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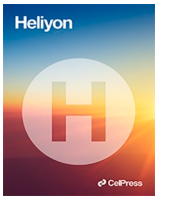

Clinical patterns and risk factors for multiorgan involvement in IgG4-Related disease patients

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ABSTRACT

Background: IgG4-related disease with multiorgan involvement predicts higher disease activity, thus, it is necessary to identify whether IgG4-related disease involves multiple organs at the early stage. To further clarify the clinical characteristics and risk factors for IgG4-related disease with multiorgan involvement, we conducted an observational study.
Methods: We retrospectively analysed the clinical data of 160 patients who were primarily diagnosed with IgG4-related disease at the First Affiliated Hospital of Zhengzhou University from January 2015 to January 2021. According to the number of involved organs, patients were divided into two groups: multiorgan involvement and nonmultiorgan involvement. Patients were divided into a multiorgan group and a nonmultiorgan group according to multiple organ involvement.
Results: There were 82 cases identified with multiorgan involvement and 78 cases diagnosed with no multiorgan involvement in this series. Most cases were elderly and male ($p > 0.05$). The most frequently affected organs in IgG4-RD were the lymph nodes (50.6 %), pancreas (38.7 %) and salivary glands (35.6 %). Multivariate analysis showed that eosinophilia, IgG4>2*ULN, lymph node involvement, salivary gland involvement and lung involvement were independent risk factors for multiorgan involvement ($p < 0.05$).
Conclusions: The main issues in clinical practice are how to accurately diagnose the disease and screen the more vulnerable organs.

1. Introduction

IgG4-related disease (IgG4-RD) is a chronic fibro-inflammatory autoimmune disease pathologically characterized by dense infiltration of lymphoplasmacytes dominated by IgG4-positive plasma cells, together with storiform fibrosis and obliterative phlebitis in the affected organs [1]. It was once considered a solitary disease with specific organ involvement, and several terms were proposed

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according to the different involved organs, such as autoimmune pancreatitis and Mikulic's disease. In 2003, Kamisawa et al. [2]. First introduced the concept of IgG4-RD and proposed that autoimmune pancreatitis is a pancreatic manifestation of IgG4-RD. Since then it has been considered a kind of systemic disorder [3].

It is currently found that IgG4-RD can affect almost every organ, involvement of retroperitoneum/aorta, the pancreato-biliary tract, salivary glands, and head and neck are the most common disease phenotypes observed [4]. In 2017, Yamada et al. [5] reported that 62.9 % of patients presented with involvement of three or more organs, and the proportion of patients with single organ involvement was only 11.4 %. Another international study involving 493 patients reported that 75.6 % of IgG4-RD patients had multiorgan ($\geq$2 organs) involvement [6].

Therefore, Carruthers et al. [6] proposed the IgG4-RD Responder Index (RI) to uniformly measure disease activity according to the number of affected organs and serum IgG4 level, and it has been confirmed as a reliable evaluation method. Serum IgG4 was removed from the RI category in a subsequent study [7]. Multiorgan involvement predicts higher disease activity, and early recognition is particularly important. However, recognition of accurate status of organs involvement is difficult because comprehensive laboratory and imaging assessments are not feasible during every visit of patient clinically. Hence, identifying risk factors that correlate well with the numbers of involved organs of IgG4-RD could be helpful.

Several studies have proposed that some predictive factors for multiorgan involvement in IgG4-RD, including higher serum IgG4 concentrations, elevation of eosinophils at baseline and Salivary gland involvement [9]. However, differences in epidemiological characteristics, serological results, and prognostic outcomes between the multiorgan group and the nonmultiorgan group need further interpretation. Besides, the predictive factors for IgG4-RD multiorgan involvement remain uncertain.

Based on data of inpatients with IgG4-RD from our hospital, for the first time, we report significant differences in clinical presentation between patients with multi-organ involvement and those without, and sought to identify the risk factors for multiorgan involvement to achieve early systematic treatment and improve the prognosis.

