

85912_Auto_Edited.docx

*Retrospective Cohort Study***Clinical characteristics and outcome of autoimmune pancreatitis based on serum immunoglobulin G4 level: A single-center, retrospective cohort study**

Zhou GZ *et al.* Clinical characteristics and outcome of AIP

Guan-Zhou Zhou, Jia-Qi Zeng, Lei Wang, Miao Liu, Ke Meng, Zi-Kai Wang, Xiu-Li Zhang, Li-Hua Peng, Bin Yan, Fei Pan

Abstract**BACKGROUND**

Autoimmune pancreatitis (AIP) has been linked with elevated immunoglobulin (Ig) G4 levels. The characteristics and outcomes of AIP based on serum markers have not been fully evaluated.

AIM

To compare clinical features, treatment efficacy, and outcome of AIP based on serum IgG4 levels and analyze predictors of relapse.

METHODS

A total of 213 patients with AIP were consecutively reviewed in our hospital from 2006 to 2021. According to the serum IgG4 level, all patients were divided into two groups, the abnormal group ($n = 148$) with a high level of IgG4 [$> 2 \times$ upper limit of normal (ULN)] and the normal group ($n = 65$). The *t*-test or Mann-Whitney U test was used to compare continuous variables. Categorical parameters were compared by the χ^2 test or

Fisher's exact test. Kaplan-Meier curves and log-rank tests were established to assess the cumulative relapse rates. Univariate and multivariate analyses were used to investigate potential risk factors of AIP relapse.

RESULTS

Compared with the normal group, the abnormal group had a higher average male age (60.3 ± 10.4 vs 56.5 ± 12.9 years, $P = 0.047$); higher level of serum total protein (72.5 ± 7.9 g/L vs 67.2 ± 7.5 g/L, $P < 0.001$), IgG4 (1420.5 ± 1110.9 mg/dL vs 252.7 ± 106.6 mg/dL, $P < 0.001$), and IgE (635.6 ± 958.1 IU/mL vs 231.7 ± 352.5 IU/mL, $P = 0.002$); and a lower level of serum complement C3 (100.6 ± 36.2 mg/dL vs 119.0 ± 45.7 mg/dL, $P = 0.050$). In addition, a lower number of cases with abnormal pancreatic duct and pancreatic atrophy (23.6% vs 37.9% , $P = 0.045$; 1.6% vs 8.6% , $P = 0.020$, respectively) and a higher rate of relapse (17.6% vs 6.2% , $P = 0.030$) were seen in the abnormal group. Multivariate analyses revealed that serum IgG4 [$> 2 \times$ ULN), hazard ratio (HR): 3.583; 95% confidence interval (CI): 1.218–10.545; $P = 0.020$] and IgA ($> 1 \times$ ULN; HR: 5.908; 95% CI: 1.199 – 29.120; $P = 0.029$) and age > 55 years (HR: 2.383; 95% CI: 1.056–5.378; $P = 0.036$) were independent risk factors of relapse.

CONCLUSION

AIP patients with high IgG4 levels have clinical features including a more active immune system and higher relapse rate. Several factors, such as IgG4 and IgA, are associated with relapse.

Key Words: Autoimmune pancreatitis; Immunoglobulin G4; Clinical characteristics; Outcome; Relapse; Cohort study

Zhou GZ, Zeng JQ, Wang L, Liu M, Meng K, Wang ZK, Zhang XL, Peng LH, Yan B, Pan F. Clinical characteristics and outcome of autoimmune pancreatitis based on serum

immunoglobulin G4 level: A single-center, retrospective cohort study. *World J Gastroenterol* 2023; In press

Core tip: Our findings suggested that patients with a high immunoglobulin (Ig) G4 level had different clinical features including a more active immune system and higher relapse rate. Patients with normal IgG4 level still require attention because they have a high incidence of jaundice and pancreatic atrophy. Some factors were identified as risk factors for relapse, such as age > 55 years [hazard ratio (HR) 2.383; 95% confidence interval (CI) 1.056-5.378; $P = 0.036$], high IgG4 level [$> 2 \times$ upper limit of normal (ULN) (HR 3.583; 95% CI 1.218-10.545; $P = 0.020$) and high IgA level ($> 1 \times$ ULN) (HR 5.908; 95% CI 1.199-29.120; $P = 0.029$).

