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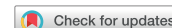


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ORIGINAL ARTICLE



Phenotyping of IgG4-related diseases based on affected organ pattern: A multicenter cohort study using cluster analysis

Takafumi Niwamoto^a, Tomohiro Handa^b , Shoko Matsui^c, Hiroshi Yamamoto^d, Hajime Yoshifuji^e, Hiroyasu Abe^f, Hisako Matsumoto^a, Yuzo Kodama^g, Tsutomu Chiba^h, Hiroshi Senoⁱ, Tsuneyo Mimori^e and Toyohiro Hirai^a

^aDepartment of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; ^bDepartment of Advanced Medicine for Respiratory Failure, Kyoto University, Kyoto, Japan; ^cHealth Administration Center, University of Toyama, Toyama, Japan; ^dFirst Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan; ^eDepartment of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; ^fDepartment of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto University, Kyoto, Japan; ^gDivision of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; ^hKansai Electric Power Hospital, Osaka, Japan; ⁱDepartment of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

ABSTRACT

Objectives: Immunoglobulin G4-related disease (IgG4-RD) is a systemic, multiorgan disease of unknown etiology. We aimed to classify IgG4-RD by a combination pattern of affected organs and identify the clinical features, including the comorbidities of each subgroup.

Methods: Patients diagnosed with IgG4-RD between April 1996 and June 2018 were enrolled from three institutes. Hierarchical cluster analysis was performed using six frequently affected organs (lacrimal gland and/or orbit, salivary gland, lung, pancreas, kidney, and retroperitoneum and/or aorta). Clinical features, such as comorbidities and outcomes, were compared between clusters.

Results: In total, 108 patients enrolled in this cohort could be stratified into five distinct subgroups: group 1, lung dominant group; group 2, retroperitoneal fibrosis and/or aortitis dominant group; group 3, salivary glands limited group; group 4, Mikulicz's disease dominant group; and group 5, autoimmune pancreatitis with systemic involvement group. There were significant between-group differences in sex (male dominant in group 1, 2, and 5), history of asthma and allergies on the respiratory tract (most frequent in group 5), and malignancy (most frequent in group 5).

Conclusion: IgG4-RD can be classified into subgroups according to the pattern of affected organs. Group 5 may have frequent complications with allergies and malignancies.

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Autoimmune pancreatitis; clinical phenotypes; cluster analysis; IgG4-related disease; Mikulicz disease

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, multiorgan disease characterized by infiltrating IgG4-positive plasma cells, fibrosis, and elevated serum IgG4 concentration [1]. Autoimmune pancreatitis (AIP) occurs predominantly in males, while the prevalence of IgG4-related lacrimal glands and salivary glanditis, also known as Mikulicz disease, in males versus females is approximately 1:1 [2–5]. It may suggest that patients with IgG4-RD have different demographics and clinical features, depending on the pattern of affected organs. It is also recognized that IgG4-RD is frequently complicated by allergic diseases [6] and malignancies [5]. The patterns and severity of affected organs and comorbidities, including allergies and malignancies, are important for selecting the appropriate treatment managements for IgG4-RD.

Cluster analysis is a method of classifying a set of objects into subgroups, where objects in the same groups are more

similar than those in other groups. In recent years, studies have reported that cluster analyses are used to classify sarcoidosis patients, according to the pattern of affected organs in order to clarify patient characteristics or to classify the patients with interstitial pneumonia into subgroups shown to be associated with prognosis [7,8]. In IgG4-RD, cluster analysis has also been performed based on age and blood marker [9] or patterns of affected organs [10]. Wallace et al. performed cluster analysis based on affected organs in 765 multinational IgG4-RD patients and classified them into four groups: (i) pancreato-hepatobiliary disease, (ii) retroperitoneal fibrosis (RPF) and/or aortitis, (iii) head and neck-limited disease, and (iv) classic Mikulicz's disease with systemic involvement. Female and Asians are more likely to develop head and neck-limited disease. Although the usefulness of cluster analysis based on affected organs in IgG4RD has been demonstrated, it remains unclear how many clusters are clinically meaningful and how those clusters are

associated with clinical features, such as malignant complications, treatment, and outcomes.

