

Original article

Differences in clinical characteristics of IgG4-related disease across age groups: a prospective study of 737 patients

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Abstract

Objective. The aim of this study was to compare the clinical characteristics of IgG4-related disease (IgG4-RD) among different age groups.

Methods. We conducted a prospective study of 737 patients who were newly diagnosed with IgG4-RD and compared detailed demographic features, organ involvements, laboratory tests, treatments and outcomes across age groups. The patients were divided into five groups according to their age at diagnosis: ≤ 39 , 40–49, 50–59, 60–69 and ≥ 70 years. The clinical characteristics of paediatric patients were also described.

Results. Sex ratio, disease duration, allergy history and clinical symptoms were significantly different across age groups. Besides, the proportions of superficial organ involvement (lacrimal gland and sinus) decreased with age, while the proportions of internal organ involvement (pancreas, biliary tract, retroperitoneal tissue, lung and prostate) increased with age, which was more prominent in male patients. Mikulicz's disease was the most common manifestation (70%) in paediatric IgG4-RD patients. Multiple Cox analysis identified that age ≤ 56 years at diagnosis was an independent risk factor of relapse.

Conclusion. We revealed the impact of age on clinical characteristics of IgG4-RD, which indicated that different management might be required among different age groups.

Key words: IgG4-related disease, age, clinical characteristics, prognosis, paediatrics

Rheumatology key messages

- Clinical characteristics of IgG4-related disease differ among age groups.
- The prevalence of internal organ involvement increases with age in IgG4-related disease.
- Younger age is independently associated with relapse of IgG4-related disease with glucocorticoid-based treatment.

Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated condition associated with fibroinflammatory lesions that

can involve almost all organs in human body, with salivary gland, lacrimal gland, pancreas, biliary tract and lymph nodes the most commonly affected sites [1–3]. Typical patients are middle-aged to elderly men [1, 4].

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It features a series of pathological characteristics such as dense lymphoplasmacytic infiltration, storiform pattern of fibrosis and massive IgG4 positive plasma cells infiltrating in the affected tissues with or without serum IgG4 elevation [5]. Glucocorticoid (GC) is the first-line therapy of IgG4-RD, and is effective in most of the patients [6, 7]. Immunosuppressants (IM) are often required in combination with GC since the relapse rate of GC monotherapy is 38.5~50% in the process of GC tapering and withdrawal stages [8–10].

With progressive advancements in medical science and health care system, the proportion of elderly people continues to rise. Previous studies have demonstrated that ageing remains the single largest risk factor for various diseases, such as cardiovascular disease, stroke, cancers and infections [11]. Besides, immunosenescence and inflammaging have been considered one of the sources of chronic inflammatory disorders and autoimmune diseases [12, 13]. In rheumatoid arthritis (RA), the proportion of ACPA negative patients, level of acute phase reactants, experience of constitutional symptoms, disease severity, choice of pharmacological treatment and prognosis were associated with age [14–17]. In SLE, clinical manifestations such as arthritis, serositis, malar rash, renal disease and 10-year survival rates were different across age groups [18–20]. In terms of IgG4-RD, younger age has been implicated as a risk factor for disease relapse [21–23]. Besides, Yamamoto *et al.* [24] have revealed laboratory differences between the elderly (>70) and non-elderly (≤ 70) in IgG4-related dacryoadenitis and sialadenitis. Although these studies have partly demonstrated the association between age and relapse or age and laboratory tests, to our knowledge, age disparities in clinical manifestations, disease severity and treatment agents in full-spectrum IgG4-RD have not been studied in detail before. Hence, based on our data of 737 patients from our cohort, we focused on the clinical characteristics and treatment outcomes among age groups. Moreover, paediatric patients were also described in order to illustrate the broad range of manifestations and emphasize awareness of IgG4-RD in paediatrics.

Methods

Patients

This prospective study enrolled patients with IgG4-RD at Peking Union Medical College Hospital between March 2011 and January 2020 (ClinicalTrials.gov ID: NCT01670695). Patients who satisfied the 2011 comprehensive criteria were included [25]. Patients with malignancies, infectious diseases, comorbid rheumatoid diseases or conditions that could mimic IgG4-RD were excluded. Finally, newly diagnosed and untreated IgG4-RD patients were included in this study ($n = 737$). After taking age distribution of patients and balanced sample size into consideration, patients were divided into five groups according to the age at diagnosis (≤ 39 , 40–49,

50–59, 60–69 and ≥ 70 years). Paediatric patients were identified as aged 17 years or younger at diagnosis. Patients' allergy history was collected by using the definitions of the European Academy of Allergy and Clinical Immunology [26], including allergic asthma, allergic rhinoconjunctivitis, allergic urticaria, atopic eczema, allergic contact dermatitis, food allergy and drug allergy. Detailed demographic parameters, organ involvements, laboratory tests, imaging studies, histological examinations, disease activity, treatment agents and outcomes were recorded. This study was approved by the Ethics Committee of Peking Union Medical College Hospital. All enrolled patients signed written informed consents.

Organ involvement

Organ involvement was assessed by reviewing patients' past medical history, symptoms, signs, laboratory tests, imaging studies and histological examinations. Involved organs were classified into superficial and internal organs according to anatomical sides [27, 28]. Superficial organs included submandibular gland, parotid gland, lacrimal gland, sinus, thyroid and skin. Internal organs referred to pituitary, lung, liver, biliary tract, pancreas, gastrointestinal tract, artery, retroperitoneal tissue, mediastinum, kidney and prostate. Lymph node was not included in either superficial or internal organs.

Laboratory tests, imaging studies and histological examinations

Laboratory tests of complete blood count, ESR, CRP, serum immunoglobulin (Ig) concentration, IgG subclasses, total IgE (T-IgE) level, complement (C3, C4), ANAs, RF, liver and renal function tests were performed and recorded at baseline (at the time of diagnosis without treatment) and in the follow-up. Proportions of B cell phenotypes were measured in 103 treatment naïve patients who were newly diagnosed by flow cytometry after staining with CD19, CD24 and CD38 as previously described [29]. B cell subsets were defined as mature naïve B cells ($CD19^+CD24^{int}CD38^{int}$), memory B cells ($CD19^+CD24^+CD38^-$), regulatory B cells ($CD19^+CD24^{hi}CD38^{hi}$) and $CD19^+CD24^-CD38^{hi}$ B cells according to literature reports [30, 31]. All patients underwent image examinations, namely ultrasonography, CT, MRI or ^{18}F -fluorodeoxyglucose PET/CT. Tissue biopsies were carried out on 434 patients according to pathology method reported before [32].

Disease activity, treatment agents and outcomes

Disease activity was evaluated by IgG4-RD responder index (RI) [33]. Treatment regime included GC monotherapy, IM monotherapy, GC combined with IM and watchful waiting (referring to no treatment or single injection of betamethasone). Relapse was defined as a recurrence or worsening of symptoms or imaging studies, with or without the re-elevation of serum IgG4 concentration. Re-elevation of serological IgG4 level alone was not

considered to be a relapse. We included 310 patients treated with GC monotherapy or GC combined with IM and analysed their relapse in the follow-up of 36 months.

Statistical analysis

Continuous normally distributed data were presented as mean and standard deviation and continuous non-normally distributed data were presented as median and interquartile range. Multiple sets of measurement data were compared with a one-way analysis of variance or multiple independent samples non-parametric test (Kruskal–Wallis test). A *post hoc* Tukey test or Dunn's test was used for multiple comparisons ($\alpha=0.05$). Categorical variables were assessed by Fisher's exact test or the χ^2 test. The χ^2 trend test was used to test the statistical significance of changes in proportions of organ involvement with age. Correlations between variables were assessed using Pearson's rank test (normally distributed) or Spearman's rank correlation test (non-normally distributed). Stepwise multiple linear regression analysis was employed to identify the potential factors associated with serum IgG4 concentration. The receiver operating characteristic curve was used to determine the predictive ability of age for relapse and the cut-off value. Propensity score matching (PSM) was performed to eliminate confounding. Potential factors such as sex, disease duration, IgG4-RD RI, involvement of superficial (salivary gland, sinus) and internal organs (pancreas, biliary tract and lung) and whether an IM was used were included as independent variables. Kaplan–Meier survival curves and log-rank tests were performed to calculate the relapse rate. Univariate and multivariate Cox regression analysis was performed to estimate the risk factors of relapse in IgG4-RD and a backward stepwise method (likelihood ratio test) was used. Statistical analysis was performed with IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). *P*-values <0.05 (two-tailed) were considered statistically significant.

