Correlation between colour Doppler activity and parenchymal alterations in salivary glands of patients with primary Sjögren's disease

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Abstract

Objective

Sjögren's disease (SjD) is a systemic autoimmune disorder characterised by chronic lymphocytic inflammation of the salivary and lacrimal glands, leading to progressive dysfunction and tissue damage. Salivary gland ultrasonography (SGUS) enables standardised, semiquantitative evaluation of glandular structure. While grey-scale (B-mode) scoring systems such as De Vita et al. and OMERACT are widely used, the recently validated colour Doppler (CD) OMERACT scoring system allows assessment of glandular vascularisation. However, its relationship with structural imaging and clinical disease activity remains uncertain. The aim of the study is to assess the correlation between CD ultrasonography and established B-mode scores, and to explore the clinical significance of vascular assessment in patients with SjD.

Methods

Sixty-three consecutive patients fulfilling the 2016 ACR/EULAR criteria for SjD underwent standardised SGUS of parotid and submandibular glands using De Vita et al., B-mode OMERACT, and CD OMERACT semiquantitative scores (0–3). Clinical, serological, and disease activity parameters were recorded and correlated using Spearman's rank coefficient.

Results

Most patients exhibited moderate to severe B-mode alterations, while higher CD grades (2–3) were less frequent. CD OMERACT scores correlated moderately with De Vita et al. ($\varrho=0.44$, $p<0.001$), B-mode OMERACT ($\varrho=0.48$, $p<0.001$), and glandular ESSDAI ($\varrho=0.43$, $p<0.001$). SjD-related lymphoma showed weak but significant correlation with CD OMERACT and moderate correlation with both B-mode scores.

Conclusion

Colour Doppler ultrasonography reflects inflammatory vascular changes paralleling structural and clinical disease activity in SjD. Although it does not yet provide independent diagnostic value, further studies are needed to define the role of Colour Doppler as a complementary tool in salivary gland ultrasonography for assessing glandular inflammation and lymphoproliferative risk.

Key words

Sjögren's syndrome, parotid gland, ultrasonography, biopsy

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Introduction

Sjögren's disease (SjD) is a systemic autoimmune disease characterised by chronic lymphocytic inflammation of the lacrimal and salivary glands, leading to progressive glandular dysfunction and tissue damage, in addition to extra-glandular manifestations (1, 2). B cell hyperactivation and chronic lymphocytic infiltration expose SjD patients to an increased risk of lymphoproliferative complications, such as MALT lymphoma (3-5).

Morphological alterations of the major salivary glands in SjD can be easily depicted by imaging techniques, particularly major salivary gland ultrasonography (SGUS), which has emerged as a valuable non-invasive tool for disease evaluation (6-8). Over the past decade, several ultrasonographic scoring systems have been proposed to semi-quantitatively assess glandular involvement in SjD, with the aim of providing standardised imaging criteria for both diagnostic and classification purposes. Although SGUS is not yet included in the 2016 ACR/EULAR classification criteria, its clinical utility and reproducibility have been widely recognised (9). To overcome heterogeneity among existing scoring systems, the Sjögren's Ultrasound Subgroup of the OMERACT working group developed a consensus-based definition of B-mode (grey-scale) SGUS features and proposed a semiquantitative 0–3 scoring system for salivary gland structural abnormalities, which is now extensively used in clinical and research settings (10). Most of these systems, however, rely exclusively on grey-scale imaging, without incorporating vascular information. Recently, the same OMERACT subgroup standardised the ultrasonographic assessment of salivary gland vascularisation and developed a consensus-based 0–3 colour Doppler (CD) scoring system to evaluate glandular vascular signals in SjD patients (11). This system demonstrated good inter-reader and excellent intra-reader reliability both in static images and in live patient exercises. Subsequent studies have confirmed that CD ultrasonography is a reliable technique for visualising intraparenchymal vasculature in SjD, though its reproducibility is highly dependent on operator experience reliability (12). Despite these advances, current literature on the clinical role of CD ultrasonography in SjD remains limited. In particular, its potential correlation with established B-mode semiquantitative scores, such as the De Vita *et al*. (13) and OMERACT systems (10), and with clinical or serological markers of glandular and extra-glandular inflammation has not been fully elucidated. The aim of the present study is therefore to evaluate the relationship between CD findings and the most widely used 0–3 semiquantitative B-mode scores (De Vita *et al*. and OMERACT) in patients with SjD, and to explore whether glandular CD assessment may provide additional information on inflammatory domains, both glandular and systemic, beyond that offered by traditional structural imaging.