INTRODUCTION

Autoimmune pancreatitis (AIP) has recently become a cause of global health concern^[1,2]. It is characterized by elevated serum immunoglobulin (Ig) G4 levels and an enlarged pancreas based on diagnostic imaging. AIP is a form of chronic pancreatitis that was initially introduced in 1995 by Yoshida *et al*^[3]. However, understanding of the pathology was limited since then until Hamano *et al* introduced the role of IgG4 in AIP^[4].

IgG4 has unique properties, unlike other immunoglobulin subtypes. Among the four IgG subclasses, IgG4 levels are the lowest, accounting for about 5% of total IgG in a healthy adult. IgG4 inhibits the formation of immune complexes through fab-arm exchange and does not affect the classical complement pathway^[5]. A correlation between the IgG4 concentration and chronic inflammatory processes and disease severity has been established; the role of IgG4 and disease pathogenicity has also been proposed in previous studies^[6,7]. Elevated IgG4 levels have also been observed in autoimmune diseases, such as rheumatoid arthritis, and patients with high IgG4 levels have shown a unique clinical profile^[8]. Although the etiology is not fully elucidated, the

role of IgG4 in AIP pathogenesis was highlighted as a potential diagnostic marker and predictor of relapse^[9-13].

A favorable response despite frequent relapse in the long term is generally seen in patients with AIP receiving steroid therapy. To date, the risk factors of relapse remain controversial. According to an epidemiological survey in Japan, > 20% of patients diagnosed with AIP experienced relapse at least once. It was less likely that the initial steroid doses and serum IgG4 level affected the appearance of relapse^[1], while another study reported a higher relapse rate in patients with AIP having high IgG4 levels^[14]. In addition, a cohort study highlighted IgG4-related sclerosing cholangitis as a predictor of relapse^[15]. In the present retrospective cohort study, we compared the clinical characteristics of patients with AIP based on the serum IgG4 level and analyzed the potential risk factors of relapse.

MATERIALS AND METHODS

Ethics

This was a single-center retrospective study performed at the First Medical Center of Chinese PLA General Hospital. The research protocol was approved by the Ethical Committee of Chinese PLA General Hospital (S2022-330-01).

Study design and population

A total of 308 patients from 2006 to 2021 were reviewed consecutively (Figure 1). Ninety-five patients were excluded due to other chief diagnoses ($n = 20$), insufficient data ($n = 31$), and non-fulfillment of the International Consensus Diagnostic Criteria (ICDC; $n = 44$). Eventually, 213 patients diagnosed with AIP according to ICDC were enrolled. All enrolled patients were divided into two groups based on serum IgG4 levels: normal group [IgG4 \leq 402 mg/dL, 2 \times upper limit of normal (ULN)] and abnormal group (IgG4 > 402 mg/dL)^[16].

Demographic characteristics of age, sex, and duration of hospitalization were evaluated. Clinical manifestations included predispositions, symptoms, such as

abdominal pain, and involvement of other organs. Weight loss was defined as > 5 kg in the past 3 mo. Extrapaneatic lesions were diagnosed by the IgG4-RD criteria, 2021^[17]. Results of blood routine examination, biochemistry, coagulation, and immunological tests were collected. Radiological findings were analyzed from computed tomography (CT), magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography/magnetic resonance cholangiopancreatography. The maximum standard uptake value (SUV-max) of positron emission tomography/CT (PET/CT) was also compared. The effectiveness of treatment was based on patient symptoms and serological and radiological results. Relapse was defined as the reoccurrence of symptoms, abnormal serological results, or the presence of imaging lesions.

