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ORIGINAL ARTICLE

Clinical and diagnostic significance of serum immunoglobulin A rheumatoid factor in primary Sjogren's syndrome

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Abstract

Objectives The aim of this study was to investigate the diagnostic accuracy of rheumatoid factor (RF) isotype for the detection of primary Sjogren's syndrome (pSS) and evaluate the clinical and serological associations of immunoglobulin (Ig) A RF in patients with pSS.

Materials and methods RF levels were measured in 77 and 37 patients with pSS and idiopathic sicca symptoms, respectively, using ELISA and analysed with respect to clinical and laboratory disease characteristics. Receiver operating characteristic curves were used to determine and compare the diagnostic accuracy of IgA RF with other diagnostic tests.

Results Serum levels of IgA RF were significantly higher in patients with pSS than in those with idiopathic sicca symptoms. IgA RF showed sensitivity, specificity, positive, and negative predictive values of 83.1, 78.4, 88.9, and 69.0%, respectively, for pSS diagnosis. IgA RF was associated with xerostomia, severe sialoscintigraphic grade, low unstimulated salivary flow rate (USFR), antinuclear antibody, high IgG and IgM/G RF levels, and low C3 levels in patients with pSS. IgA RF titres had positive correlations with sialoscintigraphic grade and IgG and IgG/M RF levels and had negative correlations with USFR and C3 levels.

Conclusion Our findings confirmed the potential of IgA RF to distinguish pSS from idiopathic sicca symptoms. The presence of IgA RF in patients with pSS was associated with significantly worse exocrine function and active serologic profile. No association between IgA RF and extra-glandular manifestations was noted.

Clinical relevance IgA RF should be the predictive and diagnostic marker in patients with pSS.

Keywords Sjogren's syndrome · Rheumatoid factor · IgA rheumatoid factor · Diagnosis · Exocrine function · Extra-glandular manifestations

Introduction

Primary Sjogren's syndrome (pSS) is a chronic systemic autoimmune disease characterised by lymphocytic infiltration and destruction of the exocrine glands, leading to immune-mediated secretory dysfunction [1]. The pathogenesis of pSS is unknown, but pSS shows B cell hyperactivity in the form of hypergammaglobulinaemia, autoantibody production, and germinal centre formation in the salivary gland [2, 3]. Rheumatoid factors (RFs) are among the autoantibodies associated with pSS. RFs are antibodies directed against the Fc portion of immunoglobulin G (IgG). RF positivity is found in 75–95% of pSS cases, whereas it is found in 50–80% of rheumatoid arthritis (RA) cases [4]. The presence of RF in patients with RA is known to predict the development of more aggressive and erosive joint diseases and extra-articular manifestations [5]. Likewise, several studies showed that RF in patients with pSS correlated with severity of glandular inflammation, numbers of extra-glandular manifestations, and active serological profile [6–8].

Although measurement of non-IgM RFs is not performed routinely in clinical practice due to technical difficulties, RFs can belong to any isotype. IgA RF has been reported with a prevalence ranging widely from 25.8 to 86% in patients with

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pSS [7–10]. A few studies have suggested the prognostic value of non-IgM RFs in pSS. The presence of IgA RF in patients with pSS is correlated with the presence of autoantibodies and hypergammaglobulinaemia. However, previous studies have shown convincing results on the extra-glandular involvement of pSS [10–12]. One study reported a correlation between the serum level of IgA RF and a number of extra-glandular manifestations [11]. On the other hand, other authors showed that IgA RF was only associated with renal disease, but found no correlation of IgA RF with other extra-glandular manifestations [12].

In clinical practice, pSS could be challenging to diagnose because of the lack of a single confirmative diagnostic test. Various classification criteria were designed mainly for clinical trials and research but are often used as diagnostic tools in individual patients with suspected pSS. However, we have encountered a few patients who failed to meet the classification criteria, but have had clinical features highly suggestive of a diagnosis of pSS. The notable examples include patients with a seronegative status of anti-Ro/La SSB) and those with early/SSB) and those with early-stage pSS when secretion of tear and saliva is not impaired. In these cases, other tests provide assistance to clinicians.

Thus, this present study aimed to answer the question on whether the serum RF isotype has a potential diagnostic value for the detection of pSS. In addition, we assessed whether serum IgA RF may serve as a prognostic factor by evaluating their association with clinical and serological characteristics.