In this study, we performed hierarchical cluster analysis based on affected organs in Japanese patients with IgG4-RD and investigated the relationship between clinical features and outcomes.

Materials and methods

Study population

A total of 108 patients diagnosed with IgG4-RD between April 1996 and June 2018 at three Japanese hospitals (Toyama University Hospital, Shinshu University Hospital and Kyoto University Hospital) were enrolled. IgG4-RD diagnosis was made based on comprehensive diagnostic criteria and diagnostic criteria for IgG4-related respiratory disease, and only definite cases were included [11,12]. Clinical information was collected from the medical records retrospectively. This study was approved by the Institutional Review Board (IRB) of Toyama University Hospital (C28-121), Shinshu University Hospital (No. 3101), and Kyoto University (R0829). The IRB also specifically waived the requirement of patient consent.

Measurements

Hierarchical cluster analysis was performed based on the involvement of six frequently affected organs (lacrimal gland and/or orbit, salivary gland, lung [lung parenchyma, mediastinal lymph nodes, bronchus and pleura], pancreas, kidney, RPF and/or aorta) and clinical information was compared between groups. Clinical information included age at diagnosis of IgG4-RD, sex, complication of malignancy during post-diagnostic follow-up, follow-up duration, treatment details (usage of systemic corticosteroids (CSs), i.e. initial dose, relapse rate and dose during treatment, and maintenance dose), serum markers (peripheral blood white blood cell count, eosinophil percentage, serum C-reactive protein, IgG, IgG4, IgE, soluble interleukin-2 receptor (sIL-2R), and outcomes. Airway diseases, mostly with allergic components (rhinitis and/or sinusitis and/or bronchial asthma) were also assessed and defined as respiratory allergies in this study. A respiratory medicine specialist diagnosed asthma at each hospital. A physician at each hospital diagnosed rhinitis and sinusitis based on symptoms and sinus computed tomography. According to previous reports [13,14], each patient's outcomes were assessed according to imaging evaluations, patient symptoms, and physical findings. They were categorized into three grades: improved, worsened, or no change. The assessment was performed at each institute by S. M., H. Y., and T. N.

Statistical analysis

The significance of differences in continuous variables between groups was determined using the Kruskal–Wallis test, and the significance of differences in frequencies was

analyzed with the Fisher's exact test. For continuous covariates, summary statistics were reported as median and interquartile range (IQR). For categorical variables, summary statistics were reported as frequencies and percentages. Six representative affected organs (lacrimal gland and/or orbit, salivary gland, lung, pancreas, kidney, RPF and/or aorta) were used as categorical variables to identify groups.

We performed a hierarchical cluster analysis based on the affected organs. To determine the number of clusters, we compared clinical features of three to six group models.

p Values <.05 were considered statistically significant. Statistical analyses were performed using JMP Pro 13.2.1 and SAS Release 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics, treatment, and outcomes

Of the 108 cases, the median age at IgG4-RD diagnosis was 65; 79 (73%) were males. Thirty-eight cases (35%) had bronchial asthma and 80 (74%) cases had respiratory allergies. Twelve cases (11%) had complication of malignancy after IgG4-RD diagnosis (colon cancer and lung cancer: three cases each, malignant lymphoma: two cases, renal cancer, urothelial cancer, laryngeal cancer and tongue cancer: one case each). Regarding the frequency of affected organs, 33 cases (31%) had lacrimal gland and/or orbital lesion, 73 cases (68%) had a salivary gland lesion, 49 cases (45%) had a lung lesion, 35 cases (32%) had a pancreas lesion (AIP), 16 cases (15%) had a kidney lesion, and 24 cases (22%) had RPF and/or aortitis. CSs were administered to 74 cases, of which 21 (28%) cases had relapsed during treatment. The median and IQR dose of CSs for initial treatment was 35 (30–40) mg/day, dose at relapse was 2 (0–8) mg/day, and the maintenance dose was 5 (3–8) mg/day. Regarding outcomes, 86 cases (84%) improved, two cases (2%) worsened, and 14 cases (14%) were unchanged (Table 1).

