	0.792
CRP, mg/L	2.21(0.91-7.28)	2.79(1.05-5.32)	2.20(0.91-7.51)	0.789
Serum globulin level, g/L	31.60(27.50-37.48)	33.30(30.80-35.33)	31.50(27.50-37.60)	0.399
AGR	1.46(1.28-1.65)	1.15(0.93-1.43)	1.49(1.29-1.65)	<b>0.001**</b>

Serum IgA level, g/L	1.99[1.35-2.79]	1.56[1.14-2.88]	2.01[1.36-2.78]	0.235
Serum IgM level, g/L	0.84[0.62-1.18]	0.77[0.62-1.34]	0.84[0.61-1.17]	0.833
Serum IgE level, IU/mL	236.80 [77.89-633.25]	320.50[169.00-701.00]	234.00[73.92-625.60]	0.172
Serum IgG level, g/L	17.42[13.70-25.50]	21.94[16.30-29.80]	17.36[13.65-24.74]	<b>0.015*</b>
Serum IgG4 level, mg/dL	584.0[273.0-1400.0]	610.0[444.0-2330.0]	565.9[269.0-1382.5]	0.065
Eosinophil count, 10 <sup>9</sup> /L	0.16[0.08-0.30]	0.26[0.10-0.47]	0.16[0.08-0.30]	0.102
Eosinophil percentage, %	2.40[1.00-4.50]	6.10[2.65-7.53]	2.30[1.00-4.30]	<b>[0.001**</b>
ANA (+), n (%)	96[15.95%]	4[13.79%]	92[16.06%]	0.948
Elevated RF, n (%)	80[13.29%]	4[13.79%]	76[13.26%]	1.000
<b>Number of involved organs</b>	3.0[2.0-5.0]	4.0[2.0-5.0]	3.0[2.0-4.3]	0.252
<b>Organ involvement</b>				
Head and neck	409 [67.94%]	22[75.86%]	387[67.54%]	0.349
Aorta	29[4.82%]	1[3.45%]	28[4.89%]	1.000
Bile duct system	102 [16.94%]	6[20.69%]	96[16.75%]	0.581
Endocranium	5[0.83%]	0[0]	5[0.87%]	1.000
Gall bladder	76[12.62%]	3[10.34%]	73[12.74%]	0.926
Heart and pericardium	6[1.00%]	0[0]	6[1.05%]	1.000
Kidney	115 [19.10%]	4[13.79%]	111[19.37%]	0.615
Lacrimal gland	249 [41.36%]	15[51.72%]	234[40.84%]	0.245
Liver	28[4.65%]	3[10.34%]	25[4.36%]	0.298
Lung	138 [22.92%]	8[27.59%]	130[22.69%]	0.540
Lymph node	289 [48.01%]	18[62.07%]	271[47.29%]	0.120

Mediastinum	2 (0.33%)	0 (0%)	2 (0.35%)	1.000
Mesenterium	11 (1.83%)	1 (3.45%)	10 (1.75%)	1.000
Middle ear and mastoid	3 (0.50%)	0 (0%)	3 (0.52%)	1.000
Orbit and peri-orbit	58 (9.63%)	4 (13.79%)	54 (9.42%)	0.649
Pancreas	167 (27.74%)	12 (41.38%)	155 (27.05%)	0.093
Parotid gland	193 (32.06%)	7 (24.14%)	186 (32.46%)	0.349
Pituitarium	3 (0.50%)	0 (0%)	3 (0.52%)	1.000
Prostate	32 (5.32%)	1 (3.45%)	31 (5.41%)	0.972
Retroperitoneum	87 (14.45%)	4 (13.79%)	83 (14.49%)	1.000
Sublingual gland	19 (3.16%)	2 (6.90%)	17 (2.97%)	0.524
Submandibular gland	342 (56.81%)	20 (68.97%)	322 (56.20%)	0.176
Thyroid	54 (8.97%)	0 (0%)	54 (9.42%)	0.098

Values are expressed as mean±standard deviation (SD), median (interquartile range, IQR), ratio or number (percentage).

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AGR, albumin to globulin ratio; RF, rheumatoid factor; ANA, anti-nuclear antibodies.

†Age, age at IgG4 related disease diagnosis.

††Allergic diseases include asthma, urticaria, eczema and allergic rhinitis.

‡Head and neck involvement includes orbit and peri-orbit, lacrimal gland, submandibular gland, parotid gland, sublingual gland and thyroid.

\* $P < 0.05$ .

\*\* $P < 0.01$ .

