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Review Article

Minor Salivary Gland Surgery and Histopathological Scoring System: A Systematic Review

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Sjögren's syndrome is a systemic autoimmune disease characterized by chronic inflammation of the exocrine glands with an associated functional deficit. The clinical picture is characterized by symptoms such as dry eyes (xerophthalmia) and dry mouth (xerostomia). The disease is defined as primary if no other autoimmune diseases are associated, otherwise, it is defined as secondary. A systematic review was made using the databases PubMed (MEDLINE), Scopus, and keywords "biopsy," "classification," "clinical pathology," "salivary glands," and "Sjogren's syndrome." The diagnosis of Sjögren's syndrome is based on a combination of clinical, serologic, instrumental, and histological features. In addition to ocular tests, a biopsy of the minor salivary glands represents one of the most relevant examinations for the diagnosis. In fact, the evaluation of specific histopathological features represents one of the most important criteria proposed in the last international consensus of 2016, which developed the most recent classification criteria for Sjögren's syndrome. Knowledge of classification criteria, minor salivary gland biopsy techniques, and histopathological features are essential for the clinician to evaluate the pathology report and make a diagnosis of Sjögren's syndrome. The aim of this review is to describe the classification criteria of the disease proposed to date, the main biopsy techniques used to analyze the minor salivary glands, and finally, the histopathological diagnostic scoring systems currently applied.

1. Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder of unknown etiology, characterized by immune-mediated damage of the salivary and lacrimal glands, resulting in xerostomia, hyposalivation, and xerophthalmia [1].

Since 1986, the world's leading experts in SS have attempted to group the main criteria for classifying the disease to align its diagnosis [2].

The diagnostic examination considered to date the most specific for the diagnosis of SS is the minor salivary gland biopsy (MSGB), whose collected sample is analyzed histopathologically by microscopic analysis to assess the presence of specific markers of SS, in accordance with the main histopathological diagnostic criteria [3].

The aim of this review is to accurately describe the classification criteria of SS that have been stated to date, the main MSGB techniques, reporting their associated complications, and, finally, to describe the histopathological diagnostic scoring systems of the disease.

The focused questions were as follows: what are the SS classification criteria and histopathological scoring systems stated to date that must be known by the clinician to make a diagnosis? What are the main MSGB techniques performed to date?

2. Materials and Methods

2.1. Eligibility Criteria. The following inclusion criteria guided the analysis of the studies:

Type of studies. Clinical trials, case-control studies, cross-sectional studies, cohort studies, narrative reviews, and systematic reviews.

Type of participants. Patients with primary and secondary SS.

Type of interventions. Assessment of SS classification criteria, histopathological scoring systems, and MSGB techniques, evaluated through case-control, cross-sectional, cohort, clinical, and review studies.

Outcome *type*. Sensitivity and specificity of SS classification criteria and histopathological scoring systems, indications, advantages, and complications of MSGB techniques. Only studies that met all inclusion criteria were included. Moreover, the following exclusion criteria were adopted: (I) abstract of articles published in non-English languages; (II) duplicate studies; (III) in vitro or animal clinical studies; (IV) not pertinent studies; (V) absence of Ethics Committee approval; and (VI) irrelevant articles.

2.2. Search Strategy. The PICO model [4] (Population, Intervention, Comparison, Outcome) was used to perform this review, through a literature search of the PubMed (MEDLINE) and Scopus electronic databases. Abstracts of studies that evaluated the sensitivity and specificity of SS classification criteria and histopathological scoring systems, indications, advantages, and complications of MSGB techniques were reviewed.

During all the systematic literature reviews, the preferred reporting items for systematic reviews and meta-analysis (PRISMA) consensus was followed [5].

2.3. Research. The medical subject heading (MeSH) terms are biopsy, classification, clinical pathology, minor salivary glands, and Sjogren's syndrome; an electronic search was carried out with PubMed (MEDLINE) and Scopus databases. The articles published in the years 2012 to 2022 were targeted. The duration of data extraction was between January 2022 and May 2022. The last search was performed on 19 July 2022. Two calibrated reviewers (M.P. and F.P.) performed the search. Disagreements and discrepancies were resolved by consensus and two other reviewers were consulted (E.K., A.S., and F.S.). All the titles and abstracts were read thoroughly from the articles searched primarily, and nonrelevant studies were excluded. The relevant articles were enlisted and scrutinized for any similar studies which matched our inclusion criteria. For extraction of pertinent results, we read full texts of the included studies, and the findings were recorded.

