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The Positive Predictive Value of a Very High Serum IgG4 Concentration for the Diagnosis of IgG4-Related Disease

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ABSTRACT. ***Objective.*** Serum IgG4 concentrations are used to evaluate a diagnosis of IgG4-related disease (IgG4-RD), but the positive predictive value (PPV) of a very high IgG4 level is uncertain. This study evaluated the PPV of a very high IgG4 concentration for diagnosing IgG4-RD.

Methods. The data warehouses of 2 large academic healthcare systems were queried for IgG4 concentration test results. Cases with serum IgG4 concentrations > 5× the upper limit of normal (ULN) were included. Cases of IgG4-RD were determined using the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria. The PPV for IgG4-RD of an IgG4 concentration > 5× ULN was estimated. Other conditions associated with very high IgG4 concentrations and specific features of IgG4-RD cases were characterized.

Results. IgG4 concentrations were available in 32,206 cases. Of these, 3039 (9.4%) had elevated IgG4 concentrations, and a final cohort of 191 (0.6%) cases had IgG4 concentrations > 5× ULN (median age 66 yrs, 72% male). The PPV of an IgG4 concentration > 5× ULN for a diagnosis of IgG4-RD was 75.4% (95% CI 68.7-81.3). In the remaining cases, elevated IgG4 concentrations were observed among patients with malignancies, autoimmune diseases, and infections.

Conclusion. The majority of cases with serum IgG4 concentrations > 5× ULN in this study had IgG4-RD. These data support the high weight placed on very high serum IgG4 concentrations in the ACR/EULAR classification criteria. However, 25% of cases with very high IgG4 concentrations had an alternative diagnosis, underscoring the importance of considering the broad differential of etiologies associated with an elevated IgG4 concentration when evaluating a patient.

Key Indexing Terms: biomarker, classification criteria, IgG4, IgG4-related disease

IgG4-related disease (IgG4-RD) is an immune-mediated inflammatory disease characterized by tumor-like lesions that are composed of lymphocytes and IgG4+ plasma cells densely embedded in fibrosis.[1-4] Serum IgG4 concentrations are an important part of the evaluation for suspected IgG4-RD; however, an elevated serum IgG4 concentration is not specific for IgG4-RD. We have previously shown that in a cohort of 380 patients with serum IgG4 test results, the positive predictive value (PPV) of an elevated serum IgG4 concentration (> 135 mg/dL) is 34%.[5] In a cohort of patients with pancreatic disease, the PPV of an elevated serum IgG4 level (> 140 mg/dL) for the diagnosis of IgG4-RD was similarly low at 36%.[6] Similar findings have been observed in other cohorts, suggesting that the PPV of any elevation in the serum IgG4 concentration is low.[7,8] However, the PPV of a very elevated serum IgG4 concentration has not been established.

Very high IgG4 concentrations are commonly observed in patients with IgG4-RD and this test is frequently used to

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establish the diagnosis of IgG4-RD.[4] Indeed, the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for IgG4-RD place a high weight on elevated serum IgG4 concentrations; of the 20 points required to be classified as IgG4-RD, 11 can be accrued if the patient has an IgG4 concentration > 5× the upper limit of normal (ULN).[9] Despite this, the PPV of a serum IgG4 concentration > 5× ULN remains unknown. The objective of this study was to estimate the PPV of a serum IgG4 concentration > 5× ULN for the diagnosis of IgG4-RD, and to characterize the association of very elevated serum IgG4 concentrations with other diseases.

METHODS

Data source, study population, and covariate ascertainment. We queried the data warehouses at 2 large healthcare systems—Stanford University and Mass General Brigham—for all IgG subclass test results from January 1, 2005, to January 1, 2021. Cases with any serum IgG4 concentration > 5× ULN were included. There was not a single "normal" range for IgG4 in this study, as the reference values changed over time at both institutions (ranging from normal values of 4-86 mg/dL to 11-157 mg/dL). We analyzed each patient and each IgG4 test value individually and included those that were > 5× ULN based on the reference range for the test done at that time. The cut-off of > 5× ULN was chosen based on the high weighting given to this value in the ACR/EULAR classification criteria for IgG4-RD.[9] We performed chart reviews and extracted demographics, BMI, smoking history, medical history, imaging, pathology, and laboratory test results of interest from the electronic medical record (EMR) of each case at the time of the highest serum IgG4 concentration. A history of atopic disease was determined by mention of asthma, atopic dermatitis or eczema, or allergic rhinitis in any of the clinical notes. Sinusitis was also determined through reference to sinus disease in clinical notes or in relevant imaging studies.

