Article

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The Significance of Serum IgG4/IgG and IgG4/IgG1 Ratio in the Diagnosis Value of IgG4-Related Diseases

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Objective: Elevated serum immunoglobulin G4 (IgG4) is one of the important features of patients with IgG4-related diseases (IgG4-RD). But diagnosing these diseases using IgG4 alone is tricky because the tests can sometimes give inaccurate results. Our research is focused on studying the ratio of IgG4 to two other substances, immunoglobulin G (IgG) and immunoglobulin G1 (IgG1), in the blood. We hope this approach will lead to more accurate diagnoses of IgG4-RD.
Methods: We conducted a study on 68 patients diagnosed with IgG4-related diseases (IgG4-RD) and 160 individuals suffering from other autoimmune diseases (AID) at our hospital between June 2018 and June 2022. Eighty healthy people who underwent physical examination in our hospital at the same time were randomly selected as controls, and medical records were collected for all subjects. The serum IgG and IgG subclasses were detected, and the IgG4/IgG and IgG4/IgG1 ratios were calculated.
Results: We found that patients with IgG4-RD have significantly higher average levels of serum IgG4 and more elevated IgG4/IgG and IgG4/IgG1 ratios compared to individuals with other AID patients and those in good health ($p < 0.001$). The receiver operating characteristic (ROC) curve analysis showed that the diagnostic effectiveness area under the curve (AUC) of the serum IgG4/IgG ratio for IgG4-RD was 0.906 (95% confidence interval [CI], 0.865–0.947) and 0.921 (95% CI, 0.876–0.965) when comparing with other AID patients and healthy individuals, respectively. The optimal cut-off value for the IgG4/IgG ratio was 0.147 (with 72.1% sensitivity and 94.4% specificity) compared with AID patients and 0.129 (with 77.9% sensitivity and 96.2% specificity) compared with healthy individuals. Similarly, the AUC of the serum IgG4/IgG1 ratio for diagnosing IgG4-RD was 0.919 (95% CI, 0.882–0.956) and 0.916 (95% CI, 0.870–0.962) when compared with patients with other AID and healthy individuals, respectively. When we divided our study participants into a high IgG4/IgG ratio group (>0.129) and a normal IgG4/IgG ratio group (≤0.129) using a cut-off point of 0.129, we found through logistic regression analysis that those with a high IgG4/IgG ratio were more likely to be associated with IgG4-RD (odds ratio [OR], 31.25; 95% CI, 15.31–63.79; $p < 0.001$). Likewise, a high IgG4/IgG1 ratio was also significantly linked to an increased risk of IgG4-RD (OR, 36.39; 95% CI, 17.57–75.38; $p < 0.001$).
Conclusions: The serum's IgG4/IgG and IgG4/IgG1 ratios are independently linked to IgG4-RD and are valuable in its diagnosis.

Keywords: IgG4/IgG ratio; IgG4/IgG1 ratio; IgG4-related diseases; autoimmune diseases

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a complex condition driven by the immune system, characterized by inflammation and fibrosis [1]. First identified in 2003, IgG4-RD is primarily defined by the enlargement of one or several organs in the body and notably high levels of IgG4. From a pathological perspective, and the disease is marked by the presence of lymphocytes, fibrosis, a condition known as occlusive phlebitis, and infiltration by eosinophils from a pathological perspective [2]. If left untreated, IgG4-RD can continually progress, forming mass-like lesions and ongoing immune inflammation. This can result in fibrosis, compression of organs and neighboring tissues, and in severe cases, could even lead to organ failure [3]. While no extensive surveys specifically focused on the prevalence of IgG4-RD, insights can be gleaned from cross-sectional studies examining the epidemiology of autoimmune pancreatitis, a condition closely related to IgG4-RD. These studies indicate a rise in the prevalence of autoimmune pancreatitis from 2.2 per 100,000 people in 2007 to 10.1 per 100,000 in 2016, which potentially signifies an increase in disease occurrence and enhanced disease recognition among healthcare professionals [4,5]. However, autoimmune pancreatitis is only one of the more than ten organs involved in IgG-RD, and even though IgG-RD is considered a rare disease, it is less rare at present. In addition to genetic factors, IgG4-RD disease may also be associated with environmental or autoimmune triggers, but overall, the mechanism is unclear [6]. Like other autoimmune diseases (AID), IgG4-RD can be divided into induced remission and maintenance remission, and the drugs used for treatment mainly include glucocorticoids, immunosuppressive agents, and monoclonal antibodies. Still, the overall therapeutic effect is poor [7].