Results

Patients' demographic features

In this study, we prospectively included a total of 737 IgG4-RD patients divided into five groups according to age at diagnosis (Fig. 1A). Male ratio increased with advancing age (Fig. 1B, *P* for trend <0.001). In addition, the demographic features are shown in Table 1. The disease duration (the time from onset to diagnosis) and frequencies of allergy history were significantly different across age groups. The number of organs involved was comparable in different age groups. At disease onset, the occurrence of lacrimal gland swelling ($P<0.001$), nausea and vomiting ($P=0.028$), jaundice ($P<0.001$) and nasal congestion ($P<0.001$) were significantly different across age groups.

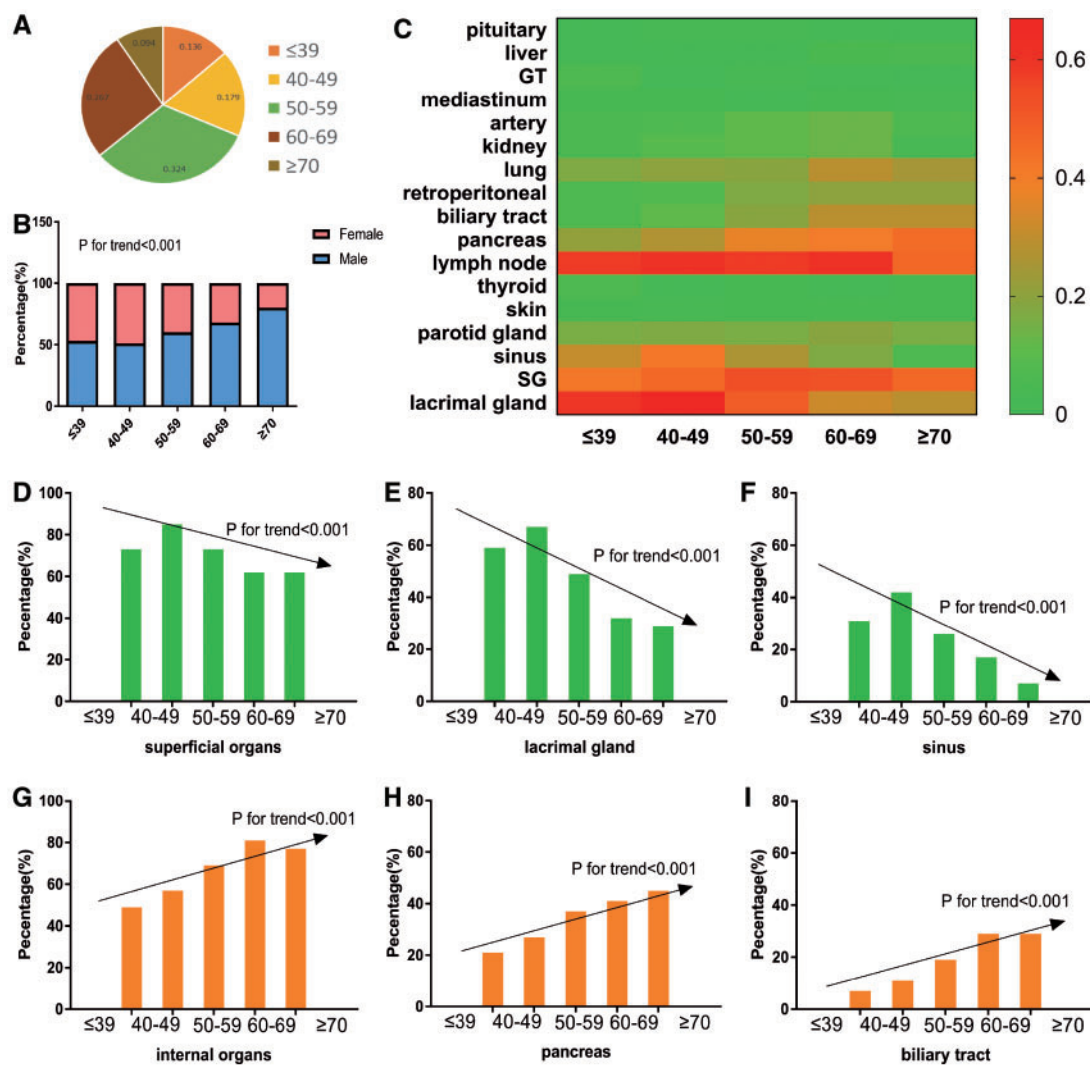
Organ involvement

In terms of organs involved in IgG4-RD, a heat map was used to elucidate and visualize the difference across age groups (Fig. 1C), showing different frequencies of organ involvement in the age groups. To further demonstrate the characteristics of organ involvement based on age disparities, we subsequently compared the proportions of superficial or internal organ involvement and analysed the change patterns across age groups. The proportions of total superficial organs (*P* for trend <0.001), lacrimal gland (*P* for trend <0.001) and sinus (*P* for trend <0.001) involvement were significantly different between age groups, all presenting downtrends with advancing age (Fig. 1D–F). However, the proportions of other superficial organ involvement were comparable in different age groups (Supplementary Fig. S1, available at *Rheumatology* online). In addition, the involvement rates of total internal organs (*P* for trend <0.001), pancreas (*P* for trend <0.001), biliary tract (*P* for trend <0.001), lung (*P* for trend $=0.022$), prostate (*P* for trend $=0.001$) and retroperitoneum (*P* for trend <0.001) were significantly different across age groups, presenting uptrends with advancing age (Fig. 1G–I and Supplementary Fig. S1, available at *Rheumatology* online). In other internal organs, the percentage involvement was not significantly different across age groups (Supplementary Fig. S1, available at *Rheumatology* online). Considering that female patients were more likely to present with superficial organ involvement, while male patients more frequently had internal organ involvement [28], we wanted to know whether this age-related organ involvement disparity was affected by the distribution of gender. Hence, we compared the organ involvements across age groups in male and female (Supplementary Fig. S2, available at *Rheumatology* online). The proportions of superficial organ (lacrimal gland and sinus) involvement decreased with age in both male and female patients. On the contrary, the proportion of internal organ involvement increased with age, and was more prominent in male patient, mainly presenting in pancreas, biliary tract, lung and retroperitoneum, while the phenomenon only occurred in biliary tract in female patients.

Laboratory findings

We further compared the laboratory tests at baseline among the five age groups. Haemoglobin ($P=0.028$), platelet ($P<0.001$), ESR ($P<0.001$), CRP ($P=0.012$), serum IgG ($P=0.001$), IgM ($P<0.001$), IgG1 ($P<0.001$), IgG3 ($P<0.001$), IgG4 ($P=0.006$) concentrations and proportions of B regulatory cells (CD19⁺CD24^{hi}CD38^{hi}) ($P=0.038$) were significantly different across age groups (Table 2).

We also performed correlation analysis between laboratory tests and age (Fig. 2). We found that ESR ($r=0.263$, $P<0.001$), CRP ($r=0.175$, $P<0.001$), serum IgG ($r=0.13$, $P<0.001$), IgG1 ($r=0.168$, $P<0.001$), IgG3 ($r=0.165$, $P<0.001$) and IgG4 concentration

Fig. 1 Age, sex and organ involvement distributions of IgG4-RD patients

(A) Age distributions of patients. (B) Sex ratio of patients across age groups. (C) Heat map: the percentages of organ involvement across age groups. (D–F) Comparison of percentages of total superficial organs (D), lacrimal gland (E) and sinus (F) involvement across age groups. (G–I) Comparison of percentages of total internal organs (G), pancreas (H) and biliary tract (I) involvement across age groups. GT: gastrointestinal tract; SG: submandibular gland.

($r = 0.106$, $P = 0.004$) were positively correlated with age. What is more, serum IgM concentration ($r = -0.184$, $P < 0.001$) and proportions of naïve B cell ($CD19^+CD24^{int}CD38^{int}$) ($r = -0.202$, $P = 0.043$) were negatively correlated with age. However, none of peripheral eosinophils, serum IgA, T-IgE, IgG2 concentrations or other B cell subsets showed statistically significant correlation with age (data not shown).

