

## A Meta-analysis of the Diagnostic Value of Minor Salivary Gland Biopsy for Primary Sjogren's Syndrome

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**Objective.** The purpose of this study is to evaluate the diagnostic performance of minor salivary gland biopsy (MSGB) for patients with primary Sjogren's syndrome (pSS).

**Methods.** We have conducted a search from Medline, Embase, and Cochrane Library databases, and performed a meta-analysis on the diagnostic accuracy of MSGB in pSS patients.

**Results.** A total of eight studies, including 583 pSS and 627 non-pSS patients, were available for the meta-analysis. The pooled sensitivity and specificity of MSGB were 75.7% (95% confidence interval [CI], 72.0~79.1) and 90.7% (88.1~92.9), respectively. The positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 9.475 (4.051~22.16), 0.266 (0.208~0.340), and 38.92

(19.12~72.21), respectively. The area under the curve was 0.901 and the Q\* index was 0.902, indicating a high diagnostic accuracy. Some between-study heterogeneity was found in the meta-analyses; however, there was no evidence of a threshold effect (Spearman correlation coefficient=0.419; p=0.301). Meta-regression showed that the study quality, sample size, study design, and diagnostic criteria were not sources of heterogeneity, and subgroup meta-analyses did not change the overall diagnostic accuracy.

**Conclusion.** Our meta-analysis of published studies demonstrates that MSGB has a high diagnostic accuracy and may play an important role in the diagnosis of pSS.

**Key Words.** Primary Sjogren's syndrome, Minor salivary gland biopsy, Diagnostic accuracy, Meta-analysis

### Introduction

Primary Sjogren's syndrome (pSS) is a chronic systemic autoimmune disease affecting the exocrine system. pSS is characterized by dry eyes and dry mouth, and lymphocytic infiltration of the salivary and lacrimal glands. Pathologic analysis of patients with pSS shows lymphocyte infiltration and destruction of the lacrimal and salivary glands. The diagnosis of pSS is made according to diagnostic criteria including a combination of several tests (1,2). Among these criteria, the classification criteria proposed by the American-European Consensus Group (AECG) are the most often used (2). Of the six diagnostic criteria in this classification, at least four should be met to conclude a diagnosis of pSS. The pathological findings in a biopsy of the labial salivary glands are among these

criteria. Any 4 of the 6 criteria must include either salivary gland biopsy or autoantibodies, and any 3 of the 4 objective criteria including histopathology should be satisfied. A positive minor salivary gland biopsy (MSGB) should have a focus score (FS) of  $\geq 1$ , defined as the presence of a cluster of at least 50 lymphocytes per 4 mm<sup>2</sup> of glandular tissue. The revised classification criteria of the American College of Rheumatology (ACR) include only objective findings such as (i) serological findings, (ii) an FS in labial salivary gland biopsies, and (iii) ocular signs (3). Detection of inflammation in MSGB is a diagnostic method for pSS in both the AECG and ACR criteria. MSGB is a simple, safe, and reliable tool for the diagnosis of pSS and is required in evaluating antibody-negative pSS patients. However, the diagnostic value of

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MSGB for the diagnosis of pSS is variable and still unclear.

The diagnostic accuracy of MSGB has been studied in the context of pSS; however, the published results are controversial (4-12). This may be due to the small sample sizes, low statistical power, and/or the presence of clinical heterogeneity. To overcome the limitations of the individual studies, resolve the inconsistencies, and reduce the likelihood of false positives or false negatives due to random errors (13), we performed a meta-analysis on the sensitivity and specificity of MSGB for the diagnosis of pSS by using published data.