IgG4 is one of the immunoglobulin G (IgG) subtypes and is mainly presented in the blood, with normal adult concentrations of serum IgG4 of approximately 80–1400 mg/L, accounting for 0.8%–11.7% of total IgG [8]. The increase of serum IgG4 concentration is one of the important features and diagnostic criteria of IgG4-RD, but its sensitivity and specificity are unsatisfactory. Elevated serum IgG4 can occur in various non-IgG4-RD diseases, including diffuse connective tissue disease, chronic infection, leukemia, and allergic diseases, resulting in poor specificity and low positive predictive value [9]. A meta-analysis showed a pooled sensitivity of 87.2% and a specificity of 82.6% for serum IgG4. However, while the specificity improved when using twice the upper limit, there was a notable decrease in sensitivity [6]. In addition, when renal damage occurs in IgG-RD, serum IgG4, complement 3, and complement 4 may decrease, causing false negatives [10,11]. Therefore, scholars are gradually focusing on other serological markers, including interleukin-6 and C-reactive protein [12]. One study suggests that the IgG4/IgG RNA ratio may play a role in distinguishing IgG4-RD from primary sclerosing cholangitis and hepatobiliary malignancies. Immunoglobulin G1 (IgG1) is the most abundant protein of IgG subtypes. However, few studies have evaluated the diagnostic value of IgG4/IgG1 in IgG4-RD [13].

Hence, our objective was to assess the effectiveness of serum IgG4/IgG and IgG4/IgG1 ratios in the diagnosis of IgG4-RD and to explore the relationship of these ratios have with IgG4-RD.

Method

Subject

Our study analyzed data from 68 patients with IgG4-RD and 160 patients with other AID who were diagnosed and treated at our hospital between June 2018 and June 2022. As a control group, we randomly selected 80 healthy individuals, matched by sex and age, who underwent physical exams during the same period. The study complied with the principles of the Declaration of Helsinki and was conducted with the approval of the ethics committee of the Capital Institute of Pediatrics (Reference number: 20170310007), and written consent was obtained from all participants. In total, we included 308 subjects based on inclusion and exclusion criteria. We retrospectively collected data such as age, gender, and levels of IgG and its subclasses concentration from all subjects' medical records.

Inclusion criteria: Participants were included if they were at least 18 years old, met the diagnostic criteria for IgG4-RD established in 2011 [14] or other AID, and completed the IgG and IgG subclasses detection.

Exclusion criteria: Patients treated with glucocorticoids or CD20 monoclonal antibodies before they visited our hospital. Patients with systemic multi-organ involvement and significant fibrosis of the affected organs, severe heart, liver, or kidney disease, chronic infection, or allergic diseases. Pregnant women and patients unable to cooperate due to mental disorders were also excluded from the study.

Data Collection

The study encompassed 308 participants, which included 68 individuals diagnosed with IgG4-RD, 160 subjects suffering from other AID, and 80 healthy control subjects. We conducted tests on serum IgG and its subclasses for all these participants. Five milliliters of fasting venous blood from each participant, which was drawn and then centrifuged. Before proceeding with the tests, specimens should be examined for clarity, ensuring there were no unidentified particles or residual fibrinogen, and confirmed that the samples were free from hemolysis.

