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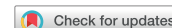


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ORIGINAL ARTICLE



Serum soluble interleukin-2 receptor as a biomarker in immunoglobulin G4-related disease

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ABSTRACT

Objectives: Serum soluble interleukin-2 (IL-2) receptor (sIL-2R) might reflect disease activity in immunoglobulin G4-related disease (IgG4-RD). We aimed to elucidate the clinical significance of blood markers, including sIL-2R, in patients with IgG4-RD.

Methods: We enrolled 59 patients with IgG4-RD and investigated the association between blood markers (white blood cells, C-reactive protein, sIL-2R, IgG, IgG4, IgE, total hemolytic complement), and clinical indices.

Results: At baseline, serum sIL-2R ($R_s = 0.532$, $p < .001$) and IgG4 ($R_s = 0.545$, $p < .001$) levels showed significant correlation to the number of organs involved. During follow-up period (median, 70 months; range, 7–195 months), 40 patients were treated with corticosteroids. Receiver operating characteristic (ROC) analysis showed that baseline sIL-2R levels most accurately predicted patients requiring glucocorticoid treatment (area under the ROC curve, 0.807). Among the 46 patients who improved, sIL-2R and IgG4 levels decreased in 42 and 41 patients, respectively. Among them, serum sIL-2R levels decreased to a normal range in 42 patients (91%), whereas IgG4 levels normalized in 19 (41%).

Conclusion: The serum sIL-2R level is a potential biomarker for IgG4-RD that may reflect the number of involved organs and may predict patients requiring glucocorticoid treatment.

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KEYWORDS

Biomarker; IgG4-related disease; soluble IL-2 receptor

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disease that can affect any organ and is histologically characterized by the infiltration of IgG4-positive lymphoplasmacytic cells [1,2]. Serum IgG4 concentrations are elevated in majority of the patients with IgG4-RD [1], but this elevation is not fully sensitive or specific for the diagnosis of IgG4-RD [2]. Although serum IgG4 generally decreases in response to systemic treatment [3], persistent elevation of serum IgG4 is not rare in patients with disease remission [4]. To date, there is no established blood marker for the diagnosis of or for disease activity evaluation in IgG4-RD.

Interleukin 2 (IL-2) receptor is expressed on T-cells rapidly after their activation and exerts its function of inducing T-cell proliferation in an autocrine and paracrine manner. Soluble IL-2 receptor (sIL-2R) is the soluble form of IL-2 receptor, and it is released from the activated T-cells [5]. Elevation of sIL-2R concentrations in several systemic

inflammatory diseases [6–8] and its reduction after corticosteroid therapy in autoimmune pancreatitis [9] suggest that sIL-2R may be a useful biomarker in IgG4-RD [10]. 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography has been reported to be useful for the detection of organ involvement and assessment of disease activity in patients with IgG4-RD [10–12]. We previously reported that total lesion glycolysis, which reflects global metabolic disease activity [13], had a significant positive correlation with serum sIL-2R, but not with serum IgG4 in IgG4-RD [10]. This study aimed to investigate the clinical utility of blood biomarkers including sIL-2R in patients with IgG4-RD.

Materials and methods

Study population

This retrospective study included 59 patients diagnosed with IgG4-RD at Toyama University Hospital, Shinshu University

Hospital, and Kyoto University Hospital, from 2002 to 2016. White blood cells, serum C-reactive protein (CRP), sIL-2R, IgG, IgG4, IgE, and total hemolytic complement (CH50) were measured at the time of diagnosis. The diagnoses were based on the comprehensive diagnostic criteria for IgG4-RD published in 2011 [14], and only definite cases were included. 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 consent.