Line charts were used to describe the patterns of change of serum T-IgE and IgG subclasses with age (Fig. 3A). Besides, we also recorded the changes of serum IgG4 level at 3, 6 and 12 months after treatment (Fig. 3B). The serum IgG1, IgG3, IgG4 and T-IgE levels peaked at 60–69 years of age and serum IgG4 level in the age group 60–69 years remained at a peak after treatment for 3, 6 and 12 months.

Furthermore, multivariate linear regression analysis was performed to identify the potential factors associated with baseline serum IgG4 level (Supplementary Table S1, available at *Rheumatology* online). As shown in Supplementary Table S1, age was independently associated with serum IgG4 level (standardized β -coefficient 0.146, $P < 0.001$). Other identified variables were sex (standardized β -coefficient 0.161, $P < 0.001$), lacrimal gland involvement (standardized β -coefficient -0.15 , $P < 0.001$) and number of involved organs (standardized β -coefficient 0.332, $P < 0.001$).

Disease activity, treatment agents and outcomes

We further compared the IgG4-RD RI of patients among the five groups (Fig. 3C) and it showed a

TABLE 1 Demographic characteristics of IgG4-RD across age groups

Clinical characteristics	All (n = 737)	Age group					P-value (compared in all groups)
		≤ 39 (n = 100)	40–49 (n = 132)	50–59 (n = 239)	60–69 (n = 197)	≥ 70 (n = 69)	
Gender, male: female	1.58: 1	1.13: 1	1.03: 1	1.49: 1	2.08: 1	3.93: 1	<0.001
Duration, median (IQR), months	12 (4–36)	12 (6–36)	12 (6–39)	12 (4–36)	12 (4–48)	6 (2–24)	0.019
Allergy history, n (%)	356 (48)	49 (49)	73 (55)	128 (54)	76 (39)	30 (44)	0.01
Number of organs involved, n (%)							
1–2	265 (36)	43 (43)	46 (35)	86 (36)	59 (30)	31 (45)	0.126
3–4	298 (40)	43 (43)	56 (42)	95 (40)	81 (41)	23 (33)	
≥ 5	174 (24)	14 (14)	30 (23)	58 (24)	57 (29)	15 (22)	
Symptoms at disease onset, n (%)							
Lacrimal gland swelling	289 (39)	49 (49)	75 (57)	101 (42)	49 (25)	15 (22)	<0.001
Submandibular gland swelling	278 (38)	30 (30)	45 (34)	102 (43)	72 (37)	29 (42)	0.169
Parotid gland swelling	79 (11)	10 (10)	13 (9)	28 (12)	22 (11)	6 (9)	0.947
Lymphadenopathy	204 (28)	38 (38)	34 (26)	68 (28)	49 (25)	15 (22)	0.106
Abdominal pain	125 (17)	11 (11)	15 (11)	45 (19)	42 (21)	12 (17)	0.069
Nausea and vomiting	57 (8)	1 (1)	7 (5)	21 (9)	20 (10)	8 (12)	0.028
Jaundice	98 (13)	4 (4)	11 (8)	30 (13)	37 (19)	16 (23)	<0.001
Nasal congestion	121 (16)	16 (16)	43 (33)	35 (15)	24 (12)	3 (4)	<0.001
Cough	75 (10)	8 (8)	14 (11)	22 (9)	24 (12)	7 (10)	0.798
Exophthalmos	28 (4)	5 (5)	7 (5)	10 (4)	4 (2)	2 (3)	0.495
Fever	37 (5)	9 (9)	6 (5)	8 (3)	8 (4)	6 (9)	0.13

IgG4-RD: IgG4-related disease; IQR: interquartile range.

significant difference in age groups ($P=0.025$). The treatment approaches were not significantly different (Fig. 3D, $P=0.39$). A total of 310 patients who were treated with GC alone or GC combined with IM were included in the study of treatment outcomes and followed up for >36 months. The receiver operating characteristic curve revealed that age ≤ 56.5 was strongly linked to disease relapse. As a result, patients were divided into young patients (age ≤ 56 , $n=173$) and elderly patients (age >56 , $n=137$). Using PSM, 119 patients from the young patients and 119 patients from the elderly patients were matched. Baseline clinical characteristics of the two groups were balanced after PSM (Supplementary Table S2, available at *Rheumatology* online). A total of 53 patients (22.3%) relapsed during the follow-up of 36 months and Kaplan–Meier survival analysis revealed that young patients (age ≤ 56) were more likely to relapse over any given month of follow-up compared with elderly patients (Fig. 3E, $P=0.029$).

Multivariate Cox analysis of 310 patients treated with GC alone or GC combined with IM identified that older age (hazard ratio 0.54, $P=0.013$) was the independent protective factor with relapse, while higher percentage of eosinophils (hazard ratio 2.44, $P<0.001$) was the independent risk factor with relapse (Table 3).

Clinical characteristics and treatment outcomes in paediatric patients

We also studied the clinical characteristics and treatment outcomes of paediatric patients (Supplementary Table S3, available at *Rheumatology* online). Ten patients (seven boys and three girls) aged from 9 to 17 years were included. Disease duration ranged from 4 to 60 months. Most patients presented with Mikulicz's disease (70%). Other manifestations were lymphadenopathy (40%), autoimmune pancreatitis (30%), IgG4-related sclerosing cholangitis (20%), lung disease (10%), sinusitis (10%), hepatopathy (10%) and thyroiditis (10%). Multiple organ involvement (two or more organ manifestations) occurred in 60% of paediatric patients. The percentage of the paediatric patients with serum IgG4 elevation was significantly lower than that in adults (70% vs 92.6%, $P=0.036$). The IgG4-RD RI ranged from 3 to 21. The majority of patients (70%) were treated with GC alone or combined with IM. In the seven patients treated with GC monotherapy or GC combined with IM, three patients (42.9%) relapsed in the follow-up.