Methods

Study population

The study was a single-centre cross-sectional study performed at Konkuk University Medical Center between May 2016 and April 2017. The study enrolled 114 patients with established pSS and suspected SS. The definitive diagnosis of pSS was made according to the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [13]. Patients who did not fulfil the ACR/EULAR classification criteria for pSS and received a diagnosis of idiopathic sicca symptoms represented the controls. More specifically, idiopathic sicca symptom was defined as a condition of persistent, non-immune-mediated dry eyes and mouth in patients without any systemic disorders potentially responsible for these symptoms. Written informed consents were provided by participants. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board for Human Research, Konkuk University Medical Center (KUH 1010776).

Clinical evaluation and laboratory tests

A standardised clinical evaluation was performed to obtain and record the following data: demographics, history of dry mouth and eyes, duration of subjective sicca symptoms, symptoms/signs suggestive of disease-related extra-glandular manifestations, comorbidities, medication use, Schirmer's test result (abnormal if ≤ 5 mm/5 min on one or both sides), and whole unstimulated salivary flow rate (USFR, abnormal if < 0.1 ml/min). Whole unstimulated saliva was collected in a sterilised plastic tube over a period of 15 min. USFR was recorded as millilitres per 15 min. Patients were instructed to refrain from intake of any food or beverage or smoke at least 1 h before collection [14]. To assess the disease activity and disease-related damage, we measured the EULAR Sjogren's syndrome disease activity index (ESSDAI) [15] and Sjogren's syndrome disease damage index (SSDDI) [16].

Routine laboratory tests included the evaluation of white blood cell (WBC), lymphocyte, haemoglobin, and platelet counts; C-reactive protein (CRP); IgG, IgA, IgM, cryoglobulin, and complement (C3, C4) levels; and erythrocyte sedimentation rate (ESR). In terms of immunological evaluation, we checked for the presence of antinuclear antibodies (ANAs) (assessed on HEp-2 cells; a titre $\geq$ 1:160 was considered positive), anti-SS-A/Ro and anti-SS-B/La antibodies (using enzyme-linked immunosorbent assay (ELISA)), and anti-cyclic citrullinated peptide (CCP) antibodies (using ELISA). The different RF isotypes (IgM, IgA, and IgG) were detected using a commercially available ELISA kit (RF ELISA Kit; Immco Diagnostics, NY, USA). According to the manufacturer's recommendations, IgA and IgG RF concentrations above 25 endotoxin units ELISA units (EU)/ml and IgM RF concentration above 12.5 IU/ml were considered positive.

Salivary gland scintigraphy

A low-energy high-resolution single-head gamma camera (E.cam, Siemens Healthcare, Erlangen, Germany) was used to obtain salivary gland scintigraphic images. Five minutes after administering technetium-99m pertechnetate (^{99m}TcO4, 250 MBq) intravenously, the anterior, right lateral, and left lateral static images were acquired. At 10 and 20 min after administering ^{99m}TcO4, three images were re-taken. At 35 min, 2 g of lemon-flavoured vitamin C was administered orally for 5 min. Post-stimulation images were then obtained in three views.

Two experienced specialists in nuclear medicine classified the patients into four scintigraphic stages according to the following criteria proposed by Schall et al.: (1) class 1 denotes normal, rapid uptake of isotope by the salivary glands within the first 10 min, a progressive increase in concentration, and prompt excretion into the oral cavity within 20–30 min; (2) class 2 is considered mild involvement, with reduced

concentration or normal uptake with a delayed secretion into the oral cavity; (3) class 3 indicates moderate involvement, with marked delay in uptake and reduced concentration and excretion; and (4) class 4 represents severe involvement, with complete absence of active concentration in the salivary glands [17].

Statistical analysis

Statistical analyses were performed using the SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL, USA). Data were expressed as median (interquartile range, IQR) or mean (standard deviation, SD) for continuous variables, as appropriate, and as absolute frequencies and percentages for categorical variables. Data were compared using unpaired Student's *t*, chi-square, and Mann–Whitney *U* tests, as appropriate. On the receiver operating characteristic (ROC) curve, the optimal cut-off value producing the best combination of sensitivity and specificity was located nearest the upper left corner of the curve. Spearman's rank correlation was used to assess the correlation between IgA RF titres and serologic parameters. p values < 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