2. Methods

2.1. Study subjects

The retrospective study was conducted on 160 patients with IgG4-RD from the First Affiliated Hospital of Zhengzhou University between January 2015 and January 2021. The diagnosis of IgG4-RD adopts the 2011 comprehensive diagnostic criteria [8]: (1) diffuse/localized organ swelling or masses; (2) elevated serum IgG4 level (>1.35 g/L); and (3) histopathological features of infiltration of IgG4+ plasma cells (>10 IgG4+ cells per high power field and ratio of IgG4+/IgG + cells >40 %). Possible IgG4-RD required (1) and (2), probable IgG4-RD required (1) and (3), and definite IgG4-RD required all of the items. Organ involvement was assessed based on signs and symptoms, laboratory detection, imaging and histopathological examinations. Disease activity was evaluated with the IgG4-RD responder index (RI) [7]. Patients with previous malignancy, active/severe infection and other autoimmune diseases were excluded. According to previous studies, the involvement of $\geq$3 organs is considered multiorgan involvement, and distal biliary stricture accompanying autoimmune pancreatitis is the only item not included in the scope of biliary involvement [9]. According to the number of involved organs, patients were divided into two groups: multiorgan involvement and nonmultiorgan involvement.

2.2. Data collection

Collected data from medical records including clinical features (gender, age, history of allergic disease, number of involved organs and disease duration). Allergic disease was diagnosed according to the criteria of the European Academy of Allergy and Clinical Immunology. Disease course was defined as the time between the onset of symptom and diagnosis. The laboratory indicators consist of liver function, C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA), complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum IgE, serum IgG, serum IgG4 and complement tests, including were analysed retrospectively. Imaging examinations such as ultrasound, CT, PET/CT or MRI are used to assess the involvement of each organ. In this study, tissue biopsies were performed on 95 patients, and the tissues were immunohistochemically stained using IgG4 antibodies. After ruling out all possible alternative diagnoses, a pathologic diagnosis of IgG4-RD was confirmed by experienced pathologists. The study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants.

2.3. Statistical analysis

The quantitative variables are described as the means $\pm$ standard deviation (SD) or medians (interquartile range, IQR). Categorical variables are presented as cases and proportions. Shapiro-Wilk test is used to distinguish whether continuous variables conform to a normal distribution. For quantitative variables, Student's t-test was performed to analyze the difference between two groups in accordance with normal distribution, Mann–Whitney *U* test was performed to analyze the difference between two groups in non-normal distribution. For categorical variables, differences between groups were analysed using chi-square test or Fisher's exact test. Univariate and multivariate Cox regression analyses (Enter method) were conducted to identify the potential risk factors for multiorgan involvement. Variables with $P < 0.1$ in the univariate analysis were enrolled in the multivariate analysis. IBM SPSS Statistics version 24.0 software was used for all the statistical analyses. Significant differences were defined as $P < 0.05$.

3. Results

3.1. Patient demographic features

Overall, 160 inpatients with IgG4-RD (113 males and 47 females) were enrolled in this study. According to the comprehensive diagnostic criteria of IgG4-RD, patients were diagnosed with definite (78, 48.8 %), probable (7, 4.3 %), and possible IgG4-RD (75, 46.9 %), respectively.

Among these 160 patients, 82 cases were confirmed with multiorgan involvement, and other 78 cases were diagnosed with no multiorgan involvement. The detailed distribution of organ involvement number was indicated as follows: one organ was involved in 19 %, two organs in 29 %, three organs in 30 %, four organs in 14 %, and five or more organs in 8 % (Supplementary Fig. S1). We observed several differences between the multiorgan involvement group and the nonmultiorgan involvement group. The demographic features of the patients are presented in Table 1.

The number of affected organs and the IgG4-RD RI score in the multiorgan involvement group were higher than those in the nonmultiorgan involvement group (median 3 vs. 2, $P < 0.001$; median 9 vs. 6, $P < 0.001$, respectively). Compared with the non-multiorgan involvement group, the multiorgan involvement group was related to a longer disease duration (median 5.5 vs. 2 months, $P < 0.001$). There was no significant difference in diagnostic status between male and female IgG4-RD patients.