The detection of serum IgG subclasses was carried out via immunonephelometry using a Siemens BN II machine (Siemens, Germany, BN II machine). The assay kit used for the serum IgG subclass tests had verified precision, accuracy, measurement range, and adult reference interval. This was confirmed with controls at varying concentrations. The detection of serum IgG, was conducted with immunonephelometry, which offers benefits such as a broad detection range, accurate results, short detection time (usually just a few minutes), and strong stability.

Statistical Analysis

We executed the statistical analysis using IBM SPSS 26.0 software (IBM Corp., Armonk, NY, USA). We represented normally distributed continuous variables as mean $\pm$ standard deviation and compared the differences among IgG-RD, other AID, and healthy controls using analysis of variance (ANOVA). The least significant difference (LSD) method was used to compare any two individual groups. Variables that didn't follow a normal distribution were represented as medians, including the 25th and 75th percentiles. Non-parametric tests were utilized to compare these variables across the three different groups. Categorical variables were presented as counts, and chi-squared tests were employed to compare groups. Receiver operating characteristic (ROC) curves were utilized to evaluate the diagnostic performance and significance of serum IgG4/IgG and IgG4/IgG1 ratios for IgG4-RD. Youden index (= sensitivity + specificity – 1) was used to evaluate the optimal cut-point of IgG4/IgG and IgG4/IgG1 ratio for diagnosing IgG4-RD, and sensitivity and specificity were determined. Following the determination of the IgG4/IgG ratio cut-off point, the study population was categorized into normal and high IgG4/IgG groups, and logistic regression was performed to analyze the association between the high IgG4/IgG group and IgG4-RD.

Similarly, the population was categorized into normal and high IgG4/IgG1 groups after determining the IgG4/IgG1 ratio cut-off point, and logistic regression was performed to analyze the correlation between high

Table 1. Clinical characteristics of the participants.

	IgG4-RD	Other AID	Healthy control	F value/χ^2	p
n	68	160	80	-	-
Age, years	36.6 ± 10.2	39.4 ± 10.9	37.8 ± 9.5	1.857	0.158
Male, n (%)	28 (41.2)	73 (45.6)	31 (39.2)	0.998	0.607
Serum IgG4, mg/L	2516 ± 1618[ab]	678 ± 267	608 ± 247	146.294	<0.001
Serum IgG4, mg/L, median (5th, 75th)	2000 (1380, 3750)[ab]	951 (709, 1050)	515 (383, 903)	155.550	<0.001
IgG4/IgG	0.179 ± 0.054[ab]	0.101 ± 0.029	0.100 ± 0.021	134.474	<0.001
IgG4/IgG1	0.305 ± 0.107[ab]	0.149 ± 0.055	0.156 ± 0.046	134.679	<0.001

a, p (the difference between IgG4-RD (immunoglobulin G4-related diseases) and other AID (autoimmune diseases) subjects) < 0.001. b, p (the difference between IgG4-RD and healthy control) < 0.001.

Table 2. IgG4/IgG ratio Optimum cut-off value and diagnostic performance for distinguishing IgG4-associated diseases from other autoimmune diseases and healthy controls.

	Cut-off	Sensitivity, %	Specificity, %	p
Other AID patients as controls	0.147	72.1	94.4	<0.001
Healthy people as controls	0.129	77.9	96.2	<0.001

IgG4/IgG1 group and IgG4-RD. Graphs were prepared by Graphpad Prism 6.0 (Graphpad Prism Software, Inc., San Diego, CA, USA). A p-value of less than 0.05 in a two-tailed test was considered statistical significance.