## Materials and Methods

### Identification of eligible studies and data extraction

We used the Medline, Embase, and Cochrane Library databases to identify articles published from January 1971 through June 2014 in which MSGB was performed in pSS patients and control subjects. In addition, all references mentioned in the selected articles were reviewed to identify studies not indexed by the electronic databases. PICO stands for Patient, Intervention, Comparison, and Outcome. PICO of this study was pSS patients (P), MSGB (I), classification criteria for pSS (C), and sensitivity, specificity (O). To incorporate concept from the PICO analysis in search strategy, the following keywords and subject terms were used in the search: "salivary gland", "biopsy", "sensitivity", "specificity", and "Sjogren's syndrome". Studies were selected for the analysis if they included (i) cases and controls (or a comparative group), (ii) sufficient data to calculate the sensitivity and specificity of MSGB, (iii) patients with pSS diagnosed on the basis of the classification criteria, and (iv) FS  $\geq 1$  as a positive MSGB result. Language restriction was applied; only English articles were included. We excluded (i) studies with overlapping data, (ii) studies with insufficient data, (iii) studies with secondary SS, and (iv) a review study. Two independent reviewers extracted data about the methods and results of meta-analysis from the original studies. Discrepancies between the reviewers were resolved by consensus or with a third reviewer. We extracted information on author(s), publication year, and the demographic characteristics of participants (ethnicity and diagnostic criteria) from each study. MSGB raw data were extracted from all primary studies to fill the four cell values of a diagnostic 2×2 table (true positives, false positives, true negatives, and false negatives). We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria to assess the quality of each study (14). The QUADAS criteria consist of a list of 14 questions, with a score of 1 given if a criterion item was fulfilled, -1 if a criterion was not achieved, and 0 if the item was unclear (14).

### Evaluation of statistical associations

Within- and between-study variations and heterogeneities were assessed by using Cochran's Q-statistic. Cochran's Q-statistic test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified by using  $I^2$  with a range from 0% to 100%, representing the proportion of between-study variability attributable to heterogeneity rather than to chance (15).  $I^2$  values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed-effects model assumes that a genetic factor has a similar effect on disease susceptibility across all studies investigated, and that observed variations among studies are caused by chance alone (16). The random-effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance (17). The random-effects model is most appropriate to use in the presence of significant between-study heterogeneity (17). We used a random-effects model to combine the sensitivity, specificity, positive and negative likelihood ratio (PLR, NLR), and diagnostic odds ratio (DOR) estimates due to heterogeneity, and analyzed the summary receiver-operating characteristic (SROC) curves. DOR is a unitary measure of diagnostic performance that encompasses both sensitivity and specificity, or both PLR and NLR, and DOR is considered a suitable global measure of accuracy for comparing the overall diagnostic accuracies of different tests (18). Because sensitivity and specificity are interdependent, independent calculations may sometimes underestimate both variables. SROC curve analysis is more appropriate because it accounts for this mutual dependence. The area under the curve (AUC) (in this case, area under the SROC curve) presents an overall summary of test performance and displays the trade-off between sensitivity and specificity, and an AUC of 1.0 (100%) indicates perfect discriminatory ability for a diagnostic test (13). In addition, the  $Q^*$  index is another useful global estimate of test accuracy for comparing SROC curves. The  $Q^*$  index is defined at the point where sensitivity equals specificity on an SROC curve, and is the point on an SROC curve intersected by the antidiagonal. A  $Q^*$  value of 1.0 indicates 100% accuracy (i.e., sensitivity and specificity of 100%) (13). Statistical manipulations for this meta-analysis were performed by using Meta-DiSc, version 1.4 (Hospital Universitario Ramon y Cajal, Madrid) (19).

### Evaluation of heterogeneity and meta-regression

A between-study heterogeneity observed in a meta-analysis indicates variability in results across studies. A threshold effect is the most important cause of heterogeneity. Different