Material and methods

Patients

Consecutive adult SjD patients, referred to the Clinic of Rheumatology, University Hospital of Udine, Italy, from January until June 2023, who fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2016 classification criteria for SjD, were recruited. The study was conducted according to a protocol approved by the Regional Ethical Committee (CEUR-2017-Os-027-ASUIUD). All patients gave oral and written informed consent for all procedures, which were carried out in accordance with the Declaration of Helsinki and with the guidelines for good clinical practice.

Clinical evaluation

Data collected included gender, age, disease duration, previous minor salivary gland biopsy, and the presence of serum anti-Ro/SSA, anti-La/SSB antibodies, and rheumatoid factor (RF). Additional clinical and serological variables were also recorded, including serum monoclonal component, complement levels (C3 and C4), presence of cryoglobulinaemia, and disease activity and patient-reported outcomes, evaluated using the EULAR Sjögren's Syndrome

Disease Activity Index (ESSDAI) and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (14). Oral and ocular dryness were assessed through both subjective and objective measures. Subjective symptoms were evaluated using the Visual Analogue Scale (VAS) for oral and ocular sicca, while objective assessment was based on the unstimulated salivary flow rate and Schirmer's test I. Unstimulated saliva was collected in pre-weighed containers, and the saliva volume was determined by weighing. Objective tests were performed on the same day as the SGUS evaluation, according to the recommended standardised procedure.

Sonographic evaluation: B-mode

The parotid glands (PGs) and submandibular glands (SMGs) were examined using a SAMSUNG RS85 ultrasound system equipped with a linear high-frequency transducer (LM4-15B). Examinations were performed by one of three expert sonographers (AZ, VM, or IG), all of whom were blinded to the patients' clinical data. The intra-rater and inter-rater reliability between the three sonographers exceeded 0.7 for both scoring systems used. The three sonographers were blinded to each other B mode and CD scores.

Both the PGs and SMGs were scanned with the patient in a supine position, the neck hyperextended, and the head slightly rotated to the opposite side. The PGs were evaluated in both longitudinal and transverse planes, while the SMGs were assessed in the longitudinal plane, following the standardised OMERACT scanning procedure. Ultrasound images were scored in real time at the patient's bedside using two B-mode four-grade semiquantitative scoring systems: the 1992 De Vita *et al*. score and the B-mode OMERACT score. The De Vita *et al*. score (13), developed by stepwise discriminant analysis, considers both anechoic/hypoechoic areas and hyperechoic bands. Grade 0 corresponds to normal homogeneous parenchyma; grade 1 indicates mild inhomogeneity with isolated small anechoic/hypoechoic areas without hyperechoic bands (definition updated for modern ultrasound technology); grade 2 reflects moderate inhomogeneity with multiple anechoic/hypoechoic areas and/or few hyperechoic bands; and grade 3 denotes severe inhomogeneity with large, confluent anechoic/hypoechoic areas and/or diffuse hyperechoic bands. The B-mode OMERACT score (10), the most recent standardised SGUS scoring system, is defined as follows: grade 0, normal parenchyma; grade 1, minimal change with mild inhomogeneity without anechoic/hypoechoic areas; grade 2, moderate change with focal anechoic/hypoechoic areas surrounded by normal tissue; and grade 3, severe change with diffuse inhomogeneity and anechoic/hypoechoic areas involving the entire gland surface.

