Clinical Characteristics and Therapeutic Response of Immunoglobulin G4-Related Disease: a Retrospective Study of 127 Chinese Patients

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Abstract

Background & Aims: Immunoglobulin G4-related disease (IgG4-RD) is a multisystem fibroinflammatory condition. The aim of the present study was to characterize the clinical features and therapeutic response of patients with IgG4-RD and identify risk factors for disease relapse.

Methods: We collected baseline data of eligible patients with IgG4-RD and analyzed clinical feature by interview and review of medical records. The patients who received medical therapy with at least 3 months follow-up were used to characterize the therapeutic response and identify risk factors for relapse.

Result: Totally 127 IgG4-RD patients, including 92 males and 35 females, were included in the present study. The median age at diagnosis was 63.0 years, ranging from 23 to 86. The pancreas, bile duct and lymph nodes were the most frequently involved organs. The serum IgG4 level was elevated in 94.5% of the patients and was correlated with the number of organs involved. Patients classified as head and neck limited group were more likely to be female. Patients classified as pancreato-hepatobiliary group had highest aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin level (all $p \leq 0.05$). Mikulicz syndrome and systemic involvement group had the highest IgG-RF score, serum globulin, IgG and IgG4 level. Among 92 patients who received medical therapy with at least 3 months follow-up, 76 received glucocorticoids (GC) alone or in combination with immunosuppressive agents and 16 patients did not take GC. 74 out of the 76 patients (97.3%) achieved remission, with 59 of them remained in remission and 15 of them relapsed. Whereas 16 patients did not take GC, among them, 6 patients achieved remission with one patient relapsed. On multivariate analysis, higher initial score of ACR/EULAR IgG4-RD Classification Criteria, GC monotherapy and GC withdrawal were independent predictors for relapse.

Conclusion: Different phenotypes of IgG4-RD showed different demographic and serological features. The risk factors of relapse were GC withdrawal, GC monotherapy and higher score of ACR/EULAR IgG4-RD Classification Criteria.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a multisystem fibroinflammatory condition characterized by male dominant, IgG4-positive plasma cell infiltration and elevated serum Immunoglobulin G4 (IgG4) levels.¹ Japanese researchers have estimated its incidence to be 0.28–1.08/100 000 inhabitants/year, with 336–1,300 patients newly diagnosed per year.² Although the epidemiological study of IgG4-RD is rarely conducted in other part of the world, increasing number of cases has been reported from other countries including China in recent years.³

Glucocorticoids is the first-line therapy for IgG4-RD and effective for most patients.⁴ However, over 30% patients relapse during the tapering or after cessation of glucocorticoids (GC).^{5,6} Till now, several risk factors for relapse in IgG4-RD patients have been identified.^{7–9} However, whether adding

immunosuppressant agents to GC could reduce the relapse rate remains controversial.^{8,10,11} Furthermore, the relationship between higher the American College of Rheumatology /the European League Against Rheumatism (ACR/EULAR) score¹² and relapse is still unknown.

Therefore, the aim of the study was to describe the clinical feature and identify risk factors for relapse in Chinese patients with IgG4-RD. We also explore the impact of different treatment strategy and higher score of ACR/EULAR IgG4-RD Classification Criteria on the rate of relapse.

Method

Study population

This was a retrospective longitudinal study of patients with IgG4-related diseases diagnosed between January 2014 and December 2020 at Beijing Friendship Hospital, Capital Medical University, China. This study was approved by the institutional ethics committee. (NO. YYXSSC-2021-097)

IgG4-related disease was diagnosed base on the Comprehensive Diagnostic Criteria for IgG4-related disease¹³:(1)Characteristic diffused swelling or masses in single or multiple organs;(2)Elevated serum IgG4 level($\geq 135\text{mg/dl}$);(3)Histopathologic presentation showing:1) Marked lymphocyte and plasmacyte infiltration and fibrosis;2) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells $> 40\%$ and >10 IgG4+ plasma cells/HPF. Patients met (1) +(2) +(3),(1) +(3), or (1)+(2) were classified as definite, probable, or possible, respectively. Patients with pancreatic involvement who did not have pathological examination were diagnosed according to the International Consensus Diagnostic Criteria (ICDC).¹⁴

The inclusion criteria to the current study were: (1) diagnosis with Ig4-RD, and (2) with complete baseline data.