Outcome ascertainment. For each case, the primary diagnosis associated with the IgG4 concentration elevation was ascertained through chart review. The diagnosis of IgG4-RD was established using the ACR/EULAR classification criteria for IgG4-RD.[9] Cases were categorized as definite IgG4-RD if they met all classification criteria for IgG4-RD, probable IgG4-RD if they met all inclusion and exclusion criteria but did not have sufficient points to be classified as definite IgG4-RD, atypical if they had nonentry criteria organ involvement but histopathologic features consistent with IgG4-RD, and possible if they had signs of symptoms of IgG4-RD but not enough evidence to fit into any of the other categories and had no alternative diagnosis.[10,11] We classified cases as IgG4-RD if they were definite, probable, or atypical. For patients without IgG4-RD, the diagnosis attributed to their elevated IgG4 concentration was determined based on review of clinical notes, as well as laboratory, imaging, and pathology results. In some cases, no diagnosis was made, and these patients were listed as "unknown."

Statistical analysis. Baseline characteristics of patients with serum IgG4 concentrations > 5× ULN were summarized. Descriptive statistics were calculated using frequencies and percentages, along with median and IQR for continuous variables. The PPV of a serum IgG4 concentration > 5× ULN for the diagnosis of IgG4-RD was calculated as the number of cases fulfilling the definition of definite, probable, or atypical IgG4-RD divided by the total number of cases identified with an IgG4 concentration > 5× ULN. The associated 95% CIs were estimated using Poisson regression. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute).

Institutional review board (IRB) approval at both institutions was provided to conduct this study (Stanford University IRB, protocol IRB-58745, and Mass General Brigham IRB, protocol 2020P003549).

RESULTS

Patient characteristics. We identified 32,206 cases with serum IgG subclass testing, including 3039 cases (9.4%) with an elevated serum IgG4 concentration and 198 cases (0.7%) with an IgG4 concentration > 5× ULN (Supplementary Table S1, available with the online version of this article). Of the 198 cases with a serum IgG4 concentration > 5× ULN, 7 cases had insufficient data to include in subsequent analyses, leaving 191 cases (0.6%) in the final combined cohort (Table 1). The total cohort of cases with a serum IgG4 concentration > 5× ULN had a median age of 66 years, was predominately male (n = 137, 71.7%), and was racially diverse (56.5% White; Table 1). The mean BMI was 26.8 and the majority of cases were never smokers (64.9%). Atopic disease and sinusitis were present in 73 (38.2%) and 45 (23.7%) cases, respectively. Characteristics of the patients with probable, atypical, and possible IgG4-RD can be found in Supplementary Table S2 and Table S3.

Primary outcome. The PPV of an IgG4 concentration > 5× ULN for a diagnosis of (1) definite; (2) probable or definite; or (3) atypical, probable, or definite IgG4-RD were 69.1% (95% CI 62.0-75.6), 74.3% (95% CI 67.5-80.4), and 75.4% (95% CI 68.7-81.3),

Table 1. Demographics and clinical characteristics of cases with a serum IgG4 level > 5x ULN.

	Total Cohort, n = 191	Stanford Cohort, n = 53	Mass General Brigham Cohort, n = 138
Age, yrs, median (IQR)	66.0 (54.4-75.0)	62.2 (44.9-70.8)	65.1 (57.0-75.8)
Sex			
Female	54 (28.3)	20 (37.7)	34 (24.6)
Male	137 (71.7)	33 (62.3)	104 (75.4)
Race/ethnicity			
White	108 (56.5)	18 (34)	90 (65.2)
Black	9 (4.7)	2 (3.8)	7 (5.1)
Hispanic[a]	12 (6.3)	10 (18.9)	2 (1.5)
Asian	46 (24.1)	21 (39.6)	25 (18.1)
Unknown	9 (4.8)	1 (1.9)	8 (5.8)
Other	16 (8.4)	10 (18.9)	6 (4.4)
BMI, kg/m^2,			
mean (SD)	26.8 (5.8)	26.0 (5.9)	27.2 (5.7)
< 25	80 (41.9)	28 (52.8)	52 (37.7)
25–29.9	50 (26.2)	16 (30.2)	34 (24.6)
≥ 30	43 (22.5)	9 (17.0)	34 (24.6)
Unknown	18 (9.4)	0 (0.0)	18 (13.0)
Smoking			
Never	124 (64.9)	36 (67.9)	88 (63.8)
Former	59 (30.9)	15 (28.3)	44 (31.9)
Current	4 (2.1)	2 (3.8)	2 (1.5)
Unknown	4 (2.1)	0 (0)	4 (2.9)
Atopic disease	73 (38.2)	22 (41.5)	51 (37)
Sinusitis	45 (23.7)	14 (26.4)	31 (22.5)
Receiving allergy immunotherapy	1 (0.5)	0 (0)	1 (0.7)

Values are n (%) unless otherwise indicated. [a] Ethnicity is recorded separately from race in the Stanford cohort, and thus cases may appear twice in this column. ULN: upper limit of normal.