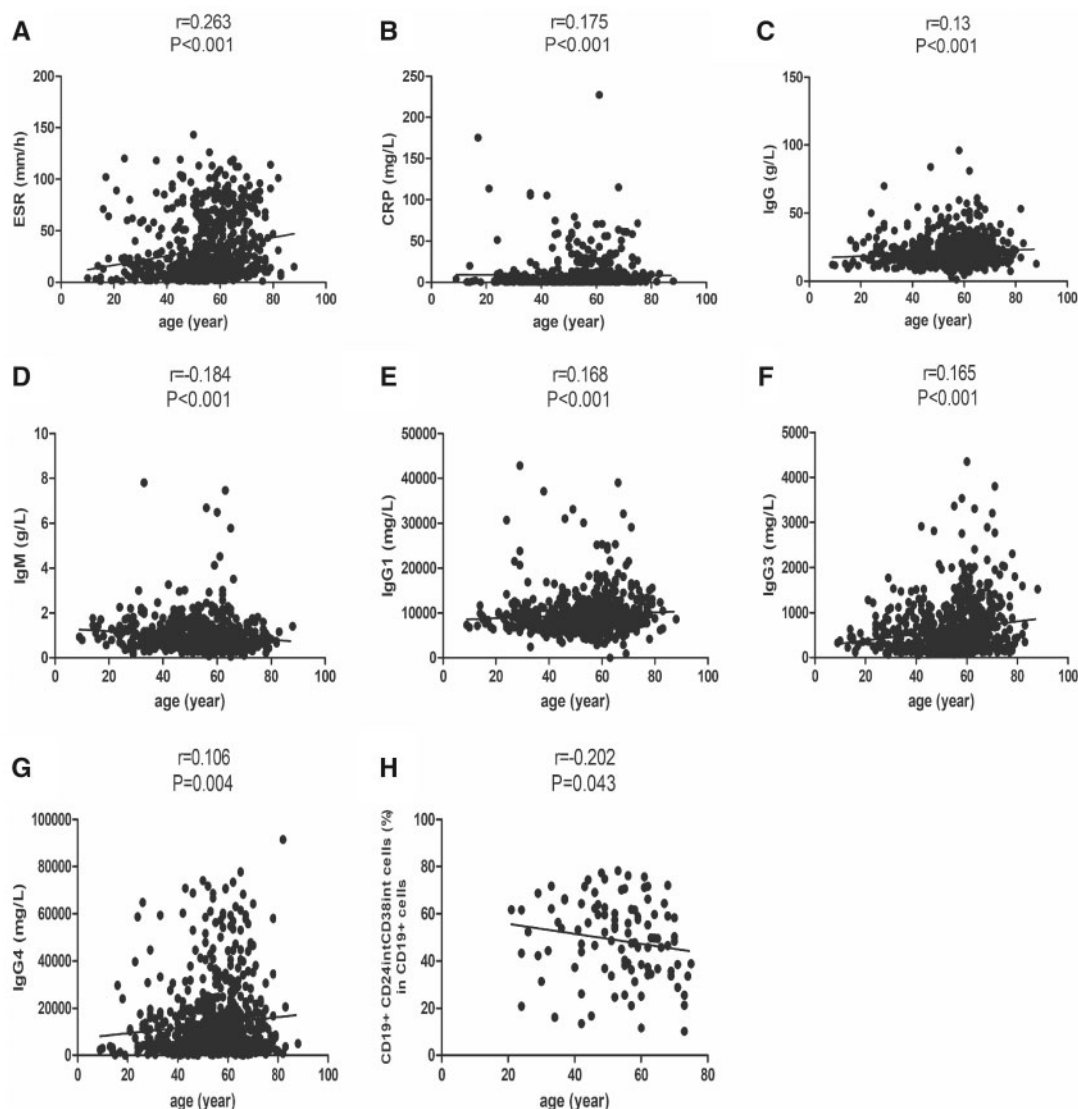
Discussion

To our knowledge, this is the largest prospective study that revealed the age disparities of IgG4-RD. We focused on demographic features, organ involvement,

TABLE 2 Baseline laboratory parameters of IgG4-RD across age groups

Laboratory parameters	All (n = 737)	Age group				P-value (compared in all groups)
		≤39 (n = 100)	40–49 (n = 132)	50–59 (n = 239)	60–69 (n = 197)	≥70 (n = 69)
HGB, mean (s.d.), g/l	134 (19)	137 (20)	138 (20)	135 (19)	131 (17)	133 (18)
WBC, mean (s.d.), 10 ⁹ /l	7.13 (2.48)	7.65 (2.61)	7.30 (2.88)	6.85 (2.12)	7.13 (2.60)	7.1 (2.29)
PLT, mean (s.d.), 10 ⁹ /l	239 (74)	276 (80)	254 (79)	239 (70)	231 (60)	226 (74)
Eosinophils, median (IQR), 10 ⁹ /l	0.2 (0.1–0.4)	0.19 (0.09–0.37)	0.2 (0.08–0.47)	0.21 (0.1–0.39)	0.2 (0.1–0.44)	0.2 (0.1–0.34)
Elevated eosinophils, n (%)	148 (20)	22 (22)	31 (23)	42 (17)	42 (22)	11 (16)
ESR, median (IQR), mm/h	19 (8–50.3)	14.5 (6–27.3)	12.5 (6–23.8)	22 (8–50)	28 (12–65)	32 (12.8–67.3)
CRP, median (IQR), mg/l	2.1 (0.8–7.1)	1.97 (0.5–6.1)	1.74 (0.7–3.5)	1.9 (0.8–6.9)	3.1 (1.2–9.4)	4.12 (1.1–7.9)
Serum IgG, median (IQR), g/l	18.2 (13.9–24.8)	17.6 (13.8–24.3)	16.2 (12.3–22.2)	18.6 (13.5–24.5)	19.8 (15.1–28.8)	18.6 (15–23.8)
Serum IgA, median (IQR), g/l	2.0 (1.4–2.7)	2.2 (1.4–2.9)	1.9 (1.4–2.6)	1.9 (1.4–2.5)	1.9 (1.3–2.7)	2.3 (1.4–3.3)
Serum IgM, median (IQR), g/l	0.8 (0.6–1.2)	1.1 (0.6–1.4)	0.9 (0.7–1.2)	0.7 (0.5–1.1)	0.7 (0.5–1.1)	0.7 (0.5–1.1)
Serum T-IgE, median (IQR), kU/l	306 (102–712)	229.5 (60.8–639.5)	259 (91.9–589)	308.5 (128.8–712)	383.5 (123.3–758.8)	331 (109.9–820.5)
Serum IgG1, median (IQR), mg/l	8715 (7190–10625)	8615 (7065–10500)	8180 (6975–9483)	8455 (6828–10200)	9480 (7700–11875)	9440 (7810–12600)
Serum IgG2, median (IQR), mg/l	5500 (4145–7295)	5460 (3910–6770)	5320 (4130–7315)	5610 (4170–7537)	5470 (3950–7230)	5540 (4490–7723)
Serum IgG3, median (IQR), mg/l	436.5 (246–813.3)	455 (243–743.8)	411.5 (222.8–660.8)	393 (240.5–645.8)	544 (287–1020)	521 (266–1140)
Serum IgG4, median (IQR), mg/l	7670 (3060–16525)	4600 (2280–13250)	6930 (2980–13500)	8530 (3260–15275)	10000 (3300–21000)	7100 (3950–17450)
CD19 ⁺ , median (IQR), % ^a	5.42 (4.09–7.67)	6.61 (5.12–8.74)	4.72 (3.57–8.26)	5.01 (2.98–7.72)	5.25 (4.32–6.4)	5.81 (3.97–6.51)
CD19 ⁺ CD24 ^{hi} CD38 ^{hi} , median (IQR), % ^b	5.26 (2.75–10.2)	6.28 (2.22–10.2)	3.97 (2.16–7.81)	5.63 (3.34–15.3)	5.27 (2.33–10.7)	5.13 (4.06–8.94)
CD19 ⁺ CD24 ^{hi} CD38 ^{hi} , median (IQR), % ^b	3.19 (0.56–6.26)	1.14 (0.08–3.82)	4.66 (1.55–7.85)	3.42 (0.61–9.51)	3.23 (0.84–6.85)	0.65 (0.19–2.92)
CD19 ⁺ CD24 ^{int} CD38 ^{int} , median (IQR), % ^b	49.7 (36.8–61.8)	55.2 (42.6–65.0)	57.9 (42.3–65.5)	50.3 (38.4–59.8)	46.5 (35.1–62.1)	36.1 (24.5–48.9)
CD19 ⁺ CD24 ^{hi} CD38 ^{hi} , median (IQR), % ^b	8.99 (4.14–19.2)	13.0 (4.1–22.3)	8.7 (4.67–15.4)	7.13 (4.67–17.0)	8.29 (3.71–18.4)	19.3 (7.83–28.6)
ANAs (+), n (%)	119 (16)	15 (15)	19 (14)	36 (15)	34 (17)	15 (22)
RF (+), n (%)	119 (16)	12 (12)	19 (14)	42 (18)	34 (17)	12 (17)

^aPercentage of CD19⁺ cells in total lymphocytes. ^bPercentage of B cell subsets in CD19⁺ cells. HGB: haemoglobin; IgG4-RD: IgG4-related disease; IQR: interquartile range; PLT: platelet; WBC: white blood cell count.

Fig. 2 Correlation analysis between age and baseline laboratory findings

(A and B) Correlations between ESR/CRP and age. (C–G) Correlations between serum levels of IgG/M/G1/G3/G4 and age. (H) Correlation between proportions of CD19⁺CD24^{int}CD38^{int} cells in CD19⁺ cells and age.

laboratory tests, disease activity, treatment agents and outcomes among different age groups.