The exclusion criteria were: (1) with concomitant other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, anca associated systematic vasculitis; (2) complicated with malignant tumors.

Baseline characteristics and follow-up information

The demographic, baseline data were collected by review of medical records: gender, age, complete blood count, erythrocyte sedimentation rate (ESR), biochemistry, serum immunoglobulin levels, IgG4 level, autoantibodies, imaging and histology. The clinical phenotypes were classified based on organ involvement as reported by Wallace et al group:¹⁵ pancreato-hepatobiliary group, retroperitoneal fibrosis and/or aortitis group, head and neck-limited group and Mikulicz syndrome with systemic involvement group.

The follow-up information was obtained by interview in person or by telephone and review of medical records. Follow-up interval were scheduled at month 1 and 3 and every 3~6 months thereafter.

Evaluation of therapeutic response

Therapeutic response to treatment with or without GC was evaluated by changes in IgG4-RD responder index (RI)¹⁶ which was the sum of score refers to the degree of disease activity in all the organ sites, all graded on a 0–3 scale. Remission was defined as IgG4-RD RI declined ≥ 2 points from baseline. Disease relapse was defined as clinical symptoms recurred or imaging findings worsened after remission on glucocorticoids therapy. Elevated serum IgG4 level alone was not regarded as disease relapse.

Statistical analyses

All statistical analyses were performed using SPSS version 26.0. Continuous variables were shown as median (interquartile range) or means with standard deviations. Categorical variables were displayed as counts and percentages. The Mann-Whitney U test was used for comparing non-normally distributed variables between different groups. The Chi-square test was applied to compare the status of categorical variables. Cox proportional hazards model was used to identify prognostic factors for relapse. The enter procedures were applied for the final model selection. The receiver operating characteristic (ROC) curve was used to determine the predictive ability of score of ACR/EULAR IgG4-RD Classification Criteria for relapse and the related cut-off values. Kaplan–Meier's curves was used to assess relative contribution of variables to disease relapse. A two-sided probability $P < 0.05$ was considered statistically significant.

Result

Demographic and baseline clinical features of IgG4-RD

Totally 164 patients diagnosed with IgG4-related disease between January 2014 and December 2020 in our institute. Finally, 127 IgG4-RD patients fulfilled the inclusion criteria and did not meet the exclusion criteria. Among them, 92 were males and 35 were females (M: F=2.62:1). The median age at diagnosis was 63.0 years, ranging from 23 to 86.

According to the 2011 Comprehensive Diagnostic Criteria¹³ for IgG4-RD, 15 (11.8%), 3 (2.3%) and 105 (82.6%) cases were diagnosed as definite, probable and possible IgG4-RD, respectively. Another 4 patients with normal serum IgG4 level were diagnosed as probable IgG4-RD according to the International Consensus Diagnostic Criteria.

In our cohort, 25 patients(19.7%)showed single organ involvement, 87 patients(68.5%)showed 2-4 organs involvement, and 15 patients(8.6%)showed more than 5 organs involvement. (Table2). Patients with 5 or over organ involvement group had higher serum IgG and IgG4 level than those with less 5 organs involvement (all $p \leq 0.05$, Table 2).The most common organ involvement was pancreas ($n=82, 64.5\%$), bile duct ($n=62, 48.8\%$), lymph nodes ($n=53, 41.7\%$), and kidney ($n=48, 37.8\%$). (Figure 2)

Table 1

shows the baseline laboratory findings for IgG4-RD patients. The median baseline serum levels of IgG level and IgG4 were elevated in this cohort (1775g/L, 9.8g/L), with 70 patients (68.6%) having increased IgG level and 120 patients (94.5%) having increased IgG4 level. Low titer ANAs were detected in 66 patients (86.8%), none of whom was positive for anti-extractable nuclear antibodies.