3.2. Clinical features

The most frequently involved organs were the lymph nodes (50.6 %), followed by the pancreas (38.7 %), salivary glands (SG) (35.6 %), lacrimal glands (LG) (31.2 %), lung (30 %), kidney (13.7 %) and bile duct (12.5 %). More than two organs involvement was observed in the majority of IgG4-RD patients, while 19 % (n = 31) had only one organ involved.

Patients with eosinophilia had a higher incidence of dacryoadenitis (61.9 % vs. 16.4 %, $P = 0.014$), submandibular sialadenitis (65.9 % vs. 49.5 %, $P = 0.007$), lymphadenopathy (55.3 % vs. 42.0 %, $P = 0.037$) and skin rash (7.4 % vs. 2.7 %, $P = 0.034$) (Fig. 1), as well as an elevated IgG4-RD RI and more organs involvement ($P < 0.05$, Table 1). Surprisingly, whether the patients had eosinophilia or not, no significant difference was observed in the incidence of allergic diseases (Table 1).

Detailed organ involvement between the multiorgan and nonmultiorgan involvement groups is shown in Fig. 2. In the multiorgan involvement group, the most common organs involved were the lymph nodes (73.1 %), salivary gland (57.3 %), and lacrimal gland (46.3 %). In the no multiorgan involvement group, the pancreas (42.3 %) was the most frequently affected organ, followed by the lymph nodes (26.9 %) and lung (20.5 %). The involvement of lymph nodes (73.1 % vs. 26.9 %, $P < 0.001$), salivary glands (57.3 % vs. 12.8 %, $P < 0.001$), lacrimal glands (46.3 % vs. 15.3 %, $P < 0.001$), lungs (39 % vs. 20.5 %, $P = 0.011$) and paranasal sinuses (19.5 % vs. 3.8 %, $P = 0.002$) was more common in patients with multiorgan involvement. Kidney involvement was more likely common in the multiorgan involvement group, but it is not considered statistically significant between the two groups (18.2 % vs. 8.9 %, $P = 0.087$).

3.3. Laboratory findings

The laboratory indicators of all patients and the two groups are displayed in Table 2. Elevated serum levels of IgG4 were observed in 153 patients (95.7 %), and 125 (78.1 %) patients had elevated serum IgG4 >2 ULN. In addition, 35/160 patients (21.8 %) exhibited eosinophilia. A total of 43/96 patients (44.8 %) exhibited hypocomplementemia, and 14/120 patients (11.7 %) were ANA-positive.

In the laboratory tests, patients with multiorgan involvement presented higher eosinophil counts and lower CRP, serum C3 and C4 levels. The incidence of eosinophilia and IgG4 >2 ULN was also higher for IgG4-RD patients associated with multiorgan involvement. However, the incidence of hypocomplementemia is not significantly different between the two groups. No significant differences were found in the levels of serum HBG, WBC, PLT, albumin, globulin, ESR, IgG, IgE or ANA positive rate.

Correlation of involved organ number with clinical and laboratory parameters.

Correlation analysis showed that the number of organs involved was positively correlated with disease duration, eosinophil count and globulin (Table 3) but negatively correlated with serum C3, C4 and CRP, as shown in Table 3. All of these results indicate that many kinds of factors are correlated with disease burden of IgG4-RD patients.

Table 1
Demographic features of IgG4-RD patients.