Laboratory data

White blood cell counts, serum CRP, sIL-2R, IgG, and IgG4 were measured in all patients at the time of diagnosis. Serum sIL-2R was measured using enzyme immunoassay (normal range 122–496 U/ml), or chemiluminescence enzyme immunoassay (normal range 145–519 U/ml). Serum IgG4 was measured using immunonephelometry. Based on the comprehensive diagnostic criteria [14], a cut-off value of 135 mg/dl was used for IgG4 to assess elevation and normalization. Serum IgE and CH50 levels were also recorded when available. The last visit was defined as the last time when both serum sIL-2R and IgG4 were measured. Changes in blood markers from the diagnosis to the last visit were assessed as follows: 10% or more increase: “increased,” 10% or more decrease: “decreased,” and others: “no change.”

Assessment of disease activity course

The global disease activity course for each patient was assessed according to imaging evaluations, patient symptoms, and physical findings, in reference to previous reports [3,10,15]. The activity at the time of diagnosis was compared with that at the last visit. Images were evaluated on the basis of changes in the size of major lesions (those with the largest diameter, associated with symptoms or functional impairment). In reference to the response evaluation criteria in solid tumors [16], at least a 30% decrease in the largest lesion diameter was judged as improved, and at least a 20% increase was judged to be worsened. In combination with changes in objective symptoms and physical findings (e.g. exophthalmos, submandibular swelling), global disease activity course was categorized into the following three grades:

Improved: improvement either in images, objective symptoms, or physical findings, and no worsening in any of these.

Worsened: development of new lesion or worsening either in images, objective symptoms, or physical findings.

No change: not meeting criteria for “improved” or “worsened”.

The assessment was performed at each institute by S. M., H. Y., and T. H.

Data analyses

To evaluate the clinical utility of the blood markers, we assessed the correlation between blood markers and the number of affected organs at the time of diagnosis, the association between blood markers at diagnosis and use of glucocorticoid during the follow-up period, and the correlation between disease activity course and changes in blood markers.

Immunostaining

The lymph node and submaxillary gland tissue specimens obtained from two patients with IgG4-RD were fixed in 10% formaldehyde and embedded in paraffin. Serial 5-mm-thick sections were cut from the blocks of paraffin-embedded tissues, and the sections were immunohistochemically stained using an automated Bond Max stainer (Leica Biosystems; Wetzlar, Germany). The following primary antibodies were used: CD25 (4C9; 1:20; Novocastra) and FOXP3 (236A/E7; 1:100; Abcam, Cambridge, MA).

Statistical analysis

The statistical analyses were performed using JMP, version 10.0 (SAS Institute Inc., Cary, NC). Continuous data are shown as median and interquartile range (IQR). The Spearman rank correlation coefficient was used to analyze the correlations between blood markers and the number of affected organs. Comparison between groups was made using Fisher’s exact probability test or Wilcoxon rank sum test. A receiver operating characteristic (ROC) analysis of biomarkers was performed to determine the threshold for predicting patients that required glucocorticoid treatment during follow up. A p value of $<.05$ was considered statistically significant.

Results

Characteristics of the patients

The characteristics of the study subjects are shown in Table 1. The median age was 65 years old, and 71% of patients were male. Thirty-four patients (58%) had a history of allergies, and 44 (75%) were symptomatic. A median of three organs were affected. The most frequently affected organs were the mediastinal lymph nodes (81%), followed by the salivary glands (64%), and lungs (53%).

Correlation between blood markers and number of affected organs

Blood marker values at diagnosis and their correlation with the number of affected organs are shown in Table 2. Serum sIL-2R ($R_s = 0.532$, $p < .001$), IgG4 ($R_s = 0.545$, $p < .001$), and IgG ($R_s = 0.435$, $p < .001$) had significant correlations with the number of affected organs (Figure 1), while other markers did not.

Clinical course of the patients

During the follow up period (median 70 months, range 7–195 months), 40 patients underwent glucocorticoid treatment, and their median (interquartile) dose was 35

Table 1. Patient characteristics.