Demographic features	Value
Male gender ,n(%)	92(72.4%)
Age at onset (years)	63(55-69)
White blood cell(10^9 /L)	5.7(4.5-7.1)
Eosinophils(%)	4.4(2.1-7.5)
ALT(U/L)	33.5(15.0-134.8)
AST(U/L)	31.9(19.8-91.3)
GGT(U/L)	102(22.0-525.0)
ALP(U/L)	140.0(74.0-392.0)
ALB (g/L)	35.9(32.3-39.0)
GLO(g/L)	34.2(30.3-40.6)
TBIL (umol/L)	18.2(10.8-70.6)
DBIL (umol/L)	5.5(2.1-37.0)
Cr (umol/L)	69.7(58.1-84.2)
IgG (g/L)	1775(1527-2357)
IgG4(g/L)	9.8(3.9-15.2)
IgG4 $\geq$ 1.35g/L, n (%)	120(94.5%)
ANA (+), n (%)	66(86.8%)*
IgG4-RD RI scores	8(6-10)
Demographics and serological features of all enrolled patients(n=127)	
#Serum immunoglobulin G test in 102 patients. *ANA test in 76 patients	

Table 2
The demographics and serological features for multiple-organ involvement patients

Demographic features	1-4 organs involved (n=116)	≥5 organs involved (n=11)	P value
Male gender, n(%)	82(70.7%)	10(90.9%)	0.1
Age at onset (mean ± SD) (years)	63.5(55-69)	60.0(58.0-68.0)	0.5
White blood cell(10^9 /L)	5.7(4.4-7.2)	5.7(4.6-6.7)	0.7
Eosinophils(%)	4.1(2.0-7.5)	5.6(2.6-6.8)	0.6
IgG (g/L)	1760.0(1510.0-2330.0)	2100(1720-3350)	0.03
IgA(g/L)	211.5(148.5-267.8)	147(110-225)	0.1
IgM(g/L)	70.2(45.4-102.0)	78.8(39.9-159.0)	0.5
IgG1(g/L)	9.2(7.2-11.8)	10.0(7.6-17.3)	0.4
IgG4(g/L)	8.0(3.8-13.8)	18.8(13.0-43.6)	0.006

The most common clinical presentations of IgG4-RD were abdominal pain (34.0%), followed by jaundice (30.7%), and glands swelling (21.5%).

The imaging feature of patients with IgG4-RD demonstrated organ enlargement of involved tissues. Local or diffuse pancreatic gland enlargement can be seen in 71 patients. Diffuse or segmental narrowing of bile duct and thickening of bile duct wall was seen in 45 patients. Lacrimal and salivary gland enlargement were commonly observed in 60 patients. Bilateral renal cortex low-density areas of the kidney were found in 10 patients.

Histopathological examinations were conducted in 55 patients, including biopsies of pancreas(n=19), submandibular glands(n=10), labial gland(n=9), neck tumor(n=4), lymph node(n=3), kidney(n=2), liver(n=2), parotid glands(n=1) and others(n=5).

Among them, 18 patients (31.1%) fulfilled the pathological diagnostic criteria of IgG4-RD.

The characteristic histopathological finding of IgG4-related disease was dense lymphocytic infiltrate and storiform fibrosis. In our cohort, the most common manifestations were lymphocytic and plasma cell infiltration (44.6%). Storiform fibrosis were observed in 6 patients (10.7%).