Sonographic evaluation: colour Doppler mode

Assessment of salivary gland vascularisation was performed according to the OMERACT consensus-based protocol for CD ultrasonography in SjD (11). Examinations were conducted after at least one hour of fasting, and participants were instructed not to smoke, eat, or brush their teeth before the evaluation, with the ambient temperature kept constant throughout the procedure. CD imaging was performed using standardised settings: CD frequency up to 9–12 MHz, pulse repetition frequency (PRF) 500–800 Hz, image depth 2.5 cm. Vascularisation was evaluated bilaterally in both PGs and SMGs, excluding signals originating from known anatomic vessels such as the facial, transverse facial, and retromandibular veins. The CD OMERACT 0–3 semiquantitative scoring system was applied, where grade 0 indicates no visible vascular signals in the glandular parenchyma, grade 1 focal dispersed vascular signals, grade 2 diffuse vascular signals detected in less than 50% of the gland, and grade 3 diffuse vascular signals in more than 50% of the glandular parenchyma.

Statistical evaluation

Statistical analysis was performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation (SD) for normally distributed continuous variables, and as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as absolute frequencies and percentages. Correlations between sonographic parameters and clinical, demographic, and laboratory variables were assessed using Spearman's rank correlation coefficient (ϱ) (15), due to the non-parametric nature of the data. The strength of the correlation was defined as follows: very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.00). A two-tailed p-value <0.05 was considered statistically significant in all analyses.

Results

Clinical and laboratory characteristics

A total of 63 consecutive patients with SjD were evaluated. The mean (±SD) age at the time of the SGUS assessment was 60.6±11.8 years, and the median (IQR) disease duration was 13 (12) years. Anti-Ro/SSA positivity accounted for 95.2%, while anti-La/SSB for 60.3% of cases. Rheumatoid factor (RF) was detected in 71.4% of patients. An abnormal unstimulated salivary flow rate was observed in 76.2% of patients, and an abnormal Schirmer's I test in 79%. Minor salivary gland biopsy (MSGB) results were available for 32 patients, of whom 75% had a positive result. 15/63 patients received a diagnosis of SjD-related lymphoma. The median (range) ESSDAI at the time of SGUS was 4 (0–22), and the mean (±SD) ESSPRI was 5.8 (± 2.2). Table I summarises the clinical and laboratory features of the patients (Table I).

Overall, 24/63 (38.1%) patients had moderate to severe disease activity (ESSDAI ≥5). 10/24 (41.6%) of these patients had a diagnosis of SjD-related lymphoma. In most of these cases (7/10, 70%), close observation was preferred over active treatment because of the indolent nature of the lymphoproliferative disease. The remaining three patients were treated with B-cell depleting agents according to haematological indications.

Table I. Demographic, clinical and laboratory features of included SjD patients.

Demographic data	
Female, n (%)	57 (90.5%)
Age at evaluation, mean (SD) years	60.6 (11.82)
Disease duration, median (IQR) years	13 (12)
Clinical indexes	
ESSDAI, median (IQR)	4 (6)
ESSDAI ≥ 5, n (%)	24 (38.1%)
ESSPRI, mean (SD)	5.8 (2.2)
ESSPRI ≥ 5, n (%)	38 (60.3%)
Positive unstimulated salivary flow, n (%)	48 (76.2%)
Positive Schirmer's I test n/N (%)	49/62 (79%)
Laboratory	
SSA positivity, n (%)	60 (95.2%)
SSB positivity, n (%)	38 (60.3%)
RF positivity, n (%)	45 (71.4%)
MC presence, n (%)	17 (27.0%)
Low C3/C4, n (%)	14 (22%)
Cryoglobulins, n (%)	8 (12.7%)
SjD-related lymphoma, n (%)	15 (28.3%)
Patients (n=63)	

SD: standard deviation; IQR: interquartile range; RF: rheumatoid factor; MC: monoclonal component; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index.