The strategies developed and used for each electronic database are presented in Table S1 (Supplementary Material).

3. Results

The primary search identified 445 articles based on MeSH terms. Following those, 147 articles were removed (7 abstracts of articles published in non-English languages, 83 duplicates, 10 in vitro or animal clinical studies, 45 because not pertinent and 2 because of the absence of Ethics Committee approval), and 298 articles were screened based on title and abstracts. The remaining 298 full-text articles were assessed for eligibility. Additionally, 261 full-text articles were further excluded because they were irrelevant articles (full-text articles aim not useful to answer focused questions, more focus on the treatment of Sjögren's syndrome, analysis of other major and/or minor salivary gland disorders, analysis of other autoimmune diseases, full-text content not corresponding to abstract). The 37 relevant articles were finally included and analyzed in the review. The PRISMA flow diagram of the review process is described in Figure 1.

3.1. Risk of Bias. The Cochrane Collaboration's tool for assessing the risk of bias was used to evaluate the reviewed articles (Table 1). Table S2 shows the criteria for judging the risk of bias in the "risk of bias" assessment tool. This review has a moderate risk of bias.

Table 2 shows the baseline characteristics of patients included in the selected studies. Evidence of studies included in this systematic review (design, inclusion and exclusion criteria, aim, and results) is shown in Table S3.

4. Discussion

4.1. Sjögren's Syndrome Classification Criteria. The classification criteria for SS have been modified several times over the years, considering cost, applicability, and non-invasiveness without reducing sensitivity and specificity, while maintaining a high level of strictness, including both clinical and laboratory manifestations [6].

During the First International Seminar on SS held in Copenhagen in May 1986, four expert groups coming from different countries suggested different sets of classification criteria for SS as follows: Californian criteria, Greek criteria, Japanese criteria, and Copenhagen criteria. In general, any set of criteria could hypothetically be able to correctly select and classify patients with SS if used by individual groups of researchers; however, the need for universally accepted classification criteria was particularly felt in the scientific community at the time [7]. This took place for the first time in 1993 by Vitali and Bombardieri [8].

Vitali's preliminary criteria for SS classification were the first to be accepted by the scientific community thanks to a study involving 26 centers in 12 different countries (11 in Europe, plus Israel) [8].

In 2002 the classification criteria were revised by the American-European Consensus Group (AECG) and widely adopted both in clinical practice and research [9].

The main difference from 1993 Vitali's criteria is represented by the necessary presence of either histological (IV)

