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REVIEW

The accuracy of Raman spectroscopy in the detection and diagnosis of oral cancer: A systematic review and meta-analysis

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Abstract

Purpose: The aim of this study was to systematically review and assess the diagnostic accuracy of Raman spectroscopy (RS) for oral cancer tissue, oral precancerous lesions, and normal oral tissue.

Methods: PubMed, Embase, Web of Science, the China National Knowledge Infrastructure, and gray literature were searched for all relevant articles published before July 2019. We used the Quality Assessment of Diagnostic Accuracy Studies tool to assess the quality of the included studies. We estimated the pooled sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratio (DOR), and established summary receiver operating characteristic (SROC) curves to identify the diagnostic accuracy of RS for oral cancer tissue, oral precancerous lesions, and normal oral tissue. In addition, the area under the curve (AUC) was reported to estimate the overall effectiveness of RS.

Results: A total of 41 articles were eligible for this meta-analysis. The coalescent sensitivity and specificity of RS in diagnosing oral cancer in vivo were 0.91 and 0.85. The positive likelihood ratio, the negative likelihood ratio, and the area under the curve were 8.01, 0.10, and 0.9284. The frozen tissue subgroup in vitro oral cancer group showed improved diagnostic accuracy with an AUC of 0.9968. The in vitro frozen tissue group also showed better diagnostic accuracy in distinguishing between oral precancerous lesions and normal oral tissues.

Conclusions: RS has the advantages of being noninvasive and able to provide real-time and in situ results, so it deserves to be studied and improved further to better serve clinical work.

KEYWORDS
diagnosis, meta-analysis, oral cancer, oral precancerous lesion, Raman spectroscopy

1 | INTRODUCTION

Oral cancer, a type of head and neck cancer, is a generic term for malignant tumors that occur in the mouth, most

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of which are characterized as squamous cell carcinoma. In particular, oral squamous cell carcinoma (OSCC), which accounts for 90% of the incidence of oral malignant lesions, is the sixth most common cancer in the world, and its risk factors include alcohol consumption, tobacco use, HPV, and EBV.[1–6] In addition, approximately 300,000 new cases of OSCC are diagnosed every year,[7] and a trend of increasing morbidity has been observed. Although modern medical technology has been progressing, only half of oral cancer patients can survive for 5 years,[8] and the prognosis, which is largely determined by an early diagnosis, is poor. Early diagnosis is now thought to improve the survival and quality of patients' lives. However, some early diagnosis methods are not satisfactory. For example, it usually takes a certain amount of time to diagnose oral cancer with histological examinations, and most of the pathological diagnostic accuracy rates for CT and MRI are not high. Therefore, there is a pressing need for a rapid and highly accurate method of diagnosing oral cancer.

Recently, Raman spectroscopy (RS), which is referred to as "molecular fingerprinting," has been used for the diagnosis of various diseases, especially cancer. RS has been shown to be highly sensitive to tissue changes.[9–11] Additionally, molecular level changes can be detected by RS. Therefore, RS can be used for the early diagnosis of oral cancer, and it has obvious advantages over traditional pathology and imaging systems.[12,13]