Characteristics	All	Multiorgan involvement	Nonmultiorgan involvement	*Statistics*	*P value*
Number of cases, n	160	82 (51.2 %)	78 (48.8 %)		
Age at diagnosis onset, years, median (IQR)	55 (46.3–63.8)	55 (47–62)	54.5 (46–64.3)	−0.400	*0.689*
Age at diagnosis, years, median (IQR)	55 (48.3–64)	55 (49–63)	55 (46–65)	−0.080	*0.936*
Disease duration, months, median (IQR)	3.5 (1–12)	5.5 (1.9–24)	2 (1–9.3)	−3.016	***0.030***
Gender				0.100	*0.751*
Male, n (%)	113 (70.6)	57 (69.5)	56 (71.8)		
Female, n (%)	47 (29.4)	25 (30.5)	22 (28.2)		
Allergy history, n (%)	37 (23.1)	16 (19.5)	21 (26.9)	1.567	*0.211*
Number of involved organs	3 (2–3)	3 (3–4)	2 (1–2)	−11.274	***0.000***
IgG4-RD RI	9 (6–9)	9 (9–12)	6 (3–6)	−11.107	***0.000***

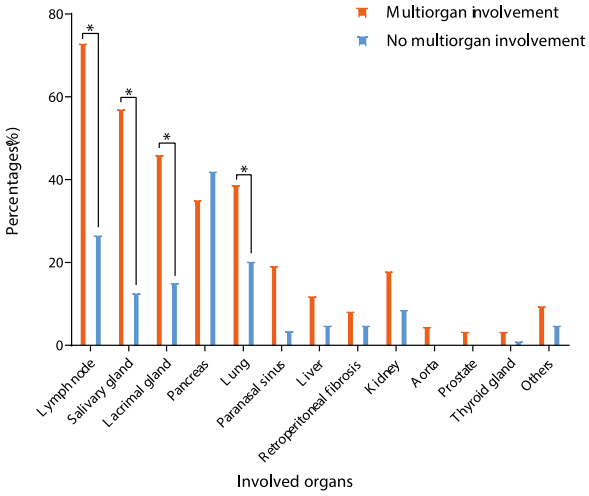

Fig. 1. Involved organs between the two groups.

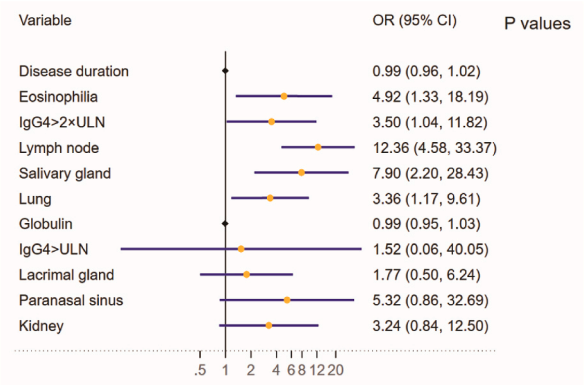

Fig. 2. Multivariate analysis of logistic regression of risk factors for multiorgan-involved patients.

3.4. Risk factors associated with multiorgan involvement

As shown in Table 4, disease duration (OR = 1.023, 95 % CI: 1.002–1.045; P = 0.032), eosinophilia (OR = 5.259, 95 % CI: 2.137–12.944; P < 0.001), IgG4>2 × ULN (OR = 4.897, 95 % CI, 2.06–11.64; P < 0.001), lymph nodes (OR = 7.403, 95 % CI: 3.679–14.896; P < 0.001), salivary gland (OR = 9.131, 95 % CI: 4.123–20.222; P < 0.001), lacrimal gland (OR = 4.75, 95 % CI: 2.237–10.084; P < 0.001), lung (OR = 2.48, 95 % CI: 1.224–5.026; P = 0.012) and paranasal sinus (OR = 6.061, 95 % CI: 1.691–21.726; P = 0.006) were more likely to be associated with multiorgan involvement in univariate logistic regression analysis.

Furthermore, eosinophilia (OR = 4.92, 95 % CI: 1.331, 18.187; P = 0.017), lymph nodes (OR = 12.36, 95 % CI: 4.579–33.368; P < 0.001), salivary gland (OR = 7.904, 95 % CI, 2.197–28.428; P = 0.002), lung (OR = 3.359, 95 % CI: 1.174–9.61; P = 0.024) and IgG4>2 × ULN (OR = 3.501, 95 % CI, 1.037–11.822; P = 0.044) remained significant in the multivariate analysis (Fig. 2).