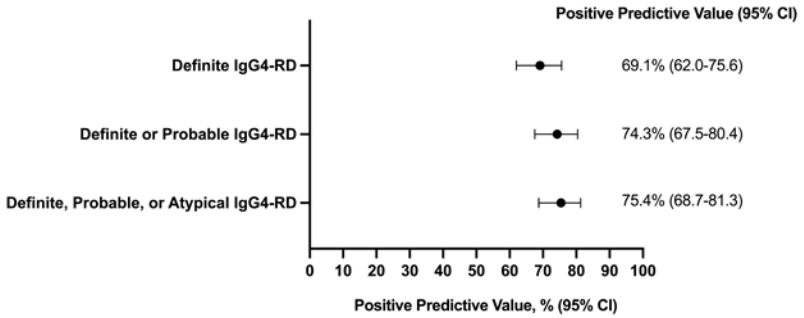

Figure. Positive predictive value of serum IgG4 > 5× ULN for the diagnosis of IgG4-RD. IgG4-RD: IgG4-related disease; ULN: upper limit of normal.

respectively (Figure). The median (IQR) IgG4 concentration among the total cohort of cases with serum IgG4 concentrations > 5× ULN was 955.4 mg/dL (619.9-1280.0) and among cases with definite IgG4-RD (n = 132) was 1021.6 mg/dL (678.5-1419.9; Table 2). Several other diseases were associated with a very elevated serum IgG4 concentration. Broadly, these

Table 2. Distribution of cases with a serum IgG4 level > 5× ULN by disorder.

Disorder	n (%)	IgG4, mg/dL, Median (IQR)
Total cohort	191 (100)	955.4 (619.9-1280.0)
IgG4-related disease	147 (77)	1001.0 (675.0-1335.0)
Definite IgG4-RD	132 (69.1)	1021.6 (678.5-1419.9)
Probable IgG4-RD	10 (5.2)	980.3 (807.8-1207.5)
Atypical IgG4-RD	2 (1)	653.2 (609.6-696.9)
Possible IgG4-RD	3 (1.6)	677.0 (623.0-971.2)
Malignancy	12 (6.3)	1257.5 (953.0-2025.5)
B-cell lymphoma	4 (2.1)	1275.0 (1131.8-1489.0)
Leukemia	3 (1.6)	1030.0 (876.0-1105.0)
POEMS syndrome	1 (0.5)	3492
Plasma cell myeloma and AL amyloidosis	1 (0.5)	2102
MGUS (monoclonal gammopathy)	1 (0.5)	2000
Cholangiocarcinoma	1 (0.5)	1240
Castleman disease	1 (0.5)	576
Autoimmune/immune-mediated	17 (8.9)	752.0 (540.0-1968.0)
Hypereosinophilic syndrome	3 (1.6)	540.0 (511.6-2702.4)
EGPA	3 (1.6)	923.0 (751.3-1847.2)
Systemic lupus erythematosus	2 (1)	760.0 (756.0-764.0)
Lymphadenopathy	2 (1)	534.1 (508.5-559.7)
Sarcoidosis	1 (0.5)	534
Rosai-Dorfman disease	1 (0.5)	2879
Primary sclerosing cholangitis	1 (0.5)	871
Postinfectious inflammatory disease	1 (0.5)	579
Evans syndrome	1 (0.5)	2835
Autoimmune hepatitis	1 (0.5)	1968
Acute disseminated encephalomyelitis	1 (0.5)	519
Infection	3 (1.6)	738.0 (645.5-758.0)
Epidural abscess with MSSA	1 (0.5)	738
MSSA bacteremia and osteomyelitis	1 (0.5)	778
Mycobacterial disease	1 (0.5)	553
Unknown	3 (1.6)	512.0 (483.0-515.5)
Other[a]	9 (4.7)	552.0 (525.0-654.7)

[a] Other includes single cases of food allergies, cystic fibrosis, bronchiolitis obliterans and bronchiectasis, chronic eosinophilic pneumonia, chronic sinusitis, noninflammatory aortic aneurysm, seasonal allergies, pediatric autoimmune neuropsychiatric disease associated with Streptococcal infection, and small fiber neuropathy. AL: amyloid light-chain; EGPA: eosinophilic granulomatosis with polyangiitis; IgG4-RD: IgG4-related disease; MGUS: monoclonal gammopathy of undetermined significance; MSSA: methicillin-susceptible *Staphylococcus aureus*; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities; ULN: upper limit of normal.

included malignancies (n = 12, 6.3%), other autoimmune or immune-mediated diseases (n = 17, 8.9%), and infections (n = 3, 1.6%; Table 2).