To date, many articles have studied the accuracy of RS in distinguishing between oral cancer and normal oral tissues. However, the experimental results and conclusions of the different studies are inconsistent. Considering the relatively high rate of fatality, high economic burden, and poor prognosis of oral cancer, it is pertinent that the accuracy of RS in the early diagnosis of oral cancer is evaluated. Herein, we seek to systematically evaluate the accuracy of RS in the diagnosis of oral cancer.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Four databases (PubMed, Embase, Web of Science, and CNKI [up to July 2019]) were systematically searched to identify all studies evaluating the accuracy of RS in the early diagnosis of oral cancer. The key terms used in the search included "head and neck neoplasm" and "Raman." The key term "head and neck neoplasms" refers to salivary gland neoplasms, maxillary sinus neoplasms, paranasal sinus neoplasms, throat neoplasms, laryngeal neoplasms, nose neoplasms, mouth neoplasms, and pharyngeal neoplasms. In addition, the term was expanded to include head neoplasms, head and neck cancer, head cancer, neck cancer, neck neoplasms, head and neck squamous cell carcinoma, HNSCC, salivary gland cancer, salivary gland adenocarcinoma, salivary adenoid cystic carcinoma, maxillary sinus cancer, paranasal sinus neoplasms, paranasal sinus cancer, larynx neoplasms, laryngeal cancer, larynx cancer, throat cancer, nose cancer, nasal cancer, mouth cancer, oral neoplasms, oral cancer, pharynx neoplasm, or pharynx cancer. In addition, the key word "Raman" was expanded to include Raman spectrum analysis, Raman spectroscopy, Raman optical activity, Raman scattering, Raman spectra, Raman spectrum, Raman spectroscope, or Raman spectrometry. We displayed the search strategy in Table 1. Gray literature, related articles, and the reference lists of the literature identified in the search were searched to identify all relevant studies, abstracts, and citations. We downloaded the full texts of all potential studies to ensure that they were eligible for inclusion.

2.2 | Selection criteria

Studies were required to meet the following criteria for inclusion: (1) all samples, including ex and in vivo samples, of oral cancer neoplasms detected by RS were from human beings, and a histopathological diagnosis was used as the gold standard. (2) A healthy control group without oral cancer was included in the studies. (3) Sufficient data were presented to establish a fourfold table including true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). (5) All subjects were examined by RS.

The exclusion criteria were as follows: (1) studies involving nonhuman subjects, (2) studies in which the reference standard excluded histopathology, (3) studies that did not have a control group or were case reports or case series, and (4) duplicate reports or reviews.

2.3 | Data extraction and quality assessment

Two reviewers independently extracted the data of each article and evaluated the quality of the article utilizing a standardized data extraction form. Disagreements were resolved by consensus. Data were extracted for the following variables: the first author's name, geographical location, number of patients, sample type, mean age of the subjects, samples and spectra, methodological and technical data such as the diagnostic algorithm, study design, RS technique, TP, TN, FP, and FN. Each study's quality was assessed in accordance with the Quality

TABLE 1 Search strategies in the study

Databases	Steps	Strategies
PubMed	#1	"Head and Neck Neoplasms"[Mesh] OR Head and Neck Neoplasms OR Head Neoplasms OR Head and Neck cancer OR Head cancer OR Neck cancer OR Neck Neoplasms OR head and neck squamous cell carcinoma OR HNSCC
	#2	""Salivary Gland Neoplasms"[Mesh] OR Salivary Gland Neoplasms OR Salivary Gland cancer OR Salivary gland adenocarcinoma OR salivary adenoid cystic carcinoma
	#3	"Maxillary Sinus Neoplasms"[Mesh] OR Maxillary Sinus Neoplasms OR Maxillary Sinus cancer OR "Paranasal Sinus Neoplasms"[Mesh] OR Paranasal Sinus Neoplasms OR Paranasal Sinus cancer
	#4	"Laryngeal Neoplasms"[Mesh] OR Laryngeal Neoplasms OR Larynx Neoplasms OR Laryngeal cancer OR Larynx cancer
	#5	throat cancer OR throat Neoplasms
	#6	"Nose Neoplasms"[Mesh] OR nose Neoplasms OR nose cancer OR nasal cancer
	#7	"Mouth Neoplasms"[Mesh] OR Mouth cancer OR oral Neoplasms OR oral cancer OR Mouth Neoplasms
	#8	"Pharyngeal Neoplasms"[Mesh] OR Pharynx Neoplasm OR Pharynx cancer OR Pharyngeal Neoplasm
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
	#10	Raman Spectrum Analysis OR Raman Spectroscopy OR Spectroscopy, Raman OR Analysis, Raman Spectrum OR Raman Optical Activity Spectroscopy OR Raman Scattering OR Scattering, Raman OR Raman spectra OR Raman spectrum OR Raman spectroscope OR Raman spectrometry OR "Spectrum Analysis, Raman"[Mesh]
	#11	#9 AND #10
Embase	#1	"Head and Neck Neoplasms" OR "Head Neoplasms" OR Head and "Neck cancer" OR "Head cancer" OR "Neck cancer" OR "Neck Neoplasms" OR "head and neck squamous cell carcinoma" OR "HNSCC" OR "Head cancer"/exp OR "Neck cancer"/exp OR "head and neck squamous cell carcinoma"/exp