Among patients with moderate to severe disease activity without SjD-related lymphoma, conventional synthetic DMARDs were used more frequently (7/14; 50%). B-cell-depleting biologic DMARDs were administered in two patients, while another two were enrolled in interventional clinical trials, following SGUS assessment. Of note, patients were not receiving corticosteroids or nonsteroidal anti-inflammatory drugs at the time of the SGUS evaluation.

Sonographic features

According to the B-mode OMERACT scoring system, the majority of patients showed moderate to severe glandular alterations (grades 2–3), observed in 71.5% of PGs and 69.9% of SMGs. A similar distribution was found using De Vita *et al*. scoring system, with grades 2–3 recorded in 63.5% of PGs and 69.9% of SMGs. CD evaluation revealed predominantly absent or mild vascular signals (grade 0 or 1) in both PGs (81.0%) and SMGs (76.2%). Higher CD grades (2–3), indicative of increased intraglandular vascularity, were observed in 15.8% of PGs and 23.8% of SMGs. The distribution of the sonographic semiquantitative scores for PGs and SMGs is summarised in Table II. Figures 1 and 2 illustrate examples of CD OMERACT scores detected in PGs and SMGs, respectively.

Correlation between vascular, structural sonographic findings and clinical-demographic indexes

De Vita *et al*. and B-mode OMERACT scores showed a moderate and statistically significant correlation with both total and glandular ESSDAI scores (ϱ=0.530 and 0.485 respectively, with $p<0.001$). CD OMERACT score showed a moderate and statistically significant correlation only with glandular ESSDAI scores (ϱ=0.431 with $p<0.001$), and not with total ESSDAI score. The correlation of SGUS scores and other ESSDAI domains was also evaluated: a weak to moderate significant correlation between SGUS scores and lymphadenopathy and biological ESSDAI domain was found, more relevant for B-mode scores. A weak significant correlation was detected also between the haematological and peripheral nervous system (PNS) ESSDAI domains and De Vita *et al*. and B-mode OMERACT scores, and cutaneous ESSDAI score and B-mode OMERACT score. No significant correlation with other ESSDAI domains and SGUS scores was detected.

Regarding the correlation between SGUS scores, a strong positive correlation was observed between the total CD OMERACT score and both the De Vita *et al*. (ϱ=0.44, $p<0.001$) and B-mode OMERACT (ϱ=0.48, $p<0.001$) scores, indicating that higher vascular signals were associated with greater parenchymal structural alteration. The total CD OMERACT for PGs showed similarly strong associations with De Vita *et al*. (ϱ=0.64, $p<0.001$) and B-mode OMERACT (ϱ=0.60, $p<0.001$) scores.

Of note, the concomitant diagnosis of a SjD-related lymphoma showed a weak yet statistically significant correlation with the CD OMERACT score, and a moderate, statistically significant correlation with both the B-mode OMERACT and De Vita *et al*. total scores (Table III).

Discussion

SGUS represents a cornerstone in the diagnosis and management of SjD, of-

Table II. Sonographic features of the parotid and submandibular glands according to De Vita *et al*., the B-mode OMERACT and Colour Doppler OMERACT scoring systems.

Semiquantitative score (0–3)	De Vita *et al*. – PG	De Vita *et al*. – SMG	B-Mode OMERACT – PG	B-Mode OMERACT – SMG	CD OMERACT – PG	CD OMERACT – SMG
Grade 0	15 (23.8%)	11 (17.5%)	9 (14.3%)	11 (17.5%)	12 (19.0%)	17 (27.0%)
Grade 1	7 (11.1%)	8 (12.7%)	8 (12.7%)	8 (12.7%)	41 (65.1%)	31 (49.2%)
Grade 2	23 (36.5%)	26 (41.3%)	27 (42.9%)	26 (41.3%)	4 (6.3%)	11 (17.5%)
Grade 3	17 (27.0%)	18 (28.6%)	18 (28.6%)	18 (28.6%)	6(9.5%)	4(6.3%)

PG: parotid gland; SMG: submandibular gland; CD: colour Doppler.