Results

Study the Clinical Characteristics of the Participants

As shown in Table 1, 68 IgG4-RD individuals, 160 other AID patients, and 80 healthy people were included. The mean age of IgG4-RD individuals was 36.6 ± 10.2 years, 28 males and 40 females; The mean serum IgG4 concentration, mean IgG4/IgG ratio and mean IgG4/IgG1 ratio of IgG4-RD individuals were 2516 ± 1618 mg/L, 0.179 ± 0.054, and 0.305 ± 0.107, respectively. The mean age of other AID subjects was 39.4 ± 10.9 years, 73 males and 87 females; The mean IgG4 concentration, mean IgG4/IgG ratio and mean IgG4/IgG1 ratio of other AID patients were 678 ± 267 mg/L, 0.101 ± 0.029, and 0.149 ± 0.055, respectively. The healthy control population was 37.8 ± 9.5 years, 31 males and 49 females. The mean serum IgG4 concentration, mean IgG4/IgG ratio and mean IgG4/IgG1 ratio in the healthy control population were 608 ± 247 mg/L, 0.100 ± 0.021, and 0.156 ± 0.046, respectively. Compared to other AID subjects and healthy participants, IgG4-RD individuals had significantly higher IgG4 concentrations, IgG4/IgG ratios, and IgG4/IgG1 ratios ($p < 0.001$). Regarding age and sex ratio, IgG4-RD individuals, other AID subjects, and healthy participants are similar ($p > 0.05$).

The Performance of IgG4/IgG Ratio

Fig. 1 illustrates the ROC curves of the IgG4/IgG ratio was used to distinguish between individuals with IgG4-RD, other AID, and healthy controls. With AID patients as controls, the area under the curve (AUC) was 0.906 (95% CI, 0.865–0.947; $p < 0.001$) for diagnosing IgG4-RD based on the serum IgG4/IgG ratio. With healthy individuals as controls, the AUC of the IgG4/IgG ratio was 0.921 (95% CI, 0.876–0.965) for diagnosing IgG4-RD. Table 2 presents the optimal cut-off value and diagnostic effectiveness of the IgG4/IgG ratio for distinguishing IgG4-RD from other AID and healthy controls. The ideal IgG4/IgG cut-point ratio for diagnosing IgG4-RD, using AID patients as controls, was 0.147 (sensitivity, 72.1%; specificity, 94.4%). When healthy individuals as controls, the optimal cut-point was 0.129 (sensitivity, 77.9%; specificity, 96.2%).

The Performance of IgG4/IgG1 Ratio

Fig. 2 demonstrates the ROC curves of the IgG4/IgG1 ratio for distinguishing IgG4-RD from other AID patients and healthy controls. With other AID patients as controls, the AUC of serum IgG4/IgG1 ratio was 0.919 (95% CI, 0.882–0.956; $p < 0.001$) when diagnosing IgG4-RD. With healthy people as controls, the AUC was 0.916 (95% CI, 0.870–0.962; $p < 0.001$) when IgG4-RD was diagnosed by ROC curve analysis. Table 3 shows the cut-off value and diagnostic performance of the IgG4/IgG1 ratio for distinguishing IgG4-RD from other AID and healthy controls. Using other AID patients as controls, the optimal cut-point of serum IgG4/IgG1 ratio was 0.244 (sensitivity, 73.5%; specificity, 96.2%). The optimal cut-point was 0.209 (sensitivity, 79.4%; specificity, 97.5%) when using healthy people as controls.

Logistic Regression

Table 4 presents the logistic regression of IgG4/IgG and IgG4/IgG1 ratios in relation to IGg4-RD. The study population was segmented into two groups based on an established tangent point (0.129): The high IgG4/IgG ratio group (>0.129) and the normal IgG4/IgG ratio group

Table 3. Optimal threshold and performance of IgG4/IgG1 ratio in differentiating IgG4-associated diseases from other autoimmune diseases and healthy controls.

	Cut-off	Sensitivity, %	Specificity, %	*p*
Other AID patients as controls	0.244	73.5	96.2	<0.001
Healthy people as controls	0.209	79.4	97.5	<0.001

Table 4. Logistic regression of IgG4/IgG and IgG4/ IgG1 ratios for IgG4-associated diseases.