4. Discussion

IgG4-related disease is newly recognized as a chronic, systemic disease that can affect almost every organ of the body synchronously or successively. It was reported that the incidence of multiple organ (≥3) involvement varied from 38 % to 78.8 % [5,10–12]. In this series, over half of the total patients were associated with multiorgan involvement. Multiorgan involvement predicts higher disease activity; thus, it is necessary to perform an evaluation of the whole body to obtain a comprehensive view of the general condition of the patients in clinical practice. Previous studies have described the status of involved organs in patients with IgG4-RD, however, these studies did not focus on the comparison between patients with multiorgan and nonmultiorgan involvement, and there is no consensus about the risk factors associated with multiorgan involvement.

There was much difference between multiorgan involvement group and nonmultiorgan involvement group in baseline demographic and clinical features. The multiorgan involvement group showed a longer disease duration. Regarding the involved organs,

Table 2
Laboratory findings between the two groups.

Variables	All	Multiorgan involvement	Nonmultiorgan involvement	Statistics	*P value*
HBG (g/L), mean (SD)	123.8 ± 18.7	125.7 ± 18	121.8 ± 19.2	−1.338	*0.183*
WBC (× 10^9/L)	6.2 (5.1–7.6)	6.2 (5.2–7.7)	6 (5–7.5)	−0.613	*0.54*
PLT (× 10^9/L)	220 (168–278)	210 (163.8–262.5)	241 (172–296)	−1.816	*0.069*
Eosinophil count (× 10^9/L)	0.25 (0.13–0.46)	0.34 (0.17–0.6)	0.2 (0.1–0.34)	−4.13	***0.000***
Eosinophilia[a], n (%)	35 (21.8)	28 (34.1)	7 (8.9)	14.821	***0.000***
Albumin (g/L), median (IQR)	38.3 (33.7–42.5)	38.6 (34.4–42.6)	37.9 (33.4–42.2)	−0.797	*0.425*
Globulin (g/L), median (IQR)	32.7 (28.4–40.6)	34.2 (28.7–41.8)	31.3 (26.6–39.2)	−1.565	*0.118*
ESR (mm/h), median (IQR)	27 (11–71)	24 (11–56)	43.5 (8.6–86.3)	−0.879	*0.379*
CRP (mg/L), median (IQR)	2.8 (1–10.1)	1.7 (0.83–6.5)	4.4 (1.4–21.8)	−2.727	***0.006***
C3 (g/L), median (IQR)	0.98 (0.77–1.3)	0.97 (0.65–1.2)	1.1 (0.83–1.45)	−2.067	***0.039***
C4 (g/L), median (IQR)	0.2 (0.14–0.27)	0.19 (0.11–0.25)	0.23 (0.2–0.36)	−2.704	***0.007***
Hypocomplementemia[b], n (%)	43 (44.8)	29 (49.2)	14 (37.8)	1.177	*0.278*
IgG (g/L), median (IQR)	17.1 (13.1–25.7)	18.8 (13.9–26.1)	16.7 (12–24.9)	−1.004	*0.315*
IgG4>ULN[c], n (%)	153 (95.7)	81 (98.7)	72 (92.3)	NA	*0.059*
IgG4>2 × ULN, n (%)	125 (78.1)	74 (90.2)	51 (65.3)	14.455	***0.000***
IgE (IU/mL)	302.7 (137.6–741.6)	297.7 (155.1–612.7)	406.9 (101.2–835.2)	−0.296	*0.767*
ANA+, n (%)[d]	14 (11.7)	6 (9.2)	8 (14.5)	0.817	*0.366*

Abbreviations: ULN, upper limit of normal.
[a] Eosinophilia was defined as an eosinophil count greater than 0.5 × 10^9/L in the peripheral blood.
[b] 96 patients were tested for Hypocomplementemia.
[c] P value is Fisher's exact test for IgG4>ULN.
[d] 120 patients were tested for ANA.

Table 3
Correlations between the number of involved organs and clinical indicators.