Statistical analysis

The *t*-test or Mann-Whitney U test was used to compare continuous variables, which were presented as mean \pm SD or median interquartile range. Categorical parameters were compared using the χ^2 test or Fisher's exact test. Kaplan-Meier curves and log-rank tests were used to assess cumulative relapse rates and univariate and multivariate Cox regression models were performed, respectively. Baseline variables that were considered clinically relevant and showed a univariate relationship with outcome were entered into the multivariate Cox regression model. Variables for inclusion were carefully chosen, considering the number of available events, to ensure the parsimony of the final model. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using GraphPad Prism 9.0 and SPSS 26.0. The statistical review of this study was performed by a biomedical statistician.

RESULTS

Demographic characteristics

Baseline data are summarized in Table 1 and Supplemental Figures 1-3. There were 65 and 148 patients in the normal and abnormal groups, respectively. There were 189

patients with type 1 AIP and 24 with type 2 AIP. The ratio of men to women was 3.06 and 3.63 in the two groups ($P = 0.722$), respectively. There was no significant difference in the mean age between the two groups (59.8 ± 11.0 years vs 57.4 ± 12.6 years, $P = 0.163$). However, the average age of men in the abnormal group was higher than that in the normal group (60.3 ± 10.4 years vs 56.5 ± 12.9 years, $P = 0.047$). The duration from onset to diagnosis (78.4 ± 71.7 d vs 93.1 ± 124.8 d, $P = 0.686$) and the days of hospitalization (16.5 ± 8.7 d vs 15.6 ± 9.0 d, $P = 0.351$) were similar between the normal and abnormal groups.

Clinical manifestations

Most patients in the normal and abnormal groups had no obvious causes before their onset (86.2% vs 84.5% , $P = 0.750$; Table 2). The frequency of patients' chief complaints including abdominal pain, jaundice, abdominal distension, and pruritus of patients was similar in the two groups (36.9% vs 42.6% , $P = 0.440$; 30.8% vs 28.4% , $P = 0.724$; 16.9% vs 20.9% , $P = 0.497$; 9.2% vs 14.9% , $P = 0.263$, respectively). It is noteworthy that seven patients in the abnormal group visited a doctor because of diarrhea, whereas no patient in the normal group went to the hospital for diarrhea (4.7% vs 0% , $P = 0.104$). The incidence of weight loss was 52.3% and 50.7% in the normal and abnormal groups, respectively ($P = 0.826$). With regard to extrapancreatic lesions, sclerosing cholangitis was the most common disease with a similar prevalence rate between the normal and abnormal groups (30.8% vs 37.2% , $P = 0.368$).

Serology results

Laboratory findings are shown in Table 3. The proportion of white blood cells was different between the two groups. Patients in the abnormal group had a higher percentage of eosinophils ($6.2 \pm 5.4\%$ vs $3.9 \pm 3.4\%$, $P = 0.001$) and a lower percentage of neutrophils ($56.1 \pm 10.3\%$ vs $61.8 \pm 11.1\%$, $P = 0.001$). The total protein level was higher in the abnormal group (72.5 ± 7.9 g/L vs 67.2 ± 7.5 g/L, $P < 0.001$) and serum albumin level was lower (36.7 ± 4.6 g/L vs 39.4 ± 5.8 g/L, $P = 0.001$). The thrombin time was also

longer in the abnormal group (17.4 ± 1.6 s vs 16.9 ± 1.2 s, $P = 0.012$). With regard to the immunological tests, patients in the abnormal group had higher levels of IgE (635.6 ± 958.1 IU/mL vs 231.7 ± 352.5 IU/mL, $P = 0.002$), four IgG subtypes (IgG1, 935.8 ± 319.9 mg/dL vs 872.6 ± 371.8 mg/dL, $P = 0.045$; IgG2, 638.6 ± 241.6 mg/dL vs 450.4 ± 174.0 mg/dL, $P < 0.001$; IgG3, 53.6 ± 58.4 mg/dL vs 42.70 ± 43.37 mg/dL, $P = 0.034$; IgG4, 1420.5 ± 1110.9 mg/dL vs 252.7 ± 106.6 mg/dL, $P < 0.001$), and two subtypes of free light chain [(FLC)- κ , 569.6 ± 252.5 mg/dL vs 306.1 ± 99.7 mg/dL, $P < 0.001$; FLC- λ , 282.5 ± 124.5 mg/dL vs 176.4 ± 63.4 mg/dL, $P < 0.001$]. A lower complement C3 level (100.6 ± 36.2 mg/dL vs 119.0 ± 45.7 mg/dL, $P = 0.050$) and a faster erythrocyte sedimentation rate (21.1 ± 20.1 mm/h vs 43.4 ± 28.6 mm/h, $P = 0.002$) were noted in the abnormal group. Positive rate of serum antinuclear antibody was similar in the normal and abnormal groups (12.5% vs 20.0% , $P = 0.298$).