The study cohort included 114 patients, in which 77 patients fulfilled the ACR/EULAR classification criteria for pSS and 37 patients for idiopathic sicca symptoms. Table 1 summarises the baseline characteristics of patients with pSS and idiopathic sicca symptoms. The mean age of the idiopathic sicca symptom group was higher than that of the pSS group [63.6 (9.5) vs. 55.8 (11.8), $p = 0.001$]. There was no difference in the current use of anticholinergic or other medications, such as antihypertensives, proton pump inhibitors, and antidepressants, that might cause sicca symptoms between pSS and control groups. Among the 77 patients with pSS, 20 (23.5%) reported Raynaud's phenomenon, 18 (23.4%) had inflammatory arthritis, 2 (2.6%) had biopsy-proven vasculitis, 8 (10.4%) had pulmonary involvement, 6 (7.8%) had peripheral nervous system involvement, and 6 (7.8%) had accompanying autoimmune thyroiditis. The median ESSDAI and SSDDI (IQR) were 3.0 (4.0) and 2.0 (2.0), respectively. Seventy (90.9%) patients with pSS were treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs). The most commonly prescribed cDMARD was hydroxychloroquine (77.9%). The other prescribed cDMARDs were methotrexate (MTX) (7.8%), azathioprine (7.8%), and sulfasalazine (1.3%). In addition, 23.4% of patients with pSS received low-dose steroids.

Table 1 Clinical and laboratory characteristics of patients with pSS and idiopathic sicca syndrome

	pSS ($n = 77$)	Idiopathic sicca syndrome ($n = 37$)	p value
Age (years), mean (SD)	56.0 (11.1)	63.3 (9.5)	0.001*
Female, *n* (%)	74 (96.1)	35 (94.5)	0.659
Duration of sicca symptoms (years), mean (SD)	6.8 (4.6)	5.9 (5.1)	0.323
Xerostomia, *n* (%)	73 (94.8)	37 (100)	0.302
Xerophthalmia, *n* (%)	71 (92.2)	33 (89.2)	0.725
Abnormal Schirmer's test, *n* (%)	58 (75.3)	28 (75.7)	0.414
USFR (ml/15 min), mean (SD)	1.9 (2.1)	3.7 (3.9)	0.029*
Abnormal USFR, *n* (%)	51 (66.2)	9 (24.3)	0.002*
Positive ANA, *n* (%)	53 (68.8)	3 (8.1)	< 0.001*
Positive anti-Ro/SSA, *n* (%)	77 (100)	0 (0)	< 0.001*
Positive anti-La/SSB, *n* (%)	41 (53.2)	1 (2.7)	< 0.001*
IgG (mg/dl), mean (SD)	1559.0 (636.3)	1342.1 (435.1)	< 0.001*
IgA (mg/dl), mean (SD)	339.1 (212.7)	257.2 (110.9)	0.035*
IgM (mg/dl), mean (SD)	99.4 (44.3)	119.5 (50.7)	0.039*
C3 (mg/dl), mean (SD)	100.0 (17.2)	112.4 (27.4)	0.026*
C4 (mg/dl), mean (SD)	22.7 (6.6)	25.8 (7.1)	0.035*
Abnormal sialoscintigraphy, *n* (%)	67 (87.0)	31 (81.6)	0.407
ESR (mm/h), mean (SD)	20.9 (15.3)	17.5 (21.2)	0.330
CRP (mg/dl), mean (SD)	0.12 (0.2)	0.3 (0.9)	0.239
ESSDAI, median (IQR)	3.0 (4.0)		
SSDDI, median (IQR)	2.0 (2.0)		

pSS primary Sjogren's syndrome, *USFR* unstimulated salivary flow rate, *ANA* antinuclear antibody, *Ig* immunoglobulin, *C* complement, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ESSDAI* Sjogren's syndrome disease activity index, *SSDDI* Sjogren's syndrome disease damage index

*Statistically significant

Detection of rheumatoid factor using the enzyme-linked immunosorbent assay

The positivity of IgA/G/M RF, which was detected using ELISA, in patients with pSS was 83.1, 63.6, and 83.1%, respectively. The corresponding values for idiopathic sicca symptoms were 21.6, 32.4, and 86.5%. IgA/G/M RF levels in patients with pSS and idiopathic sicca symptoms are shown in Fig. 1. IgA and IgG RF levels were significantly higher in the pSS [median (IQR); 131.9 (273.1) and 20.5 (18.8), respectively] than in the idiopathic sicca symptom group [14.1 (15.7) and 17.3 (18.9), respectively]. There was no significant difference in terms of IgM RF levels between patients with pSS and idiopathic sicca symptoms [median (IQR); 23.8 (25.4) and 20.5 (18.8), respectively].