	Numbers of involved organ	
Parameters	Spearman r	P value
Age at diagnosis onset, years	0.019	0.812
Age at diagnosis, years	0.037	0.643
Disease duration, months	0.200	**0.011**
HBG (g/L), mean (SD)	0.012	0.885
WBC(× 10^9/L), mean (SD)	−0.050	0.535
PLT (× 10^9/L), mean (SD)	−0.126	0.114
Eosinophil count (× 10^9/L)	0.300	**0.000**
Albumin (g/L), median (IQR)	0.004	0.961
Globulin (g/L), median (IQR)	0.161	**0.042**
ESR (mm/h), median (IQR)	−0.024	0.823
CRP (mg/L), median (IQR)	−0.181	**0.034**
C3 (g/L), median (IQR)	−0.257	**0.011**
C4 (g/L), median (IQR)	−0.317	**0.002**
IgG (g/L)	0.153	0.145
IgE (IU/mL)	−0.015	0.916

lymph node, salivary gland, lacrimal gland, paranasal sinus and lung involvement were relatively more common in multiorgan involvement. With continuous progression in the field of IgG4-RD, there have been some differences in the prevalence of affected organs in previous studies [5,12]. However, lymph nodes, salivary glands, lacrimal glands and pancreas were the most commonly affected sites in many researches [13]. In our study, lymph nodes were the most frequently involved organs, followed by the pancreas, salivary glands (61.0 %) and lacrimal glands (47.5 %). Other affected organs included the lung, retroperitoneal fibrosis, kidney, and paranasal sinus. This phenomenon manifested the systemic nature of IgG4-RD. Therefore, systemic evaluation should be emphasized for IgG4-RD before initiating therapy.

Eosinophilia, lymph nodes, salivary gland, lung involvement and IgG4>2 × ULN were risk factors for multiorgan involvement in patients with IgG4-RD. It was reported that eosinophilia is seen in approximately 11–38 % of IgG4-RD patients [11,14]. Recently, several studies have found that eosinophil count was positively correlated with the level of serum IgG4 [14,15], and some studies directly pointed out that eosinophil count was positively related to the number of involved organs [11]. Consistently, our study also demonstrated that there was a positive relationship between peripheral eosinophil counts and the number of involved organs in IgG4-RD patients. In terms of pathogenesis, an activated Th2 cell response is expressed in IgG4-RD, and Th2 cytokines, mainly interleukin IL-4 and IL-13, promote the production of IgG4 and cause eosinophilia at the same time [16]. In addition, the release of IL-2 activated by eosinophils can also promote the production of IgG4, which is traditionally considered to be related to the number of affected organs [17].

It has been widely accepted that the serum cut-off value of IgG4 level >1.35 g/L is used for diagnosing IgG4-RD, and reports show

Table 4
Univariate logistic regression analysis of risk factors for multiorgan-involved patients.

Variables	Univariate analysis		
	OR	95%CI	*P value*
Gender			
Male	1		*Ref*
Female	1.116	0.565,2.207	*0.751*
Age at diagnosis onset, years	0.996	0.972,1.020	*0.748*
Age at diagnosis, years	1.0	0.975,1.024	*0.969*
Disease duration, months,	1.023	1.002,1.045	***0.032***
Allergy history	0.623	0.296,1.311	*0.213*
Eosinophilia	5.259	2.137,12.944	***0.000***
Globulin (g/L)	1.025	0.998,1.054	***0.075***
IgG4>ULN, n (%)	6.75	0.794,57.41	***0.080***
IgG4>2 × ULN, n (%)	4.897	2.06,11.64	***0.000***
Affected organs			
Lymph node	7.403	3.679,14.896	***0.000***
Salivary gland	9.131	4.123,20.222	***0.000***
Lacrimal gland	4.75	2.237,10.084	***0.000***
Pancreas	0.746	0.394,1.412	*0.368*
Lung	2.480	1.224,5.026	***0.012***
Bile duct	1.5	0.578,3.894	*0.405*
Paranasal sinus	6.061	1.691,21.726	***0.006***
Kidney	2.271	0.872,5.914	***0.093***
Liver	2.569	0.771,8.566	*0.125*
Retroperitoneal fibrosis	1.727	0.485,6.147	*0.399*