Radiology examinations

AIP can be categorized as diffuse or focal type based on the extent of pancreatic enlargement in the radiological examinations (Table 4). In the normal group, 33 of 58 (56.9%) cases were diffuse type and 16 (27.6%) were focal type. In the abnormal group, 86 (67.7%) of 127 cases were diffuse type and 24 (18.9%) were focal type. The capsule-like rim was observed in 10 (17.2%) and 30 (23.6%) cases in the normal and abnormal groups, respectively ($P = 0.328$). Pancreatic duct images showed that the prevalence of abnormalities (stricture or dilatation) was significantly higher in the normal group (37.9% vs 23.6% ; $P = 0.045$). Hypodense kidney lesions were seen in 11 (8.7%) cases in the abnormal group and four (6.9%) cases in the normal group ($P = 0.683$). The incidence of pancreatic atrophy was significantly higher in the normal group (8.6% vs 1.6% , $P = 0.020$). The two groups had similar SUV-max according to PET/CT [normal group: 4.55 (3.725 – 6.25) vs abnormal group: 5.35 (4.025 – 6.475), $P=0.260$].

Remission and relapse

Different therapies for AIP were given to patients in the two groups (Table 5, $P = 0.029$). In the normal group, 26 (40.0%) patients received steroid monotherapy, 14 (21.5%) received steroids plus immunomodulators, 12 (18.5%) underwent endoscopy or surgery, and 13 (20.0%) received other therapies such as hepatic protectors. The median duration and dose of prednisolone therapy were 8 (6–9) wk and 40 (30–50) mg/d. In the abnormal group, 81 (54.7%) patients received steroid monotherapy, 30 (20.3%) received steroids plus immunomodulators, nine (6.1%) underwent endoscopy or surgery, and 28 (18.9%) received other therapies. The median duration and dose of prednisolone therapy were 8 (6–9) wk ($P = 0.200$) and 42.5 (40–100) mg/d ($P = 0.750$). Only three patients in the abnormal group did not achieve remission; all of whom received steroid monotherapy: one patient had persistent symptoms and two had prolonged abnormal transaminase levels.

During the median follow-up period of 53 mo, 30 patients experienced at least one episode of relapse in the normal and abnormal groups [4 (6.9%) vs 26 (19.1%), $P = 0.031$]. Of the 26 patients in the abnormal group, five (19.2%) had a relapse in extrapancreatic organs ($P = 0.337$). ¹ The cumulative relapse rates at 1 and 3 years were 3.8% and 11.0%, respectively, for the abnormal group and 2.0% and 6.9%, respectively, for the normal group (log-rank test, $P = 0.023$, Figure 2). Among the 30 patients with relapse, one (25.0%) of four in the normal group and 15 (57.7%) of 26 in the abnormal group received steroid monotherapy as their initial treatment ($P = 0.129$). Four (15.4%) of 26 relapse cases in the abnormal group experienced more than one relapse ($P = 0.399$). The median relapse duration in the normal and abnormal groups was 25 (13.5–52.3) and 43 (16.3–72) mo, respectively ($P = 0.442$). Three (75.0%) of four cases in the normal group and 20 (76.9%) of 26 cases in the abnormal group received corticosteroids for relapse ($P = 0.410$). All patients responded well to treatment.