Secondary analysis. Among the 144 cases with definite, probable, or atypical IgG4-RD and a serum IgG4 concentration > 5× ULN, the majority (88.9%) had multiorgan involvement, with a median of 3 organ systems involved (Supplementary Table S4, available with the online version of this article). The pancreas (51.4%), salivary glands (50%), lacrimal glands (33.8%), and kidneys (31%) were the most commonly involved organs. The most commonly elevated or abnormal additional laboratory tests, among those assessed, were total IgG (88.6%), IgE (77.4%), erythrocyte sedimentation rate (64.2%), and the κ:λ free light chain ratio (54.5%; Supplementary Table S4).

DISCUSSION

In this retrospective analysis, we found that the majority of cases with a serum IgG4 concentration > 5× ULN had IgG4-RD, with a PPV of 75% for IgG4-RD. This is substantially higher than the PPV associated with a serum IgG4 greater than the ULN, which ranges from 18% to 36%.[5-8] This suggests that a very elevated serum IgG4 concentration is highly predictive of IgG4-RD, and our findings support the high weight associated with an IgG4 concentration > 5× ULN in the ACR/EULAR classification criteria for IgG4-RD. However, these results also highlight the need for appropriate adherence to the inclusion and exclusion criteria to ensure that other conditions that can also present with very elevated serum IgG4 concentrations are not misclassified as IgG4-RD. These include (1) malignancies such as lymphoma, leukemia, and myeloma; (2) autoimmune and immune-mediated diseases such as eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus, and sarcoidosis; and (3) infectious diseases such as those caused by *Staphylococcus aureus* and *Mycobacterium*. Given that 25% of patients with a serum IgG4 concentration > 5× ULN in our study did not have IgG4-RD, our study underscores the importance of not anchoring on the diagnosis of IgG4-RD based solely on a laboratory result. This may be particularly important in the case of lymphoma and other malignancies, which can closely mimic IgG4-RD. We were not able to ascertain whether very elevated serum IgG4 concentrations were associated with more severe IgG4-RD or unfavorable outcomes, but this is an area of interest for future research.

Our study supports prior work that demonstrates an association between higher concentrations of serum IgG4 and multiorgan involvement of IgG4-RD.[12] Further, we have previously shown an association between elevated serum IgG4 and the "Mikulicz and Systemic" subgroup of IgG4-RD, involving organs such as the submandibular glands and lacrimal glands, along with more widespread disease.[13] Our current study provides further evidence for this association in a racially diverse, multicenter cohort of patients with IgG4-RD with very elevated serum IgG4 concentrations. We also demonstrate that what has been described as the "proliferative" subtype of IgG4-RD prevails in this cohort of patients with very elevated serum IgG4 concentrations.[4]

This study has several strengths. First, we used 2 real-world databases from large healthcare systems in different geographic areas in the US, which enabled us to create a cohort of diverse patients with serum IgG4 concentrations > 5× ULN. Second, because of linkage to EMRs, we were able to manually review all charts to obtain patient level data and ascertain a diagnosis in almost all cases.

Despite these strengths, this study has certain limitations. First, the retrospective nature of the study limited our ability to obtain complete data in some cases, but these were few. Second, serum IgG subclass testing in these cases was performed for clinical indication. Thus, it is conceivable that our estimated PPV is an overestimate. For instance, if every patient with lymphoma had serum IgG4 routinely checked, the PPV of a very elevated IgG4 concentration for IgG4-RD may be lower than what we observed. Third, this study was conducted in 2 large healthcare systems that include centers specializing in IgG4-RD care. The patient population may, therefore, not be generalizable and the PPV may be an overestimate. However, these systems also included community hospitals and other facilities not associated with IgG4-RD centers. Fourth, we were not able to calculate sensitivity and specificity of serum IgG4 concentrations > 5× ULN, as this would have required identification of all patients with IgG4-RD with negative test results (in this case, defined by a serum IgG4 concentration < 5× ULN), which we did not ascertain. Fifth, both institutions used ELISA-based testing to quantify serum IgG4 concentrations, and there may have been some variability across assays. However, our primary analysis is based on identifying cases with a result of > 5× ULN and therefore standardized to the assay's reference range.

In this multicenter, retrospective study, we observed that a majority of patients with a serum IgG4 concentration > 5× ULN had IgG4-RD, with a PPV of 75% for IgG4-RD. These data support the significant weight placed on very elevated serum IgG4 in the IgG4-RD classification criteria. However, it is notable that 25% of patients with an IgG4 concentration ≥ 5× ULN had no identifiable cause or an alternative diagnosis, underscoring the importance of considering a broad differential when evaluating a patient with a very high IgG4 concentration for IgG4-RD.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly in order to protect the privacy and protected health information of individuals who participated in the study.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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