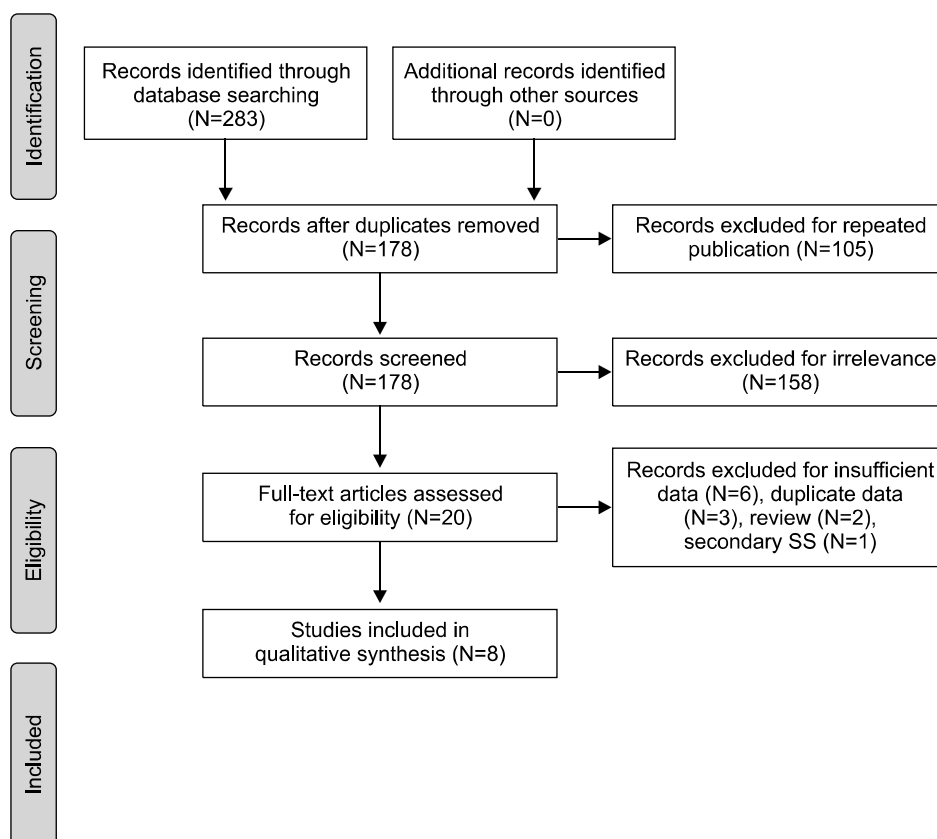
sensitivities and specificities due to various study conditions cause different threshold effects. We checked the Spearman correlation coefficient between the logit of sensitivity and logit of 1-specificity to assess the presence of a threshold effect. To examine the potential source of heterogeneity observed in the meta-analysis, subgroup analysis and meta-regression were

performed with the following covariates: (i) study quality, (ii) sample size, (iii) study design, and (iv) diagnostic criteria.

## Results

### Studies included in the meta-analysis

We identified 283 studies through electronic and manual



**Figure 1.** Flow diagram of study selection.

**Table 1.** Characteristics of individual studies included in the meta-analysis

Author	Country	Diagnostic criteria	pSS	Non-pSS	Study design	Cut-off	TP	TN	FN	FP	Anti-Ro (%)	Anti-La (%)	Study quality*
Cornec, 2013 (5)	France	Expert Opinion	78	80	Prospective	FS $\geq 1$	63	67	15	13	56.4 <sup>†</sup>	Na	10
Obinata, 2010 (6)	Japan	Revised Japanese criteria	36	37	Retrospective	FS $\geq 1$	23	34	13	3	Na	Na	12
Nakamura, 2010 (7)	Japan	AECG	63	49	Retrospective	FS $\geq 1$	58	30	5	19	58.7	17.5	11
Milic, 2009 (8)	Serbia	AECG	107	28	Prospective	FS $\geq 1$	70	28	37	0	Na	Na	10
Yazisiz, 2009 (9)	Turkey	AECG	99	54	Retrospective	FS $\geq 1$	78	54	21	0	17.7	8.3	10
Caporali, 2008 (10)	Italy	AECG	124	254	Retrospective	Cumulative FS $\geq 1$	87	248	37	6	80.6	29.6	11
Teppo, 2007 (11)	Finland	AECG	60	100	Retrospective	FS $\geq 1$	49	83	11	17	Na	Na	11
Kessel, 2006 (12)	Israel	AECG	16	25	Prospective	FS $\geq 1$	15	25	1	0	62.5	37.5	9

AECG: American-European Consensus Group criteria, pSS: primary Sjogren's syndrome, FS: focal score, TP: true positive, FP: false positive, FN: false negative, TN: true negative, Na: not available. \*Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria. <sup>†</sup>Anti-Ro or La positivity.