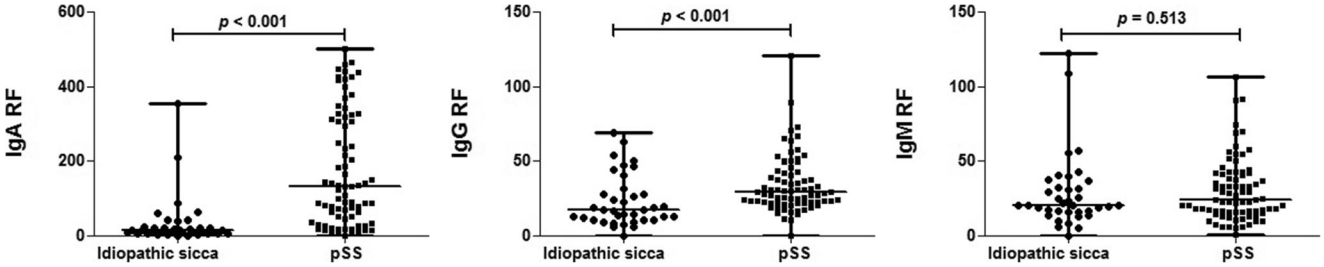

Fig. 1 IgA RF (**a**), IgG RF (**b**), and IgM RF (**c**) in patients with primary Sjogren's syndrome (pSS) and idiopathic sicca symptoms. Serum IgA, IgG, and IgM RF levels were measured using enzyme-linked immunosorbent assay (ELISA) in patients with pSS ($n = 77$) and idiopathic sicca symptoms ($n = 37$). Each symbol represents the RF level in a single patient's serum. *RF* rheumatoid factor, *pSS* primary Sjogren's syndrome

Diagnostic value of immunoglobulin A rheumatoid factor

We used the ROC curve analysis to compare the diagnostic value of IgA RF detection with those of other diagnostic tests for pSS (Fig. 2). By setting an IgA RF cut-off value of 25 EU/ml [area under the curve (AUC) 0.867; 95% CI 0.795, 0.938], IgA RF had 83.1% sensitivity and 78.4% specificity, with positive and negative predictive values of 88.9 and 69.0%, respectively. Among the RF isotypes detected using ELISA, IgA RF showed the best diagnostic accuracy. Table 2 summarises the diagnostic accuracy of IgA RF detection compared to that of IgG/IgM RF detection by ELISA, Schirmer's test, USFR measurement, and sialoscintigraphy. Schirmer's test and sialoscintigraphy were less specific compared to IgA RF detection ($p < 0.001$, both). USFR and Schirmer's test showed lower sensitivity compared to IgA RF detection ($p = 0.011$ and $p = 0.035$, respectively).

Associations between clinical manifestations and IgA RF positivity in primary Sjogren's syndrome

The clinical characteristics of pSS according to IgA RF status are shown in Table 3. There was no difference in the current use of anticholinergic or other medications that might cause sicca symptoms between IgA RF positive and negative pSS patients. The seropositivity of IgA RF was significantly associated with higher prevalence of subjective symptoms of dry mouth ($p = 0.014$) and abnormal USFR ($p = 0.027$). The pSS patients with seropositive IgA RF showed a significantly lower USFR ($p = 0.039$) and a higher scintigraphic grade of both parotid and submandibular glands compared to those with seronegative IgA RF ($p = 0.019$ and $p = 0.002$, respectively). The laboratory and immunological features of pSS according to the IgA RF status are shown in Table 4. IgA RF-positive patients with pSS had more