	B	S.E.	Wald	*p* value	OR (95% CI)
High IgG4/IgG (normal IgG4/IgG as the reference[#]), Unadjusted	3.459	0.363	90.782	<0.001	31.80 (15.61, 64.79)
High IgG4/IgG (normal IgG4/IgG as the reference[#]), Model 1*	3.442	0.364	89.386	<0.001	31.25 (15.31, 63.79)
High IgG4/IgG1 (normal IgG4/IgG as the reference[#]), Unadjusted	3.594	0.372	93.595	<0.001	36.39 (17.57, 75.38)
High IgG4/IgG1 (normal IgG4/IgG as the reference[#]), Model 1*	3.573	0.372	92.223	<0.001	35.63 (17.18, 73.88)

*Adjust for age and sex. [#]Using 0.129 as the tangent point, the normal IgG4/IgG to high IgG4/IgG was distinguished. Using 0.209 as the tangent point, normal IgG4/IgG1 and high IgG4/IgG1 ratios were distinguished.

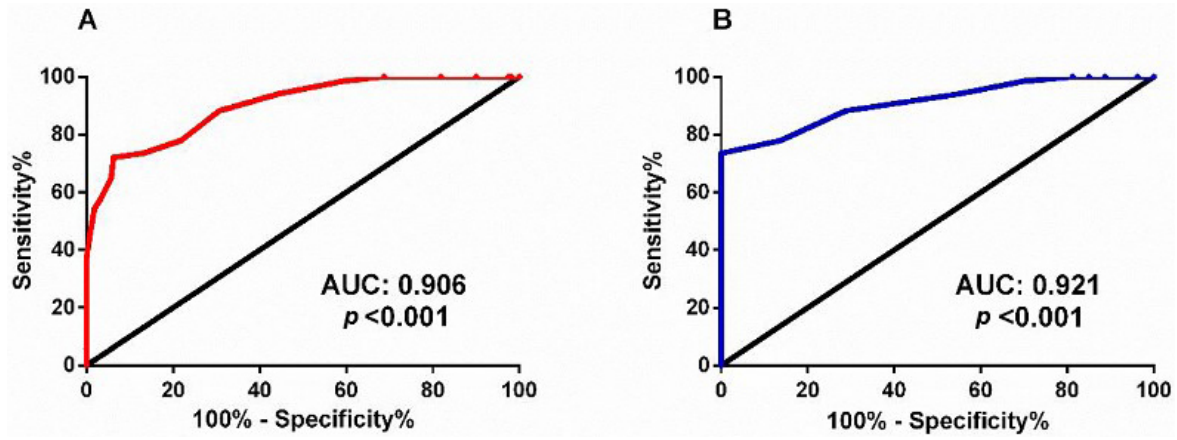

Fig. 1. Serum IgG4 (immunoglobulin G4)/IgG ratio distinguishing IgG4-associated diseases from other autoimmune diseases and healthy controls. (A) Serum IgG4/IgG ratio differentiates IgG4-associated diseases from other autoimmune diseases. AUC (area under the curve) (95% CI), 0.906 (0.865, 0.947); $p < 0.001$. (B) IgG4/IgG ratio distinguishes IgG4-associated diseases from healthy controls. AUC (95% CI), 0.921 (0.876, 0.965); $p < 0.001$.