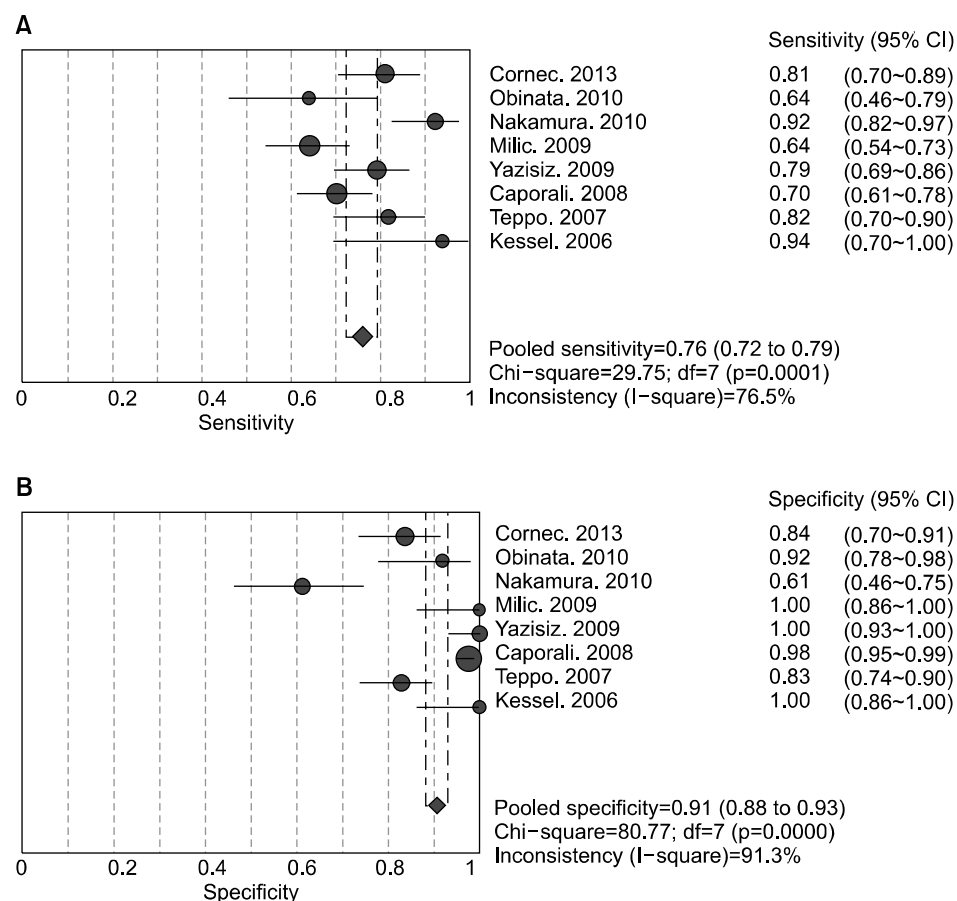
searching, and 20 were selected for a full-text review on the basis of the title and abstract. Twelve of these studies were excluded because six had insufficient data, three had duplicate data, two were reviews, and one included secondary Sjogren's syndrome (Figure 1). Thus, eight studies that reported on the diagnostic accuracy of MSGB met our inclusion criteria, including a total of 583 pSS and 627 non-pSS patients (4-12).