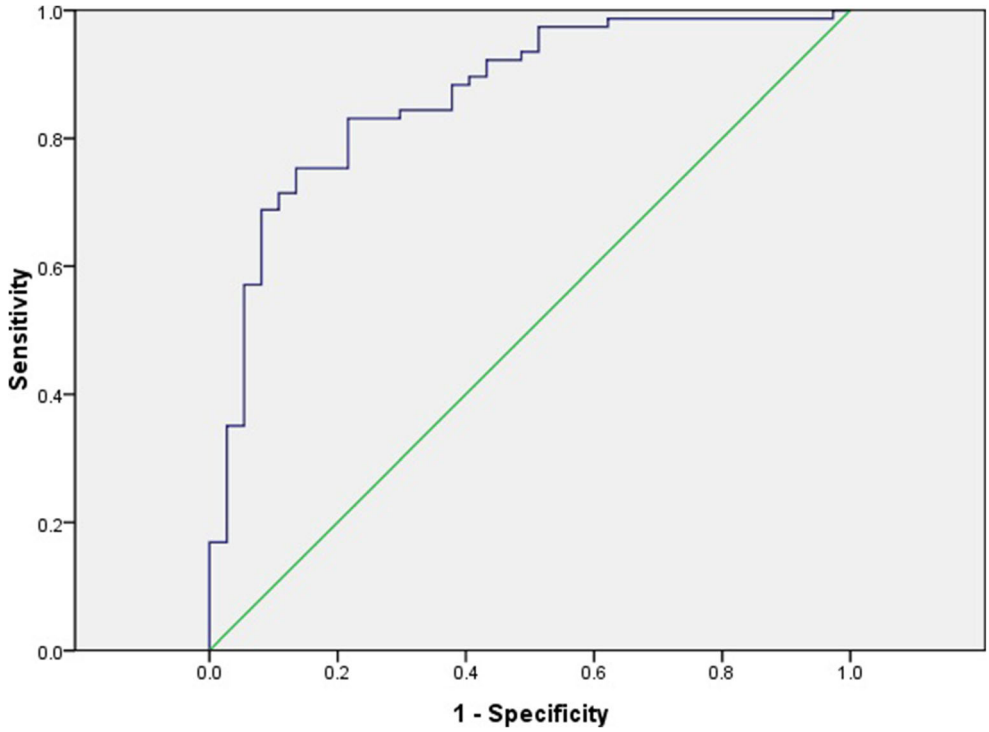

Fig. 2 Receiver operating characteristic (ROC) curve showing the diagnostic accuracy of serum IgA rheumatoid factor (RF) for primary Sjogren's syndrome. ROC curve illustrates the diagnostic accuracy of serum IgA RF. The area under the curve of the ROC curve was 0.867 (95% CI 0.795, 0.938). The diagonal line represents the reference line of no discrimination from the left bottom to the top right corner

Table 2 Diagnostic accuracy of serum IgA RF for pSS

	Sensitivity	Specificity	PPV	NPV
Serum IgA RF by ELISA	83.1	78.4	88.9	69.0
Serum IgG RF by ELISA	63.6	67.6	80.3	47.2
Serum IgM RF by ELISA	83.1	13.5	66.7	27.8
Schirmer's test ≤ 5 ml/15 min	75.3	17.6	67.4	24.0
USFR ≤ 1.5 ml/15 min	66.2	67.9	85.0	42.2
Sialoscintigraphy	94.4	8.8	68.4	42.9

PPV positive predictive value, *NPV* negative predictive value, *RF* rheumatoid factor, *USFR* unstimulated salivary flow rate

ANA ≥ 1:160 ($p = 0.002$); high titres of IgG RF ($p = 0.005$), IgM RF ($p = 0.002$), and IgG levels ($p = 0.001$); and low C3 levels ($p = 0.009$).

There was no association of IgA RF with age, symptom duration, extra-glandular involvement, ESSDAI, or SSDDI. Eighteen patients (23.4%) had inflammatory arthritis based on clinical or ultrasonographic examination. Inflammatory arthritis was not associated with the presence, titres, and isotypes of RFs. Anti-CCP occurred much more frequently in pSS patients with inflammatory arthritis than in those without inflammatory arthritis (75 vs. 17.4%, $p = 0.002$). Renal involvement (two patients with renal tubular acidosis and one with glomerulonephritis) was found in 3.9% of patients with pSS. There was no association between renal involvement and IgA RF status.

Table 3 Association with clinical features in patients with serum IgA RF-positive pSS

	Positive IgA RF ($n = 64$)	Negative IgA RF ($n = 13$)	*p* value
Age (years), median (IQR)	58.0 (55.4)	54.5 (55.1)	0.789
Female, *n* (%)	63 (98.4)	13 (100)	1.00
Duration of sicca symptoms (years), median (IQR)	5.0 (6.5)	11 (5.3)	0.349
Xerostomia, *n* (%)	63 (98.4)	10 (76.9)	0.014*
Xerophthalmia, *n* (%)	59 (92.1)	12 (92.3)	1.00
Lung involvement, *n* (%)	8 (12.5)	0 (0)	0.388
PNS involvement, *n* (%)	4 (6.3)	2 (15.4)	0.266
Inflammatory arthritis, *n* (%)	14 (21.9)	4 (30.8)	0.488
Renal disease, *n* (%)	3 (4.7)	0 (0)	1.000
Raynaud's phenomenon, *n* (%)	16 (25)	4 (30.8)	0.732
Lymphoma, *n* (%)	2 (3.1)	0 (0)	1.000
ESSDAI, median (IQR)	3.0 (5.75)	3.0 (1.75)	0.847
SSDDI, median (IQR)	2.0 (1.75)	3.0 (1.0)	0.822
Abnormal Schirmer's test, *n* (%)	51 (79.7)	7 (53.8)	0.075
Abnormal USFR, *n* (%)	46 (71.9)	5 (38.5)	0.027*
USFR (ml/15 min), median (IQR)	1.3 (2.0)	2.3 (2.8)	0.039*
Sialoscintigraphic classes 3 and 4, *n* (%)	49 (76.6)	6 (46.2)	0.042*
Parotid scintigraphic class, median (IQR)	3 (1)	2 (2)	0.019*
Submandibular scintigraphic class, median (IQR)	3 (1)	2 (2)	0.002*