(Continues)

TABLE 1 (Continued)

Databases	Steps	Strategies
	#2	"Salivary Gland Neoplasms" OR "Salivary Gland cancer" OR "Salivary gland adenocarcinoma" OR "salivary adenoid cystic carcinoma" OR "Salivary Gland cancer"/exp
	#3	"Maxillary Sinus Neoplasms" OR "Maxillary Sinus cancer" OR "Paranasal Sinus Neoplasms" OR "Paranasal Sinus cancer" OR "Maxillary Sinus Neoplasms"/exp OR "paranasal sinus tumor"/exp
	#4	"Laryngeal Neoplasms" OR "Larynx Neoplasms" OR "Laryngeal cancer" OR "Larynx cancer" OR "larynx tumor"/exp
	#5	"throat cancer" OR "throat Neoplasms"
	#6	"nose Neoplasms" OR "nose cancer" OR "nasal cancer" OR "nose tumor"/exp
	#7	"Mouth cancer "OR "oral Neoplasms" OR "oral cancer" OR "Mouth Neoplasms" OR "mouth tumor"/exp
	#8	"Pharynx Neoplasm" OR "Pharynx cancer" OR "Pharyngeal Neoplasm" OR "Pharynx cancer"/exp
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
	#10	"raman spectrum analysis" OR "raman spectroscopy" OR "raman optical activity spectroscopy" OR "raman scattering" OR "raman spectra" OR "raman spectrum" OR "raman spectroscope" OR "raman spectrometry" OR "raman spectrometry"/exp
	#11	#9 AND #10
CNKI	#1	Head and neck neoplasms
	#2	Nasopharyngeal neoplasm
	#3	Oral cancer
	#4	Laryngeal cancer
	#5	#1 OR #2 OR #3 OR #4
	#6	Raman spectroscopy
	#7	#5 AND #6
Web of science	#1	Head and Neck Neoplasms OR Head Neoplasms OR Head and Neck cancer OR Head cancer OR Neck cancer OR Neck Neoplasms OR head and neck squamous cell carcinoma OR HNSCC

TABLE 1 (Continued)

Databases	Steps	Strategies
	#2	Salivary Gland Neoplasms OR Salivary Gland cancer OR Salivary gland adenocarcinoma OR salivary adenoid cystic carcinoma
	#3	Maxillary Sinus Neoplasms OR Maxillary Sinus cancer OR Paranasal Sinus Neoplasms OR Paranasal Sinus cancer
	#4	Laryngeal Neoplasms OR Larynx Neoplasms OR Laryngeal cancer OR Larynx cancer
	#5	throat cancer OR throat Neoplasms
	#6	nose Neoplasms OR nose cancer OR nasal cancer
	#7	Mouth cancer OR oral Neoplasms OR oral cancer OR Mouth Neoplasms
	#8	Pharynx Neoplasm OR Pharynx cancer OR Pharyngeal Neoplasm
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
	#10	Raman Spectrum Analysis OR Raman Spectroscopy OR Spectroscopy, Raman OR Analysis, Raman Spectrum OR Raman Optical Activity Spectroscopy OR Raman Scattering OR Scattering, Raman OR Raman spectra OR Raman spectrum OR Raman spectroscope OR Raman spectrometry
	#11	#9 AND #10

Assessment of Diagnostic Accuracy Studies (QUADAS).[14,15] The number of "Yes" responses in each study assessment was defined as the score of the study's quality.

2.4 | Data synthesis and statistical analysis

Data analyses were carried out by Meta-DiSc1.4 and Stata 12.0 software.