Of these studies, four were done in Europe, two in the Middle East, and two in Asia. Six studies used the AEGC criteria for pSS diagnosis (2) and two employed other criteria (5,6). A positive MSGB was defined as indicating a lymphocytic infiltrate with FS  $\geq 1$ , except for one study that used a cumulative FS of  $\geq 1$  from multi-level sections of gland (10). Table 1 shows the characteristic features of the participants in the

**Table 2.** Summary results of the meta-analysis

Subgroup	Population	Study no.	N		Sensitivity	Specificity	PLR	NLR	DOR
			pSS	Non-pSS					
All combined	Overall	8	583	627	0.757 (0.720~0.791)	0.907 (0.881~0.929)	9.475 (4.051~22.16)	0.266 (0.208~0.340)	38.92 (19.12~72.21)
Study quality	QUADAS > 11	4	283	440	0.767 (0.712~0.815)	0.898 (0.866~0.924)	6.888 (2.288~20.73)	0.274 (0.193~0.389)	31.01 (13.33~72.14)
	QUADAS $\leq 10$	4	300	187	0.748 (0.695~0.796)	0.929 (0.882~0.962)	23.59 (2.600~214.0)	0.246 (0.154~0.395)	101.27 (14.71~696.9)
Study design	Prospective	3	201	133	0.729 (0.662~0.789)	0.900 (0.835~0.946)	14.23 (2.033~99.74)	0.247 (0.121~0.502)	62.03 (9.287~414.4)
	Retrospective	5	382	494	0.772 (0.727~0.813)	0.909 (0.880~0.933)	9.020 (2.803~29.02)	0.261 (0.196~0.347)	37.60 (15.21~92.92)

pSS: primary Sjogren's syndrome, PLR: positive likelihood ratio, NLR: negative likelihood ratio, DOR: diagnostic OR, QUADAS: Quality Assessment of Diagnostic Accuracy Studies criteria.



**Figure 2.** Sensitivity (A) and specificity (B) estimates for minor salivary gland biopsy for the diagnosis of primary Sjogren's syndrome. Circles and lines represent point estimates and 95% confidence intervals, respectively. Circled areas represent relative study sizes.

studies included in the meta-analysis, as well as the quality assessments of the diagnostic accuracy reported in those studies. Four studies had a QUADAS score of  $\leq 10$ , whereas four had a higher QUADAS score of  $> 11$ .