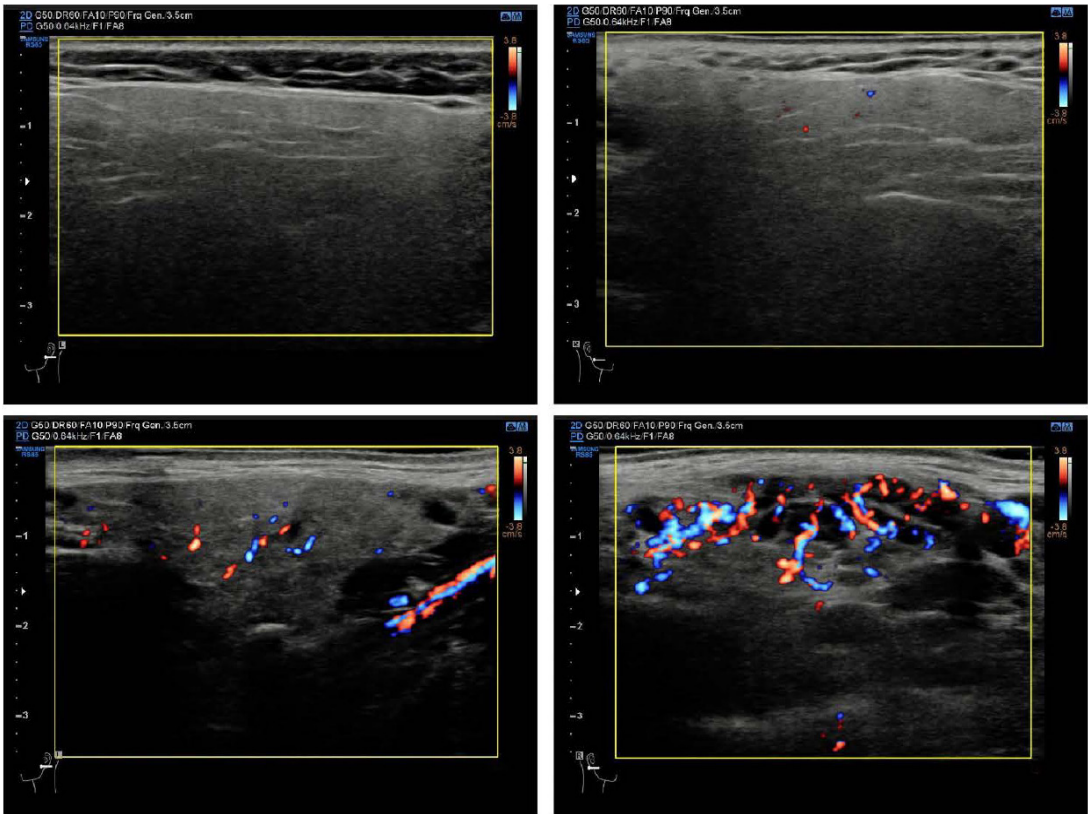

Fig. 1. Representative examples of CD OMERACT semiquantitative system in parotid glands.
First row, left to right: grade 0; grade 1.
Second row, left to right: grade 2; grade 3.