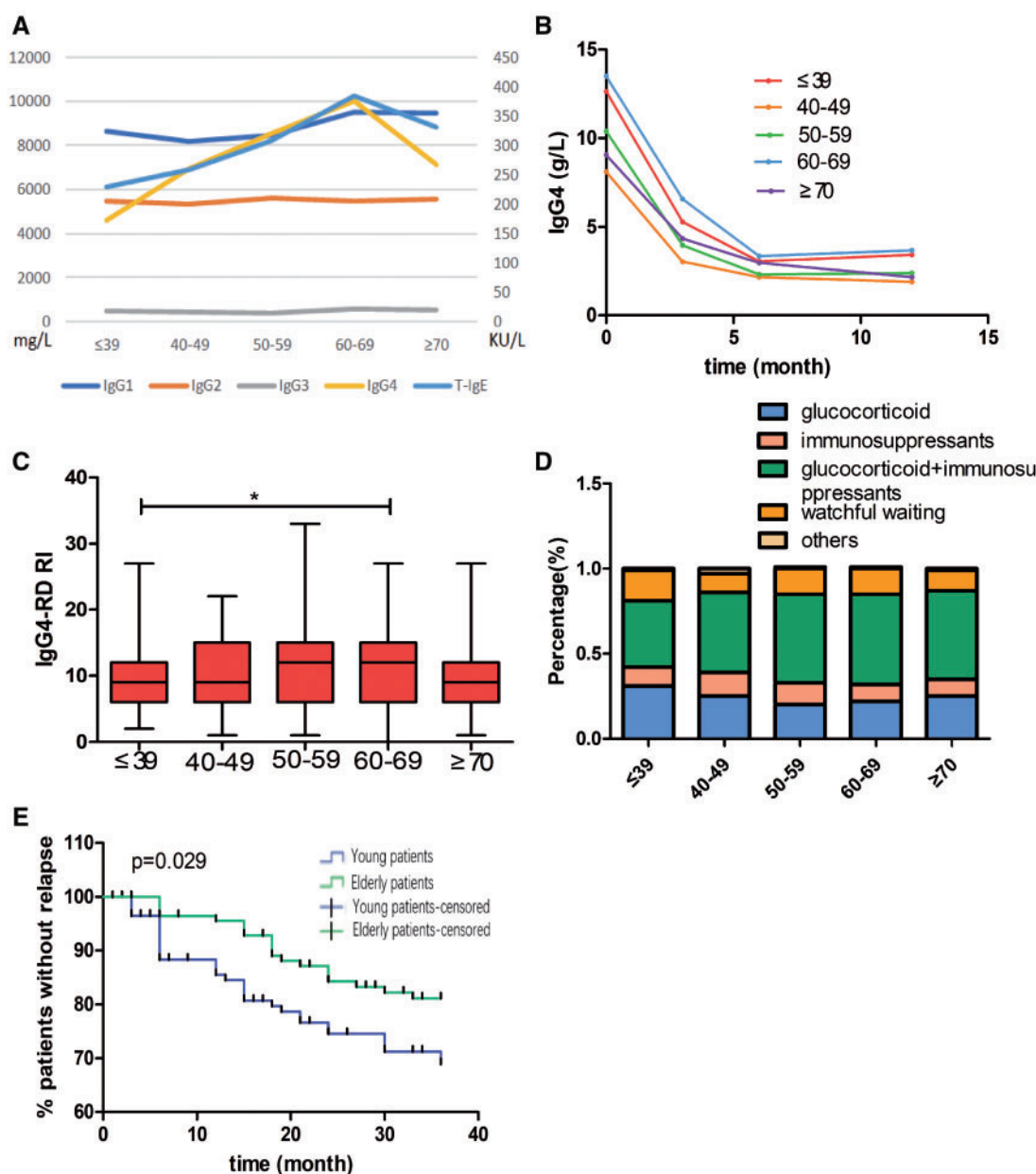
The demographic features of the five groups were different. Our work revealed male predominance in older groups, which was consistent with other reports [24, 28]. IgG4-RD has long been considered to be accompanied with allergic conditions [34, 35]. Although we found the frequencies of allergy history were significantly different across age groups, we did not find any statistical discrepancies in eosinophils and T-IgE that related to allergic inflammation. Of note, Yamamoto *et al.* [24] reported that both level of serum IgE and peripheral count of eosinophils were significantly lower or tended to be lower in the elderly-onset (>70) group.

IgG4-RD is a systemic disease characterized by multiple site involvement. Superficial organ involvements

such as lacrimal gland and sinus were less common with advancing age, while the involvements of submandibular gland, parotid gland and skin showed no difference across age groups. As for internal organs, the proportions of pancreas, biliary tract, retroperitoneum, prostate and lung involvement increased with age, indicating that these internal organs were more likely to be damaged by IgG4-RD in the older patients. Besides, the phenomenon that the proportion of internal organ involvement increased with age was more prominent in male patients. Therefore, extra attention is needed and it is particularly necessary to perform a comprehensive and systemic evaluation to obtain a full view of organ involvement in clinical practice, especially for elderly men.

A comparison of laboratory tests revealed that ESR, CRP, serum IgG, IgM, IgG1, IgG3 and IgG4 levels were

Fig. 3 Levels of IgG subclasses and T-IgE, IgG4-RD RI, treatment approaches and treatment outcomes across age groups



(A) Median values of serum IgG subclasses and T-IgE across age groups. (B) Median values of serum IgG4 at baseline or after treatment for 3, 6 and 12 months. (C) Boxplots of IgG4-RD RI across age groups. (D) Percentage of treatment approaches across age groups. (E) Kaplan-Meier survival curve of patients without relapse between young patients (age ≤56) and elderly patients (age >56). IgG4-RD: IgG4-related disease; RI: responder index; T-IgE: total IgE.

significantly different across age groups. Besides, ESR, CRP, serum IgG, IgG1, IgG3 and IgG4 levels were positively correlated with age. Consistent with our data, Wallace *et al.* [36] reported that patients with elevated serum IgG4 concentration tend to be older, with more organ involvements, with higher serum IgG, IgG1, IgG2 and IgG3 levels and lower complement levels. An age-

dependent physiological process might contribute to the observed age-related increase in ESR, CRP and IgG subclasses. It has been reported that the production of acute-phase proteins, pro-inflammatory cytokines, such as IL-6 and TNF- α , reactive oxygen species and autoantibodies increased in multiple tissues with advancing age [13, 37]. Yamamoto *et al.* [24] found no significant

TABLE 3 Univariate, multivariate cox analysis and forest plot of potential factors associated with relapse in IgG4-RD

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex	1.01 (0.62–1.63)	0.975	—	—
Age	0.54 (0.33–0.88)	0.013	0.54 (0.33–0.88)	0.013
Duration	1.08 (0.67–1.73)	0.756	—	—
Serum IgG4	1.15 (0.71–1.85)	0.572	—	—
IgG4-RD RI	0.81 (0.50–1.32)	0.395	—	—
Superficial organ	1.43 (0.83–2.47)	0.193	—	—
Internal organ	0.85 (0.52–1.39)	0.527	—	—
Pancreas	0.68 (0.42–1.11)	0.12	0.64 (0.39–1.05)	0.075
Biliary tract	0.77 (0.45–1.33)	0.352	—	—
Salivary gland	1.14 (0.71–1.84)	0.58	—	—
Lacrimal gland	1.53 (0.97–2.44)	0.07	—	—
Retroperitoneal	0.56 (0.29–1.09)	0.086	—	—
Lung	1.43 (0.87–2.34)	0.157	—	—
Sinus	1.63 (1.01–2.63)	0.046	—	—
EO%	2.32 (1.46–3.69)	<0.001	2.44 (1.53–3.90)	<0.001
GC + IM	0.76 (0.48–1.20)	0.232	—	—

P-values shown in bold are statistically significant. EO: eosinophils; GC+IM: glucocorticoid combined with immunosuppressant; HR: hazard ratio; IgG4-RD: IgG4-related disease.

difference in serum IgG, IgG4 level and CRP between older (>70) and younger (≤70) patients. The discrepancy between the two studies possibly derived from different grouping criteria, different ethnic groups or relatively smaller sample size in the other study. Multiple linear regression analysis revealed that older age, male sex, lacrimal gland involvement and more involved organs were independently associated with higher serum IgG4 level, while artery involvement was independently associated with lower serum IgG4 level. The standardized β -coefficient indicated that the number of involved organs showed the strongest association with serum IgG4 level. Consistently, Wang *et al.* [28] revealed higher IgG4 level was associated with older age, male sex, higher baseline IgG4 RI and Mikulicz's disease. Besides, Wallace *et al.* [36] reported that patients with elevated serum IgG4 concentration tend to be older, with more organ involvements, with higher serum IgG subclass levels and lower complement levels. Zhang and Stone [21] mentioned in a review article that IgG4-RD of a 'proliferative type' affecting epithelial gland and tissues (dacryoadenitis, sialadenitis and pancreatitis, etc.) tends to have higher serum IgG1, IgG4 and IgE levels than that of a 'fibrotic type' originating from extra-glandular sites (such as aortitis). Our study (Peng *et al.*) [38] revealed IgG4-RD with aortitis/periaortitis and periarteritis (PAO/PA) had a lower level of serum IgG4 than IgG4-RD without PAO/PA.