Determination of the groups and frequency of affected organs in each group

We investigated the optimal number of clusters in this study population by comparing different models with three to six clusters. First, the four groups model showed a similar pattern to the previous study [10] containing an RPF and/or aorta dominant group, salivary glands limited group, Mikulicz disease dominant group, and AIP with systemic involvement group (Supplementary Table 1). Although in this analysis, group 1 (Supplementary Table 1) was considered to correspond to the “RPF and/or aorta-dominant group” in the previous study [10], most cases here involved the lung (63%), and in only 43% of patients did it involve the RPF and/or aorta, which suggests that this group did not really represent RPF and/or aorta-dominant group”. Next, patients were divided into five clusters. The RPF and/or aorta dominant group in four cluster analysis were subdivided into two distinct groups of lung dominant (85% of

the patients had lung lesions) and RPF and/or aorta dominant ones (100% of the patients had RPF and/or aorta lesions) (Supplementary Figure 1). Further division into six groups generated no distinct subgroup. Finally, division into three clusters led to combining the RPF and/or aorta with the salivary glands groups in four cluster analyses, which dampened the groups' characteristics. Therefore, five was considered to be the most appropriate number of clustering, and clinical features were compared among the five groups.

Table 1. Patient characteristics, treatment, and outcomes.

Total number of the subjects	108
Age, Median (IQR)	65 (57–74)
Male gender, <i>n</i> (%)	79 (73%)
Bronchial asthma, <i>n</i> (%)	38 (35%)
Respiratory allergies, <i>n</i> (%)	80 (74%)
Malignancy, <i>n</i> (%) ^a	12 (11%)
Organ involvement, <i>n</i> (%)	
Lacrimal gland/orbit	33 (31%)
Salivary gland	73 (68%)
Lung	49 (45%)
Pancreas	35 (32%)
Kidney	16 (15%)
RPF/periarterial lesion	24 (22%)
Follow-up duration, M, Median (IQR)	74 (34–107)
Body weight, kg, Median (IQR)	59.1 (52.2–68.1)
CSs administration, <i>n</i> (%)	74 (69%)
Relapse during treatment, <i>n</i> (%)	21 (28%)
Initial dose of CSs, mg/day, Median (IQR)	35 (30–40)
CSs dose at relapse, mg/day, Median (IQR)	2 (0–8)
Maintenance dose of CSs, mg/day, Median (IQR)	5 (3–8)
Outcomes, <i>n</i> (%)	
Improved	86 (84%)
Worsened	2 (2%)
No change	14 (14%)

Data are expressed as median (IQR) or number (%).

RPF: retroperitoneal fibrosis; CSs: corticosteroids; IQR: interquartile range.

^aColon cancer and lung cancer: three cases each, malignant lymphoma: two cases, renal cancer, urothelial cancer, laryngeal cancer and tongue cancer: one case each.

Cases with lacrimal gland and/or orbital lesions were classified into group 4 or 5; cases with lung lesions were classified into groups 1, 4, or 5; and cases with AIP was classified into groups 2 or 5 (Table 2).

Comparison of clinical characteristics, blood markers, and treatment among clusters

The comparisons of patient characteristics and comorbidities among different clusters are shown in Table 3. There were significant differences in sex and complications from bronchial asthma, respiratory allergies, and malignancies. Males were predominant in groups 1, 2, and 5, while gender distributions were equal in groups 3 and 4. Malignancies were the most frequent in group 5. Bronchial asthma and allergies were frequent in groups 4 and 5. Three cases with AIP classified into group 2 had no complications of cancer or allergies. The number of affected organs was significantly different among the groups, and highest in group 5 (Table 2).

There was no significant differences in laboratory data, but serum IgG4 tended to be higher in group 5 than in the others (Table 4).

Treatment details are shown in Table 5. There were no significant treatment differences between groups. When target organs for the treatment were analyzed in each group, representative organs were the most or the second-most frequent target in groups 2–5, while in group 1, the kidneys and RPFs, but not the lungs, were the frequent treatment targets (Supplementary Table 2). Immunosuppressants were used in 6 out of 108 cases. We observed no significant difference in the frequency of immunosuppressant use (Table 5).