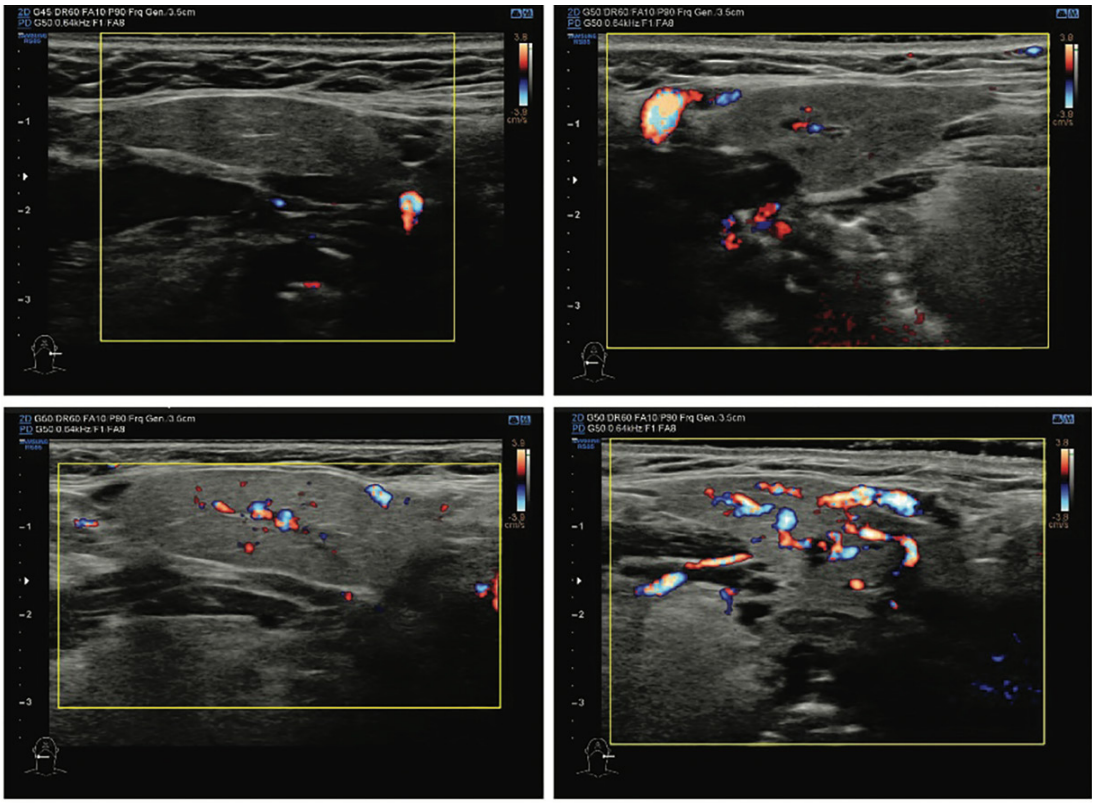

Fig. 2. Representative examples of CD OMERACT semiquantitative system in submandibular glands.
First row, left to right: grade 0; grade 1.
Second row, left to right: grade 2; grade 3.

fering a non-invasive, repeatable, and real-time evaluation of major salivary glands, which are the main target organs of the disease. Semi-quantitative B-mode scoring systems, such as those proposed by De Vita *et al*. and by the OMERACT working group, have enabled standardised assessment of glandular structural involvement (10, 13). SGUS scores have been shown to correlate with histopathological, serological and clinical markers of disease activity,

Table III. Correlation coefficients between scoring systems and main clinical features and indexes are expressed as Spearman's rho and related *p*-value.

	De Vita *et al*.		B-Mode OMERACT		CD OMERACT	
	p	Spearman's rho	*p*	Spearman's rho	*p*	Spearman's rho
Disease duration	0.883	0.019	0.908	-0.015	0.549	-0.077
Age at evaluation	0.204	0.165	0.311	0.132	0.244	0.149
ESSDAI total	**<0.001**	**0.530****	**<0.001**	**0.485****	0.075	0.226
ESSDAI glandular	**<0.001**	**0.448****	**<0.001**	**0.451****	**<0.001**	**0.431****
ESSDAI lymphadenopathy	**0.001**	**0.408****	**0.046**	**0.256***	**0.021**	**0.288***
ESSDAI haematological	**0.006**	**0.346***	**0.017**	**0.306***	0.291	0.135
ESSDAI biological	**<0.001**	**0.458****	**<0.001**	**0.472****	**0.046**	**0.251***
ESSDAI cutaneous	0.528	0.085	**0.020**	**0.297***	0.516	0.083
ESSDAI PNS	**0.015**	**0.315***	0.054	0.078	0.119	0.198
ESSPRI (total)	0.989	0.002	0.295	-0.141	0.851	-0.025
VAS global sicca	0.527	0.085	0.851	0.025	0.814	0.031
Lymphoma	**<0.001**	**0.542****	**<0.001**	**0.511****	**0.010**	**0.321***