that serum IgG4 concentrations were associated with disease activity [18,19]. It seems that the more organs involved in IgG4-RD, the more serum IgG4 rised. Carruthers et al. [20] reported a median serum IgG4 concentration of 6.9 g/L in patients with multiorgan involvement compared to 2.3 g/L in those with single-organ involvement. Consistently, in a Chinese study, serum IgG4 levels in patients with multiple-organ involvement were significantly higher than those in patients with single-organ involvement. Moreover, a moderate positive correlation between serum IgG4 levels and the number of affected organs in IgG4-RD patients was revealed by Spearman's rank test [21]. Up to now, the role of elevated serum IgG4 in IgG4-RD still needs further illustration. IgG4 has traditionally been thought to induce an anti-inflammatory rather than a proinflammatory response, driven by the lack of ability of this IgG subtype to activate complement and Fcγ receptors. However, IgG4 was unable to form hemimolecules and immune complexes suggesting that they may be the products of inflammatory stimuli, with long or repeated antigen exposure leading to increased serum IgG4 concentrations [22,23]. The existence of elevated IgG4 means that there is active and extensive destructive inflammation in the process of disease. In total, its high level may reflect increased disease activity.

This study shows that the presence of lymphadenopathy in IgG4-RD patients indicates high disease activity and progression to multiorgan involvement, which is consistent with Takanashi et al. [24]. Although several researches have revealed that patients with IgG4-associated lymphadenopathy tend to progress to extranodal lesions, IgG4-associated lymphadenopathy without any other organ involvement is rare [25]. The underlying mechanisms of this phenomenon may be the diffusion of the inflammation of nearby involved organs. The other explanation may be that lymph nodes are the origin of inflammation, which promotes the activation of immune cells and further release of cytokines, leading to an increase in serum IgG4 and promoting the development and spread of inflammation.

The salivary gland is also a risk factor for multiorgan involvement. More recently, an international study group analysed the largest international patient cohorts of IgG4-RD using potential category analysis (LCA) and finally described four phenotypes of IgG4-RD, including the hepatopancreatobiliary group, the retroperitoneal and aortic group, the head and neck restricted group, and the Mikulicz and whole body group. In the fourth group, males were dominant, presenting with typical Mikulicz's syndrome of systemic involvement, with the highest serum IgG4 level and a higher number of involved organs [26]. As previous studies mentioned, salivary gland involvement in patients meant more affected organs and a higher serum IgG4 level and IgE level as well as a higher incidence of eosinophilia [27]. Moreover, Martín-Nares et al. [28] found patients with major salivary gland swelling had a higher probability of lymphadenopathy and lung involvement, which implied that patients with these involved organs may have the ability to influence more organs.

There are some limitations of our study. One limitation of this study is a retrospective analysis; another limitation is that it is concluded basing on a single-center population study indicating a selection bias. Furthermore, since IgG4 was not accurately quantified in our center, the diagnosis of IgG4-RD was not according to the latest 2019 diagnostic criteria. The improvement of pathological diagnosis and multicenter validation are what we need to do in the future.

In summary, peripheral eosinophilia; serum IgG4; and affected organs of lymph nodes, salivary glands and lungs were associated with multiorgan involvement. We recommend that patients who are vulnerable to multiorgan involvement have a comprehensive inspection for evidence of subclinical disease and clarify the extent of organ involvement at diagnosis, which emphasizes the necessity and urgency of treatment.

5. Ethics approval statement

The study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University.

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Data availability statement

The data associated with this study has not been deposited into a publicly available repository. The data used and/or analysed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Hang Ding: Writing – original draft. **Lin Zhou:** Conceptualization. **Linlin Zheng:** Data curation. **Jiahui Wang:** Methodology. **Yongpeng Zhai:** Methodology. **Xinyi Zhou:** Resources. **Ping Zhao:** Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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