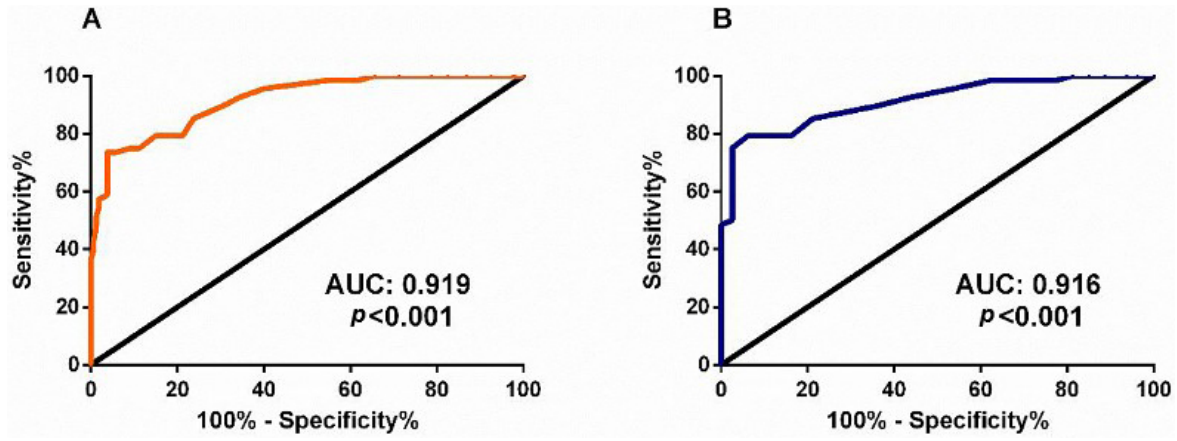

Fig. 2. ROC (receiver operating characteristic) curve of IgG4/IgG1 ratio differentiating IgG4-associated diseases from other autoimmune diseases and healthy controls. (A) Serum IgG4/IgG1 ratio identifies IgG4-associated diseases from other autoimmune diseases. AUC (95% CI), 0.919 (0.882, 0.956); $p < 0.001$. (B) Serum IgG4/IgG1 ratio identifies IgG4-associated diseases from healthy controls. AUC (95% CI), 0.916 (0.870, 0.962); $p < 0.001$.

(≤0.129). According to the logistic regression analysis, the high IgG4/IgG ratio group demonstrated an increased risk of IgG4-RD in comparison to the normal IgG4/IgG group (odds ratio [OR] 31.80; 95% confidence interval [CI], ranging from 15.61 to 64.79). This association remained significant in Model 1, which corroborated the increased risk of IgG4-RD with high IgG4/IgG ratios (OR, 31.25; 95% CI, 15.31–63.79; $p < 0.001$). A similar tangent point was applied to classify the study population into the high IgG4/IgG1 ratio group (>0.209) and the normal IgG4/IgG1 ratio group (≤0.209). The logistic regression findings indicated a significant association between the high IgG4/IgG1 ratio group and increased risk of IgG4-RD compared to the normal IgG4/IgG1 ratio group (OR, 36.39; 95% CI, 17.57–75.38). This association was still evident in Model 1, affirming the increased risk of IgG4-RD with high IgG4/IgG ratios (OR, 35.63; 95% CI, 17.18–73.88; $p < 0.001$).

Discussion

Our findings indicate that serum IgG4/IgG and IgG4/IgG1 ratios are valuable diagnostic tools for IgG4-RD, particularly when utilizing other AID patients and healthy people as controls. Furthermore, a distinct correlation exists between elevated serum IgG4/IgG and IgG4/IgG1 ratios were associated with IgG4-RD. IgG4-RD is recently recognized as an autoimmune disorder typified by elevated IgG4 concentrations and fibrosis affecting multiple organs [15]. Over the past decade, researchers have progressively outlined the pathogenesis and clinical characteristics of IgG4-RD, delving into its diagnosis and treatment and establishing guidelines and consensus [14,16]. Nevertheless, our understanding of IgG4-RD's pathogenesis remains in its early stages, and the treatment options are still relatively constrained. There need to be more large-scale population-based studies on IgG4-RD in China. A Japanese study reported on the prevalence of autoimmune pancreatitis, a disease subtype of IgG4-RD. The findings suggested a prevalence rate of 10.1 per 100,000 individuals in 2016, underlining the need for clinical attention to this disorder [5]. The same study also noted a higher prevalence in men compared to women (ratio, 2.94:1), and the disease was mainly found among middle-aged and elderly individuals, and the disease was found primarily in middle-aged and elderly individuals [5]. Our study found a similar age pattern in the IgG4-RD population but a predominance of females. Another Japanese study indicated a gender ratio of 2.5:1 for men to women with IgG4-RD [17]. This discrepancy underscores the need for further verification through large-scale, multiethnic studies.