To obtain the diagnostic accuracy of RS for oral cancer, we calculated the sensibility, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic threshold, diagnostic odds ratio (DOR), and 95% confidence interval (CI). To merge the differences between the studies, we chose a random effects model (DerSimonian–Laird method) instead of a fixed effects model (Mantel–Haenszel method). The common population from which all studies in the meta-analysis were from was determined by a settled effect model. In addition, a stochastic effects model (DerSimonian–Laird method) suggested that these studies are from different populations, which may lead to deviations in the results.[16,17]

Given that the threshold may have an effect on the results, a summary receiver operating characteristic (SROC) curve was calculated, and a threshold analysis was carried out; in addition, we calculated the area under the curve (AUC) to estimate the overall effectiveness of the RS. The SROC curves did not exhibit a shoulder peak, indicating that thresholds may have no effect on the result. When the AUC value is between 0.9 and 1, the diagnostic effect is defined. It is favorable when the AUC value falls between 0.8 and 0.9. The diagnostic effect is fair when the AUC value is between 0.7 and 0.8. In addition, when the AUC value falls between 0.6 and 0.7, the diagnostic effect is poor. When the AUC falls between 0.5

and 0.6, the diagnostic method is considered to be ineffective.[18]

To further investigate heterogeneity, subgroup analyses were performed using the DerSimonian-Laird test (Q statistic), the chi-square test, and the inconsistency index (I^2) statistic. I^2 index is a better measure than DerSimonian-Laird test (Q statistic) when low numbers of trials are included. The Q stat tests have been noted as being inconsistent in meta-analyses with low numbers of trials. The I^2 index is a proposed better measure of consistency between trials in a meta-analysis, and it aims to show variability across studies is due to heterogeneity and not chance.[19] Hence, we used the Q statistic to describe the presence or absence of heterogeneity, and we used the I^2 index to classify the degree of heterogeneity for accurate result.[16] When the I^2 index is greater than 50% and the p value is less than .05,[17] the degree of heterogeneity was thought to be significant. A sensitivity analysis was carried out to assess the robustness of the combined results. If substantial heterogeneity existed, a meta-regression analysis and subgroup analysis were carried out to investigate the heterogeneity.

The Deeks' funnel plot asymmetry test was conducted in Stata12.0 to assess publication bias. When the p value was less than .05,[20] publication bias was considered to exist.

3 | RESULTS

3.1 | Study selection

Through the initial literature search, we retrieved 955 articles, and 219 of them were excluded because they were duplicates. Then, 109 articles about oral cancer were selected after the article titles and abstracts were read. After the full texts were read, 68 articles were excluded because of a lack of data and relevance. Finally, 41 studies that were eligible for inclusion in this meta-analysis were selected. All articles were written in English, except one article,[21] which was published in Chinese. No other studies were identified as relevant publications by examining the literature reference lists. A flow diagram of the study selection process is presented in Figure 1.

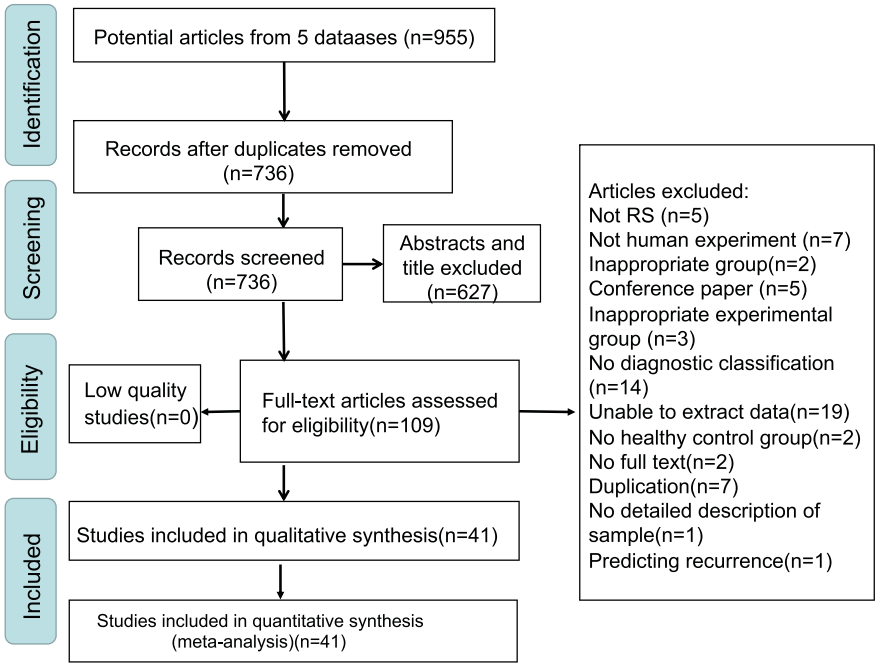
3.2 | Description of studies included in the review