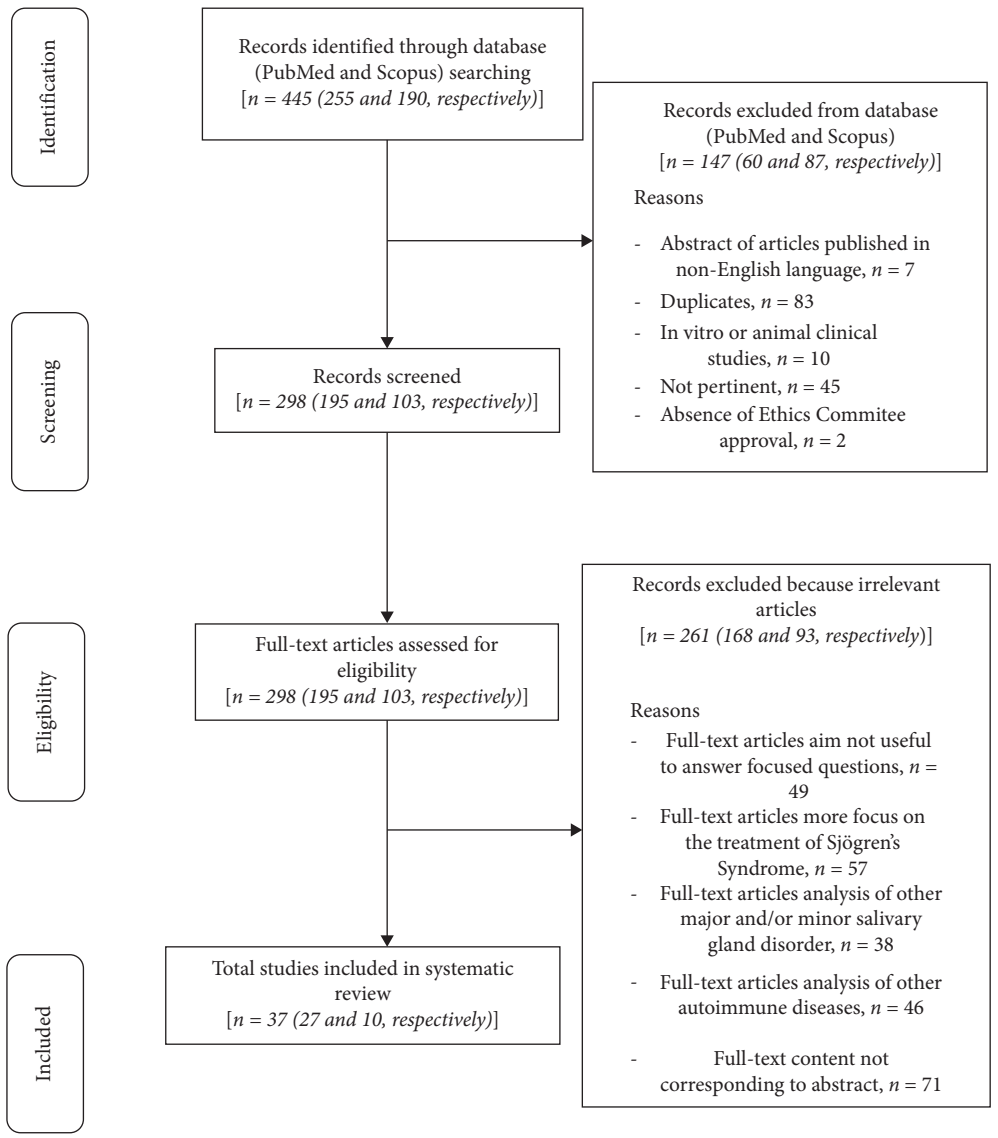

Figure 1: Flow chart of the systematic review process.

Table 1: The risk of bias in studies is represented by the green symbol, low risk of bias, and the yellow symbol, high risk of bias.

	Adequate sequence generated	Allocation concealment	Blinding	Incomplete outcome data	Registration outcome data
Baldini et al. [6]	⊖	⊖	⊖	✓	✓
Vitali and Bombardieri [7]	⊖	⊖	⊖	✓	✓
Vitali et al. [8]	✓	⊖	⊖	✓	✓
Vitali et al. [9]	⊖	⊖	⊖	✓	✓
Shiboski et al. [10]	⊖	✓	⊖	✓	✓

Table 1: Continued.

	Adequate sequence generated	Allocation concealment	Blinding	Incomplete outcome data	Registration outcome data
Rasmussen et al. [11]					
Van nimwegen et al. [12]					
Shiboski et al. [13]					
Rasmusssen et al. [14]					
Billings et al. [15]					
Bautista-Vargas et al. [16]					
Wijaya et al. [17]					
Chisholm and Mason [18]					
Greenspan et al. [19]					
Fox [20]					
Marx et al. [21]					
Delgado and Mosqueda [22]					
Richards et al. [23]					
Seoane et al. [24]					
Peloro et al. [25]					
Guevara-gutiérrez et al. [26]					
Teppo and Revonta [27]					

Table 1: Continued.

	Adequate sequence generated	Allocation concealment	Blinding	Incomplete outcome data	Registration outcome data
Comini et al. [28]	⊖	⊖	⊖	✓	✓
Syed et al. [29]	✓	⊖	⊖	✓	✓
Friedman et al. [30]	⊖	✓	✓	✓	✓
Tarpley et al. [31]	⊖	⊖	⊖	✓	✓
Costa et al. [32]	✓	✓	✓	✓	✓
Chen et al. [33]	⊖	⊖	⊖	✓	✓
Daniels et al. [34]	✓	⊖	⊖	✓	✓
Barone et al. [35]	⊖	⊖	⊖	✓	✓
Han et al. [36]	⊖	⊖	⊖	✓	✓
Kapsogeorgou et al. [37]	⊖	⊖	⊖	✓	✓
Rooper et al. [38]	⊖	⊖	⊖	✓	✓
Carubbi et al. [39]	✓	⊖	⊖	✓	✓
Fragkioudaki et al. [40]	⊖	⊖	⊖	✓	✓
Berardicurti et al. [41]	⊖	⊖	⊖	✓	✓
Stergiou et al. [42]	⊖	⊖	⊖	✓	✓

or serological (VI) criteria for the definition of SS. In addition, the diagnostic test procedures, the positivity parameters of sialography and scintigraphy, and some exclusion criteria have been more precisely defined.