RF rheumatoid factor, *PNS* peripheral nervous system, *USFR* unstimulated salivary flow rate, *ESSDAI* Sjogren's syndrome disease activity index, *SSDDI* Sjogren's syndrome disease damage index

*Statistically significant

Table 4 Association with laboratory and immunological features in patients with IgA RF-positive pSS

	Positive IgA RF ($n = 64$)	Negative IgA RF ($n = 13$)	*p* value
Positive ANA, *n* (%)	49 (76.6)	4 (30.8)	0.002*
Positive anti-Ro/SSA, *n* (%)	64 (100)	13 (100)	1.00
Positive anti-La/SSB, *n* (%)	35 (54.7)	6 (46.2)	0.574
IgA RF by ELISA (EU/ml), median (IQR)	138.3 (280.8)	13.0 (7.0)	< 0.001*
IgG RF by ELISA (EU/ml), median (IQR)	30.1 (20.4)	23.2 (10.2)	0.005*
IgM RF by ELISA (IU/ml), median (IQR)	28.1 (23.8)	17.6 (16.6)	0.002*
Positive anti-CCP, *n* (%)	8 (12.5)	2 (15.4)	0.453
IgG, median (IQR), mg/dl	1672.0 (565.0)	1300.0 (434.0)	0.001*
IgA (mg/dl), median (IQR)	323.0 (199.0)	212.0 (101.5)	0.121
IgM (mg/dl), median (IQR)	92.5 (55.0)	114.0 (65.0)	0.301
C3 (mg/dl), median (IQR)	94.6 (18.6)	106.9 (26.4)	0.009*
C4 (mg/dl), median (IQR)	22.5 (7.4)	23.6 (6.4)	0.401
Leukopenia (< 4/mm^3), *n* (%)	10 (15.6)	1 (7.7)	0.678
ESR (mm/h), median (IQR)	21.0 (19.5)	15.0 (24.0)	0.142
CRP (mg/dl), median (IQR)	0.05 (0.07)	0.06 (0.25)	0.601

RF rheumatoid factor, *ANA* antinuclear antibody, *CCP* cyclic citrullinated peptide, *Ig* immunoglobulin, *C* complement, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

*Statistically significant

The variables that were found to be significantly associated with IgA RF seropositivity in patients with pSS at the univariate level were evaluated in pairwise correlation analyses (Fig. 3). As assessed using ELISA, IgA RF levels tended to correlate with IgG RF levels ($r = 0.351$, $p = 0.002$), Ig M RF levels ($r = 0.408$, $p < 0.001$), and IgG levels ($r = 0.516$, $p < 0.001$). IgA RF levels were inversely correlated with USFR ($r = -0.243$, $p = 0.033$) and C3 levels ($r = -0.371$, $p = 0.002$). IgA RF levels were correlated with the sialoscintigraphic grade of both parotid ($r = 0.234$, $p = 0.041$) and submandibular ($r = 0.325$, $p = 0.004$) glands.