The serum IgG1, IgG3, IgG4 and T-IgE levels peaked at 60–69 years of age, which was in accord with IgG4-RD RI. It was reported that healthy populations aged between 18 and 39 had the highest levels of IgG2 and IgG4, and those aged between 10 and 17 had the highest level of IgE [39], indicating that age-related changes

of immunoglobulins in IgG4-RD patients may also derived from disease severity. In addition, the probability of total internal organ involvement as well as single internal organ involvement (biliary tract, retroperitoneum, lung, kidney and artery) peaked at 60–69 years of age, suggesting that extra attention and comprehensive evaluation were required in this population.

In our clinical practice, the treatment approaches (the proportion of patients treated with GC or GC combined with IM) were not significantly different across age groups. Kaplan–Meier survival analysis suggested that younger age at onset was associated with relapse. Moreover, the result of multivariate Cox analysis revealed that age was associated with relapse, which was in accordance with two studies that focused on predictors of recurrence in Mikulicz's disease or IgG4-RD [22, 23]. Multivariate Cox analysis also identified that higher proportions of eosinophils were a risk predictor associated with relapse, which was in accord with other studies [40–41].

As for paediatric patients of IgG4-RD, our cohort showed a male dominance, which was different from that of 64% girls in a systematic review [42]. The most commonly affected organ in that review was orbital disease, followed by IgG4-related pancreatitis, cholangitis and pulmonary disease. By comparison, our patients showed that Mikulicz's disease was the most common manifestation, followed by lymphadenopathy, autoimmune pancreatitis and IgG4-related sclerosing cholangitis. Consistent with a previous report, the proportion of the IgG4-RD paediatric patients with elevated IgG4 serum concentration was 70% [42].

Why the disease phenotypes differ depending on age of diagnosis remains a matter of conjecture. IgG4-RD is

a multifactorial disease, and the different characteristics of age groups might originate from immunosenescence, inflammaging and difference of hormone levels, such as oestrogen. Immunosenescence was involved in both innate and adaptive immune systems [37]. Chronic antigenic stimulants accumulated as people got older, which remodelled the immune system by there being fewer naïve cells and increased dysfunctional memory cells. It was reported that the number of T regulatory cells increased with age though function degenerated [13]. Besides, there was a progressive reduction of the TCR repertoire and decreased proliferation of T cells *in vitro* with age [43–46]. As for B cells, the number of B regulatory cell as well as their functions were decreased with age [13]. In the innate immune system, previous studies have demonstrated that myeloid skewing, impairment of neutrophil chemotaxis and effector function, defects in NK cells and monocyte dysregulation were associated with age [13, 47]. Inflammaging was characterized by a variety of senescence-associated secretory phenotypes, such as proinflammatory cytokines, chemokines, growth factors and proteases, secreted by senescent cells [48]. Both the dysregulation of the immune system and cellular senescence contributed to the proinflammatory environment.

There were a few limitations in this study. First, though PSM was performed between young and elderly patients, it could only control known variables, which might cause residual confounding in some degree. Second, pathology tests were carried out in 58.9% of patients; the rest of the patients were diagnosed based on typical clinical presentations, imaging studies and serum IgG4 level. Third, a different sex ratio might affect superficial or internal organ involvement across age groups. As a result, we compared the proportions of affected organs separately in both male and female patients (Supplementary Fig. S2 available at *Rheumatology* online) and the results were consistent with that in the whole population.

In conclusion, our study revealed the differences in demographic features, organ involvements, laboratory tests, treatment agents and outcomes across age groups. The proportions of superficial organ involvement (lacrimal gland and sinus) decreased with age while the percentages of internal organ involvement (pancreas, biliary tract, retroperitoneal, lung and prostate) increased with age. Younger age at onset (≤ 56) was an independent risk factor of relapse in IgG4-RD patients based on GC therapy. Therefore, evaluation and treatment strategies should be given according to the clinical characteristics of different age groups.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Linear regression analysis of clinical variables associated with serum IgG4 concentration.

variables	Unstandardized β coefficient (SD)	Standardized β coefficient	P-value
Age (years)	0.013 (0.003)	0.146	<0.001
Sex (male)	0.402 (0.089)	0.161	<0.001
Lacrimal gland involvement	0.547 (0.096)	0.226	<0.001
Arteries involvement	-0.58 (0.135)	-0.15	<0.001
Number of involved organs	0.24 (0.027)	0.332	<0.001

Age, sex, disease duration, allergy history, IgG4-RD RI, number of involved organs and the involvement of pancreas, bile duct, submandibular gland, lacrimal gland, parotid gland, sinus, retroperitoneum, arteries and lung were included for stepwise multiple linear regression analysis. IgG4 levels were logarithmically transformed so that the residual error followed a normal distribution.

Supplementary Table S2. Baseline clinical characteristics of young patients (age $\leq$ 56) and elderly patients (age>56) before and after PSM.

	Pre-PSM			Post-PSM		
	Young patients (n=173)	Elderly patients (n=137)	P-value	Young patients (n=119)	Elderly patients (n=119)	P-value
Sex (male), n (%)	103 (59.5)	95 (69.3)	0.074	79 (66.4)	80 (67.2)	0.891
Duration, (months)	12 (6-24)	12 (3-36)	0.648	12 (5-24)	12 (3-36)	0.586
Number of organs involved	3 (2-5)	4 (3-5)	0.138	4 (2-5)	4 (2-5)	0.679

IgG4-RD RI	12 (9-15)	12 (9-18)	0.138	12 (9-15)	12 (9-15)	0.997
Organ involvement						
Superficial organs	128 (74)	87 (63.5)	0.047	82 (68.9)	78 (65.5)	0.581
Internal organs	106 (61.3)	115 (83.9)	<0.001	86 (72.3)	97 (81.5)	0.091
Pancreas	64 (37)	62 (45.3)	0.141	47 (39.5)	51 (42.9)	0.598
Biliary tract	35 (20.2)	50 (36.5)	0.001	34 (28.6)	38 (31.9)	0.572
Salivary gland	101 (58.4)	80 (58.4)	0.998	69 (58)	71 (59.7)	0.792
Retroperitoneal	30 (17.3)	33 (24.1)	0.143	27 (22.7)	29 (24.4)	0.76
Lung	37 (21.4)	45 (32.8)	0.023	31 (26.1)	34 (28.6)	0.663
Sinus	57 (32.9)	24 (17.5)	0.002	27 (22.7)	23 (19.3)	0.524
GC+IM	101 (58.4)	80 (58.4)	0.998	70 (58.8)	72 (60.5)	0.792

PSM: Propensity score matching; GC: glucocorticoid; IM: Immunosuppressant.

Supplementary Table S3. Clinical characteristics and treatment outcomes of IgG4-RD in pediatrics.

case	Age (year)	Sex (M/F)	Duration (month)	Organ manifestation	Allergy history	Serum IgG4 (mg/L)	IgG4-RD RI	treatment	outcomes
Case 1	9	F	36	Mikulicz' s disease lung disease sinusitis	Y	2300	12	Pred 20mg/d, MTX 5mg/w	Pred tapered and maintained in a low (5mg/d) dose of pred, MTX and MMF.
Case 2	10	M	36	Mikulicz' s disease lymphadenopathy	Y	2980	9	Pred 30mg, MTX 7.5mg/w	Pred tapered and maintained in a low (5mg/d) dose of pred and MTX.