In 2012, new classification criteria for SS were proposed to simplify the diagnosis, given the lack of standardization of old diagnostic criteria and the emergence of biological agents as potential treatments (Table 3). These criteria address individuals with signs/symptoms suggestive of SS [10].

Notably, Rasmussen et al. compared the 2012 ACR classification criteria with those of the 2002 AECG in a well-characterized cohort of patients with SS to evaluate the performance of the simplified classification. The two classifications achieved concordant results in most cases. From a clinical or biological point of view, there seems to be no

Table 2: Baseline characteristics of patients included in the selected studies.

Authors	*N* of patients	% Women	Mean age (years), mean (SD or range)	Ethnicity or countries of origin	% of pSS cases	% of sSS cases or other diseases
Baldini et al. [6]	NR as a nonsystematic review					
Vitali et al. [7]	NR as a nonsystematic review					
Vitali et al. [8]	480	48.54% (pSS) 39.37% (sSS)	54 ± 14 (pSS) 56 ± 13 (sSS)	11 European countries plus Israel (descriptive statistics are not shown)	51.25%	41.87%
Vitali et al. [9]	180	41.11% (pSS)	58.1 ± 14.9 (pSS)	10 European countries (descriptive statistics are not shown)	42.22%	No distinction between pSS and sSS
Shiboski et al. [10]	1,618	92.27%	54 (21–90)	Argentina (17%), China (15%), Denmark (20%), Japan (15%), United Kingdom (7%), USA (26%)	No distinction between pSS and sSS	No distinction between pSS and sSS
Rasmussen et al. [11]	837	91%	55 (12–86)	Caucasian (74%), African-American (2%), Asian (1%), Native American (2%), Pacific Islander (0.1%)	No distinction between pSS and sSS	No distinction between pSS and sSS
Van Nimwegen et al. [12]	114	94% (pSS) 86% (sSS)	52.3 ± 15.3 (pSS) 50.2 ± 12.6 (sSS)	Netherlands (descriptive statistics are not shown)	29.82%	70.17%
Shiboski et al. [13]	1,578	NR	NR	Argentina, China, Denmark, Japan, United Kingdom, USA (descriptive statistics are not shown)	No distinction between pSS and sSS	No distinction between pSS and sSS
Rasmusssen et al. [14]	1,703	93.3% (SS)	56.5 (47–65) (SS)	Caucasian (65.2%), African-American (3.6%), native American (27.2%), Asian (2.9%)	26.13%	No distinction between pSS and sSS
Billings et al. [15]	1,303	92.2% (SS)	53 (7–81) (SS)	Caucasian (74.2%), African-American (11.9%), Asian (7.2%), other (6.7%)	53.80%	No distinction between pSS and sSS
Bautista-Vargas et al. [16]	NR as a nonsystematic review					
Wijaya et al. [17]	23	91.30% (pSS)	50.2 (40.6–73.4%)	NR	39.13%	No distinction between pSS and sSS
Chisholm et al. [18]	40	20% (pSS)	65 (pSS)	NR	25%	25% (rheumatoid arthritis) 15% (Osteoarthritis) 15% (Reiter's disease) 10% (psoriatic arthritis) 10% (scleroderma)
Greenspan et al. [19]	43	NR	NR	NR	100%	No distinction between pSS and sSS
Fox et al. [20]	NR					
Marx et al. [21]	77	NR	NR	African-American (35.06%), Caucasian (5.19%)	46.75% (SS)	40.26% (sarcoidosis) 6.49% (sialosis) 6.49% (lymphoma)
Delgado et al. [22]	19	36.84%	32	Peru (100%)	0%	100% (secondary amyloidosis)

Table 2: Continued.