Discussion

The present study confirmed clinical phenotypic characteristics of IgA RF-positive pSS, and the application of IgA RF detection in a cohort of patients with sicca symptoms to detect

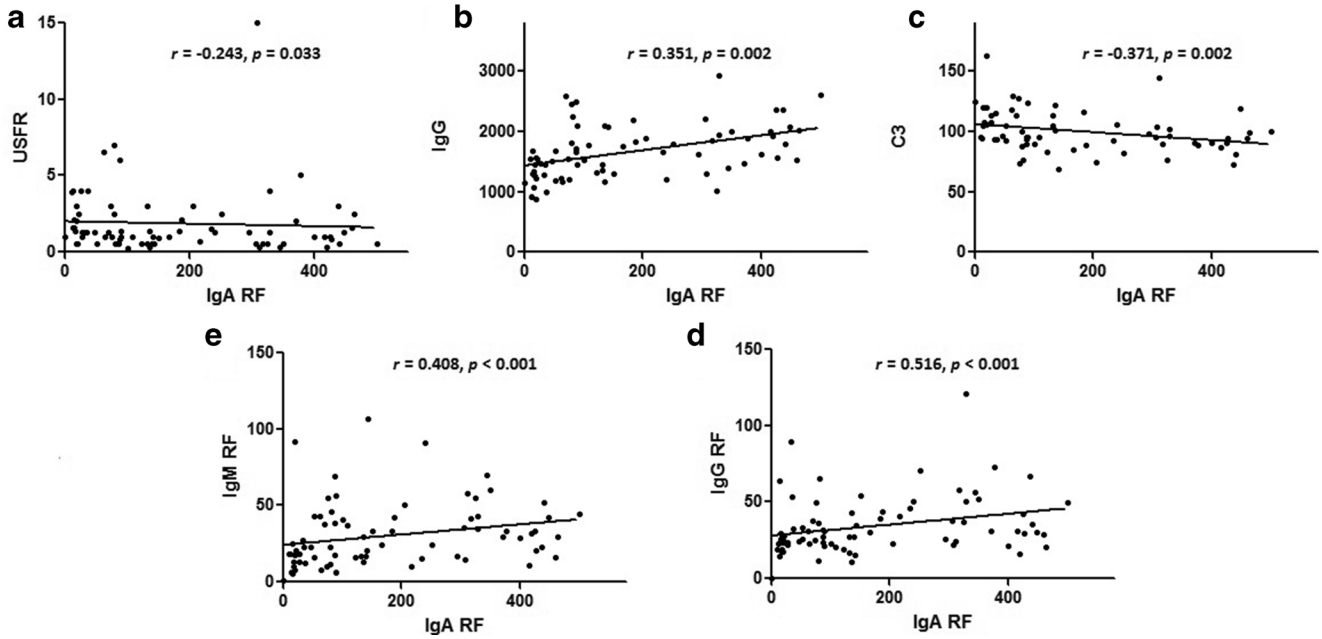

Fig. 3 Correlation between serum IgA RF and USFR (**a**), IgG (**b**), C3 (**c**), IgM RF (**d**), and IgG RF (**e**) in patients with primary Sjogren's syndrome. Each dot represents individual value (correlation coefficient and *p* value by Spearman's rank correlation test). *RF* rheumatoid factor, *USFR* unstimulated salivary flow rate, *Ig* immunoglobulin, *C* complement

pSS. RFs were initially described by Waaler and Rose in 1940, but there is little information about the mechanisms underlying their production, physiological functions, and pathological effects [4]. RFs are frequently detected in patients with RA, connective tissue disease, and various infectious diseases. pSS is typically associated with RFs at high frequencies (75–95%) [4, 18]. The presence of RF in pSS was found to be associated with serologic positivity for anti-Ro/SSA and anti-La/SSB, hypergammaglobulinaemia, cryoglobulinaemia, and systemic diseases [19–22]. Several studies further identified that RF was an independent predictor for lymphoma development [23, 24]. Although IgM RFs are the most frequently observed isotype and the measurement of non-IgM RF levels is not widely used in clinical practice, a few studies identified that IgA RF had a predictive value for the development and disease severity of RA and juvenile idiopathic arthritis (JIA) [25–27]. However, there is little data related to the clinical features of IgA RF-positive pSS patients.

Consistent with previous reports [9], we confirmed that IgA RF was associated with active serologic profile, including high ANA, IgM RF, IgG RF, and IgG levels and low C3 levels. A proposed model of the generation of RF suggested that a strong and disease-specific humoral autoimmune reaction might proceed within a host, who had a certain genetic background, and produce RF. Firstly, the specific production of an autoimmune response after tissue destruction and initiation of inflammation results in the production of distinct autoantibodies, such as anti-Ro/SSA and anti-La/SSB. Then, enhanced immune complexes generated through protective and autoimmune responses exaggerate the initial immune response and result in RF production [18]. In some individuals, the exaggerated B cell activation could cause lymphomagenesis. The presence of IgA RF could reflect polyclonal B cell activation, which is a distinctive characteristic of pSS.