Of all the included articles, 25[1,22–45] studies had data available for extraction for an oral cancer group, 3 studies[46–48] had data available for an oral precancerous lesion group, and 13 studies[21,49–60] had data available for both groups. We used histopathological samples as the gold standard for all studies.

Among the 38 studies in the oral cancer group, 5[33,53,54,56,60] studies evaluated in vivo tissue, whereas 33[1,21–32,34–45,49–52,55,57–59] studies evaluated in vitro samples. in vitro samples can be categorized as tissues (n = 13),[1,21,22,24,26,27,30,39,43–45,50,55] bio fluids (n = 15),[23,25,31,32,35–37,40–42,49,51,57–59] and exfoliated cells (n = 6),[25,28,29,34,38,52] and the tissue group can be divided into a fresh tissue group (n = 5),[21,22,30,45,55] frozen tissue group (n = 7),[1,24,26,27,39,44,50] and dehydrated tissue group (n = 1)[43] (one study[25] had subgroups). A variety of diagnostic algorithms were used to analyze the RS results; most studies used principal component analysis (PCA) and linear discriminate analysis (LDA; n = 14)[1,22,24,25,30,31,39–41,45,52,57,58,60] or principal component (PC)-LDA (n = 12),[23,28,29,33–38,49,51,59] and other studies used a hybrid Gaussian process (HGP) with PCA (n = 1),[26] a Gaussian process (GP) with PCA (n = 1),[27] factorial discriminant analysis (FDA) with PCA (n = 1),[1] maximum representation and discrimination feature (MRDF) sparse multinomial logistic regression (SMLR; n = 3),[53,54,56] discriminant function analysis (DFA) with PCA (n = 1),[21] a support vector machine (SVM; n = 4),[41–43,55] LDA with an artificial neural network (ANN; n = 1),[32] ConvNets (n = 1),[45] PCA and SVM (n = 2),[41,45] BP for chaos (n = 1),[44] and PCA with discriminant analysis (DA; n = 1)[50] (three studies[1,41,45] had subgroups). The applied Raman spectral range was divided into two categories, including the fingerprint region (FP; n = 35)[1,21,23–30,32–45,50–60] and high wavenumber (HW; n = 4)[22,31,36,49](one study[36] had subgroups).

Of all the 15 studies in the oral precancerous lesion group, 4[53,54,56,60] studies evaluated tissue in vivo, whereas 11[21,46–52,55,57–59] studies evaluated samples in vitro. in vitro samples can be categorized as tissues (n = 3),[21,50,55] bio fluids (n = 5),[36,49,51,57,58] and exfoliated cells (n = 3),[47,48,52] and tissues can be categorized as fresh tissues (n = 2)[21,55] or frozen tissues (n = 1).[50] A variety of diagnostic algorithms were carried out to analyze the RS results; most of the studies used principal component analysis (PCA) and linear discriminate analysis (LDA; n = 4)[52,57,58,60] or principal component (PC)-LDA (n = 5),[46–49,59] and other studies used maximum representation and discrimination feature (MRDF) sparse multinomial logistic regression (SMLR; n = 3),[53,54,56] PCA with discriminant function analysis (DFA; n = 1),[21] a support vector machine (SVM; n = 1),[55] and PCA with discriminant analysis (DA; n = 1).[50] All of the applied Raman spectral ranges were FP, except for one study,[49] it was HW.

FIGURE 1 Study flow diagram



The details of each study are shown in Table 2.

3.3 | Assessment of study quality

All the studies that met the QUADAS guidelines were included. In addition, all the QUADAS items were used to estimate the quality of the studies.[15] The detailed evaluation results are shown in Table 3.