Authors	*N* of patients	% Women	Mean age (years), mean (SD or range)	Ethnicity or countries of origin	% of pSS cases	% of sSS cases or other diseases
Richards et al. [23]	58	NR	20–72	UK (100%)	0%	100% (secondary amyloidosis)
Seoane et al. [24]	NR					
Peloro et al. [25]	NR					
Guevara-Gutiérrez et al. [26]	50	NR	NR	NR	100% (SS)	0%
Teppo et al. [27]	191	81%	53 (20–85)	Finland (100%)	38% (SS)	63% (non-SS)
Comini et al. [28]	569	NR	NR	Italy (100%)	NR	NR
Syed et al. [29]	400	NR	NR	Canada (descriptive statistics are not shown)	NR	NR
Friedman et al. [30]	NR					
Tarpley et al. [31]	96	NR	NR	USA (descriptive statistics are not shown)	NR	NR
Costa et al. [32]	166	NR	NR	France (descriptive statistics are not shown)	NR	NR
Chen et al. [33]	28	92.86% (SS) 100% (non-SS)	44.86 ± 11.18 (SS) 47.71 ± 8.09 (non-SS)	NR	50% (SS)	50% (non-SS)
Daniels et al. [34]	1787	93%	54 (21–90)	USA (26%), Denmark (20%), Argentina (17%), Japan (15%), China (15%), UK (7%)	NR	5% (sSS)
Barone et al. [35]	NR as a nonsystematic review					
Han et al. [36]	1 (case report)	100%	55	China (100%)	100% (SS)	100% (AOSD)
Kapsogeorgou et al. [37]	NR as a nonsystematic review					
Rooper et al. [38]	NR as a nonsystematic review					
Carubbi et al. [39]	104	94.23%	52	NR	100%	0%
Fragkioudaki et al. [40]	473	94.49% (pSS) 100% (pSS NHL) 91.78% (pSS NHL MALT)	51.6 ± 13.2 (pSS) 52.1 ± 16.2 (pSS NHL) 49.9 ± 12.7 (pSS NHL MALT)	Greece (100%)	80.55% (pSS)	4.02% (pSS NHL) 15.43% (pSS NHL MALT)
Berardicurti et al. [41]	NR as a systematic review					
Stergiou et al. [42]	NR as a nonsystematic review					

NR: not reported; SS, Sjögren's syndrome; pSS, primary Sjögren's syndrome; sSS, secondary Sjögren's syndrome; AOSD, adult-onset still's disease; NHL, non-Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue.

advantage in using the new ACR criteria over the old AECG criteria [11]. Although both classifications present very similar items, the AECG criteria allow the substitution of some items and the use of dry eyes and oral symptoms to classify patients, while the ACR criteria are based exclusively on objective tests in association with the symptoms considered [12].

Consequently, the need for an international consensus on the classification criteria for SS led researchers from the SICCA team (ACR) and the EULAR (European League Against Rheumatism) task force on SS to form an international group with the aim of developing shared primary SS classification criteria combining the features of the ACR and AECG classifications, using methods consistent with those recommended by the ACR and EULAR [13].

These recent criteria describe the key shared features defining the disorder and they represent the common language to be used in the future to make scientific communication easier, more correct, and reproducible, favoring the exchange of information, and stimulating the development of collaborative studies (Table 4) [13].

Table 3: 2012 classification criteria for SS by ACR [10].

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the following 3 objective features: (1) positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer ≥1 : 320) (2) labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm^2 (using histopathologic definitions and focus score assessment methods as previously described) (3) keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that the individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years) (using ocular staining score as previously described)
Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: (i) history of head and neck radiation treatment (ii) hepatitis C infection (iii) acquired immunodeficiency syndrome (iv) sarcoidosis (v) amyloidosis (vi) graft versus host disease (vii) IgG4-related disease*

*Exclusion criteria: rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or other connective tissue diseases. ANA = antinuclear antibody.

Table 4: 2016 classification criteria for primary SS by ACR/EULAR [13].