Number of patients	59
Age at diagnosis	65 (57–71)
Male gender	42 (71%)
History of allergies (rhinitis, bronchial asthma)	34 (58%)
Symptomatic	44 (75%)
Number of affected organs	3 (2–5)
Affected organs	
Mediastinal lymph nodes ^a	48 (81%)
Salivary gland	38 (64%)
Lung	31 (53%)
Pancreas	26 (44%)
Lacrimal gland	21 (36%)
Kidney	15 (25%)
Retroperitoneum	13 (22%)
Prostate	11 (26% of males)
Sinus	9 (15%)
Sclerosing cholangitis	2 (3%)
Others ^b	9 (15%)

Data are expressed as median (interquartile range) or number (%).

^aIncluding 17 patients with extrathoracic lymph node involvement.

^bOne case each; orbit, pituitary gland, nasal mucosa, pharynx, thyroid, aorta, skin, liver, and bladder.

Table 2. Blood marker values at diagnosis and their correlation with the number of affected organs ($n = 59$).

Blood markers (normal values)	Blood marker value ^a	r_s	p value
WBC/ μ l (3200–9400)	6190 (4935–7125)	0.034	.797
Eo, % (3–5)	5.0 (2.5–8.9)	0.188	.154
CRP, mg/dl (<0.2)	(0.0–0.3)	0.026	.844
sIL-2R ^b , U/ml	959 (549–1350)	0.532	<.001
IgG, mg/dl (826–1840)	2241 (1739–3099)	0.435	<.001
IgG4, mg/dl (4.8–105)	661 (371–1430)	0.545	<.001
IgE ^c , IU/ml (<170)	551 (228–1112)	–0.153	.256
CH50 ^d , U/ml (28–51)	41 (28–47)	–0.275	.062

^aData are expressed as median (interquartile range).

^bNormal range was 122–496 U/ml using enzyme immunoassay, and 145–519 U/ml using chemiluminescence enzyme immunoassay.

^c $n = 57$.

^d $n = 47$.

WBC: white blood cells; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor; IgG4: immunoglobulin G4; IgE: Immunoglobulin E; CH50: 50% hemolytic complement. Analysis was performed with the Spearman rank correlation coefficient.

(30–40) mg/d on converting to prednisolone. All patients treated with glucocorticoid showed improvement, but six patients relapsed after the steroid was reduced to 10 mg/d (IQR 6–10 mg/d), and two other patients developed malignant lymphoma. The disease activity course for IgG4-RD was evaluated in 57 patients, excluding the two patients with malignant lymphoma. At the last visit, 46 showed improvement, nine patients showed a stable clinical course compared with that at the time of diagnosis, whereas two indicated worsened condition.

Blood markers at diagnosis and glucocorticoid use during follow up

Comparison of clinical findings (age at diagnosis, sex, presence or absence of symptoms, allergy, each organ involvement, and number of affected organs) and blood markers at diagnosis showed that there was a significant difference in the number of affected organs ($p < .05$), serum sIL-2R ($p < .001$), IgG4 ($p < .05$), IgG ($p < .05$), and CRP ($p < .05$) between patients treated and not treated with glucocorticoid. The predictive power of the blood markers with regard to glucocorticoid use during the follow up period was assessed based on ROC curves. ROC analysis showed that baseline sIL-2R provided the most accurate prediction of patients who required glucocorticoid treatment (area under ROC [AUC] = 0.807, $p = .0001$). The best cut-off value was 1046 U/ml for sIL-2R, with a sensitivity of 60% and a specificity of 95%, respectively, to discriminate patients who required glucocorticoid treatment. In contrast, serum IgG4 had a low accuracy, with an AUC of 0.674 (Figure 2).