Univariate and multivariate analyses

¹ Univariate and multivariate Cox regression models were performed to predict the risk factors for AIP relapse (Figure 3). Univariate analyses revealed an association between

relapse and age > 55 years [hazard ratio (HR): 2.254; 95% confidence interval (CI): 1.074-4.731; $P = 0.032$]. Similarly, serum IgG4 levels (> 402 mg/dL, $2 \times$ ULN) and IgA levels (> 400 mg/dL, $1 \times$ ULN) were significant contributors to relapse (IgG4, HR: 3.381, 95% CI: 1.176-9.726, $P = 0.024$; IgA, HR: 6.271, 95% CI: 1.294-30.389, $P = 0.023$). Patients with a thickened bile duct seen on imaging scans also showed a higher risk of relapse (HR: 2.619; 95% CI: 1.096-6.258, $P = 0.030$). The presence of some clinical symptoms such as abdominal pain, type of parenchymal imaging, type of managements, initial dose of steroid and absence of maintenance therapy, were not significantly different between the relapse and non-relapse groups. Using multivariate analyses, we identified three significant independent predictors of relapse, IgG4 levels (> 402 mg/dL; HR: 3.583, 95% CI: 1.218-10.545; $P = 0.020$), IgA levels (> 400 mg/dL; HR: 5.908; 95% CI: 1.199-29.120; $P = 0.029$), and age > 55 years (HR: 2.383, 95% CI 1.056-5.378; $P = 0.036$).

DISCUSSION

AIP is characterized by elevated IgG4 levels in the blood and abundant infiltration of IgG4-positive plasma cells and lymphocytes in tissues. Serum IgG4 has been recognized as an established diagnostic biomarker for AIP^[1,2,18]. In 2011, the ICDC formally defined a cut-off with $2 \times$ ULN of IgG4 as a diagnostic criterion for AIP. A sensitivity of 53%-81% and specificity of 90%-99% were reported in studies adopting this cutoff criterion^[16,19-21]. Considering the unique features of IgG4, patients with high IgG4 levels may have a unique clinical profile and prognosis. Previous studies have shown that AIP had a favorable but short-term prognosis following steroid therapy, with a relapse rate of 24%-63%^[22-25]. Patients at a higher risk of relapse had higher serum IgG4 and alkaline phosphatase concentrations. The involvement of other organs, such as the bile duct and salivary glands, are also recognized as risk factors^[12,23,26].

Epidemiological studies revealed that AIP mainly affected elderly adults, especially those > 60 years, with a male predominance, which was also seen in our study^[1,27]. In the abnormal group, the average age of male patients was higher compared with the normal group. No significant differences were noted among women with AIP. Similar

findings were reported in previous studies^[28,29]. Despite the unclear mechanism, a positive correlation was noted between age and serum IgG4 level with gender preference, which may partly explain the higher incidence rate of AIP in elderly men.

Similar to acute pancreatitis, the enlargement of the pancreas stimulates nerve endings on its capsule, leading the most common symptom of abdominal pain in patients. In addition, jaundice was obvious in patients due to the involvement of other organs, such as the bile duct, or the compression by swollen pancreatic parenchyma. Patients in the normal group had a higher incidence of jaundice with no significant differences. Although little is known about its actual mechanism, it reminds us that patients with obstructive jaundice and normal IgG4 levels are likely to be diagnosed with AIP rather than pancreatic carcinoma. Seven patients in the abnormal group had a rare initial symptom of diarrhea, which partly attributes to the abnormal digestive function of the pancreas.

