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

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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, obliterator phlebitis and IgG4-positive plasma cell infiltration in tissue [1-3]. As a recently recognized fibrolumamatory 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 $P<0.1$ 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±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±12.1 years at IgG4-RD diagnosis and 56.8±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 ($P<0.1$): 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], $P=0.001$) 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)-κB 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 comparativley 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
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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References

1. Ahn SS, Song JJ, Park YB, et al. Malignancies in Korean patients with immunoglobulin G4-related disease. Int J Rheum Dis. 2017;20:1028–35.
2. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Modern Pathology; An Official Journal of the United States Canadian Academy of Pathology Inc. 2012;25:1181.
3. Tang H, Yang H, Zhang P, et al. Malignancy and IgG4-related disease: the incidence, related factors and prognosis from a prospective cohort study in China. Sci Rep. 2020;10:4910.
4. Culver EL, Chapman RW. IgG4-related hepatobiliary disease: an overview. Nat Rev Gastroenterol Hepatol. 2016;13:601–12.
5. Cortazar FB, Stone JH. IgG4-related disease and the kidney. Nat Rev Nephrol. 2015;11:599–609.
6. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4-related disease. Mod Rheumatol. 2012;22:414–8.
7. Wallace ZS, Wallace CJ, Lu N, et al. Association of IgG4-Related Disease With History of Malignancy. Arthritis Rheumatology. 2016;68:2283–9.
8. Sekiguchi H, Horie R, Kanai M, et al. IgG4-Related Disease: Retrospective Analysis of One Hundred Sixty-Six Patients. Arthritis Rheumatol. 2016;68:2290–9.
9. Huggett MT, Culver EL, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. 2014;109:1675–83.
10. Asano J, Watanabe T, Oguchi T, et al. Association Between Immunoglobulin G4-related Disease and Malignancy within 12 Years after Diagnosis: An Analysis after Longterm Followup. J Rheumatol. 2015;42:2135–42.
11. Hart PA, Law RJ, Dierkhising RA, et al. Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. Pancreas. 2014;43:417.
12. Hirano K, et al. Incidence of Malignancies in Patients with IgG4-related Disease. Intern Med. 2014;53:171–6.
13. Inoue D, Yoshida K, Yoneda N, et al. IgG4-Related Disease: Dataset of 235 Consecutive Patients. Medicine. 2015;94:e680.
14. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European league against rheumatism classification criteria for IgG4-related disease. Ann Rheum Dis. 2020;79:77–87.
15. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115–32.
16. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
17. Yajima R, Takano K, Konno T, et al. Mechanism of fibrogenesis in submandibular glands in patients with IgG4-RD. J Mol Histol. 2018;49:577–87.
18. Pua KH, Chew CL, Lane DP, et al. Inflammation-associated genomic instability in cancer. Genome Instability Disease. 2020;1:1–9.
19. Fest J, Ruiter R, Mulder M, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer—a population-based cohort study. Int J Cancer. 2020;146:692–98.
20. Gouravani M, Khalili N, Razi S, et al. The NLRP3 inflammasome: a therapeutic target for inflammation-associated cancers. Expert Rev Clin Immunol. 2020;16:175–87.
21. Gupta R, Khosroshahi A, Shinagare S, et al. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a retrospective analysis of pancreatic resections. Pancreas. 2013;42:506–10.
22. Bledsoe JR, Wallace ZS, Stone JH, et al. Lymphomas in IgG4-related disease: clinicopathologic features in a Western population. Virchows Arch. 2018;472:839–52.
23. Kawaji Y, Nagata H, Muramatsu A, et al. Diffuse large B cell lymphoma with chromosomal translocation t(14;19)(q32;q13) occurring in IgG4-related disease. Ann Hematol. 2019;98:1785–87.
24. Gaetane N, Elena P, Michele B, et al. Lymphomas complicating primary Sjögren's syndrome: from autoimmunity to lymphoma. Rheumatology 2019; kez052.
25. Fallah M, Liu X, Ji J, et al. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Ann Oncol. 2014;25:2025–30.
26. Tanaka A, Moriyama M, Nakashima H, et al. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. Arthritis Rheumatology. 2012;64:254–63.
27. Grados A, Ebbo M, Piperoglou C, et al. T Cell Polarization toward TH2/TFH2 and TH17/TFH17 in Patients with IgG4-Related Disease. Front Immunol. 2017;8:235.
28. Conde L, Bracci PM, Halperin E, Skibola CF. A search for overlapping genetic susceptibility loci between non-Hodgkin lymphoma and autoimmune diseases. Genomics. 2011;98:9–14.
29. Vardhana S, Younes A. The immune microenvironment in Hodgkin lymphoma: T cells, B cells, and immune checkpoints. Haematologica. 2016;101:794–802.
30. Khurana A, Ansell SM. Role of Microenvironment in Non-Hodgkin Lymphoma: Understanding the Composition and Biology. The Cancer Journal. 2020;26:206–16.
31. Schneider A, Hirth M, et al. Risk of Cancer in Patients with Autoimmune Pancreatitis: A Single-Center Experience from Germany. Digestion. 2017;95:172–80.
32. Rosaria GM, Gilda V, Mansour S, et al. Bidirectional Mast Cell–Eosinophil Interactions in Inflammatory Disorders and Cancer. Frontiers in Medicine. 2017;4:103.
33. Leighton SEJ, Teo JGC, Leung SF, et al. Prevalence and prognostic significance of tumor-associated tissue eosinophilia in nasopharyngeal carcinoma. Cancer. 2015;77:436–40.
34. Kurose N, Mizuguchi S, Ohkanemasa Y, et al. Adenosquamous carcinoma of the uterine cervix displaying tumor-associated tissue eosinophilia. SAGE Open Medical Case Rep. 2019;7:1–5.
35. Hu G, Wang S, Zhong K, et al. Tumor-associated tissue eosinophilia predicts favorable clinical outcome in solid tumors: a meta-analysis. BMC Cancer. 2020;20:454.