**Table 2** Standardized prevalence ratios for malignancy in the IgG4-RD cohort compared to the Chinese general population

Stratification variables	Observed malignancies, n	Chinese prevalence, %	Expected malignancies, n	SPR (95%CI)
<b>Total</b>	29	0.556	3.347	8.66 [5.84, 12.31]
<b>Sex</b>				
Male	18	0.2778	1.672	10.77 [6.41, 16.86]
Female	11	0.2214	1.333	8.25 [4.14, 14.66]
<b>Malignancy</b>				
Lung	8	0.0656	0.395	20.25 [8.77, 39.66]
Lymphoma	3	0.0117	0.070	42.86 [8.79, 123.88]
Thyroid	3	0.0299	0.180	16.67 [3.44, 48.47]
Cervix	3	0.0233	0.140	21.43 [4.42, 62.21]
Bladder	2	0.0173	0.104	19.23 [2.33, 69.07]
Stomach	2	0.0648	0.390	5.13 [0.62, 18.44]

Abbreviations: IgG4-RD, IgG4 related disease; SPR, standardized prevalence ratio; 95%CI, 95% confidence interval.

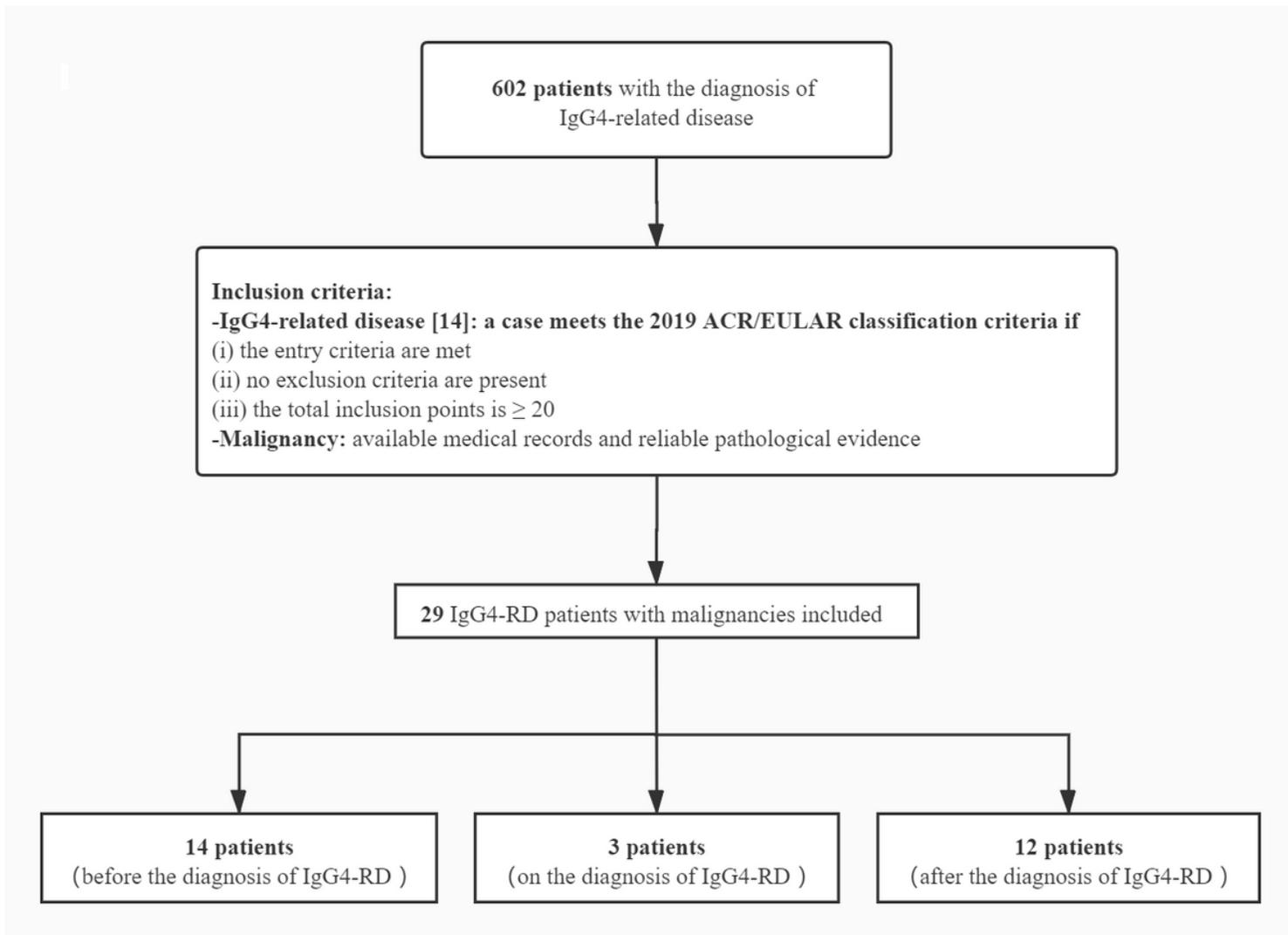
**Table 3** ORs of related factors for malignancy in IgG4-RD patients: logistic regression analysis

Variables	Univariate analysis				Multivariate analysis			
	Odds ratio (OR)	95%CI	Wald Z	P-value	Odds ratio (OR)	95%CI	Wald Z	P-value
Age at IgG4-RD diagnosis	1.028	0.996-1.062	3.028	0.082				
Eosinophil percentage	1.101	1.042-1.164	11.627	0.001	1.096	1.019-1.179	6.057	<b>0.016*</b>
Albumin to globulin ratio	0.112	0.040-0.308	17.946	0.001	0.185	0.061-0.567	8.744	<b>0.002**</b>
Autoimmune pancreatitis	1.904	0.889-4.077	2.744	0.098	2.400	1.038-5.549	4.187	<b>0.041*</b>

\* $P \leq 0.05$ .