CD: colour Doppler; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; PNS: peripheral nervous system.
*weak correlation; **moderate correlation.

including lymphocytic infiltrate and autoantibody positivity (16-18). Although SGUS is not yet part of the 2016 ACR/EULAR classification criteria, numerous studies have demonstrated that its inclusion improves diagnostic sensitivity and specificity without compromising accuracy (19, 20).

In recent years, the OMERACT group has extended SGUS evaluation to CD imaging, standardising the assessment of salivary gland vascularisation as a potential marker of parenchymal inflammation. However, the clinical relevance and additive value of CD in comparison with established B-mode systems remain to be clarified (11, 12, 21).

In the present study, CD evaluation revealed predominantly mild vascular signals (grades 0–1) in both PGs and SMGs, with only a minority of patients showing higher vascular grades (2–3). This pattern suggests that, in most patients, glandular vascular activity is limited, consistent with the chronic and fibrotic stage of glandular damage typically observed in long-standing SjD. These findings align with previous studies showing that vascular hyperaemia is more evident during active inflammatory phases but decreases as fibrosis becomes predominant (22).

Conversely, other reports have described increased CD activity associated with parenchymal inhomogeneity, indicating that, in some cases, vascular signals may reflect tissue remodelling (23). In our cohort, higher CD grades were associated with a lymphoproliferative profile. Patients with increased vascularisation often had biopsy-proven lymphoma or high-risk lymphoproliferative lesions such as LESA or MALT-type infiltrates, together with serological markers of B-cell activation, including RF positivity, hypocomplementaemia, and cryoglobulinaemia (24-26). These findings support the hypothesis that increased intraglandular vascularity may reflect an underlying proliferative or inflammatory milieu, consistent with previous reports linking focal vascularised lesions to lymphoma development in SjD (27-29).

From a quantitative perspective, total CD OMERACT scores correlated moderately with both B-mode De Vita *et al*. and OMERACT scores, and with glandular ESSDAI, suggesting that vascular activity parallels structural damage and local inflammation. However, the strength of these associations was comparable to that between the B-mode systems themselves, indicating that CD does not currently provide clear additional information beyond structural scoring.

At present, the clinical application of CD in SjD remains limited. Nevertheless, CD might represent a valuable complementary tool to assess disease dynamics over time. Its ability to detect changes in glandular vascularity could be particularly relevant for monitoring the response to therapeutic interventions targeting inflammatory or lymphoproliferative activity. Future longitudinal studies are warranted to confirm whether variations in CD scores correlate with clinical improvement or histopathological changes following treatment.

This study has some limitations. The sample size was relatively small, and the cross-sectional design prevents conclusions about causality or longitudinal evolution. Moreover, the absence of histopathological correlation for all patients limits the interpretation of vascular findings in terms of underlying tissue pathology. Nonetheless, the correlation between SjD-related lymphoma and SGUS measures was evaluated in relation to the histological assessment of major salivary gland parenchyma, rather than to other known peripheral laboratory risk factors for lymphoma development. In summary, CD evaluation in SjD correlates with established grey-scale scores and with glandular disease activity but does not yet appear to provide independent diagnostic information. Its role may lie in complementing SGUS to characterise inflammatory and lymphoproliferative patterns and to monitor therapeutic response. Larger, multicentre, and longitudinal studies are needed to validate the reproducibility, prognostic value, and potential clinical integration of CD scoring in routine SjD assessment.

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