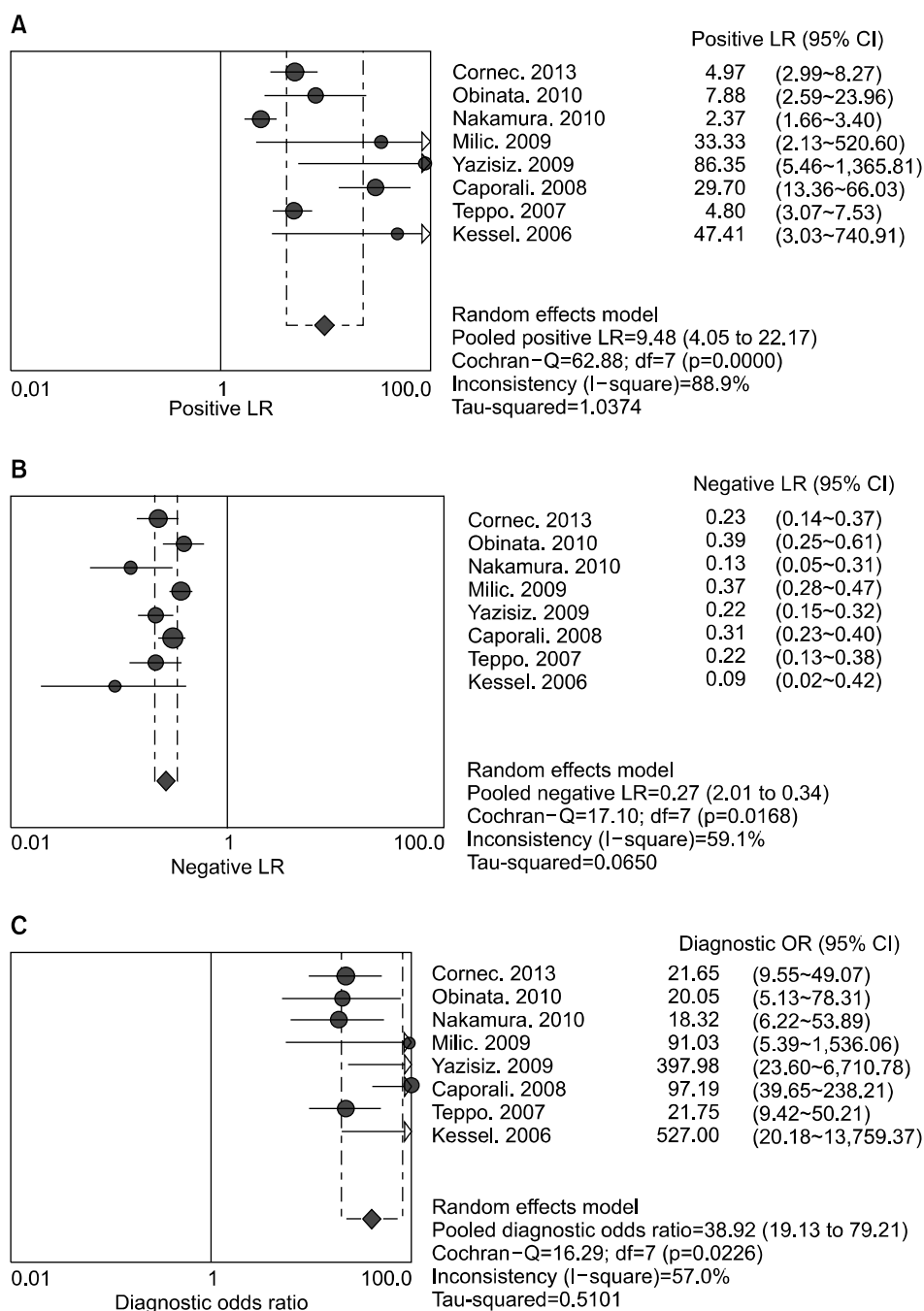
### Diagnostic accuracy of MSGB for pSS

When all eight studies were considered together, the sensitivity estimates of MSGB ranged from 63.5% to 93.7% and the specificity estimates ranged from 83.8% to 100% (Table 1). The pooled sensitivity and specificity of MSGB were 75.7% (95%

CI, 72.0~79.1) and 90.7% (88.1~92.9), respectively (Table 2, Figure 2). In summary, the PLR, NLR, and DOR of MSGB were 9.475 (4.051~22.16), 0.266 (0.208~0.340), and 38.92 (19.12~72.21), respectively (Table 2, Figure 3). Figure 4 shows the performance of MSGB testing in the form of SROC curves. The AUC of MSGB was 0.902 and the  $Q^*$  index was 0.833, indicating a high diagnostic accuracy (Table 3).

### Diagnostic accuracy of MSGB in subgroup analysis

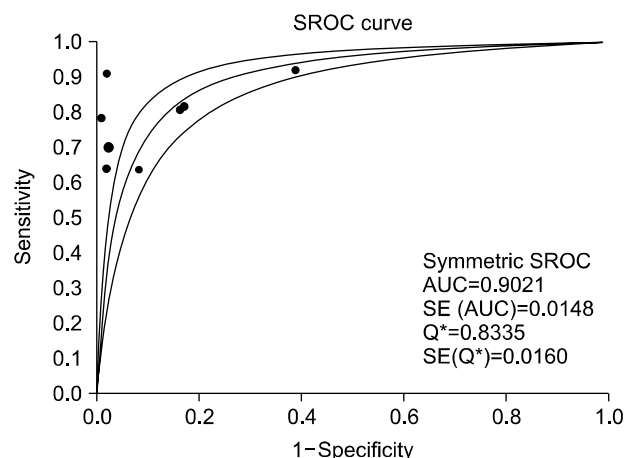
A subgroup analysis was conducted according to study qual-



**Figure 3.** Positive (A) and negative (B) likelihood ratios, and diagnostic odds ratio (C) estimates for minor salivary gland biopsy for the diagnosis of primary Sjogren's syndrome. Circles and lines represent point estimates and 95% confidence intervals, respectively. Circled areas represent the relative study size.