Of the 38 studies that were identified through our search and included in the oral cancer group, 13[26,27,33,35,37,52–54,56–60] had an overall quality score of 11 (78.6% YES rate), and 15[21,22,25,30,34,36,38,41,42,44,45,49–51,55] had a score of 10 (71.4% YES rate). In addition, 10[1,23,24,28,29,31,32,39,41,43] studies scored only a 9 (64.3% YES rate). Of the 15 studies in the precancerous lesion group, 10[47,48,52–54,56–60] had an overall quality score of 11 (78.6% YES rate), and 5[21,46,49,50,55] had a score of 10 (71.4% YES rate). There were no low-quality articles in all the articles selected. To obtain an extensive amount of data, we fully investigated all 41 studies.

3.4 | Pooled results

3.4.1 | In vivo group

Oral cancer group

Five[33,53,54,56,60] of the included studies assessed tissues in vivo, and their coalescent sensibility and specificity results for RS were 0.91 (95% CI [0.89, 0.92], $p = .0000$, $I^2 = 96.9\%$) and 0.85 (95% CI [0.84, 0.86], $p = .0000$, $I^2 = 94.7\%$), respectively (Figure S1). The coalescent PLR and NLR were 8.01 (95% CI [4.65, 13.81]) and 0.10 (95% CI [0.05, 0.20]), respectively. The DOR was 85.72 (95% CI [28.65, 256.47]). The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9284.

Oral precancerous lesion group

Four[53,54,56,60] studies examined tissues in vivo. The coalescent sensibility and specificity for RS were 0.96 (95% CI [0.94, 0.98], $p = .0000$, $I^2 = 87.3\%$) and 0.95 (95% CI [0.93, 0.96], $p = .0000$, $I^2 = 89.0\%$), respectively (Figure S1). The pooled PLR and NLR were 25.85 (95% CI [9.18, 72.78]) and 0.04 (95% CI [0.01, 0.15]), respectively. The DOR was 839.25 (95% CI [274.50, 2,565.92]), which demonstrates very high accuracy. The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9932.

3.4.2 | Tissue/ex vivo group

Oral cancer group

Thirteen[1,21,22,24,26,27,30,39,43–45,50,55] studies examined tissues in vitro. The coalescent sensibility and specificity for RS were 0.96 (95% CI [0.96, 0.97], $p = .0000$, $I^2 = 87.1\%$) and 0.92 (95% CI [0.92–0.93], $p = .0000$, $I^2 = 91.6\%$), respectively (Figure S2). The pooled PLR and NLR were 17.35 (95% CI [11.19, 26.90]) and 0.04 (95% CI [0.02, 0.07]), respectively. The DOR was 693.59 (95% CI [295.33,