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm^2	3
Anti-SS-A/anti-Ro positive	3
Ocular staining score (OSS) ≥ 5 (or van bijsterveld score (vBS) ≥ 4) in at least one eye	1
Schirmer's test ≤ 5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1

Individuals with signs and/or symptoms suggestive of SS who have a *total score of* ≥ 4 for the above items meet the criteria for primary SS. Inclusions: symptoms of oral or ocular dryness or 1 extraglandular manifestation of SS. Exclusions: history of head/neck irradiation, active hepatitis C (+PCR), HIV, sarcoidosis, amyloidosis, graft versus host disease, IgG4 syndrome.

The new criteria consider oral and ocular symptoms as the main requirement of eligibility for the evaluation of the presence of SS, rather than as useful items for the classification criteria. Importantly, sialography and salivary scintigraphy were omitted and the possibility of considering the use of the ocular staining score (OSS) as an alternative to the van Bijsterveld score (VBS) was introduced [14]. In addition, compared to the AECG criteria, some exclusion conditions for SS assessment such as IgG-related disease and hepatitis C infection were updated [15].

4.2. Minor Salivary Gland Biopsy Techniques. Currently, MSGB is crucial for the diagnosis and prognosis of SS [16]. Several techniques have been proposed for performing MSGB, mainly of the lower labial mucosa, to collect a sufficient volume of glandular structures with minimal surgical trauma, and reduce local postoperative complications, especially midterm and longterm paresthesia [17]. The main complication is surgical site paresthesia, followed by intraoperative and postoperative bleeding, local postoperative pain, and discomfort, swelling, ecchymosis, surgical wound infection, dehiscence, and, finally, keloid formation [16]. Therefore, it would be recommended to use a biopsy technique that minimizes bleeding and injury to peripheral nerve endings, thereby reducing the occurrence of intraoperative and postoperative complications, especially hyposensitivity events to the outer and inner labial surfaces [17].

Hereafter, there is a summary of the main minor salivary gland biopsy techniques described in the literature to date, highlighting each of the main complications reported (Table 5).

Chisholm and Mason proposed a 3×1 cm elliptical incision reaching the muscular layer of the lower lip, reporting no major postoperative complications [18].

Greenspan described a linear incision of approximately 1.5–2 cm on the lower labial mucosa, parallel to the vermilion border and lateral to the midline, reporting chronic hypesthesia in some cases [19].

Fox suggested the application of midpalpebral calazio forceps to circumscribe the labial incision area, without reporting information on the number of cases with postoperative complications [20].

Marx reintroduced Greenspan's technique, but suggested a 3×0.75 cm incision, reporting cases of labial hypesthesia [21].

Delgado and Mosqueda suggested a 10 mm longitudinal incision on the lower labial mucosa, anterior to the inferior canine, without reporting postoperative complications [22].

Richards described a single linear horizontal mucosal incision of approximately 1 cm, reporting some cases of postsurgical superficial hyposensitivity [23].

Table 5: MSGB techniques summary.

Authors	MSGB techniques	Potential complications
Chisholm and Mason [18]	3 × 1 cm elliptical incision reaching the muscular layer of the lower lip	The authors report no complications
Greenspan et al. [19]	Linear incision of approximately 1.5–2 cm on the lower labial mucosa, parallel to the vermilion border and lateral to the midline	Chronic hypesthesia for several months
Fox [20]	Circumscription of the labial incision area by a midpalpebral calazio forceps	No data regarding the number of cases with postoperative complications
Marx et al. [21]	3 × 0.75 cm elliptical incision reaching the muscular layer of the lower lip	Partial loss of labial sensitivity
Delgado and Mosqueda [22]	10 mm longitudinal incision on the labial mucosa, anterior to the inferior canine	Authors report no complications
Richards et al. [23]	Single linear horizontal incision of the mucosal tissue of approximately 1 cm	Reduced postsurgical surface sensitivity
Seoane et al. [24]	Elliptical horizontal incision of 1 cm × 4 mm	No data regarding the number of cases with postoperative complications
Peloro et al. [25]	X-marks technique: highlight salivary gland papules with a surgical pen, perform a superficial incision of the labial mucosa of 1.5–2 mm, and, finally, a second incision perpendicular to the first one	No data regarding the number of cases with postoperative complications
Guevara-gutiérrez et al. [26]	Punch biopsy technique: lightly penetrate the epithelium of the lower lip using a 4 mm diameter punch scalpel, between the midline and the labial commissure	Modest transient hyposensitivity of the lower lip
Teppo and Revonta [27]	2-3 mm horizontal microincisions, shelling the glands came to the surface and gently removing them with scissors and surgical forceps	Pyogenic granuloma of biopsy wound
Comini et al. [28]	Extraction of the minor salivary glands using a sharp-tipped needle	The authors report no complications

Seoane performed a 1 cm × 4 mm horizontal elliptical incision, using calazio forceps, without reporting information on possible postoperative complications [24].