Analysis of the serological results revealed that patients in the abnormal group had a significantly higher total protein level and lower albumin level, indicating a high globulin concentration, along with higher IgG and IgE levels. IgG is a major component of globulin and can be divided into four subclasses based on its structure. It activates the complement system and regulates phagocytosis^[30]. In the abnormal group, except for IgG4, the levels of three subclasses of IgG were significantly higher. Some studies have demonstrated an association between IgG1 and the immunopathogenesis of AIP^[31,32]. Further studies about the specific mechanism and the relation between each subclass and AIP are required. A strong relationship between allergic diseases and AIP has been identified^[33]. Considering the role of IgE in allergic disorders and high levels noted in AIP, especially in the abnormal group, IgE may play a role in the pathogenesis of AIP^[13,30,34]. Patients in the abnormal group also had a higher level of two FLC subtypes (FLC- κ and FLC- λ). FLCs are produced during immunoglobulin synthesis and can be detected under normal physiological conditions as they are not bound to the heavy chains. It is speculated that the accumulation of FLC is attributed to the polyclonal activation of B cells. Previous studies have also proposed their role in other

autoimmune disorders; thus, FLCs may be a biomarker for AIP^[35]. Additionally, those patients with high serum IgG4 levels had a faster erythrocyte sedimentation rate and a lower complement level. Overall, these immunological findings suggest enhanced antibody biosynthesis and a more active immune system in the patient with high IgG4 levels.

Pancreatic findings such as diffuse enlargement or focal low-density mass in radiology are often the typical features indicative of AIP. Although unusual, a low-attenuating rim-like capsule is also regarded as a specific characteristic of AIP. The proportion of different radiological types was similar between the two groups, which implies that there is no relationship between serum IgG4 levels and radiological types, as reported in a previous study^[36]. Imaging scans of the pancreatic duct showed that AIP may have diffuse narrowing of the duct with long or multifocal strictures^[12,16]. Unexpectedly, the proportion of patients with an abnormality in the pancreatic duct was higher in the normal group, probably due to the limited sample size. A higher rate of atrophy was seen in the normal group, which requires careful attention to avoid the replacement of parenchyma cells by fibrous tissue as the disease progresses and leads to pancreatic dysfunction.

Patients in the two groups received varied treatments. In the abnormal group, a higher number of patients received steroid monotherapy, whereas endoscopy or surgery was more common in the normal group. It is possible that the physician's choice of endoscopy or surgery is for biopsy when patients have normal IgG4 levels to exclude cancer diagnosis. Thus, we need simpler and more accurate methods for diagnosis of AIP and to better distinguish it from cancer. To date, the relationship between serum IgG4 level and relapse is controversial. Some studies have demonstrated that an elevated serum IgG4 level is a predictor for relapse^[37-39], whereas other studies have reported contrasting findings^[23,40]. ⁸ In the present study, patients in the abnormal group were significantly more likely to experience relapse. Additionally, approximately 20% of patients in the abnormal group had one relapse in the extrapancreatic organs and > 15% of patients had at least two relapses, higher than the

normal group. This necessitates further attention to investigate the relationship between high IgG4 levels and AIP.

Previous studies have revealed some controversial predictors of relapse, such as pancreatic enlargement, initial prednisolone dose, and involvement of extrapancreatic organs^[1,15,23,41,42]. According to a UK-based study, the relapse rate of patients with elevated serum levels of IgG4 ($> 2 \times \text{ULN}$) was twice than that of another group ($\text{IgG4} \leq 2 \times \text{ULN}$)^[33]. Similar results were also reported in subsequent studies^[42-44]. In the present study, serum IgG4 levels seemed to be an independent risk factor for relapse. Although the specific mechanism remains unclear, the focus on IgG4 should increase owing to its potential effect on the pathogenesis, diagnosis, and prognosis. The concentration of IgA was recognized as an independent risk factor for relapse, which emphasized the association between an active immune system and relapse. IgA is the predominant antibody present at mucosal surfaces, supporting its prominent role in host defense against pathogens. Augmented presence of IgA immune complexes can result in excessive neutrophil activation, potentially leading to severe tissue damage in autoimmune diseases like IgA nephropathy and inflammatory bowel disease^[45-47]. A higher IgA level was also reported in IgG4-related disease or calcific pancreatitis^[48-50]. However, the elevated serum IgA levels were associated with a lower incidence of relapse of IgG4-related disease in a Japanese study. Multicenter and large sample studies are required to clarify the association between these potential risk factors and AIP. AIP is known to occur more commonly among elderly people. In our analyses, patients over the age of 55 years presented a higher risk of relapse. Maintenance therapy was recommended in various studies to prevent relapse^[1,51], while in our study, the absence of maintenance therapy did not seem to be a predictor of relapse.