In the present study, we identified IgA RFs in 80.1% of pSS patients in our cohort, whereas only 20.1% of patients with idiopathic sicca symptoms had IgA RFs. The presence of IgA RF was associated with significantly worse functional impairment of the salivary secretion, as evidenced by low USFR, severe sialoscintigraphic grade, and high prevalence of xerostomia. Although sialoscintigraphy has been excluded from the new ACR/EUAR classification criteria due to its low accuracy in diagnosing pSS, sialoscintigraphy could be used to evaluate the severe salivary glandular involvement in pSS [28, 29]. Güne et al. demonstrated that quantitative salivary gland scintigraphy may be a useful method for evaluating salivary gland dysfunction and also for determining disease severity in pSS [29]. Among the isotypes of RF, IgA RF is locally produced in the salivary glands, and inflammation and destruction of the salivary glands could lead to increased IgA RF levels in patients with pSS [30–32]. It is uncertain whether IgA RF has a pathogenic role or whether it is a result of the secondary immune response in patients with pSS. However, the presence and the increased IgA RF levels could predict more severe inflammation and destruction of the exocrine glands in patients with pSS. Therefore, the presence of IgA in patients with pSS could be a predictive marker for severe exocrine dysfunction and active serologic status.

A previously published study reported a correlation between the concentration of IgA RF and the number of extra-

glandular manifestations [11], whereas another study demonstrated that IgA RF was associated with renal disease in patients with pSS [12]. However, we could not find any association between the presence of IgA RF and extra-glandular manifestations. We found a similar frequency of extra-glandular manifestations, such as lung involvement, peripheral nervous system involvement, arthritis, leukopenia, kidney involvement, and Raynaud's phenomenon, in patients with pSS compared with previous studies [33–35]. In particular, in a previous study that reported an association between IgA RF and renal involvement, the prevalence of renal involvement (16%) was much higher than that observed in other previous studies (0.9–7.5%) [33–35] and in our study (3.9%). However, the number of patients enrolled in the present study and previously published studies was relatively small; hence, a further large study is needed to more clearly elucidate the association of IgA RF with extra-glandular manifestations.

Unlike the association observed between IgA RF and RA as well as JIA, no relation was observed between inflammatory arthritis and IgA RF in patients with pSS in this study. The positive association of anti-CCP antibodies with non-erosive arthritis was revealed in previously published studies [36, 37]. Not surprisingly, anti-CCP was present much more frequently in patients with pSS who had inflammatory arthritis. In a recent study conducted in the Netherlands, hypergammaglobulinaemia and increased IgG levels occurred much less frequently in the polyarthritis group than in the polyarthritis negative group [38]. On the contrary, we could not find an association between inflammatory arthritis and increased IgG levels representing pronounced B cell activation.

We confirmed the potential of IgA RF to distinguish pSS from idiopathic sicca symptoms with good sensitivity and specificity. Most patients in the control group presenting sicca symptoms and positive RF or ANA were referred to our clinic. Therefore, the control group had a high positive rate of IgM RF. However, in comparison to IgM RF detected by ELISA, IgA RF showed a better diagnostic accuracy in pSS. In the new classification criteria for pSS, the decision to exclude ANA and RF as initial candidate items was based on the analyses showing that an extremely small number of individuals who met the ACR classification criteria were negative for anti-SSA/SSB (anti-Ro/La) but positive for ANA (titre $\geq$ 1:320) and RF [13]. However, non-IgM RF has not been routinely measured and evaluated in previous studies. Therefore, further studies are needed to reveal a diagnostic role of IgA RF in pSS.

Our study presented several limitations. First, this study was a single-centre study, and the number of patients included was relatively small. The statistical power was limited by the small sample size of 13 patients with IgA RF-negative pSS. Further research in a large cohort of pSS patients is mandatory to confirm the diagnostic and clinical roles of IgA RF. Second, we could not evaluate the association between IgA RF seropositivity and focus score in salivary gland biopsies, because only few patients underwent lip biopsies. Our study assessed the relationship between IgA RF and exocrine gland dysfunction based on USFR measurement and sialoscintigraphy. Therefore, the correlation between the pathologic findings of sialoadenitis and IgA RF should be investigated in future studies.

The presence of IgA RF was associated with significantly worse exocrine function and active serologic profile of pSS. Indeed, our findings confirmed the potential of IgA RF to distinguish pSS from idiopathic sicca symptoms with good sensitivity and specificity. We suggest IgA RF as an additional clinical predictive and diagnostic marker for pSS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all the individual participants included in the study.

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