TABLE 2 General information of the studies included in the review

(A) Oral Cancer Group												
Reference	**Country**	**N1**	**N2**	**N3**	**Mean age**	**Sample type**	**Diagnostic algorithm**	**TP**	**FP**	**FN**	**TN**	**Spectral range**
Barroso, E. M. 2018[22]	US	7	9	2033	U	EV: Tissue (fresh)	PCA-LDA	966	132	51	884	HW
Brindha, E.2016(a)[23]	India	U	20	U	U	EV:Blood	PC-LDA	8	3	2	7	FP
Brindha, E.2016(b)[23]	India	U	20	U	U	EV: Saliva	PC-LDA	7	3	3	7	FP
Brindha, E.2016(c)[23]	India	U	20	U	U	EV: Urine	PC-LDA	7	2	3	8	FP
Brindha, E.2017[49]	India	U	197	U	U	EV: Urine	PC-LDA	109	2	8	78	HW
Cals, F. 2018[24]	Holland	10	25	720	U	EV: Tissue (frozen)	PCA-LDA	54	22	0	291	FP
Connolly, J. M.2016(a)[25]	Ireland	18	36	180	U	EV: Saliva	PCA-LDA	80	39	10	51	FP
Connolly, J. M.2016(b)[25]	Ireland	10	20	120	U	EV: Exfoliated cells	PCA-LDA	41	29	19	31	FP
Chundayil, M. G.2019[50]	India	U	37	290	60.9 ± 10.6	EV: Tissue (frozen)	PCA-DA	81	1	0	208	FP
Deshmukh, A.2011(a)[1]	India	25	U	362	U	EV: Tissue (frozen)	PCA-LDA	116	0	12	234	FP
Deshmukh, A.2011(b)[1]	India	25	U	362	U	EV: Tissue (frozen)	PCA-FDA	127	0	1	234	FP
Du, Z.2013(A)[26]	China	45	U	183	U	EV: Tissue (frozen)	PCA-HGP	57	21	7	98	FP
Du, Z.2013(B)[27]	China	41	U	765	U	EV: Tissue (frozen)	PCA-GP	526	0	0	134	FP
Elumalai, B.2014[51]	India	167	167	U	U	EV: Urine	PC-LDA	81	1	12	73	FP
Ghosh, A.2018[52]	India	15	15	62	U	EV:Exfoliated cells	PCA-LDA	45	4	3	10	FP
Hole, A.2017[28]	India	U	U	243	U	EV: Exfoliated Cells	PC-LDA	143	5	12	83	FP
Hole, A.2018[29]	India	U	44	243	U	EV: Exfoliated Cells	PC-LDA	143	5	12	83	FP
Knipfer, C.2014[30]	Germany	12	U	72	60.9 ± 10.6	EV: Tissue (fresh)	PCA-LDA	31	2	5	34	FP
Krishna, H.2013(A)[53]	India	239	U	605	U	IV	MRDF-SMLR	333	16	4	252	FP
Krishna, H.2013(B)[54]	India	199	U	802	U	IV:	MRDF-SMLR	484	17	31	270	FP
Li, Yi.2010[55]	China	138	138	138	U	EV: Tissue (fresh)	SVM	106	0	0	32	FP
Majumder, S. K.2010[56]	India	164	U	674	U	IV	MRDF-SMLR	406	8	0	260	FP
Rekha, P.2016[58]	India	83	83	U	U	EV: Saliva	PCA-LDA	50	8	10	15	FP
Rekha, P.2015[57]	India	91	91	U	U	EV: Blood	PCA-LDA	60	5	1	25	FP

TABLE 2 (Continued)