Correlation between disease activity course and changes in blood markers

Among 46 patients who showed clinical improvement, most showed a 10% or higher decrease in serum sIL-2R, IgG4, and IgG (Figure 3). Serum sIL-2R and IgG4 decreased in

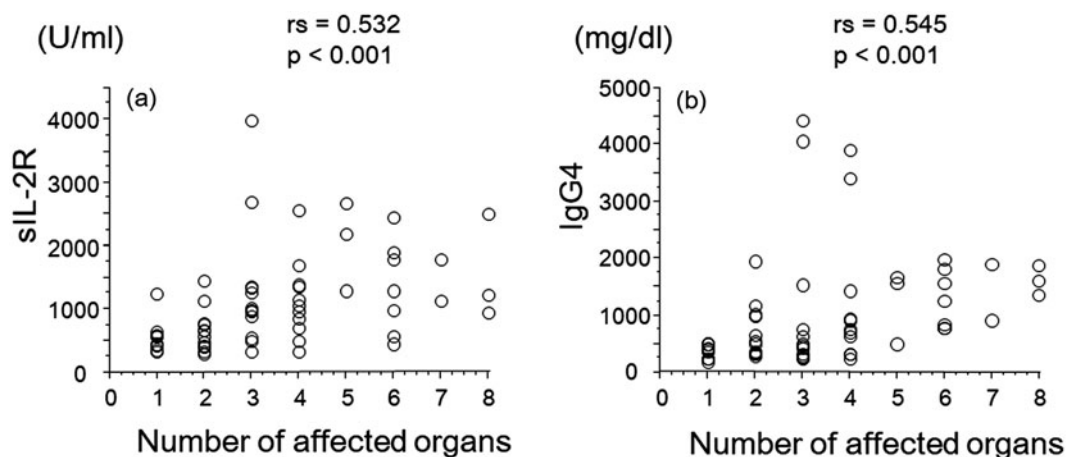


Figure 1. Correlations between number of affected organs and blood markers. The number of affected organs had significant positive correlations with serum soluble IL-2 receptor (sIL-2R) (a: $R_s = 0.532$, $p < .0001$) and serum IgG4 (b: $R_s = 0.545$, $p < .0001$). Spearman's rank correlation coefficient was used in the statistical analysis.

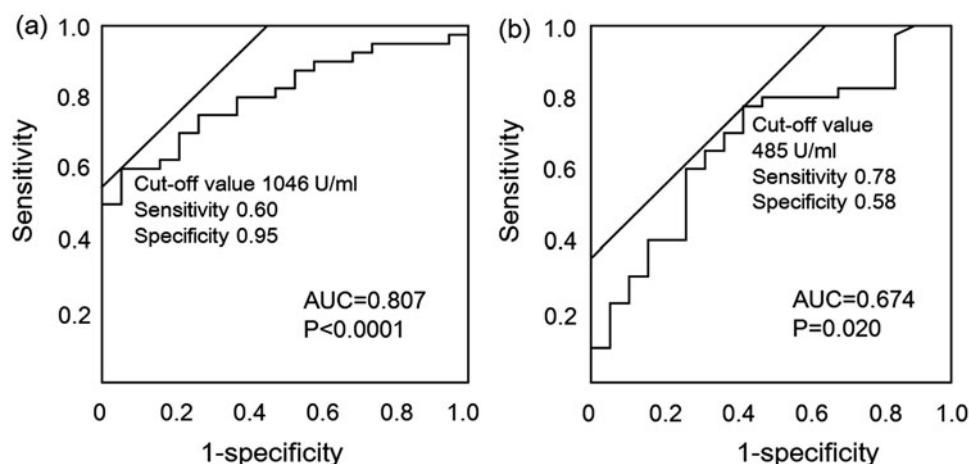


Figure 2. Capacity of the blood markers at diagnosis to discriminate patients who required systemic glucocorticoid treatment during the clinical course. Receiver operating characteristic analysis showed that serum sIL-2R had more accuracy (a: AUC = 0.807, $p < .0001$), than serum IgG4 (b: AUC = 0.674, $p < .05$) in discriminating patients who required systemic glucocorticoid treatment during the clinical course. AUC: area under ROC curve.