Features of different clinical phenotypes of IgG4-RD

The clinical phenotypes were classified based on organ involvement as reported by Wallace et al.¹⁵ In our cohort, 59, 6, 15, and 47 patients belonged to the pancreato-hepatobiliary group, retroperitoneal fibrosis

and/or aortitis group, head and neck-limited group and Mikulicz syndrome with systemic involvement group, respectively. (Table 3)

Table 3
Demographics and serological features for 127 IgG4-related disease patients divided by different clinical phenotype

Demographic features	Pancreato-hepato-biliary(n=59)	RPF/Aorta(n=6)	Head and neck-limited (n=15)	Mikulicz and systemic (n=47)	P value
Male gender, n(%)	47(79.7%)	6(100%)	7(46.7%)	32(68.1%)	0.03
Age at onset (years)	64.0(55.0-69.0)	61.0(55.8-65.5)	62.0(54.0-72.0)	63.0(56.0-70.0)	0.9
WBC(10^9 /L)	5.5(4.5-6.9)	9.6(6.6-11.0)	6.1(4.6-7.4)	5.5(4.2-7.3)	0.02
Eosinophils(%)	4.5(2.0-7.6)	3.3(1.8-4.3)	4.3(1.7-8.3)	4.5(2.6-7.7)	0.7
ALT(U/L)	90(32.0-175.0)	17.0(12.8-35.3)	17(14.0-24.5)	20.0(12.8-83.3)	0.00
AST(U/L)	71.4(26.0-130.5)	16.8(15.3-22.2)	21.6(18.8-25.7)	25.0(18.3-81.5)	0.00
ALP(U/L)	316.5(159.5-555.8)	98.0(78.5-103.0)	76.0(66.5-93.0)	79.0(66.0-283.5)	0.00
GGT(U/L)	373.0(70.0-817.0)	45.5(32.3-88.8)	23.0(17.0-31.0)	32.0(15.0-236.0)	0.00
TBIL (umol/L)	53.9(15.9-148.1)	9.8(8.5-12.3)	10.8(8.4-13.1)	14.5(9.8-32.2)	0.00
DBIL (umol/L)	27.0(4.4-98.0)	1.9(1.5-2.7)	1.8(1.5-2.3)	3.3(1.9-12.9)	0.00
ALB (g/L)	35.5(32.2-38.4)	38.2(35.4-41.5)	38.6(36.8-41.0)	35.7(30.5-39.2)	0.03
GLO (g/L)	32.2(29.5-37.7)	34.1(29.7-40.0)	32.6(30.0-42.8)	37.0(32.3-48.6)	0.01
Cr (umol/L)	69.2(54.8-77.5)	110.1(79.8-140.1)	74.4(62.5-91.0)	69.0(56.8-89.5)	0.01
IgG (g/L)	1680.0(1475.0-2065.0)	1540(1315.0-1870.0)	1545.0(1240.0-2227.5)	2020.0 (1680.0-2850.0)	0.01
IgG4(g/L)	10.3(0.54-53.7)	3.0(1.7-6.8)	8.2 (3.9-20.6)	13.0(4.5-22.1)	0.01

Table 4
The Demographics and baseline features of patients with IgG4-related disease treated with GC or GC+IM

Demographic features	GC (n=51)	GC+IM (n=23)	P value
Male gender ,n(%)	37(72.5%)	17(73.9%)	0.54
Age at onset (mean $\pm$ SD) (years)	61.0(55-69)	64 (52-66)	0.2
White blood cell(10^9 /L)	5.4(4.1-7.4)	5.5(4.7-7.3)	0.7
Eosinophils(%)	5.4(1.9-7.8)	4.3(2.7-6.5)	0.7
IgG (g/L)	1790(1580-2540)	1970(1730-2605)	0.2
IgA(g/L)	163.0(115.0-242.0)	206.5 (109.0-257.8)	0.5
IgM(g/L)	72.6(45.4-105.0)	68.0(40.1-87.0)	0.8
IgG4(g/L)	9.8(3.8-16.6)	13.2(5.7-20.6)	0.1
IgG4-RD RI scores	8(6-12)	8(6-14)	0.1

Table 5
The demographics and baseline features for relapse and non-relapse patients