36. Kienzl M, Hasenoehrl C, Valadez-Cosmes P, Maitz K, Sarsembayeva A, Sturm E, Heinemann A, Kargl J, Schicho R. IL-33 reduces tumor growth in models of colorectal cancer with the help of eosinophils. Oncoimmunology. 2020;9:1776059.

37. Zhao H, Chen Q, Alam A, et al. The role of osteopontin in the progression of solid organ tumour. Cell Death Dis. 2018;9:356.

38. Bozkaya Y, Erdem GU, Demirci NS, et al. Prognostic importance of albumin to globulin ratio in metastatic gastric cancer patients. Curr Med Res Opin. 2019;35:275–82.

39. Yoshino Y, Taguchi A, Shimizuguchi T, et al. A low albumin to globulin ratio with a high serum globulin level is a prognostic marker for poor survival in cervical cancer patients treated with radiation based therapy. Int J Gynecol Cancer. 2019;29:17–22.

Tables

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

| Variables                        | Total (n=602) | IgG4-RD with malignancies (n=29) | IgG4-RD without malignancies (n=573) | \(P\)-value |
|---------------------------------|--------------|----------------------------------|-------------------------------------|-------------|
| **Demographic data**           |              |                                  |                                     |             |
| Age†, years                     | 54.6±13.4    | 58.9±12.1                        | 54.4±13.4                           | 0.081       |
| Male:Female                     | 359:243      | 18:11                            | 341:232                             | 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       |
| **Personal history**            |              |                                  |                                     |             |
| 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       |
| **Past medical history**        |              |                                  |                                     |             |
| 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       |
| **Laboratory results**          |              |                                  |                                     |             |
| 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       | 31.6±27.50-37.48 | 33.3±30.80-35.33               | 31.5±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                      | **0.001**   |
| 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) | 0.015* |
| **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, 10^9/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) | **0.001**** |
| **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 |
| **Number of involved organs** | 3.0 (2.0-5.0) | 4.0 (2.0-5.0) | 3.0 (2.0-4.3) | 0.252 |

**Organ involvement**

| **Head and neck** | 409 (67.94%) | 22 (75.86%) | 387 (67.54%) | 0.349 |
| **Aorta** | 29 (4.82%) | 10 (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 |
| Tissue       | Cases | Prevalence | Controls | Prevalence | OR    |
|--------------|-------|------------|----------|------------|-------|
| Pancreas     | 167   | 27.74%     | 12       | 41.38%     | 0.093 |
| Parotid gland| 193   | 32.06%     | 7        | 24.14%     | 0.349 |
| Pituitary    | 3     | 0.50%      | 0        | 0          | 1.000 |
| Prostate     | 32    | 5.32%      | 1        | 3.45%      | 0.972 |
| Retroperitoneum | 87 | 14.45%     | 4        | 13.79%     | 1.000 |
| Sublingual gland | 19 | 3.16%      | 2        | 6.90%      | 0.524 |
| Submandibular gland | 342 | 56.81%     | 20       | 68.97%     | 0.176 |
| Thyroid      | 54    | 8.97%      | 0        | 0          | 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) |
|--------------------------|--------------------------|-----------------------|--------------------------|-------------|
| Total                    | 29                       | 0.556                 | 3.347                    | 8.66, 5.84, 12.31 |
| Sex                      |                          |                       |                          |             |
| Male                     | 18                       | 0.2778                | 1.672                    | 10.77, 6.41, 16.86 |
| Female                   | 11                       | 0.2214                | 1.333                    | 8.25, 4.14, 14.66 |
| Malignancy               |                          |                       |                          |             |
| 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                              |
| 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                                |
| Albumin to globulin ratio         | 0.112               | 0.040-0.308                           | 17.946                | 0.001                                |
| Autoimmune pancreatitis           | 1.904               | 0.889-4.077                           | 2.744                 | 0.098                                |
|                                   | 0.185               | 0.061-0.567                           | 8.744                 | 0.001**                              |
|                                   | 2.400               | 1.038-5.549                           | 4.187                 | 0.041*                               |

*P<0.05.

**P<0.01.