Table 2. Frequency of affected organs in each group.

	Group 1 Lung dominant	Group 2 RPF/Ao dominant	Group 3 Salivary glands limited	Group 4 Mikulicz dominant	Group 5 AIP with systemic	<i>p</i> Value
Total number	26	9	22	18	33	
Lacrimal gland/orbit, <i>n</i> (%)	0 (0%)	0 (0%)	0 (0%)	18 (100%)	15 (45%)	<.001
Salivary gland, <i>n</i> (%)	14 (54%)	1 (11%)	21 (95%)	15 (83%)	22 (67%)	<.001
Lung, <i>n</i> (%)	22 (85%)	0 (0%)	0 (0%)	7 (39%)	20 (61%)	<.001
Pancreas, <i>n</i> (%)	0 (0%)	3 (33%)	0 (0%)	0 (0%)	32 (97%)	<.001
Kidney, <i>n</i> (%)	3 (12%)	0 (0%)	4 (18%)	0 (0%)	9 (27%)	.058
RPF/periarterial lesion, <i>n</i> (%)	6 (23%)	9 (100%)	0 (0%)	4 (22%)	5 (15%)	<.001
Affected organ, <i>n</i> ; Median (IQR)	2 (1–2.25)	1 (1–2)	1 (1–1)	2 (2–3)	3 (2–4)	<.001

RPF: retroperitoneal fibrosis; AIP: autoimmune pancreatitis; IQR: interquartile range.

Table 3. Comparisons of patient characteristics and comorbidities among groups.

	Group 1 Lung dominant	Group 2 RPF/Ao dominant	Group 3 Salivary glands limited	Group 4 Mikulicz dominant	Group 5 AIP with systemic	<i>p</i> Value
Total number	26	9	22	18	33	
Age, year, Median (IQR)	70 (64–77)	65 (61–70)	67 (57–74)	59 (48–70)	63 (56–75)	.070
Male gender, <i>n</i> (%)	22 (84%)	7 (78%)	12 (55%)	10 (56%)	28 (85%)	.029
Bronchial asthma, <i>n</i> (%)	6 (23%)	1 (11%)	4 (18%)	8 (44%)	19 (58%)	.006
Respiratory allergies, <i>n</i> (%)	15 (58%)	3 (33%)	15 (68%)	15 (83%)	32 (97%)	<.001
Malignancy, <i>n</i> (%)	3 (12%)	1 (11%)	0 (0%)	0 (0%)	8 (36%)	.023

Data are expressed as median (IQR) or number (%).

RPF: retroperitoneal fibrosis; AIP: autoimmune pancreatitis; IQR: interquartile range.

Table 4. Comparison of blood markers among groups.

	All	Group 1 Lung dominant	Group 2 RPF/Ao dominant	Group 3 Salivary glands limited	Group 4 Mikulicz dominant	Group 5 AIP with systemic	<i>p</i> Value
WBC/ μ L	6110 (5003–7223)	5740 (4728–6928)	6130 (5055–6830)	5635 (4903–7373)	6670 (5280–8950)	6360 (5600–7805)	.250
Eo %	5.0 (2.8–9.0)	4.2 (2.0–7.1)	4.0 (2.4–11.0)	5.3 (2.0–10.4)	4.0 (2.78–7.4)	8.5 (3.2–10.3)	.290
CRP mg/dL	0.1 (0.1–0.4)	0.3 (0.1–0.7)	0.1 (0.0–0.3)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.2 (0.0–0.4)	.496
IgG mg/dL	2180 (1727–3112)	2437 (1780–3596)	1946 (1631–2466)	1966 (1564–3125)	2026 (1558–2391)	2245 (1802–3490)	.197
IgG4 mg/dL	613 (322–1160)	441 (239–882)	424 (281–735)	560 (310–819)	578 (455–1213)	896 (509–1580)	.063
IgE IU/mL	482 (240–1100)	674 (323–1392)	439 (160–1139)	381 (180–1181)	544 (191–1068)	400 (242–986)	.500
sIL-2R U/mL	860 (533–1334)	957 (569–1447)	995 (568–1540)	540 (382–1071)	578 (439–785)	996 (609–1350)	.080

Data are expressed as median (IQR).