Peloro described the X-marks technique: with a surgical pen, the papules of the salivary glands are highlighted, followed by a superficial incision of the labial mucosa of 1.5–2 mm and, finally, a second incision perpendicular to the first. There is no data on occurring postoperative complications [25].

Guevara-Gutierrez et al. proposed the Punch Biopsy technique: with a 4 mm diameter punch scalpel, the epithelium of the lower lip is lightly penetrated, between the midline and the labial commissure, reporting cases of a modest transient hyposensitivity of the lower lip [26].

Teppo and Revonta described 2-3 mm horizontal microincisions on the lower labial mucosa, subsequently shelling out the glands that had come to the surface and gently removing them with scissors and surgical forceps [27].

Finally, Comini et al. used a sharp-tipped needle to extract the minor salivary glands, without reporting complications [28].

Based on the literature review, there is a high heterogeneity of used MSGB techniques, in fact, most authors have described different techniques depending on their clinical and experimental experience.

Regardless, Syed et al. [29] performed a technique like Fox [20] and Seoane [24], using chalazion forceps, without reporting complications in more than 400 patients. The main advantages related to the use of forceps were tissue stabilization, vascular compression, improved view of the operative field, and finally easier extrusion of minor salivary glands.

Instead, Friedman et al. [30] used a technique like Delgado and Mosqueda [22], with reduced incision size to 5–7 mm, reporting mild complications in a total of 118 patients.

4.3. Histopathological Diagnostic Criteria of SS. The grade of glandular involvement and the histopathological diagnosis of SS is made according to the criteria of one of the three main grading systems available today (Table 6).

They are the system of Chisholm and Mason [18], described in 1968, including 5 grades (0 to 4), based on the presence of minimal or moderate lymphocytic infiltration and/or lymphocytic foci; the system of Greenspan and Daniels [19], described in 1974, introducing the concept of focus score (FS), defined as the number of lymphocytic foci in a 4 mm^2 area of normal-appearing tissue, and establishing the concept of focal lymphocytic sialadenitis (FLS) as the presence of FS > 1; and, the system of Tarpley [31], also described in 1974, adding the concepts of acinar destruction and fibrosis.

In the Chisholm and Mason scoring system, the authors established the criteria in their study and used the definition of "*focus*," which is an aggregate of 50 or more lymphocytes [18]. An accurate and detailed histopathological assessment is possible by analyzing four to seven salivary gland secretory

Table 6: SS histopathological scoring system.

Chisholm and Mason scoring system	Grade	Lymphocytes/4 mm^2
	0	Absent
	1	Light infiltration
	2	Moderate infiltration or less than one focus
	3	1 focus
	4	More than 1 focus
Greenspan and daniels scoring system	FS	Lymphocytes/4 mm^2
	1	1 focus
	2	2 foci
	3	3 foci
	4	4 foci (thus up to 10 foci)
	12	Confluent infiltrate
Tarpley scoring system	Class	Lymphocytes/4 mm^2
	0	Normal
	1	1 or 2 aggregates (minimal infiltration)
	2	≥ 3 aggregates of round cells per lobule
	3	Diffuse infiltration with partial destruction of the acinar tissue with or without fibrosis
	4	Diffuse infiltration, with or without fibrosis, and complete destruction of the lobular architecture

units due to the frequent heterogeneous distribution of the inflammatory infiltrate and related glandular damage [16]. Chisholm and Mason scoring system is based on the degree of lymphocyte infiltration per 4 mm^2 of salivary tissue: 0 = absent, 1 = mild infiltration, 2 = moderate infiltration or less than one focus, 3 = 1 focus, 4 = >1 focus [30]. Since then, this grading system has been widely used by pathologists, demonstrating a sensitivity and specificity for SS of 72.1% and 80%, respectively [33].