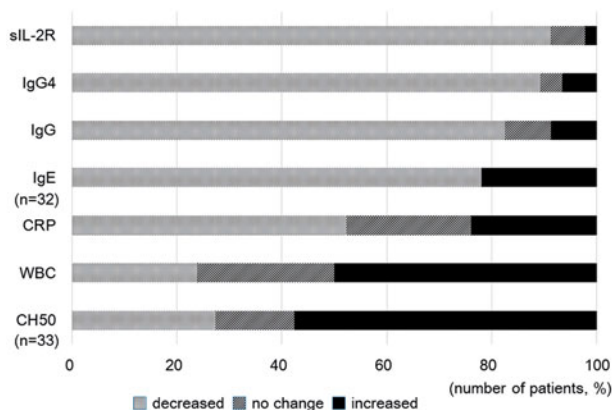


Figure 3. Changes in blood markers in patients who improved ($n = 46$). Change in the blood marker levels from the time of diagnosis to the last visit in patients who improved is shown. Levels of serum sIL-2R, IgG4, and IgG showed a $\geq 10\%$ decrease in most patients.

42 (91%) and 41 (89%) patients. In patients who exhibited improvement, serum sIL-2R and IgG4 were elevated at diagnosis in 37 (80%) and 46 (100%) patients, respectively. Among these patients, the minimal values for serum sIL-2R and IgG4 decreased to a normal range during the clinical course in 42 (91%) and 19 (41%) patients, respectively (Table 3). In the two patients whose condition worsened, serum sIL-2R increased in both patients at the last visit, although it was once normalized in one patient during the clinical course. In these patients, serum IgG4 increased in one patient and decreased in the other at the last visit.

Immunohistochemical staining

Both CD25 and Foxp3 antibodies were positively stained in numerous mononuclear cells in inguinal lymph node tissue obtained from a patient with IgG4-RD, whose serum sIL-2R concentration was 754 U/ml and serum IgG4 concentration was 349 mg/dl (Figure 4). The findings were also confirmed in the submaxillary gland tissue obtained from another patient.

Serial changes in blood marker levels in patients who developed malignancies during the clinical course

A 60-year-old female patient with lacrimal, salivary, lung parenchymal, mediastinal, and renal lesions was treated with prednisolone 30 mg/d. Serum IgG4 levels showed a constant decrease, whereas serum sIL-2R levels increased again during the clinical course. The patient suddenly died due to hemoptysis, and necropsy led to the diagnosis of malignant lymphoma infiltrating the trachea. Another patient who developed lymphoma also showed similar trend in these marker levels. The diagnosis of the patients was based on histology, and there was no evidence of malignant lymphoma at diagnosis. In contrast, in four other patients diagnosed with colorectal or prostate cancer, no obvious change was observed in serum sIL-2R or IgG4 levels.

Discussion

In IgG4-RD, serum IgG4 is the most widely used biomarker, and some previous reports showed that its serum levels reflect disease activity and treatment response [3,17]. However, the role of IgG4 in the pathogenesis of IgG4-RD remains unclear. IgG4 is traditionally considered an anti-inflammatory immunoglobulin, which is induced in response to Treg activation and following IL-10 release [1,18]. It is now considered unlikely that IgG4 itself is the primary element driving the pathophysiology of IgG4-RD [2]. Despite the lack of established biomarker in IgG4-RD, some studies have suggested that serum sIL-2R levels might be a useful biomarker to reflect disease activity in IgG4-RD [9,13]. This study aimed to elucidate the clinical significance of serum biomarkers, including sIL-2R. We showed that both serum sIL-2R and serum IgG4 levels correlated significantly with the number of affected organs in patients with IgG4-RD. In addition, we showed for the first time that serum sIL-2R levels had a high accuracy in predicting glucocorticoid requirement during the clinical course. The immunohistochemical staining of biopsied tissues obtained from

Table 3. Minimal values of sIL-2R and IgG4 during clinical course.