Demographic features	Total follow-up patients(n=74)	Remission patients(n=59)	Relapse patients (n=15)	P value
Male gender ,n(%)	54(73.0%)	40(67.8%)	14(93.3%)	0.05
Age at onset (years)	60.2(23-79)	63(56-68)	64(52-66)	0.3
White blood cell(10^9 /L)	5.8(1.0-12.2)	5.3(4.2-7.3)	5.5(4.7-7.3)	0.7
Eosinophils(%)	5.5(0.07-19.6)	4.6(2.25-7.65)	4.3(2.7-6.5)	0.4
IgG (g/L)	2189.7(1010.0-5590.0)	1795.0(1570.0-2357.0)	1970(1730-2605)	0.3
IgA(g/L)	190.0(56.1-432.0)	187.0(116.5-254.0)	206.5(109.0-257.8)	0.8
IgM(g/L)	77.1(20.1-227.0)	69.9(43.6-101.5)	68.0(40.1-87.0)	0.8
IgG4	15.6(0.54-73.2)	10.9(4.1-17.7)	13.2(5.7-20.6)	0.3
IgG4-RD RI scores	10.0(2-36)	8(6-12)	8(6-14)	0.2

Patients from head and neck limited group were more likely to be female (53.3%) than patients in the other groups. The highest aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl

transpeptidase (GGT), bilirubin level was observed in pancreato-hepatobiliary group (all $p \leq 0.05$). Mikulicz syndrome and systemic involvement group had the highest IgG-Rf score, serum globulin, IgG and IgG4 level. (Table 3)

Therapeutic response in patients with more than 3-months follow-up.

Out of the 127 patients, 29 patients followed up for less than 3 months, 6 patients received surgical treatment. Finally, 92 patients did not undergo surgery and had at least 3 months follow-up, with a median follow-up period of 17 months (interquartile range: 8–33 months).

Among 76 GC monotherapy or Combination therapy patients, 74 patients (97.3%) achieved remission, with 59 of them remained in remission and 15 of them relapsed. The Mann-Whitney U test shown no statistical difference in baseline data between relapse and non-relapse patients.

Among these GC-treated patients, steroid-induced necrosis of femoral head was observed in one patient, and poor glycemic control was reported in 7 patients. Gastrointestinal side effect, edema and poor blood pressure control occurred in one, two and three patients, respectively, which were regarded as steroid-related. GC and GC+ Immunosuppressive agents (IM) groups showed no statistical difference in side effects.

Another 16 patients did not take glucocorticoids (GC) therapy. Among them, 6 patients achieved remission with one patient relapsed.

Comparison of cumulative relapse rate in patients with different treatment regimen

Among 74 GC-treated response patients, 50 patients received GC monotherapy (67.6%) and 24 patients (31.4%) received GC and IM combination therapy. The Kaplan–Meier curve showed that the cumulative relapse rates in the GC monotherapy group were higher than that in the combination therapy group (Log rank test, $p=0.01$). There were no statistically significant differences between the GC monotherapy and GC+IM combination therapy groups in demographic features and baseline laboratory findings and initial GC dose.

In the maintenance treatment stage, 7 out of 17 glucocorticoids withdrawal patients, (41.2%) suffered from relapse. The cumulative relapse rate was significantly higher for GC withdrawal patients (Log rank: $p=0.01$). (Figure 3)

Comparison of cumulative relapse rate in patients with different score of ACR/EULAR IgG4-RD Classification Criteria level

Cox regression analysis demonstrated that higher initial score of ACR/EULAR IgG4-RD Classification Criteria were associated with relapse in patients with IgG4-RD (Table 6). The ROC curve shown that the maximum score cutoff set by using Youden's index was 33.5 (sensitivity 73.3%, specificity 69.5%). The

Kaplan-Meier plotting and log-rank test demonstrated that the score of ACR/EULAR IgG4-RD Classification Criteria ≥ 33.5 group had higher cumulative rate (Log rank: $p=0.01$). (Figure 3)