Individuals with IgG4-RD often exhibit significantly increased IgG4 levels. Additionally, IgG4-positive plasma cells and lymphocytes can be detected in the affected organ tissues, indicating IgG4's involvement in this disease [18]. However, elevated IgG4 concentrations are not unique to IgG4-RD. They can also be observed in conditions like chronic infections, allergies, and tumors, indicating the need for improving diagnostic precision using IgG4 levels. For instance, a U.S. study investigating the utility of heightened IgG4 levels for distinguishing IgG4-RD from cholangiocarcinoma yielded promising results, with a sensitivity of 71% and a specificity of 87% [19]. In Japan, a study encompassing 132 IgG4-RD patients suggested effective diagnostic outcomes, with a sensitivity of 97.0% and a specificity of 79.6% for diagnosing IgG4-RD [20]. Furthermore, potential biomarkers such as anti-galectin-3 antibodies, annexin A11, and serum complement 5 have been identified, which could aid in diagnosing and monitoring the progression of the disease. Yet, the usefulness and dependability of these biomarkers still need to be substantiated further [6].

Recently, a study showed that the IgG4/IgG ratio was correlated with the number of IgG4-positive plasmacyte in pathological tissues [21], suggesting that the IgG4/IgG ratio may be useful for diagnosing IgG4-RD. This study revealed that when other AID patients and healthy individuals were used as control groups, the areas under the ROC curve for IgG4/IgG ratio in diagnosing IgG4-RD amounted to 0.906 (95% CI, 0.865–0.947) and 0.921 (95% CI, 0.876–0.965). Similarly, a retrospective study found that the IgG4/IgG ratio had an AUC of 0.970, a sensitivity of 94.7%, and a specificity of 91.6% [22]. In addition, in a study of 773 patients with increased IgG4 concentrations, the cut-off point for IgG4/IgG diagnosis was 0.295, with a sensitivity of 80% and specificity of 88.8% [23]. We also found that the IgG4/IgG ratio was associated with IgG4-RD.

Elevated concentrations of other IgG subclasses can also be observed in IgG4-RD individuals [24], with IgG1 being the most abundant of the IgG subclasses. We found that IgG4/IgG1 ratio also had a high diagnostic value for individuals with IgG4-RD, and the AUC of IgG4/IgG1 ratio for diagnosing IgG4-RD was 0.919 (95% CI, 0.882–0.956) and 0.916 (95% CI, 0.870–0.962) in other AID patients and healthy controls, respectively. IgG1 was also involved in IgG4-RD, and there is evidence that IgG1 can act in conjunction with IgG4 to influence IgG4-RD progression with annexin A11 [25]. Furthermore, indications have been made that the extent of penetration by IgG1-positive cells could potentially impact the disease prognosis compared to that of IgG4 [26].

This study is subject to several limitations. Firstly, the immunoturbidimetric method of Siemens in Germany was utilized to measure serum IgG4 concentrations. Evidence suggests different detection methods might yield varied serum IgG4 results [27]. Therefore, one must be cautious when comparing the outcomes of this research with those from other studies that used different detection methods. Secondly, the study population comprises Chinese hospital patients. Ethnic variations can significantly influence results. Thus, such differences should be considered when contrasting these findings with those from differ-

ent ethnic people. Lastly, this research is a cross-sectional study conducted in a single center. Future longitudinal research with larger sample sizes across multiple centers is warranted to confirm and expand upon these findings.

Conclusions

To summarize, the ratios of serum IgG4/IgG and IgG4/IgG1 hold significant independent correlations with IgG4-RD. These ratios carry the substantial diagnostic potential for IgG4-RD.

Abbreviations

IgG4, immunoglobulin G4; IgG4-RD, IgG4-related diseases; IgG, immunoglobulin G; IgG1, immunoglobulin G1; AID, autoimmune diseases; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; OR, odds ratio.

Availability of Data and Materials

All data generated or analyzed during this study are included in the article.

Author Contributions

WW and HF contributed to the study concept and design. WW and YL contributed to the acquisition of data. WW, YL and HF performed the statistical analysis. WW and HF were involved in interpretation of the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was approved by the ethics committee of Capital Institute of Pediatrics (the reference number: 20170310007). Written informed consent was provided by all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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