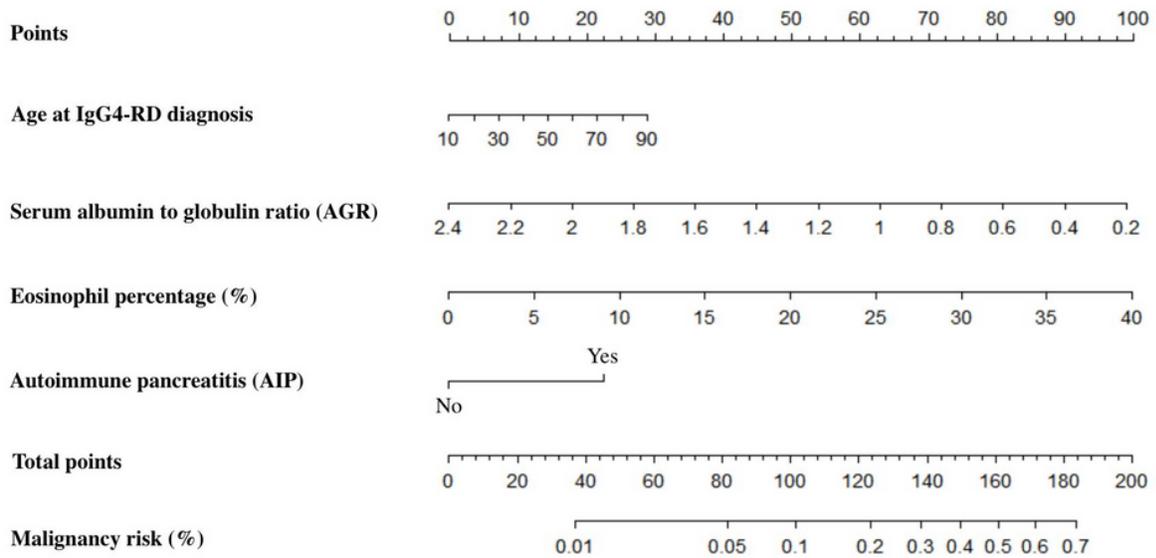
\*\* $P \leq 0.01$ .

## Figures



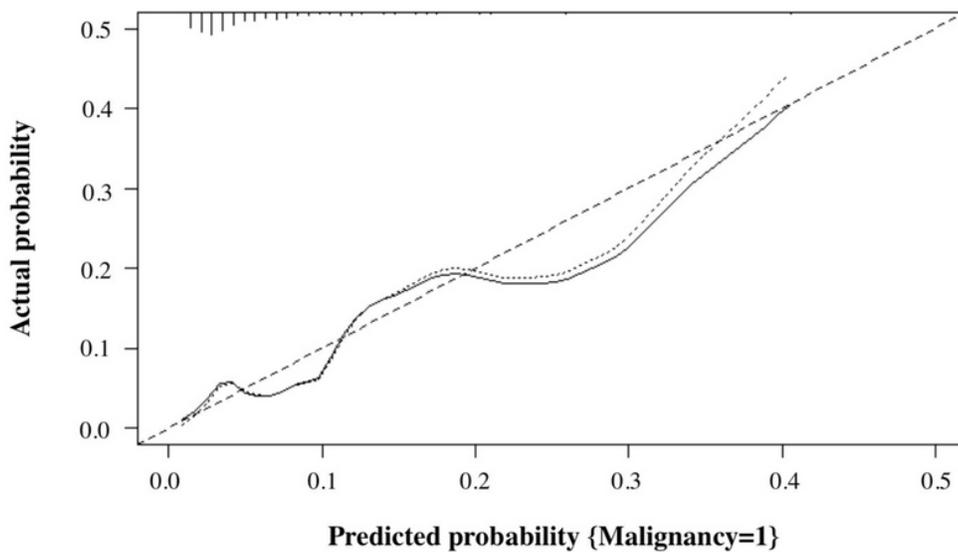
**Figure 1**

Flowchart of the inclusion of patients with immunoglobulin G4-related disease (IgG4-RD) and malignancy in this study.



**Figure 2**

The nomogram for predicting malignancy risk of IgG4-RD.



B=1000 repetitions, boot  
 Mean absolute error=0.014  
 Mean squared error=0.00032  
 0.9 Quantile of absolute error=0.027  
 c index=0.738

**Figure 3**

Calibration curve of the prediction model for malignancy risk. The calibration curve showed good agreement between the actual probability and the predicted probability by our nomogram. Harrell's C statistic was 0.738 (95%CI 0.635-0.842).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryarthritisresearchtherapy.docx](#)