ity, study design, sample size, and diagnostic criteria (Tables 2 and 3). In studies with QUADAS >11, the pooled sensitivity and specificity of sialography were 76.7% (95% CI, 71.3~81.5) and 89.8% (86.6~92.4), respectively, and those for studies with QUADAS ≤10 were 74.8 (69.5~79.6) and 92.9 (88.2~96.2), respectively (Table 2). In summary, the PLR, NLR, and DOR of MSGB were 6.888 (2.288~20.73),

0.274 (0.193~0.3890), and 31.01 (13.33~72.14), respectively, in high-quality studies, and those for low-quality studies were 23.59 (2.600~214.0), 0.246 (0.154~0.395), and 101.2 (14.71~696.9), respectively (Table 2). The AUC of high-quality studies was 0.903 and the Q\* index was 0.835. The AUC of low-quality studies was 0.886 and the Q\* index was 0.816, which indicated that the diagnostic accuracy is comparable between the high- and low-quality studies (Table 3). A similar pattern was found in the subgroup analyses according to other variables (Tables 2 and 3).



**Figure 4.** Summary receiver-operating characteristic curves for minor salivary gland biopsy for the diagnosis of primary Sjogren's syndrome. Solid circles represent individual studies included in this meta-analysis. The curve shown is a regression line that summarizes the overall diagnostic accuracy. SE (AUC): standard error of the area under the curve, Q\*: an index defined by the point on the SROC curve where the sensitivity and specificity are equal, SE(Q\*): Q\* index standard error.

### Heterogeneity

Some between-study heterogeneity was found in the meta-analyses of MSGB results. A typical “shoulder arm” pattern in an SROC space suggests the presence of a threshold effect; however, this pattern was not found in the SROC curve. Furthermore, a Spearman rank correlation test showed no evidence of a threshold effect (Spearman correlation coefficient=0.2674;  $p=0.488$ ). We explored the heterogeneity arising from factors other than a threshold effect. Meta-regression showed that study quality, sample size, study design, and diagnostic criteria were not sources of heterogeneity in the meta-analysis (Table 4). The cut-off values of MSGB were not same among the reports. Thus, we performed a Spearman rank correlation test for a threshold effect. Spearman rank correlation test showed no presence of a threshold effect in the meta-analysis (Spearman correlation coefficient=0.419;  $p=0.301$ ).

**Table 3.** Estimates of summary receiver operating characteristic curve parameters

Subgroup	Population	Study no.	Numbers		AUC	SE(AUC)	Q*	SE(Q*)
			pSS	Non-pSS				
All combined	Overall	8	583	627	0.902	0.014	0.833	0.016
Study quality	QUADAS>11	4	283	440	0.903	0.019	0.835	0.020
	QUADAS≤10	4	300	187	0.886	0.032	0.816	0.033
Study design	Prospective	3	201	133	0.881	0.032	0.818	0.033
	Retrospective	5	382	494	0.905	0.017	0.836	0.018

AUC: area under the curve, SE: standard error, QUADAS: Quality Assessment of Diagnostic Accuracy Studies criteria, NA: not available.

**Table 4.** Meta-regression analysis of potential sources of heterogeneity

Covariates	Coefficient	SE	RDOR (95% CI)	p-value
QUADAS	-1.477	1.517	0.23 (0.00~156.4)	0.433
Sample size	-0.598	0.925	0.55 (0.01~29.47)	0.584
Study design	-0.407	0.670	0.67 (0.00~879.7)	0.830
Diagnostic criteria	1.464	0.824	4.32 (0.12~150.1)	0.217

SE: standard error, RDOR: relative diagnostic odds ratio, QUADAS: Quality Assessment of Diagnostic Accuracy Studies criteria.

### Discussion

The diagnosis of pSS is often difficult because it is a heterogeneous disease with widely varying clinical and serological features, including organ-specific and systemic findings. None of the laboratory markers is known to be both sensitive and specific, and there is no single test that has sufficient accuracy to diagnose pSS (1,2). The current diagnosis of pSS is based on a combination of clinical and laboratory findings. The diagnostic criteria of the AECG, in which MSGB plays an important role, are the most often used and widely accepted criteria for the diagnosis of pSS (2). MSGB is a simple, safe, and reliable method for the diagnosis of pSS. A positive histopathology finding of MSGB is focal lymphocytic sialoadenitis in minor salivary glands, with an FS of  $\geq 1$  (2). However, the diagnostic value of MSGB for pSS needs to be further defined because the sensitivity and specificity of MSGB for pSS is unclear (20).