Table 6

Univariate and multivariable cox regression analysis of predictive factors for relapse in IgG4-related disease

Variable	Univariate analysis			Multivariate analysis		
	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI
Demographics						
Male, n (%)	0.10	5.29	0.69-40.32			
Age at onset, years	0.64	0.93	0.94-1.04			
Number of involved organs (≥ 5)	0.04	3.02	1.07-8.53			
Lacrimal gland	0.14	1.54	0.86-2.73			
Parotid	0.91	1.03	0.60-1.76			
Submandibular gland	0.79	0.93	0.56-1.56			
Lung	0.18	0.50	0.18-1.38			
Retroperitoneal fibrosis	0.37	1.34	0.71-2.52			
Pancreas	0.07	4.02	0.90-17.87			
Bile duct	0.07	1.65	0.96-2.85			
Lymph node	0.34	0.78	0.46-1.30			
Kidney	0.34	1.67	0.58-4.83			
IgG4, median (IQR), g/l	0.08	1.03	1.00-1.06			
Serum IgG4 level ≥ 5 ULN	0.15	2.50	0.70-8.88			
IgG4-RD RI scores, median (IQR)	0.04	1.06	1.00-1.12	0.83	0.99	0.91-1.07
Score of ACR/EULAR IgG4-RD Classification Criteria	0.004	1.07	1.02-1.11	0.01	1.10	1.02-1.19

Variable	Univariate analysis			Multivariate analysis		
	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI
Score of ACR/EULAR IgG4-RD Classification Criteria ≥ 20	0.55	0.54	0.07-4.08			
Combination therapy n (%)	0.04	0.12	0.02-0.93	0.04	0.12	0.02-0.94
Complete glucocorticoids withdrawal	0.02	3.35	1.21-9.29	0.02	3.83	1.25-11.68

Predictors of IgG4-RD relapse

Univariate analysis revealed that higher IgG4-RD RI scores at the baseline, the higher initial score of ACR/EULAR IgG4-RD Classification Criteria, over five organs involvement, GC-monotherapy and GC withdrawal were associated with relapse. Multivariate analysis using a Cox regression analysis further clarified that the higher initial score of ACR/EULAR IgG4-RD Classification Criteria, GC monotherapy and GC withdrawal were significant independent predictors of relapse in patients with IgG4-RD. (Table 6)

Discussion

Our findings validated that four clinical phenotypes of IgG4-RD patients shared different demographic and serological features. As for therapeutic response, most patient achieve remission with GC monotherapy or combination therapy. GC withdrawal, GC monotherapy and higher score of ACR/EULAR IgG4-RD Classification Criteria were associated with disease relapse.

In our cohort, the median age of onset in our cohort was 63 years old, and the ratio of male to female was 2.62:1, which was basically consistent with previous studies by other Chinese authors (median age:53.1,M:F=2.3:1).¹⁷The most common affected organ was pancreas which was different from some research.^{8,17}This difference may attribute to the fact that our center has advantages of subject in gastroenterology.

Patients with multiple organ involvement had higher level of baseline serum IgG and IgG4. It suggests that we should consider the possibility of multiple organ involvement if we observe the patients with significant increase of IgG4 or IgG4.

Our study revealed that patients from head and neck limited group were more likely to be female. Mikulicz syndrome with systemic involvement group had the highest serum globulin, IgG and IgG4 level. These findings were in line with an Italian cohort and two international cross-sectional cohorts.^{15,18} It also validated that some demographics and serological features were quite different between each clinical phenotype.¹⁵It may provide physicians a new insight to this clinical classification of IgG4-RD.

Our result demonstrated that 97.4% patients(n=74) response to glucocorticoids therapy, only 2 patients did not achieve remission. 6 patients with milder degree of pancreas enlargement achieved remission without GC treatment and the rest of 10 patient who did not take GC therapy were failed to achieve remission. It is widely accepted that glucocorticoids is the treatment of choice for IgG4-RD and effective for most patients.⁴ Several studies had reported that patients with IgG4-RD who are not treated with GC are less likely to achieve remission.^{19,20} Our finding indicated that majority of IgG4-RD patients with moderate-severe and/or multiple organ involvement may not benefit from the “Watchful waiting” strategy.