	Improved ^a , <i>n</i> = 46	No change ^a , <i>n</i> = 9	Worsened ^a , <i>n</i> = 2
Minimal sIL-2R, U/ml	286 (151–380)	500 (292–645)	225, 535
Number of patients with normalized sIL-2R levels ^b	42 (91%)	5 (56%)	1 (50%)
Minimal IgG4, mg/dl	145 (95–367)	359 (115–644)	79, 277
Number of patients with normalized IgG4 levels ^c	19 (41%)	2 (22%)	1 (50%)

Data are expressed as median (interquartile range) or number (%).

^aThe global disease activity course from the time of diagnosis to the last visit.

^bBelow 496 U/ml for enzyme immunoassay and below 519 U/ml for chemiluminescence enzyme immunoassay.

^cBelow 135 mg/dl.

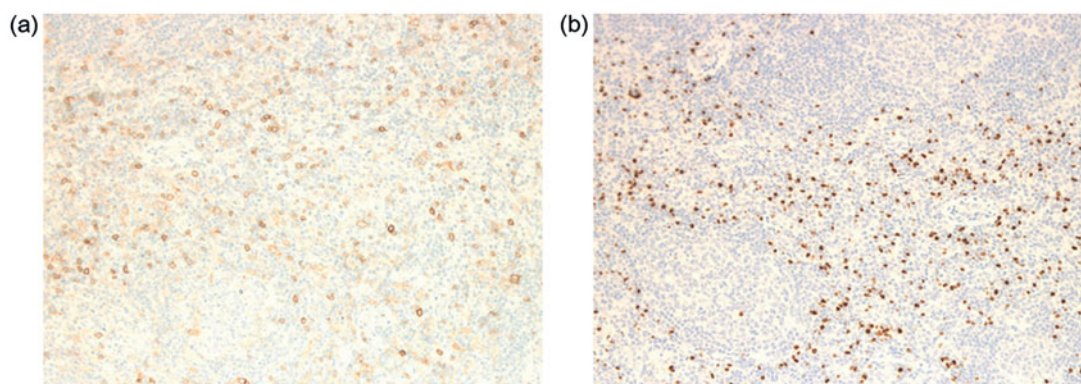


Figure 4. Immunological stain of inguinal lymph node from a patient with IgG4-RD. Both CD25 (a) and Foxp3 (b) were positively stained in numerous infiltrated mononuclear cells.

two patients with IgG4-RD showed that numerous cells were positive for CD25 and Foxp3.

Generally, systemic treatment is not indicated in all patients with IgG4-RD. However, aggressive treatment is indicated in cases with vital organ involvement because IgG4-RD can lead to organ dysfunction. In our institute, we use systemic glucocorticoids in patients with vital organ involvements with functional impairment or in those with overt symptoms that impair the quality of life. Here, the number of organs involved and levels of sIL-2R were significantly associated with glucocorticoid use. Serum sIL-2R may reflect massive organ involvement with dysfunction or active progressive disease, increasing the need for glucocorticoid treatment during the clinical course. For example, a patient with lachrymal gland involvement and mild exophthalmos, whose serum sIL-2R was 473 U/ml, was monitored without treatment and the lesion improved spontaneously. In contrast, a patient with lachrymal gland and lung involvement, whose serum sIL-2R was 1450 U/ml exhibited moderate exophthalmos and required treatment with systemic glucocorticoid. Further investigation is necessary to determine whether serum sIL-2R can be used to help the treatment decision in patients with IgG4-RD.