RPF: retroperitoneal fibrosis; AIP: autoimmune pancreatitis; WBC: white blood cell, Eo: eosinophil percentage; CRP: C-reactive protein; IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; sIL-2R: soluble interleukin-2 receptor; IQR: interquartile range.

Table 5. Comparison of treatment and outcomes among groups.

	Group 1 Lung dominant	Group 2 RPF/Ao dominant	Group 3 Salivary glands limited	Group 4 Mikulicz dominant	Group 5 AIP with systemic	<i>p</i> Value
Total	26	9	22	18	33	
Follow-up duration, M; Median (IQR)	59 (18–95)	90 (59–106)	61 (20–84)	75 (35–117)	90 (47–125)	.080
Body weight, kg; Median (IQR)	65.6 (55.0–73.8)	59.0 (45.0–71.6)	58.5 (51.1–67.1)	59.8 (51.7–67.0)	55.6 (50.0–61.5)	.171
CSs administration, <i>n</i> (%)	17 (65%)	8 (89%)	11(50%)	13 (72%)	25(76%)	.381
Relapse during treatment, <i>n</i> (%)	3 (17%)	2 (22%)	2 (9%)	8 (44%)	6 (18%)	.121
Initial dose of CSs, mg/day, Median (IQR)	30 (22.5–36)	35 (30–40)	35 (30–40)	30 (30–33.5)	35 (30–40)	.267
CSs dose at relapse, mg/day, Median (IQR)	1 (0–15)	1 (0–2)	4 (4–4)	5.8 (0.5–7.9)	2 (0–17.5)	.852
Maintenance dose of CSs, mg/day, Median (IQR)	6.3 (4–10)	5 (2.3–7.5)	6 (5–8)	5 (2–10)	5 (2.5–5)	.271
Immunosuppressant use, <i>n</i> (%) [*]	0 (0%)	1 (11%)	1 (5%)	3 (17%)	1 (3%)	.150
Outcomes, <i>n</i> (%)						.968
Improved	21 (88%)	8 (89%)	15 (75%)	16 (89%)	26 (84%)	
Worsened	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (3%)	
No change	3 (13%)	1 (11%)	4 (20%)	2 (11%)	4 (13%)	

^{*}One case of azathioprine use in groups 2 and 3; one case of mizoribine, salazosulfapyridine, and azathioprine use in group 4; and one case of tacrolimus use in group 5.

Data are expressed as median (IQR) or number (%).

RPF: retroperitoneal fibrosis; AIP: autoimmune pancreatitis; CSs: corticosteroids; IQR: interquartile range.

Discussion

In this study, we performed cluster analysis of IgG4-RDs based on affected organs and found that they could be classified into five distinct groups. In addition to the four groups in the previous study, the lung dominant group was extracted. The number of women was relatively high in the salivary gland limited group and the Mikulicz dominant group, and the frequency of allergies was high in the Mikulicz dominant group and the AIP dominant group. The AIP dominant group showed the highest frequency of malignancies after IgG4-RD diagnosis. There was no significant difference in the frequency of the need for steroid treatment or the clinical outcome.

There were significant differences in sex, coexistence in bronchial asthma, respiratory allergies, and malignancies between groups (Table 3). In contrast to other groups, gender frequencies were almost equal in groups 3 and 4. This reflects the fact that male predominance, generally seen in IgG4-RD, was not clear in patients with lacrimal and salivary gland lesions [2,5].