4

In this study, the relapse rate was 20.3% which was consistent with some researches.^{8,9} Cox regression showed that GC withdrawal, GC monotherapy and higher score of ACR/EULAR IgG4-RD Classification Criteria were independent prognostic factors for relapse. It is accepted that GC withdrawal is associated with disease relapse.^{9,21,22} In our cohort, 7 patients relapsed within median 4.3 months after glucocorticoids withdrawal. (OR 3.189, 95% CI 1.571–6.474, P=0.001).

So far, the role of combination therapy in relapse still remains controversial. Several studies have reported that combination therapy associated with a lower relapse rate.^{9,11,23} Our study also revealed that patients who took GC+IM therapy were less likely to relapse than GC monotherapy group (OR 0.12, 95% CI 0.02-0.94, P=0.04). On the contrary, a recently cohort shown that GC+IM therapy was not the risk factor of relapse.⁸ This doubt may attribute to different types and maintenance period of IM between medical centers. Standardized immunosuppressive agent treatment are urgently needed for IgG4-RD patients in the future.

Our univariate analysis shown that higher score of ACR/EULAR IgG4-RD Classification Criteria was also associated with disease relapse (OR 1.10, 95% CI 1.02-1.99, P=0.01). It seems that patients with higher score of ACR/EULAR IgG4-RD Classification Criteria are likely to relapse and should own more attention. Score of ACR/EULAR IgG4-RD Classification Criteria was calculated as the sum of several weighted criteria including clinical findings, serological results, radiological assessments and pathological interpretations.¹² Higher score implied patients may have more organ involvement, higher serum IgG4 level or baseline IgG4-RD RI score. Some of those components (more organ involvement, higher serum IgG4 level) were reported as the risk relapse factors.^{9,24} It may explain the relationship between higher score of ACR/EULAR IgG4-RD Classification Criteria and relapse.

Our study has several limitations. Firstly, this is a single-center and retrospective study. Large sample size and long duration follow-up studies are required to define the prognosis of the condition. Secondly, our cohort have different spectrum of organ involvement; therefore, a multicenter study might help us better recognize the disease.

In conclusion, GC withdrawal, GC monotherapy were the risk factor of relapse. For the first time, this study described that higher score of ACR/EULAR IgG4-RD Classification Criteria may associated with relapse.

Declarations

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No

Authors' contribution

WA and ZW contributed equally to this work. WA, ZW, XO participated in the design of the study. WA, ZW, HY, XW, DW, XZ, QW, YW and HM performed recruitment of patients and collected clinical data. WA and ML did the statistical analysis. WA drafted the manuscript. ZW helped to draft the manuscript. WA, ZW, TD, PL and JJ revised it critically for intellectual content. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Beijing Friendship Hospital, Capital Medical University (NO. YYXSSC-2021-097). Informed and written consent was obtained for the study from all patients.

Consent for publication

All authors agreed on the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The flowchart for all patient enrollment.

Figure 2

Organ involvement in 127 patients with IgG4-related disease

Figure 3

Analysis for 74 response to therapy patients in this study

a) Initial prednisone dose for non relapse and relapse patients. b) The cumulative relapse rate of GC maintenance and withdrawal groups. c) Initial prednisone dose for GC and GC+IM patients. d) The cumulative relapse rate of GC and GC+IM groups

Figure 4

The relapse of patients with higher Score of ACR/EULAR IgG4-RD Classification Criteria

a) The receiver operating characteristic (ROC) curve of Score of ACR/EULAR IgG4-RD Classification Criteria for relapse and the related cut-off values. b) Comparison of the cumulative relapse rates of GC monotherapy and GC + IM therapy during the GC tapering stage.