There were several limitations to our study. Firstly, it was a single-center retrospective study. Secondly, we only analyzed clinical factors to predict relapse. The possible genetic and environmental factors that may contribute to relapse were not considered. Additionally, the long duration of follow-up increased the risk of recall bias.

CONCLUSION

Patients with high IgG4 levels have a unique clinical profile and are at a higher risk of relapse of AIP. Normal IgG4 levels rendered diagnosis challenging, thereby reinforcing the need for a thorough understanding of the disease. Relapse of AIP is related to age and serum IgG4 and IgA levels. An active immune system is strongly related to high IgG4 levels and the risk of relapse. Long-term and multicenter studies are needed to confirm the risk factors for relapse.

ARTICLE HIGHLIGHTS

Research background

The role of immunoglobulin (Ig) G4 in the pathogenesis, diagnosis and prognosis of autoimmune pancreatitis (AIP) has received attention and patients with high levels of IgG4 have unique properties. There is still controversy about the predictors of AIP relapse, such as high IgG4 level, radiological type and steroid use.

Research motivation

To predict the relapse of AIP and identify the properties of patients with different IgG4 level, especially those with normal IgG4 level.

Research objectives

We determined some predictors of relapse and identified unique characteristics of patients with different IgG4 levels. Further studies about improving the diagnosis algorithm of AIP and predicting the relapse are needed.

Research methods

We conducted a retrospective cohort study, including patients with normal IgG4 level ($n = 65$) and high IgG4 level ($n = 148$), and compared their clinical characteristics. We

also performed univariate and multivariate Cox regression models to investigate the risk factors of relapse.

Research results

Patients with high IgG4 levels had a higher average male age; a higher level of serum total protein, IgG4, and IgE; and a lower level of serum complement C3. In addition, a lower number of cases with abnormal pancreatic duct and pancreatic atrophy and a higher rate of relapse were noted in the abnormal group. Multivariate analyses revealed that serum IgG4 ($> 2 \times$ upper limit of normal, ULN) and IgA ($> 1 \times$ ULN) and age > 55 years were independent risk factors of relapse.

Research conclusions

Patients with high IgG4 levels had different clinical features including a more active immune system and a higher relapse rate. Some factors were identified as risk factors of relapse, such as age > 55 years, high IgG4 ($> 2 \times$ ULN) and IgA level ($> 1 \times$ ULN).

Research perspectives

Further research with large samples should be conducted to verify the predictors of relapse.

5%

SIMILARITY INDEX

PRIMARY SOURCES

- | | | |
|---|--|-----------------|
| 1 | www.ncbi.nlm.nih.gov
Internet | 114 words — 2% |
| 2 | f6publishing.blob.core.windows.net
Internet | 19 words — < 1% |
| 3 | ir.ymlib.yonsei.ac.kr
Internet | 15 words — < 1% |
| 4 | Won Gi Jeong, Yun-Hyeon Kim. "Survival impact of fibrotic interstitial lung abnormalities in resected stage IA non-small cell lung cancer", The British Journal of Radiology, 2023
Crossref | 13 words — < 1% |
| 5 | ar.iiarjournals.org
Internet | 13 words — < 1% |
| 6 | www.science.gov
Internet | 13 words — < 1% |
| 7 | "Abstracts", Journal of Arrhythmia, 2023
Crossref | 12 words — < 1% |
| 8 | Claire Deroy, Diego Rossetti, Guillaume Ragetly, Juan Hernandez, Cyrill Poncet. "Comparison between double-pigtail ureteral stents and ureteral bypass | 12 words — < 1% |

devices for treatment of ureterolithiasis in cats", Journal of the American Veterinary Medical Association, 2017

Crossref

9	pure-test.amc.nl Internet	12 words — < 1%
10	www.pubmedcentral.nih.gov Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS