Ultrasonographic scores and parotid histopathology in Sjögren's disease: challenges in lymphoma identification

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Abstract

Objective

The role of major salivary gland ultrasound (SGUS) in evaluating Sjögren's disease (SjD) continues to be debated. This study aims to assess the effectiveness of two SGUS scores (OMERACT and Hocevar et al.) in identifying lymphoma in SjD patients. A secondary aim is to explore the correlation between SGUS findings and histological characteristics of the parotid salivary glands.

Methods

Consecutive adult SjD patients with a clinical indication for parotid gland biopsy between September 2018 and October 2023 were included. Ultrasound images were anonymised and assessed according to the OMERACT and Hocevar et al. scores. The histological assessment performed by the pathologist included the evaluation of lymphoma presence, focus score (FS), lymphoepithelial lesions (LELs), germinal centres (GCs), multiple focal lymphocytic sialadenitis/lymphoepithelial sialadenitis (MESA/LESA), and features of non-specific sialadenitis.

Results

Among the 57 patients included in the study, 24 (42%) were diagnosed with lymphoma. Neither the OMERACT nor the Hocevar et al. score were effective in identifying lymphoma (OMERACT score: odds ratio 1.10, 95% CI: 0.91-1.34; p=0.305; Hocevar et al. score: odds ratio 1.03, 95% CI: 0.97-1.10; p=0.300). In the remaining 33 patients without lymphoma diagnosis but at higher risk of lymphoma development, regression analysis showed significant associations between ultrasound scores and histopathological features. LELs were linked to higher OMERACT (β=3.57, 95% CI:1.53-5.61; p=0.001) and Hocevar et al. scores (β=8.16, 95% CI: 1.45-14.87; p=0.019). Additionally, the FS was correlated with both OMERACT (β=0.26, 95% CI: 0.09-0.43; p=0.004) and Hocevar et al. scores (β=0.57, 95% CI: 0.03-1.12; p=0.040).

Conclusion

The current SGUS scores seem not to allow identifying lymphoma in SjD patients with high clinical suspicion. However, the correlation between advanced histological lesions and SGUS scores raises the opportunity of developing new SGUS scores with a prognostic rather than diagnostic or classificatory significance.

Key words

Sjögren's disease, lymphoma, utrasound, histopathology, parotid gland

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Introduction

Sjögren's disease (SjD) is a chronic systemic autoimmune disease characterised by a wide spectrum of manifestations, extending from exocrine to extra-glandular involvement (1). SjD predominantly involves exocrine glands (typically salivary and lacrimal glands), which are associated with the sicca symptoms. The glandular inflammation exposes SjD patients to an increased risk of lymphoma (2), the highest among various autoimmune diseases (3). The extra-nodal marginal zone lymphoma (MZL) of the mucosa-associated lymphoid tissue (MALT) histotype (4-6) appears to be the more frequent B-cell Non-Hodgkin Lymphoma histotype (7-16). Lymphoma early identification and prevention in SjD remains a major unmet need (17).

Morphological changes of salivary glands in SjD are depicted by ultrasonography (18) and salivary gland ultrasound (SGUS) is increasingly applied in SjD management to evaluate salivary gland structural abnormalities and parenchymal lesions of the major salivary glands (19-22). Multiple SGUS scoring systems have been suggested, incorporating parameters such as hypoechoic areas, hyperechoic bands, gland volume, contour regularity, and the clarity of the posterior glandular border. Each scoring system utilises and considers a distinct combination of the parameters along with varying cutoff values.

Over the years, various scoring system have been proposed, starting with the De Vita *et al*. score (23), and including the more recent Hocevar *et al*. score (0-48) (24) and Milic *et al*. score (0-12) (25). To improve the standardisation of the methodology, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) SGUS task force proposed a new four-grade semiquantitative score with good/excellent agreement results (26, 27). SGUS is not included in the SjD classification criteria (28); however, this non-irradiating and inexpensive technique can detect parenchymal lesions of the major salivary glands (19-21). This technique enables precise identification of abnormalities and target histological sampling by ultrasound-guided core needle biopsy (US-guided CNB), as recently proposed (29-32), allowing the collection of tissue directly from the parotid glands (33).

Histopathological features such as germinal centres (GCs), lymphoepithelial lesions (LELs) and focus score (FS) are observed in both minor (labial) and major (parotid) salivary glands. The presence of GCs and LELs may reflect the B-lymphocyte hyperactivity in SjD (34-36) and are recognised as cardinal lesions suggestive of SjD pathology in the major salivary glands (37).

The use of parotid biopsies has expanded with the introduction of US-guided CNB, which have shown comparable outcomes to traditional incisional parotid biopsies (38). Furthermore, parotid gland biopsies offer several advantages, including the ability to perform repeated biopsies on the same gland and a higher likelihood of detecting lymphoproliferative disorders compared to labial gland biopsies, since the major salivary glands are the main site of lymphoma development in SjD (39).

The correlation between histopathological and SGUS features remains incompletely elucidated in the literature, as well as the role of the SGUS scores in the identification of lymphoma. Traditionally, the presence of hyperechoic bands is considered indicative of glandular fibrosis (20), while hypoechoic areas are regarded as indicative of inflammation (40). However, there are no definitive studies that have correlated histopathological variables with ultrasonographic findings. Mossel *et al*. evaluated the associations between SGUS and histopathology, showing that evaluations of the parotid glands by histopathology, salivary flow, and SGUS assess different (or at best partly related) constructs (41). In particular, SGUS and histopathology may capture related inflammatory processes, while salivary flow often does not assess the same construct as parotid gland histopathology, nor parotid gland ultrasonography (41).

The study aims to evaluate the correlation of the OMERACT and Hocevar *et al*. scores with the diagnosis of lymphoma in patients with SjD. The secondary

objective is to assess the correlation between ultrasonographic findings and histological features of the parotid salivary glands, focusing on inflammatory infiltrates and elementary lesions within a cohort of patients with SjD.

Methods

Study design

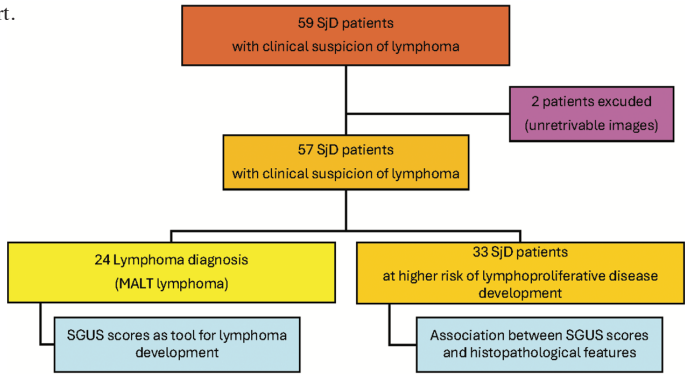
This study used a retrospective cohort study design. Patients with clinical diagnosis of SjD and fulfilment of the ACR/EULAR the classification criteria (28) who underwent parotid gland biopsy for clinical indication (*i.e.* high risk of lymphoma for the presence of parotid swelling and/or cryoglobulinaemic vasculitis) (17, 42) between September 2018 and October 2023 were selected for this study.

Informed consent was obtained from each patient in accordance with the Declaration of Helsinki and with local guidelines for good clinical practice. The study was conducted according to a protocol approved by the Regional Ethical Committee (CEUR- 2017-Os-027- ASUIUD). The exclusion criteria include the absence of ultrasound images, a time gap of more than 6 months between the salivary gland biopsy and ultrasound examination, the presence of other autoimmune diseases associated with SjD, and the presence of positive hepatitis C serology.

Clinical and laboratory assessment

Patients' clinical data were retrieved from the medical charts, including age, gender, disease duration, presence of xerostomia and xerophthalmia, as well as involvement of the nervous system, history of parotid swelling, arthritis, purpura, Raynaud's phenomenon, and pulmonary involvement. Laboratory data were also collected, including positivity for serum antibodies (ANA, anti-SSA/Ro, anti-SSB/La antibodies, rheumatoid factor), cryoglobulin, hypocomplementaemia, leukopenia, thrombocytopenia, hypergammaglobulinaemia, presence of a monoclonal component. The listed parameters will be defined and evaluated according to the definitions of the international validated disease activity score EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (43).

Fig. 1. Study flowchart.



Major salivary gland ultrasound

Ultrasound images stored in the facility's computer systems and belonging to enrolled patients have been retrieved and anonymised. The ultrasound images were obtained by a rheumatologist (AZ) and a radiologist (ML) with extensive experience (*i.e.* 10 years) in SjD-related ultrasonography with linear high-frequency transducers (RS85, probe LM4-15B (Samsung, Seoul, South Korea) or Affiniti 70G, probe L18-5 (Philips, Amsterdam, the Netherlands)). For each image, an assessment of the degree of ultrasonographic involvement was assessed according to the OMERACT (26) and Hocevar *et al.* (44) scores. The intra-rater and inter-rater reliability were almost perfect and substantial, respectively, as reported in previous study (27).

To better explore the ability to identify lymphoma patients and the correlation between the histopathological features and the ultrasonographic lesions, we specifically applied the ultrasonographic score also to the biopsied gland, allowing for a direct comparison between histopathological findings and the ultrasonographic score of the same parotid gland. In this scenario, the Hocevar et al. score was therefore applied only to the biopsied gland, with a possible range of 0 to 13 for parotid glands, and the OMERACT score ranged from 0 to 3.

Histological assessment

Histological preparations of major salivary glands obtained through surgical biopsy or CNB have been evaluated by the histopathologist (EP) with over 10 years of experience.

Histopathological assessment was used to determine the presence of lymphoma and, additionally, to evaluate the Focus Score (FS), the presence of lymphoepithelial lesions (LELs), germinal centres (GCs), multiple focal lymphocytic sialadenitis/lymphoepithelial sialadenitis (MESA/LESA), and non-specific features of sialadenitis (such as fibrotic area, duct dilatation, adipose replacement area) (45).

Statistical analysis

Patient demographic and clinical characteristics were presented with absolute values and percentages for categorical variables and means or medians (standard deviation [SD] or interquartile ranges [IQRs]) for continuous variables. The Shapiro-Wilk test was used to assess whether data were normally or nonnormally distributed. Univariate logistic regressions were performed to explore variables associated to the presence of lymphoma, estimating the odds ratios (ORs) and 95% confidence intervals (CIs). Univariate linear regressions were performed to estimate the association between the OMERACT and Hocevar *et al.* scores and histopathological features, by calculating the β (linear regression coefficient) and 95% CIs. Analyses were performed by STATA 18.

Results

Demographic and clinical characteristics

During the observational period, 59 patients underwent parotid gland biopsy. Two patients were excluded due to unretrievable ultrasound images. Consequently, 57 patients were included (Fig. 1).

Fifty out of 57 (80%) patients were female. The mean age at biopsy was 55

years (SD 15.5) after a median disease duration of 4 years (IQR 1–11). The interval between SGUS assessment and biopsy had a median of 3 months (IQR 0-6). Clinically, the cohort exhibited a mean ESSDAI score of 7 (SD 4). A history of parotid gland swelling was reported in 50 (88%) of patients, and xerostomia and xerophthalmia were present in 41 (72%) and 38 (67%) of the cohort, respectively. Other systemic manifestations included cutaneous purpura in 10 (18%), arthritis in 10 (18%), Raynaud's phenomenon in 7 (12%), and lung involvement in 5 (9%). Twenty-four out of 57 (42%) of the SjD patients were diagnosed with lymphoma by salivary gland biopsy.

Histopathologically, the majority of the cohort exhibited significant glandular involvement, with a FS ≥1 observed in 45 (82%) of the biopsies. LELs were present in 43 (81%), and GCs in 40 (75%) of the patients. MESA/LESA was identified in 20 (35%), while non-specific features of sialadenitis were observed in 4 (7%) of the cases.

Ultrasonographic assessment showed a median OMERACT score of 9 (IQR 8-10) and a median Hocevar *et al*. score of 28 (IQR 25-35). Complete demographic, serological and clinical characteristics of the cohort are presented in Table I.

Table I. Demographic and clinical features.

Patients (n=57)	
Demographic data	
Female, n (%)	50 (88%)
Age at biopsy, mean (SD) years	55 (15.5)
Age at SjD diagnosis, median (IQR) years	48 (38-56)
Disease duration, median (SD) years	4 (1-11)
Time between ultrasound and biopsy, median (IQR), months	3 (0-9)
Clinical features	
ESSDAI, mean (SD)	7 (4)
Xerostomia, n (%)	41 (72%)
Xeropthalmia, n (%)	38 (67%)
CNS involvement, n (%)	1 (2%)
PNS involvement, n (%)	5 (9%)
Parotid gland swelling history, n (%)	50 (88%)
Arthritis, n (%)	10 (18%)
Cutaneous purpura, n (%)	10 (18%)
Raynaud's phenomena, n (%)	7 (12%)
Lung involvement, n (%)	5 (9%)
Lymphoma diagnosis, n (%)	24 (42%)
Laboratory	
Leukopenia, n (%)	18 (32%)
Thrombocytopenia, n (%)	4 (7%)
Hypergammaglobulinaemia, n (%)	35 (61%)
Monoclonal component, n (%)	15 (26%)
Hypocomplementaemia C3, n (%)	11 (19%)
Hypocomplementaemia C4, n (%)	17 (30%)
ANA positivity, n (%)	56 (98%)
SSA positivity, n (%)	51 (89%)
SSB positivity, n (%)	31 (54%)
RF positivity, n (%	41 (72%)
Cryoglobulin, n (%)	9 (16%)
Histopathological features	
FS ≥1, n (%)	45 (82%) *2 missing values
LELs, n (%)	46 (81%)
GCs, n (%)	43 (75%)
MESA/LESA, n (%)	20 (35%)
Non-specific features of sialadenitis, n (%)	4 (7%)
Ultrasonographic assessment	
OMERACT score (0-12), median (IQR)	9 (8-10)
Biopsied gland OMERACT score (0-3), median (IQR)	3 (2-3)
Hocevar *et al*. score (0-48), median (IQR)	28 (25-35)
Biopsied gland Hocevar *et al*. score (0-13), median (IQR)	9 (7-10)

CNS: central nervous system; PNS: peripheral nervous system; ANA: antinuclear antibody; RF: rheumatoid factor; FS focus score; LELs: lympho-epithelial lesions; GCs: germinal centres; MESA/LESA: multiple focal lymphocytic sialadenitis/lymphoepithelial sialadenitis.

The ultrasonographic scores as a tool for lymphoma detection

According to the parotid biopsy, 24 patients were diagnosed with lymphoma (Fig. 2). All cases were identified as extra-nodal MZL-MALT lymphoma. The mean age at the time of biopsy was 62.0 years (SD 14.2). The median disease duration was 7 years (IQR 2.7–11). The mean ESSDAI score was 8 (SD 4). Regarding clinical manifestations, xerostomia and xerophthalmia were reported in 17 (71%) and 19 (79%) patients, respectively. Among the clinical features, parotid gland swelling was observed in the vast majority of patients (22/24, 92%).

Among the patients with a new diagnosis of lymphoma, SGUS evaluation revealed a median OMERACT score of 10 (IQR 8–12) and a median Hocevar *et al*. score of 31 (IQR 24–38). In particular, for the biopsied gland, the median Hocevar *et al*. score was 9 (IQR 8–11), while for the OMERACT was 3 (IQR 2-3). Focusing on the OMERACT score, 17/24 (71%) showed a grade 3 in the biopsied gland, while the remaining 7/24 (29%) showed suspicious focal lesions at the SGUS examination.

The ability of SGUS scores to identify lymphoma was evaluated. The odds ratio (OR) for the OMERACT score in detecting lymphoma was 1.10 (95% CI: 0.91–1.34; p=0.305). For the biopsied gland, the OMERACT score yielded an OR of 1.72 (95% CI: 0.79–3.72; p=0.171). Similarly, the Hocevar et al. score showed an OR of 1.03 (95% CI: 0.97–1.10; p=0.300). The biopsied gland Hocevar *et al*. score also did not show a significant association with lymphoma identification, with an OR of 1.13 (95% CI: 0.91–1.41; p=0.280) (Table II).

Association between ultrasonography score and histopathological analysis

Of the initial cohort, we perform this analysis on 33 SjD patients without

lymphoma diagnosis. Twenty-nine out of 33 (88%) patients were female. The mean age at biopsy was 49.8 years (SD 14.4) after a median disease duration of 2 years (IQR 0–9) and the median ESSDAI score was 4 (IQR 3–8). A significant proportion of patients experienced xerostomia 24 (73%) and xerophthalmia 19 (58%), while 23 (85%) had a history of parotid gland swelling. Arthritis was present in 5 (15%) of patients, cutaneous purpura in 4 (12%), and Raynaud's phenomenon in 3 (9%). Lung involvement occurred in only one patient (3%).

In this cohort of 33 SjD patients at higher risk of lymphoma, relevant ultrasonographic abnormalities were observed. The median OMERACT score was 8 (IQR 8–10), with 51.5% of patients exhibiting severe parotid gland involvement (grade 3) in the biopsied gland. The median Hocevar *et al*. score for the overall ultrasonographic evaluation was 28 (IQR 25–33). In particular, the Hocevar *et al*. score for the biopsied gland alone had a median value of 9 (IQR 7–10). Complete demographic, serological and clinical characteristics of the cohort are presented in Supplementary Table S1.

The combined regression analysis of the OMERACT and Hocevar *et al*. scores revealed that several histopathological features were significantly associated with SGUS findings in patients with SjD. The presence of LELs were associated with a significant increase in both the OMERACT score (β=3.57, 95% CI: 1.53–5.61; *p*=0.001) and the Hocevar *et al*. score (β=8.16, 95% CI: 1.45–14.87; *p*=0.019). FS also showed a significant positive correlation with both scoring systems. The regression coefficient for the OMERACT score was 0.26 (95% CI: 0.09–0.43; *p*=0.004), while for the Hocevar *et al*. score it was 0.57 (95% CI: 0.03–1.12; *p*=0.040), indicating that higher FS values are associated with increased ultrasonographic abnormalities. MESA/LESA was significantly associated with the OMERACT score (β=2.30, 95% CI: 0.46–4.15; *p*=0.016), and showed a trend towards significance with the Hocevar et al. score (β=5.52, 95% CI: -0.28–11.32; *p*=0.062).

In contrast, the presence of GCs was not significantly associated with either scoring system (OMERACT score: β=1.86, 95% CI: -0.26–3.98; *p*=0.083; Hocevar *et al*. score: β=4.46, 95% CI: -2.08–11.00; *p*=0.174). Non-specific features of sialadenitis did not show a significant correlation with either ultrasonographic score (OMERACT score: β=3.09, 95% CI: -3.49–9.66; *p*=0.341; Hocevar *et al*. score: β=9.22, 95% CI: -13.08–31.52; *p*=0.401). Complete data are reported in the Tables IIIA and IIIB.

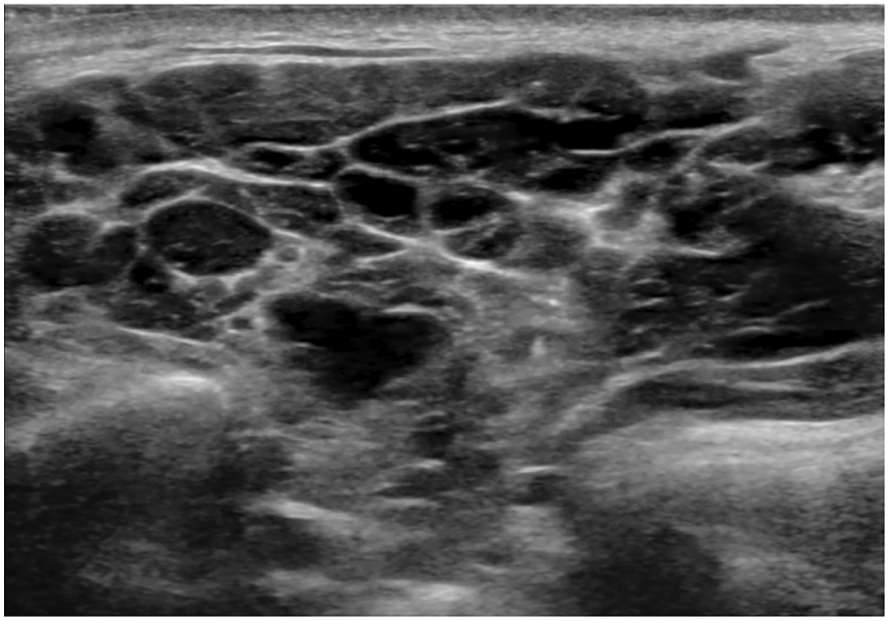


Fig. 2. Ultrasonographic image of a parotid gland of a patient diagnosed with lymphoma.

Table II. Lymphoma identification ability of ultrasonographic scores.

	Odds ratio	95% CI	*p*-value
OMERACT score	1.10	0.91-1.34	0.305
Hocevar *et al*. score	1.03	0.97-1.10	0.300
Biopsied gland OMERACT score	1.72	0.79-3.72	0.171
Biopsied gland Hocevar *et al*. score	1.13	0.91-1.41	0.280

Table IIIA. Regression model of OMERACT score.

Risk factor	β	95% CI	*p*-value
FS	0.26	0.09-0.43	0.004
LELs	3.57	1.53-5.61	0.001
GCs	1.86	-0.26-3.98	0.083
MESA/LESA	2.30	0.46-4.15	0.016
Non-specific features of sialadenitis	3.09	-3.49-9.66	0.341

Table IIIB. Regression model of HOCEVAR *et al*. score

Risk factor	β	95% CI	*p*-value
FS	0.57	0.03-1.12	0.040
LELs	8.16	1.45-14.87	0.019
GCs	4.46	-2.08-11.00	0.174
MESA/LESA	5.52	-0.28-11.32	0.062
Non-specific features of sialadenitis	9.22	-13.08-31.52	0.401

LELs: lympho-epithelial lesions; GCs: germinal centres; MESA/LESA: multiple focal lymphocytic sialadenitis/lymphoepithelial sialadenitis; FS: focus score.

Discussion

Parotid swelling and cryoglobulinaemic vasculitis are the two clinical key risk factors for lymphoma in patients

with SjD (17, 46). Non-Hodgkin's lymphoma and in particular extra-nodal MZL-MALT lymphoma is undoubtedly the most severe complication in the course of SjD, affecting approximately 5-10% of patients with SjD, with the onset of lymphoproliferation involving the major salivary glands in 60% of cases (39). SGUS imaging of these structures offers excellent visualisation of the glandular parenchyma and demonstrates high intra- and inter-operator reliability, even among non-experts (27). This makes SGUS a valuable tool for stratifying patients who may require major salivary gland biopsy.

Currently, most of the available scores serve diagnostic and classification purposes, while evidence of their prognostic role is limited.

In this study, we evaluated whether the most commonly used SGUS scores for major salivary glands in SjD (*i.e.* OMERACT (26) and Hocevar *et al.* (44) scores) could be useful in improving the accuracy of patient selection with SjD at clinical risk of lymphoma due to glandular swelling or cryoglobulinaemic vasculitis. The study demonstrated that while ultrasonographic assessments are valuable for evaluating glandular involvement, their ability to identify lymphoma in this subgroup of SjD at higher risk remains limited. In fact, both the Hocevar *et al.* score and the OMERACT score, whether evaluated across all four glands or at the level of the biopsied gland, do not provide added value in identifying lymphoma. Thus, the use of SGUS scores with prognostic significance in SjD deserves further prospective studies.

Recent studies have highlighted the significance of sonographic features in identifying lymphoma in the major salivary glands in SjD (22). To enhance the diagnostic accuracy of SGUS for lymphoma detection in SjD, several refinements to the scoring system could be proposed. Specifically, the scoring system could be expanded to incorporate "suspicious" ultrasound features in cases of focal lesions, such as very hypoechoic echogenicity, homogeneity, oval shape, well-defined margins, the presence of septa, colour Doppler vascularisation, and posterior acoustic enhancement. The concurrent presence of multiple features, particularly six or more, has demonstrated strong predictive value for lymphoma and could be integrated as a diagnostic criterion (22). In the absence of focal lesions, greater emphasis could be placed on the analysis of diffuse inhomogeneous glandular patterns as a distinguishing feature.

Nevertheless, the study has demonstrated a significant correlation between relevant histopathological lesions and the scores applied, underscoring the potential of SGUS as an objective tool to evaluate the glandular response in clinical trials.

The implications of our findings must be interpreted within the context of several limitations, including the retrospective design of the study, as well as the absence of control groups or data on initial disease conditions. Another limitation derives from the clinical necessity to perform parotid gland biopsies primarily based on suspicion of lymphoma. This may create a selection bias, as the cohort largely consists of individuals with biologically active disease and advanced lymphoproliferation in the parotid glands, often presenting with visible glandular swelling. Therefore, the correlation observed between ultrasonographic scores, and histopathological features may reflect the severity of the disease stage. The majority of our patients exhibited high ultrasonographic scores (*i.e.* OMERACT scores of 2 and 3), while those with lower scores (*i.e.* OMERACT scores of 0 and 1) were underrepresented. Future studies should aim to include also patients with lower ultrasonographic scores, to determine if similar correlations are maintained across all disease stages.

In conclusion, our findings demonstrate that the OMERACT and Hocevar *et al.* scores are not able to identify lymphoma in SjD patients at higher risk for the presence of parotid swelling and/or cryoglobulinaemic vasculitis. Nevertheless, the correlation between the elementary histological lesions and ultrasound scores highlights the opportunity of developing dedicated scores in the near future for risk stratification of lymphoma and monitoring the response to therapy.

References

1. GOULES AV, TZIOUFAS AG: Primary Sjögren's syndrome: clinical phenotypes, outcome and the development of biomarkers. *Immunol Res* 2017; 65: 331-44. https://doi.org/10.1007/s12026-016-8844-4
2. ZINTZARAS E, VOULGARELIS M, MOUTSOPOULOS HM: The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005; 165: 2337-44. https://doi.org/10.1001/archinte.165.20.2337
3. LIANG Y, YANG Z, QIN B, ZHONG R: Primary Sjögren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis* 2014; 73: 1151-56. https://doi.org/10.1136/annrheumdis-2013-203305
4. ZUCCA E, BERTONI F, CAVALLI F: Pathogenesis and treatment of extranodal lymphomas: The fascinating model of mucosa-associated lymphoid tissue lymphoma. *Haematologica* 2003; 88: 841-44.
5. NAKAMURA S, PONZONI M: Marginal zone B-cell lymphoma: lessons from Western and Eastern diagnostic approaches. *Pathology* 2020; 52: 15-29. https://doi.org/10.1016/j.pathol.2019.08.012
6. DE VITA S, GANDOLFO S, ZANDONELLA CALLEGHER S, ZABOTTI A, QUARTUCCIO L: The evaluation of disease activity in Sjögren's syndrome based on the degree of MALT involvement: glandular swelling and cryoglobulinaemia compared to ESSDAI in a cohort study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S150-56.
7. ANAYA JM, MCGUFF HS, BANKS PM, TALAL N: Clinicopathological factors relating malignant lymphoma with Sjögren's syndrome. *Semin Arthritis Rheum* 1996; 25: 337-46. https://doi.org/10.1016/s0049-0172(96)80019-9
8. KRUIZE AA, HENÉ RJ, VAN DER HEIDE A *et al.*: Long-term followup of patients with Sjögren's syndrome. *Arthritis Rheum* 1996; 39: 297-303. https://doi.org/10.1002/art.1780390219
9. ROYER B, CAZALS-HATEM D, SIBILIA J *et al.*: Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997; 90: 766-75.
10. VOULGARELIS M, DAFNI UG, ISENBERG DA, MOUTSOPOULOS HM: Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's syndrome. *Arthritis Rheum* 1999; 42: 1765-72. https://doi.org/10.1002/1529-0131(199908)42:8<1765::AID-ANR28>3.0.CO;2-V
11. MARTENS PB, PILLEMER SR, JACOBSSON LT, O'FALLON WM, MATTESON EL: Survivorship in a population-based cohort of patients with Sjögren's syndrome, 1976-1992. *J Rheumatol* 1999; 26: 1296-300.
12. PERTOVAARA M, PUKKALA E, LAIPPALA P, MIETTINEN A, PASTERNACK A: A longitudinal cohort study of Finnish patients with primary Sjögren's syndrome: clinical, immunological, and epidemiological aspects. *Ann Rheum Dis* 2001; 60: 467-72. https://doi.org/10.1136/ard.60.5.467
13. THEANDER E, HENRIKSSON G, LJUNGBERG

O, MANDL T, MANTHORPE R, JACOBSSON LTH: Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006; 65: 796-803. https://doi.org/10.1136/ard.2005.041186

14. THEANDER E, VASAITIS L, BAECKLUND E *et al*.: Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. *Ann Rheum Dis* 2011; 70: 1363-68. https://doi.org/10.1136/ard.2010.144782
15. JOHNSEN SJ, BRUN JG, GØRANSSON LG *et al*.: Risk of non-Hodgkin's lymphoma in primary Sjögren's syndrome: a population-based study. *Arthritis Care Res* (Hoboken) 2013; 65: 816-21. https://doi.org/10.1002/acr.21887
16. QUARTUCCIO L, ISOLA M, BALDINI C *et al*.: Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: Results of a multicenter study. *J Autoimmun* 2014; 51: 75-80. https://doi.org/10.1016/j.jaut.2013.10.002
17. DE VITA S, ISOLA M, BALDINI C *et al*.: Predicting lymphoma in Sjögren's syndrome and the pathogenetic role of parotid microenvironment through precise parotid swelling recording. *Rheumatology* (Oxford) 2023; 62: 1586-93. https://doi.org/10.1093/rheumatology/keac470
18. ATKINSON C, FULLER J, HUANG B: Cross-sectional imaging techniques and normal anatomy of the salivary glands. *Neuroimaging Clin N Am* 2018; 28: 137-58. https://doi.org/10.1016/j.nic.2018.01.001
19. VAN GINKEL MS, GLAUDEMANS AWJM, VAN DER VEGT B *et al*.: Imaging in primary Sjögren's syndrome. *J Clin Med* 2020; 9: 1-21. https://doi.org/10.3390/jcm9082492
20. ZABOTTI A, ZANDONELLA CALLEGHER S *et al*.: Hyperechoic bands detected by salivary gland ultrasonography are related to salivary impairment in established Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S146-52.
21. ZANDONELLA CALLEGHER S, ZABOTTI A *et al*.: Normal-appearing salivary gland ultrasonography identifies a milder phenotype of primary Sjögren's syndrome. *Front Med* 2020; 7: 602354. https://doi.org/10.3389/fmed.2020.602354
22. LORENZON M, TULIPANO DI FRANCO F *et al*.: Sonographic features of lymphoma of the major salivary glands diagnosed with ultrasound-guided core needle biopsy in Sjögren's syndrome. *Clin Exp Rheumatol* 2021; 39 (Suppl. 133): S175-83. https://doi.org/10.55563/clinexprheumatol/4c36nr
23. DE VITA S, LORENZON G, ROSSI G, SABELLA M, FOSSALUZZA V: Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-56.
24. HOCEVAR A, RAINER S, ROZMAN B, ZOR P, TOMSIC M: Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome. Evaluation of a novel scoring system. *Eur J Radiol* 2007; 63: 379-83. https://doi.org/10.1016/j.ejrad.2007.02.003
25. MILIC V, PETROVIC R, BORICIC I *et al*.: Ultrasonography of major salivary glands could be an alternative tool to sialoscintigraphy in the American-European classification criteria for primary Sjögren's syndrome. *Rheumatology* (Oxford) 2012; 51: 1081-85. https://doi.org/10.1093/rheumatology/ker431
26. JOUSSE-JOULIN S, D'AGOSTINO MA, NICOLAS C *et al*.: Video clip assessment of a salivary gland ultrasound scoring system in Sjögren's syndrome using consensual definitions: an OMERACT ultrasound working group reliability exercise. *Ann Rheum Dis* 2019; 78: 967-73. https://doi.org/10.1136/annrheumdis-2019-215024
27. ZABOTTI A, ZANDONELLA CALLEGHER S *et al*.: Salivary gland ultrasonography in Sjögren's syndrome: a European multicenter reliability exercise for the HarmonicSS Project. *Front Med* 2020; 7: 581248. https://doi.org/10.3389/fmed.2020.581248
28. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017; 69: 35-45. https://doi.org/10.1002/art.39859
29. BAER AN, GRADER-BECK T, ANTIOCHOS B, BIRNBAUM J, FRADIN JM: Ultrasound-guided biopsy of suspected salivary gland lymphoma in Sjögren's syndrome. *Arthritis Care Res* (Hoboken) 2021; 73(6): 849-55. https://doi.org/10.1002/acr.24203.
30. ZABOTTI A, ZANDONELLA CALLEGHER S *et al*.: Ultrasound-guided core needle biopsy compared with open biopsy: a new diagnostic approach to salivary gland enlargement in Sjögren's syndrome? *Rheumatology* (Oxford) 2021; 60(3): 1282-90. https://doi.org/10.1093/rheumatology/keaa441
31. MANFRÈ V, GIOVANNINI I, ZANDONELLA CALLEGHER S *et al*.: Ultrasound and bioptic investigation of patients with primary Sjögren's syndrome. *J Clin Med* 2021; 10(6): 1171. https://doi.org/10.3390/jcm10061171
32. GIOVANNINI I, LORENZON M, MANFRÈ V *et al*.: Safety, patient acceptance and diagnostic accuracy of ultrasound core needle biopsy of parotid or submandibular glands in primary Sjögren's syndrome with suspected salivary gland lymphoma. *RMD Open* 2022; 8: e001901. https://doi.org/10.1136/rmdopen-2021-001901
33. DE VITA S, ZABOTTI A, TOMMASINI A, DÖRNER T, QUARTUCCIO L: The importance of studying the parotid glands in primary Sjögren's syndrome: the right tissue at the right time. *Clin Exp Rheumatol* 2022; 40(12): 2233-36. https://doi.org/10.55563/clinexprheumatol/c9uh02
34. NOCTURNE G, MARIETTE X: B cells in the pathogenesis of primary Sjögren syndrome. *Nat Rev Rheumatol* 2018; 14: 133-35. https://doi.org/10.1038/nrrheum.2018.1
35. PIJPE J, KALK WWI, VAN DER WAL JE *et al*.: Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. *Rheumatology* (Oxford) 2007; 46: 335-41. https://doi.org/10.1093/rheumatology/kel266
36. LONGHINO S, CHATZIS LG, DAL POZZOLO R *et al*.: Sjögren's syndrome: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(12): 2343-56. https://doi.org/10.55563/clinexprheumatol/255qsx
37. PRINGLE S, VERSTAPPEN GM, VAN GINKEL MS *et al*.: Lymphoepithelial lesions in the salivary glands of primary Sjögren's syndrome patients: the perfect storm? *Clin Exp Rheumatol* 2022; 40(12): 2434-42. https://doi.org/10.55563/clinexprheumatol/06an99
38. DEROO L, GENBRUGGE E, DOCHY F *et al*.: Ultrasound-guided core needle biopsy and incisional biopsy of the parotid gland are comparable in diagnosis of primary Sjögren's syndrome. *Rheumatology* (Oxford) 2023; 62: 2765-72. https://doi.org/10.1093/rheumatology/keac714
39. RETAMOZO S, BRITO-ZERÓN P, RAMOS-CASALS M: Prognostic markers of lymphoma development in primary Sjögren syndrome. *Lupus* 2019; 28: 923-36. https://doi.org/10.1177/0961203319857132
40. MILIC V, COLIC J, CIRKOVIC A, STANOJLOVIC S, DAMJANOV N: Disease activity and damage in patients with primary Sjögren's syndrome: Prognostic value of salivary gland ultrasonography. *PLoS One* 2019; 14: e0226498. https://doi.org/10.1371/journal.pone.0226498
41. MOSSEL E, VAN GINKEL MS, HAACKE EA *et al*.: Histopathology, salivary flow and ultrasonography of the parotid gland: three complementary measurements in primary Sjögren's syndrome. *Rheumatology* (Oxford) 2022; 61: 2472-82. https://doi.org/10.1093/rheumatology/keab781
42. DE VITA S, QUARTUCCIO L, SALVIN S, CORAZZA L, ZABOTTI A, FABRIS M: Cryoglobulinaemia related to Sjögren's syndrome or HCV infection: differences based on the pattern of bone marrow involvement, lymphoma evolution and laboratory tests after parotidectomy. *Rheumatology* (Oxford) 2012; 51: 627-33. https://doi.org/10.1093/rheumatology/ker407
43. SEROR R, BOWMAN SJ, BRITO-ZERON P *et al*.: EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. *RMD Open* 2015; 1: e000022. https://doi.org/10.1136/rmdopen-2014-000022
44. HOCEVAR A, AMBROZIC A, ROZMAN B, KVEDER T, TOMSIC M: Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome. Diagnostic value of a novel scoring system. *Rheumatology* (Oxford) 2005; 44: 768-72. https://doi.org/10.1093/rheumatology/keh588
45. ZABOTTI A, GIOVANNINI I, LONGHINO S *et al*.: Nuts and bolts of salivary gland pathology in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2023; 41(12): 2525-37. https://doi.org/10.55563/clinexprheumatol/fcjoqx
46. ZANDONELLA CALLEGHER S, GIOVANNINI I *et al*.: Sjögren syndrome: looking forward to the future. *Ther Adv Musculoskelet Dis* 2022; 14: 1759720X221100295. https://doi.org/10.1177/1759720X221100295