Malignancies were most commonly observed in group 5, and no malignancy was seen in groups 3 or 4. To the best of our knowledge, this is the first study to show association between specific disease phenotype and malignancies in IgG4-RD. The cancer incidence rate with IgG4-RD reported

in the previous study is 9.5–13.9% (median observation period: 2.8–6.1 years) [15–19], while the cancer incidence rate with group 5 is 36% (median observation period of this cohort: 6.2 years, median observation period of group 5: 7.5 years), which is high even with the difference in observation period. In general, when malignancy and autoimmune or inflammatory disease are associated, two mechanisms can be considered [20]. One is that persistent inflammation due to autoimmune disease induces malignancies. In this scenario, carcinogenesis is induced on the basis of activity and duration of the autoimmune disease [21]. Another mechanism is that malignancies cause autoimmune diseases as paraneoplastic syndrome, as in dermatomyositis associated with malignancy [22]; in this case, it is expected that malignancy precedes or is diagnosed at the same time as autoimmune diseases. Otherwise, the risk of the malignancy may be most frequent within 1 year after the diagnosis of the autoimmune disease, and the clinical features of the autoimmune disease is improved after the treatment of the malignant tumor. In this cohort, 4 out of 12 cases developed malignancies within 1 year after the diagnosis of IgG4-RD and 5 cases developed malignancies >3 years after the diagnosis of IgG4-RD. In group 5, three out of eight cases developed cancer within 1 year and two developed cancer after 3 years or more. Therefore, it remains unclear what

mechanism was involved in the development of malignancies in group 5. Regarding AIP complications, such as allergies and malignancies, Shiokawa et al. reported that about half the AIP patients were positive for laminin 511-E8 antibody and antibody-negative patients have high incidences of allergies and malignancies [23]. Although the measurement for laminin 511-E8 antibody has not been conducted in this cohort, the common condition behind group 5 may be related to the frequency of complications.

Complications of bronchial asthma and respiratory allergy were common in groups 4 and 5. Regarding the definition of allergic disease, atopy was not included in this study's analysis because it was reported that there is no significant difference in morbidity between IgG4-RD patients and healthy people [6]. Previous report has suggested that allergies are associated with head and neck lesions and lung lesions [24]. Although the reason why allergies are associated with head and neck lesions and lung lesions is unknown, it might be because of the fact that the eye and airways are exposed to external environments and common mechanisms may be involved in the development of allergy and IgG4-related disease of these organs. In this cohort, AIPs also had correlation with allergies; this result is different from that of a previous report [24]. This may be because of the common autoantibodies, such as laminin 511-E8 antibody, involved in the development of pancreatic lesions and allergies; however, further studies are needed.

We speculated whether allergies and malignancies are associated with group 5 or with AIP itself. The absence of allergies and malignancies in three cases with AIP classified into group 2 may suggest that group 5, but not AIP, is associated with these complications.

Regarding blood markers, despite differences in the frequency of allergies between groups, serum Eo and IgE showed no significant difference among the groups (Table 4). In IgG4RD, it is hypothesized that allergic mechanisms are involved in the secretion of Th2 cytokines, followed by activation of eosinophils and B cells, and increase in IgE production [25]. However, Della-Torre et al. reported that a subset of nonatopic patients had elevated peripheral blood Eo and IgE concentrations, and speculated that Eo and IgE elevations are not caused by the background allergic disease, but by the inherent inflammatory characteristics of the IgG4-RD immune response itself [6]. This is consistent with the result of the present study where an increase in Eo and IgE levels did not correlate with the presence or absence of background allergic diseases.

We observed no significant difference among the groups for the IgG4 and sIL-2R values in this cohort, but the values of group 5 tended to be high. These values have been reported to correlate with the number of affected organs of IgG4-RD [26]. Therefore, increased level of blood IgG4 and sIL-2R in group 5 was considered to reflect high number of affected organs in this group (Table 3). There was no significant difference in treatment between the clusters in this study, but in Group 4, the relapse numbers were slightly higher comparatively, and more abundant in orbital lesions compared to other affected organs. Furthermore, the use of

immunosuppressants tended to be higher in Group 4 (Table 5). Therefore, more intense or prolonged treatment might be necessary in Group 4 than in other groups.

In this cohort, despite the difference in the frequency of malignancies, there was no significant difference in the prognosis between the groups (Table 5). This may be because cancer screening was regularly performed and the early detection of cancer was made. Although long term prognosis of IgG4-RD remains unclear, cancer is a life-threatening disease which may affect prognosis in IgG4-RD. Therefore, the identification of a group with a high risk of cancer is clinically important.