Greenspan and Daniels developed FS in 1974 as an extension of the system of Chisholm and Mason, proposing the quantification of the number of foci per 4 mm^2 of the tissue section, adjacent to normal glandular parenchyma [34]. In their publication, the authors stated a maximum FS of 10 to be quantified [19]. The FS has been validated as a histologic index of severity in primary SS for salivary gland involvement. Several studies in the literature have shown a correlation between the presence of an elevated FS and indices of local or systemic disease activity; however, the FS, though providing information on the extent of cellular infiltration, does not assess the size of foci: for larger or confluent foci, an FS of 12 is arbitrarily assigned [35]. This could be a problem in clinical trials because slight variations in foci size may not be accurately assessed [35].

High FS is related to severe glandular damage, with a consequent reduction of stimulated and unstimulated salivary flow, to serological positivity of anti-SSA/B and ANA antibodies, and to specific extraglandular features, such as Raynaud's phenomenon, reactive vasculitis, variable lymph node enlargement, splenomegaly, progressive leukopenia, and dry keratoconjunctivitis [36, 37]. Recently, it has been shown that an FS greater than 3 might be related to the development of non-Hodgkin's B-cell lymphoma [37]. In addition, other parameters were evaluated: the number of plasma cells in each focus, the proportions of plasma cells as a percentage of total cells in each focus, and finally, mast cells, also stained with toluidine blue [36]. In the Greenspan and Daniels scoring system, degrees of acinar depletion, fatty infiltration, and fibrosis were also assessed on a scale of 0 to 3 and, finally, the number of germinal centers, epimyoepithelial islands, and perivascular foci were included in the analysis [19]. It was found that a biopsy grade of 4 was sufficient evidence of salivary gland involvement in the presence of SS. However, because of marked variation in the degree of involvement from glandular lobe to glandular lobe in SS, the authors recommended the examination of four to seven labial glands [19].

Tarpley scoring system is based on the degree of lymphocyte infiltration per 4 mm^2 of salivary glandular tissue, dividing it into classes: 0 = normal, 1 = 1 or 2 aggregates (minimal infiltration); 2 = ≥3 aggregates of round cells per lobule; 3 = diffuse infiltration with partial destruction of acinar tissue with or without fibrosis; 4 = diffuse infiltration, with or without fibrosis, and complete destruction of lobular architecture [31]. In Tarpley's system, an aggregate is composed of approximately 50 cells (lymphocytes, plasma cells, or histiocytes) and, in addition, the concept of acinar destruction and fibrosis has been introduced [39]. Although it is not employed at the same level as the other two systems, it has been used in some studies to predict the risk of lymphoma and to assess the prevalence of SS [40]. The prognostic role of MSGB in SS is given by the presence of ectopic germinal centers (GCs) as they contribute to determine the degree of B-cell proliferation and maturation, the generation of somatic hypermutations, and the development of class-switch recombinations [41]. Immune cell infiltration greater degree and ectopic GCs greater number are associated with anti-SSA/B autoantibodies higher prevalence, increased disease severity, extraglandular manifestations, and the onset of MALT lymphoma [42].

5. Conclusions

In conclusion, MSGB represents an essential test to diagnose SS, adopting a mini-invasive biopsy technique that reduces

as much as possible intraoperative and postoperative complications. The classification criteria of SS are the combination of positive items needed to make a correct diagnosis of primary and secondary SS, including the association between high FS values, serological positivity of SSA/B and ANA autoantibodies, and the presence of glandular and extraglandular signs of SS. The clinician's knowledge of the classification criteria is fundamental for an efficient diagnostic management of the disease.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

F.S. and E.K. conceptualized the study; F.S. and E.K. developed methodology; A.S. designed software; A.S. and E.K. validated the data; F.S. formally analyzed the data; E.K. investigated the data and collected resources; A.S. and F.S. curated the data; M.P. and F.P. wrote and prepared the original draft; F.S., A.S., and E.K. wrote, reviewed, and edited the article; E.K. and F.P. visualized the data; F.S. and E.K. supervised the study; F.S. and A.S. administered the project. All authors have read and agreed to the published version of the manuscript.

Supplementary Materials

Table S1: search strategies for electronic databases; Table S2: baseline characteristics of patients included in the selected studies; Table S3: evidence of studies included in this systematic review. (*Supplementary Materials*)

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