Immunohistochemical staining of biopsied specimens obtained from two patients showed that both CD25 and Foxp3 were positively stained in numerous infiltrated cells. CD25 is expressed by peripheral CD4-positive T-cells following cellular activation. However, CD25 expression by CD4-positive cells is also a marker to identify Treg cells [19]. Nakanuma et al. [20] have reported that many Treg cells are found around the affected bile ducts and portal tracts in patients with IgG4-related sclerosing cholangitis. In contrast

to classic autoimmune conditions, the activation of Treg is indicated by increased expression of Foxp3 in tissues, as well as an increase in the number of Treg cells in the blood of patients with IgG4-RD [1]. The result of immunohistochemistry in this study suggested that at least some proportion of serum sIL-2R derived from Treg cells infiltrated affected organs. Treg cells secrete anti-inflammatory cytokines such as IL-10 and TGF- β [21,22], and these cytokines have been shown to be up-regulated in lymphocytes of the affected organs in IgG4-RD [23,24]. IL-10 shifts the balance between IgG4 and IgE, favoring IgG4 [1], while TGF- β is a major profibrotic cytokine. In addition to these anti-inflammatory cytokines, Treg cells can also express pro-inflammatory cytokines such as IL-17A, under inflammatory conditions [21]. Although the role of Treg cells in the development of IgG4-RD remains unclear, in the active phase of IgG4-RD, Treg cells may secrete a variety of cytokines that contribute to IgG4 production and fibrosis, which are characteristic pathological features of IgG4-RD. Further investigation is necessary to elucidate the role of Treg cells and cellular source of serum sIL-2R in IgG4-RD.

In this study, most of the patients showed improvement, and only two patients worsened. In patients who improved, serum IgG4 normalized only in 41% of the patients, whereas serum sIL-2R decreased to a normal range in 91%. A previous study showed that serum IgG4 levels were not normalized in 63% of the patients after treatment with glucocorticoids, including those in remission [4]. Despite the lower sensitivity of serum sIL-2R (80% in this study) compared with serum IgG4 (100%) at diagnosis, sIL-2R might be more sensitive for assessing the remission of the disease.

In this study, malignant diseases developed in six patients (two with malignant lymphoma, three with colorectal cancer, and one with prostate cancer) after the diagnosis of IgG4-RD. In the two patients who developed malignant lymphoma, serum IgG4 decreased constantly, while sIL-2R increased again after the development of lymphoma. A previous study from Japan reported malignancies in 11 out of 106 patients (10.4%) with IgG4-RD, including two patients with malignant lymphoma [25]. Another study followed 111 patients with IgG4-RD mainly consisting of autoimmune pancreatitis, and three patients developed non-Hodgkin lymphoma during the observational period. The authors calculated that the standardized incidence rate of malignant lymphoma was 16-fold higher in patients with IgG4-RD than in the general population [26]. The trend of serum IgG4 and sIL-2R in patients who developed malignant lymphoma in this study suggested that a dissociated increase in sIL-2R levels in patients with stable IgG4-RD may occasionally be associated with the development of malignant lymphoma, even though the dissociation of the markers does not necessarily mean the development of malignant lymphoma. Despite the potential usefulness of the serum sIL-2R level as a biomarker to reflect disease activity in IgG4-RD, it should be noted that this level also increases in patients with malignant lymphoma.

The current study has some limitations despite the positive outcome. First, it is a retrospective study with a limited number of patients. The study participants may have higher frequency of lung involvement than general population of IgG4-RD, possibly because the study directors at the three institutes were respiratory physicians. Second, the change in blood markers with glucocorticoid treatment was not directly assessed. In addition, the interval for the measurement of blood markers also varied for each patient. Third, other potential biomarkers such as circulating plasmablasts/plasma cells [27] were not measured. Despite these limitations, this is the first study to show the potential use of serum sIL-2R levels in monitoring the disease and predicting the need for glucocorticoid use in patients with IgG4-RD. Further prospective and larger studies are required to investigate the clinical utility of serum sIL-2R, and its pathophysiological role in IgG4-RD.

In conclusion, serum sIL-2R levels showed positive association with the number of affected organs and predicted glucocorticoid requirement in IgG4-RD. The change in serum sIL-2R over time was concordant to the clinical course of the patients. Serum sIL-2R may be a useful biomarker in IgG4-RD.

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Conflict of interest

None.

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