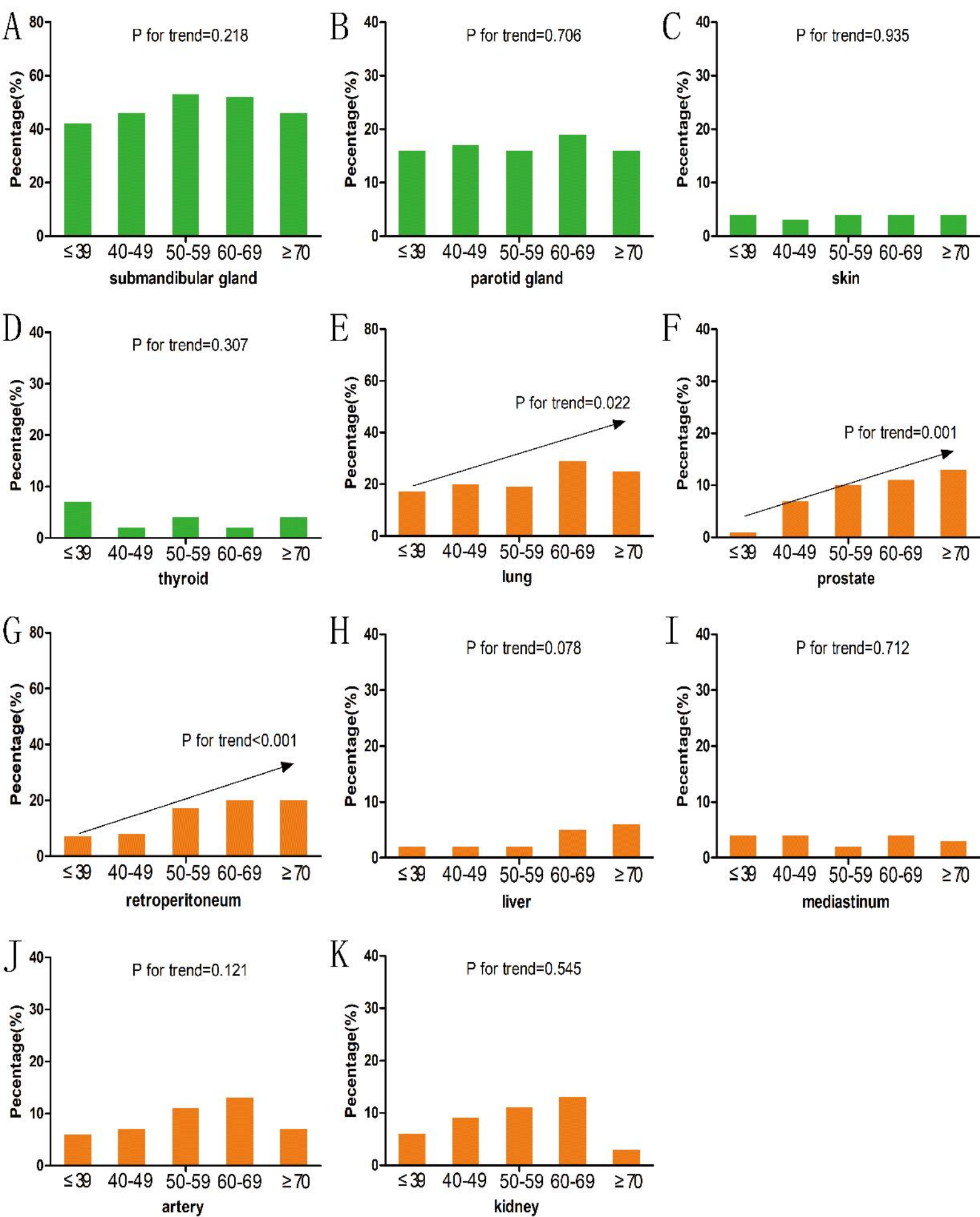
Case 3	14	M	4	AIP IgG4-SC lymphadenopathy	N	1620	12	Pred 20mg/d and UDCA (750mg/d)	Relapsed after pred tapering and required a low (5mg/d) maintenance dose of pred and UDCA.
Case 4	14	M	36	Mikulicz' s disease	Y	3170	3	Diprosan 1ml, Iguratimod Tablets	Maintained in AZA (50mg/d)
Case 5	14	F	36	Mikulicz' s disease	N	2880	3	N	Lost to follow up
Case 6	15	M	4	lymphadenopathy	Y	191	3	Pred 40mg/d	Relapsed after pred tapering and required a low (10mg/d) maintenance dose of pred, MTX and Iguratimod Tablets
Case 7	15	M	60	Mikulicz' s disease lymphadenopathy	Y	333	12	Pred 30mg/d MTX 10mg/w	Relapsed after pred tapering and required a low (2.5 or 5 mg/d) maintenance dose of pred, MTX and Iguratimod Tablets
Case 8	16	M	12	AIP IgG4-SC Hepatopathy Mikulicz' s disease	N	29700	21	MP 48mg/d, MMF 1.5g/d	MP taperd and maintained in a low dose of 8mg/d and added retaximab
Case 9	16	F	48	thyroiditis	N	2610	3	Euthyrox	Watchful waiting and Euthyrox
Case 10	17	M	4	AIP Mikulicz' s disease	N	1280	6	MP 80mg/d × 3d	Lost to follow up

M: male; F: female; Y: Yes; N: No; Mikulicz disease: IgG4-related orbital and submandibular disease; AIP: autoimmune pancreatitis; IgG4-SC: IgG4-related sclerosing cholangitis; Pred: prednisone; MTX: methotrexate; MMF: mycophenolate mofetil; UDCA: ursodeoxycholic acid; AZA: azathioprine; MP: methylprednisolone.

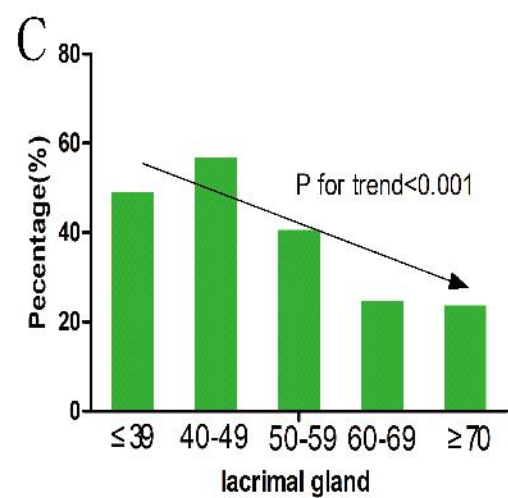
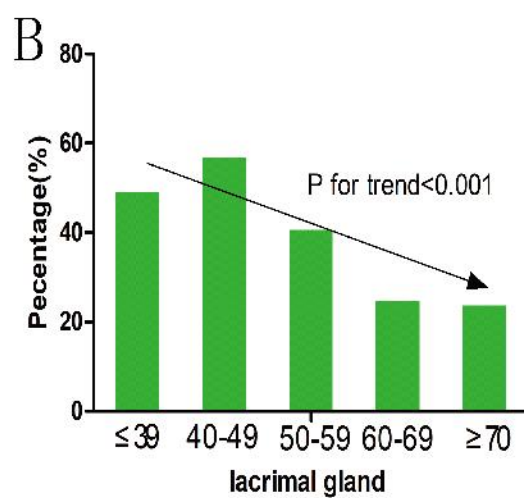
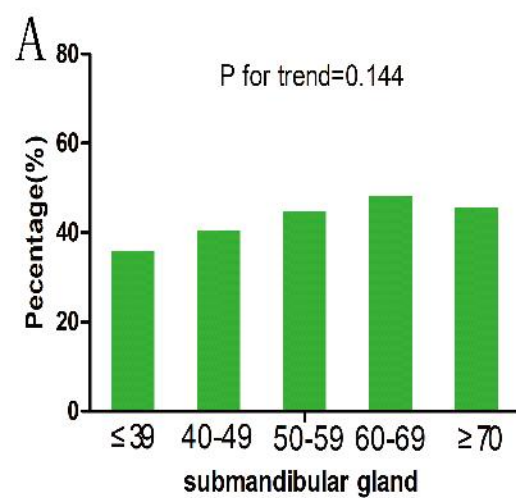
Supplementary figure legend

Supplementary Figure S1. Different organ involvement across age groups.