Analysis of the treatment target organs showed that the lung was not the main target of treatment in group 1, in which lung lesions were most frequently noted (Supplementary Table 2). This was in contrast to other groups in which the organ most frequently noted with lesions was the main target of treatment. This may be because many of the IgG4-related respiratory diseases do not exhibit respiratory symptoms or hypoxemia and often accompany other organ lesions, making it rare for the lung itself to be a therapeutic target [27]. Further studies are also needed to determine whether there is a difference in the disease characteristics of the same organ (e.g. lung lesion) among different clusters.

There are some limitations in this study. First, this study comprised small number of patients and all patients were limited to Japanese. However, this makes it possible to compare between clusters on the same ethnic background. Second, because the responsible physicians at the three institutions are respiratory physicians, they may have been biased towards selecting the affected organs. However, all the facilities are general hospitals with their own specialized organ lesion treatment departments. The frequency of lung lesions in this cohort was 45%, which was slightly higher compared with than those of previous reports (17.6% [28], 23.4% [29]). However, previous reports indicated only bilateral parenchymal lesions as lung lesions, and Matsui reported [30] that the inclusion of mediastinal and bronchial lesions, as in this cohort, will be more frequent. Therefore, we reason that this study population was not strongly biased. Third, regarding treatment, there is no standardizes protocol for adjusting steroids or adding immunosuppressive drugs. Therefore, a larger-scale study, with a standard treatment protocol, should be conducted. Fourth, this study is a retrospective study and has some data deficiencies. Fifth, each organ lesion lacks a detailed description (e.g. respiratory function and detailed imaging findings in lung lesions), and an inter-group comparison between groups was impossible. Despite these limitations, this study suggested that IgG4-RD can be classified into distinct subgroups on the basis of the pattern of affected organs and each subgroup may have characteristic clinical features.

In conclusion, we classified IgG4-RD into five groups according to the affected organs. Although the appropriate number of clusters may differ between cohorts, IgG4-RDs can be classified by the pattern of affected organs. Clinical

characteristics were found in each group, suggesting the usefulness of clustering in clinical practice and IgG4-RD research.

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Conflict of interest

None.

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ORCID

Tomohiro Handa  <http://orcid.org/0000-0002-3378-6412>

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Supplementary Table 2: Target organs of treatment

	Group 1	Group 2	Group 3	Group 4	Group 5	<i>p</i> value
	Lung dominant	RPF/Ao dominant	Salivary glands limited	Mikulicz dominant	AIP with systemic	
Lacrimal gland	0/0	0/0	0/0	9/18	4/15	<0.001
/orbit, n (%)	(-%)	(-%)	(-%)	(50%)	(27%)	
Salivary gland, n (%)	5/14 (36%)	0/1 (0%)	11/21 (52%)	3/15 (20%)	6/22 (27%)	0.021
Lung, n (%)	5/22 (23%)	0/0 (-%)	0/0 (-%)	3/7 (43%)	3/20 (15%)	0.147
Pancreas, n (%)	0/0 (-%)	1/3 (33%)	0/0 (-%)	0/0 (-%)	15/32 (47%)	<0.001
Kidney, n (%)	3/3 (100%)	0/0 (-%)	2/4 (50%)	0/0 (-%)	5/9 (56%)	0.460
RPF/periarterial lesion, n (%)	4/6 (67%)	7/9 (78%)	0/0 (-%)	2/4 (50%)	2/5 (40%)	<0.001

No. of treatment target / No. of organ involvement. Abbreviations: RPF Retroperitoneal fibrosis, AIP Autoimmune pancreatitis

Supplementary Table 1: Frequency of affected organs in each group (divided into four groups)