Studies on the diagnostic accuracy of MSGB for the diagnosis of pSS have reported inconsistent findings (4-12), which may be due to false positives, false negatives, or a low statistical power because of the small sample size. Meta-analysis integrates previous research and increases statistical power and resolution by pooling the results of independent analyses (21), and thus provides a powerful means of overcoming the problems of small sample size and inadequate statistical power.

This study is the first to assess the diagnostic value of MSGB for pSS by using meta-analysis. This meta-analysis of eight studies including 583 patients and 627 controls showed the pooled overall sensitivity, specificity, PLR, NLR, DOR, and SROC of MSGB. SROC analysis was used to show the overall accuracy of MSGB. MSGB is more specific (90.7%) than sensitive (75.7%). The specificity of MSGB was relatively high, whereas its sensitivity was moderate and suboptimal. The DOR is the ratio of the odds of positivity in diseased subjects relative to the odds of positivity in control subjects. Higher values of DOR indicate a better discriminatory test performance. The DOR value was 38.92, which means that MSGB could be a useful test in the diagnosis of pSS. MSGB had a high PLR (9.475), indicating that it is moderately helpful for the diagnosis of pSS, although it is not enough to use as a rule-in test. However, MSGB had a suboptimal NPL (0.266); thus, it is not suitable for excluding pSS. These values suggest that negative results in MSGB could not be used alone for making a diagnosis. The result of MSGB should be interpreted in conjunction with clinical and laboratory findings. When sensitivity and specificity were considered simultaneously, the AUC of MSGB was 0.902 and the  $Q^*$  index

was 0.833, indicating a good diagnostic performance. A subgroup meta-analysis according to the diagnostic criteria, study quality, sample size, and study design did not change the overall diagnostic accuracy. This study provides evidence that MSGB has a high diagnostic accuracy and plays an important role in the identification of pSS.

However, the present study has several limitations. First, between-study heterogeneity was encountered in this meta-analysis. The analyzed studies included heterogeneous groups of patients and controls. This between-study heterogeneity may have affected the results of this meta-analysis, which may be compounded by the limited information provided on clinical status and disease severity in the populations involved. We tried to overcome this limitation by using a random-effects model that incorporates uncertainties arising due to between-study variation and by performing a subgroup analysis and meta-regression. The meta-regression showed that the results of the overall analysis did not significantly differ when subgroups were included, and there was no presence of threshold effect in the meta-analysis. However, we could not analyze using age, sex, autoantibodies, and clinical features due to limited data. Second, the analyzed studies included varying levels of disease severity, and the pSS severity level was unclear. The diagnostic accuracy of MSGB may be different in the advanced stage of the disease (22). Further research is required to examine how the diagnostic accuracy measures change with the activity or clinical features of the disease. Third, the classification criteria of pSS contains MSGB (2), thus a bias of circular reasoning due to the classification criteria of pSS including histopathology may affect this meta-analysis. To evaluate more accurate diagnostic value of MSGB for pSS, further research using studies with classification criteria which do not include MSGB, like Obinata et al.'s study (6), is needed. Nevertheless, this meta-analysis also has its strengths. The number of pSS patients from the individual studies ranged from 16 to 124; however, this pooled analysis included a total of 583 pSS patients and 627 controls. In comparison with the individual studies, we were able to provide more accurate data on the diagnostic tests by increasing the statistical power and resolution through pooling the results of independent analyses.

### Conclusion

Our meta-analysis of current evidence demonstrates that MSGB has a high diagnostic accuracy and plays an important role in the diagnosis of pSS. However, considering the limitations of and the heterogeneity in this study, further studies with high quality and including a large population are needed

to definitively determine the diagnostic value of MSGB for pSS.

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