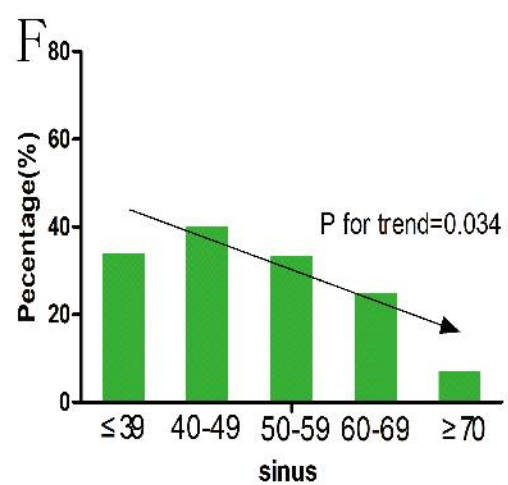
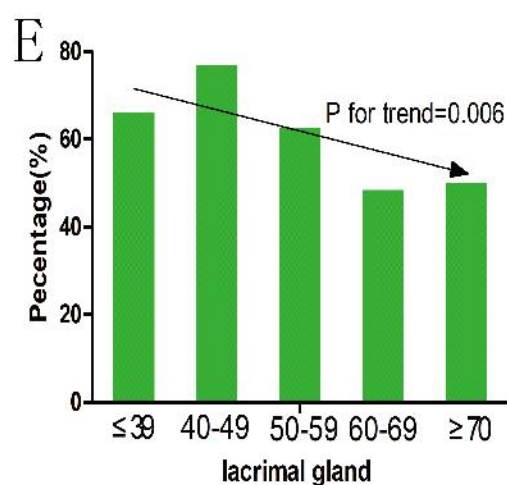
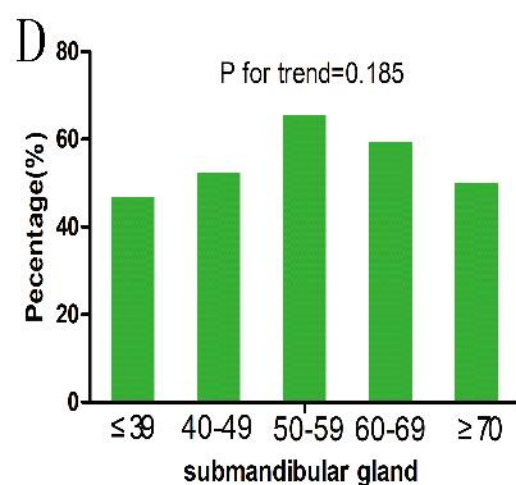
Supplementary Figure S2. Different organ involvement in male and female patients across age groups.



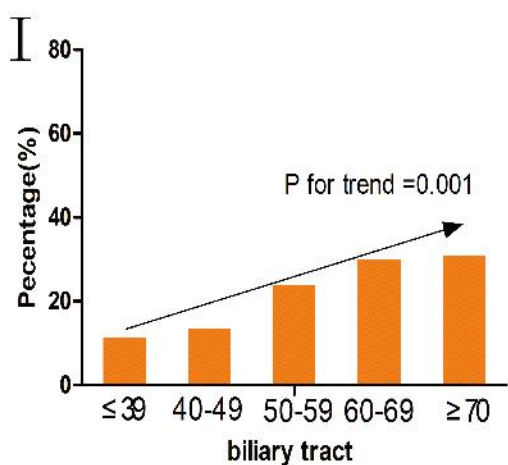
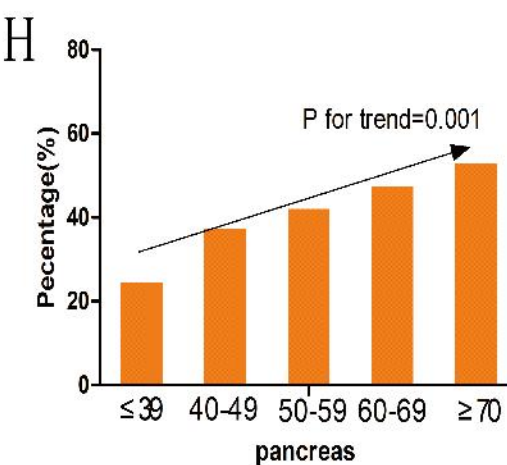
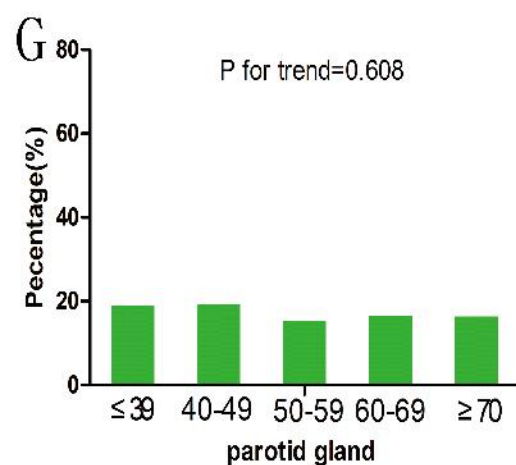
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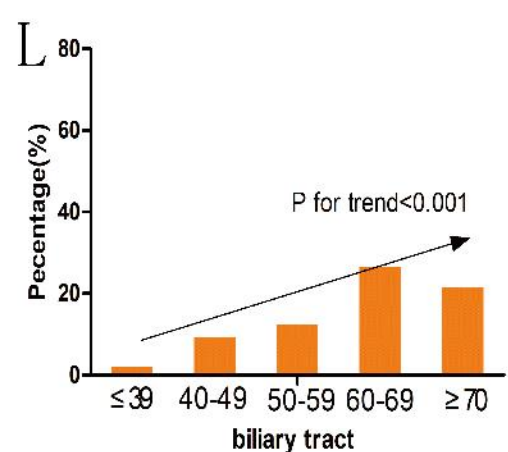
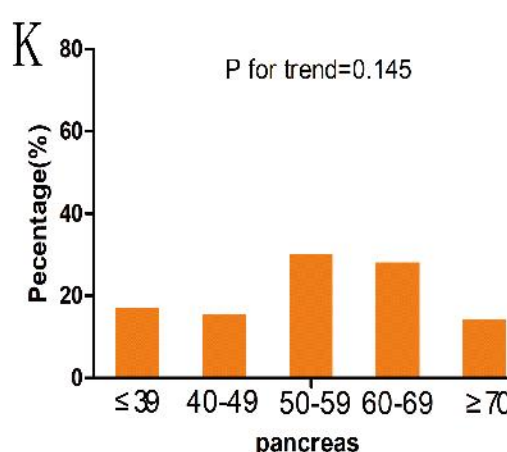
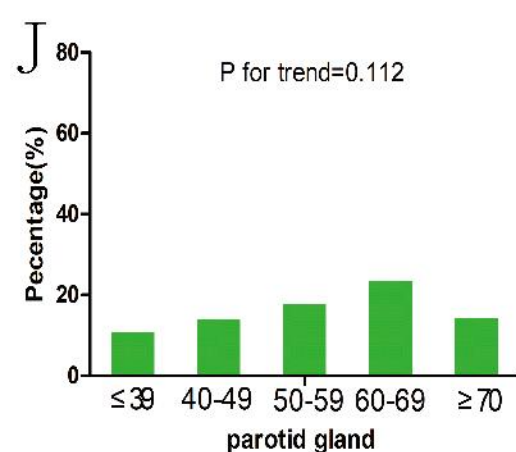
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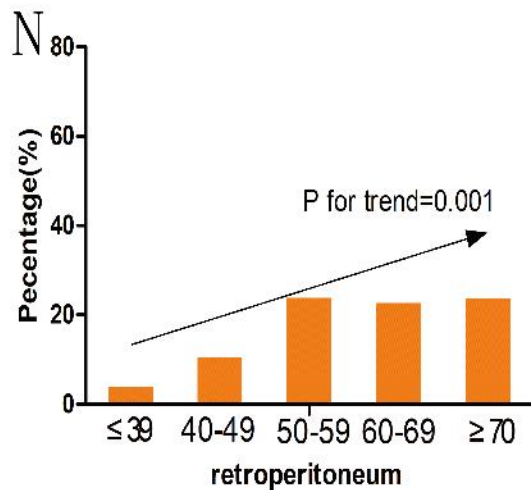
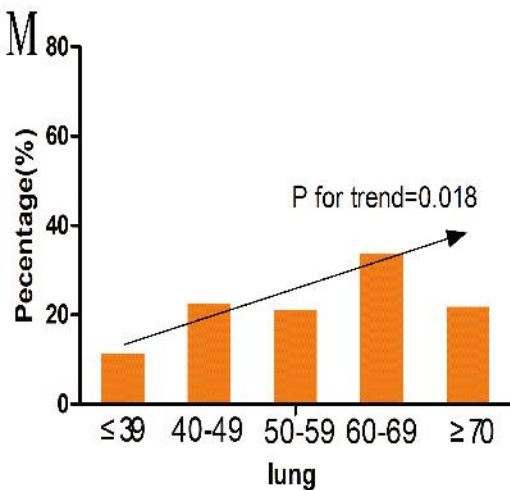
Male



Female



Male



Female