	All	Group 1	Group 2	Group 3	Group 4	<i>p</i> value
		RPF/Ao dominant	Salivary glands limited	Mikulicz dominant	AIP with systemic	
Total number	108	35	22	18	33	
Lacrimal gland /orbit, n (%)	33 (31%)	0 (0%)	0 (0%)	18 (100%)	15 (45%)	<0.001
Salivary gland, n (%)	73 (68%)	15 (43%)	21 (95%)	15 (83%)	22 (67%)	<0.001
Lung, n (%)	49 (45%)	22 (63%)	0 (0%)	7 (39%)	20 (61%)	<0.001
Pancreas, n (%)	35 (32%)	3 (9%)	0 (0%)	0 (0%)	32 (97%)	<0.001
Kidney, n (%)	16 (15%)	3 (9%)	4 (18%)	0 (0%)	9 (27%)	0.058
RPF/periarterial lesion, n (%)	24 (22%)	15 (43%)	0 (0%)	4 (22%)	5 (15%)	<0.001

Abbreviations: RPF: Retroperitoneal fibrosis, AIP: Autoimmune pancreatitis

Supplementary figure 1. Comparison of models with three to six clusters.

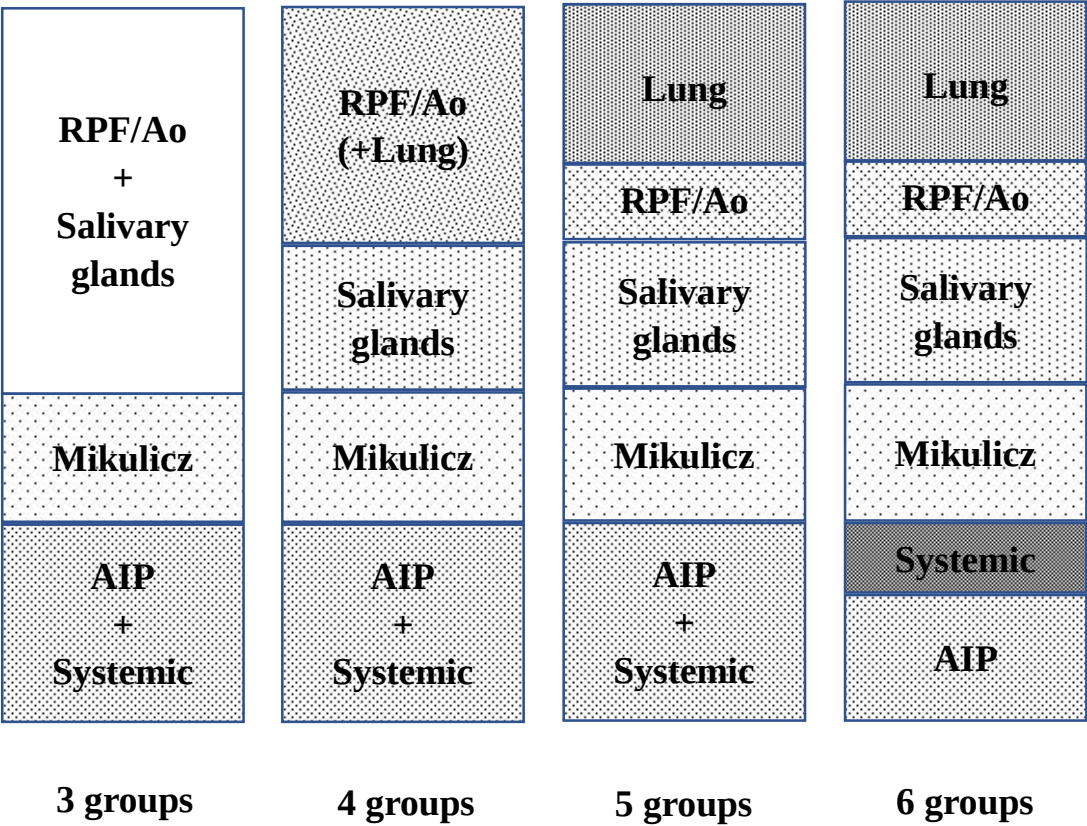


Figure legends: Four group models showed patterns similar to those noted in the previous study containing an RPF and/or aorta dominant group, salivary glands limited group, Mikulicz disease dominant group, and AIP with systemic involvement group. In the model with five clusters, the RPF and/or aorta dominant group in four cluster model were subdivided into two distinct groups of lung dominant and RPF and/or aorta dominant ones. Further division into six clusters generated no clinically meaningful subgroup.