(A) Oral Cancer Group												
Reference	**Country**	**N1**	**N2**	**N3**	**Mean age**	**Sample type**	**Diagnostic algorithm**	**TP**	**FP**	**FN**	**TN**	**Spectral range**
Pachaiappan, R.2017(A)[31]	India	64	64	U	U	EV:Blood	PCA-LDA	29	5	5	25	HW
Pachaiappan, R.2017(B)(a)[32]	India	48	48	U	U	EV:Blood	LDA-ANN	16	1	0	31	FP
Pachaiappan, R.2017(B)(b)[32]	India	48	48	U	U	EV:Blood	LDA-ANN	15	3	2	28	FP
Sahu, A.2013(a)[35]	India	70	70	691	U	EV:Blood	PC-LDA	404	9	127	151	FP
Sahu, A.2013(b)[35]	India	30	14	288	U	EV: Blood (Buccal mucosa)	PC-LDA	117	4	11	156	FP
Sahu, A.2013(c)[35]	India	56	40	563	U	EV: Blood (tongue)	PC-LDA	305	24	98	136	FP
Sahu, A.2014(a)[37]	India	86	86	258	50.68 ± 12.56	EV:Blood	PC-LDA	48	6	21	11	FP
Sahu, A.2014(b)[37]	India	53	53	159	U	EV: Blood (Buccal mucosa)	PC-LDA	30	6	6	11	FP
Sahu, A.2014 (c)[37]	India	40	40	150	U	EV: Blood (tongue)	PC-LDA	22	5	11	12	FP
Sahu, A.2015(A)(a)[36]	India	86	86	258	50.68 ± 12.56	EV:Blood	PC-LDA	56	4	13	13	FP
Sahu, A.2015(A)(b)[36]	India	53	53	159	U	EV: Blood (Buccal mucosa)	PC-LDA	31	4	5	13	FP
Sahu, A.2015(A)(c)[36]	India	40	40	150	U	EV: Blood (tongue)	PC-LDA	26	6	7	11	FP
Sahu, A.2015(A)(d)[36]	India	86	86	258	50.68 ± 12.56	EV:Blood	PC-LDA	47	8	22	9	HW
Sahu, A.2015(A)(e)[36]	India	53	53	159	U	EV: Blood (Buccal mucosa)	PC-LDA	27	6	9	11	HW
Sahu, A.2015(A)(f)[36]	India	40	40	150	U	EV: Blood (tongue)	PC-LDA	14	10	19	7	HW
Sahu, A.2015(B)[38]	India	26	26	151	U	EV: Exfoliated cells	PC-LDA	69	4	9	69	FP
Sahu, A.2015(C)[59]	India	246	246	U	U	EV: Blood	PC-LDA	101	13	19	113	FP
Sahu, A.2016(a)[33]	India	U	U	786	U	IV	PC-LDA	177	72	23	514	FP
Sahu, A.2016(b)[33]	India	U	U	319	U	IV	PC-LDA	14	64	4	237	FP
Sahu, A.2016 (c)[33]	India	U	U	499	U	IV	PC-LDA	103	67	36	293	FP
Sahu, A.2016 (d)[33]	India	157	157	1,603	U	IV	PC-LDA	275	257	82	989	FP
Sahu, A.2019[34]	India	52	U	298	U	EV:Exfoliated cells	PC-LDA	75	29	46	158	FP
Singh, S. P.2012(B)[39]	India	U	U	120	U	EV: Tissue (frozen)	PCA-LDA	33	3	7	77	FP
Singh, S. P.2012(C)[60]	India	U	U	349	U	IV	PCA-LDA	198	16	26	109	FP
Tan.Y.2017(A)[40]	China	280	280	280		EV: Blood	PCA-LDA	107	25	28	120	FP
Tan.Y.2017(B)(a)[41]	China	U	80	80	U	EV: Blood	SVM	34	16	1	29	FP
Tan.Y.2017(B)(b)[41]	China	U	80	80	U	EV: Blood	PCA-SVM	27	11	8	34	FP
Tan.Y.2017(B)(c)[41]	China	U	280	280	U	EV: Blood	PCA-LDA	107	25	28	120	FP

(Continues)

TABLE 2 (Continued)

(A) Oral Cancer Group												
Reference	**Country**	**N1**	**N2**	**N3**	**Mean age**	**Sample type**	**Diagnostic algorithm**	**TP**	**FP**	**FN**	**TN**	**Spectral range**
Xue, L.2015[21]	China	138	138	U	61 ± 11	EV: Tissu (fresh)	PCA-DFA	106	0	0	32	FP
Yan, B.2015(a)[42]	China	51	51	254	U	EV: Blood (PA)	SVM	78	10	23	143	FP
Yan, B.2015(b)[42]	China	52	52	258	U	EV: Blood (WT)	SVM	78	14	27	139	FP
Yan, B.2015(c)[42]	China	50	50	248	U	EV: Blood (MEC)	SVM	91	4	4	149	FP
Yan, B.2011[43]	China	60	U	181	U	EV: Tissue (dehydrated)	SVM	118	3	1	59	FP
Yu, M.2019(a)[45]	China	12	24	288	U	EV: Tissu (fresh)	ConvNets	143	8	1	136	FP
Yu, M.2019(b)[45]	China	12	24	288	U	EV: Tissu (fresh)	PCA-SVM (RBF)	132	15	12	129	FP
Yu, M.2019(c)[45]	China	12	24	288	U	EV: Tissu (fresh)	PCA-SVM (polynomial)	139	8	5	136	FP
Yu, M.2019(d)[45]	China	12	24	288	U	EV: Tissu (fresh)	PCA-LDA	141	17	3	127	FP
Yaogai Hu.2008[44]	China	22	22	22	U	EV: Tissue (frozen)	BP-Chaos	8	0	0	14	FP
(B) Oral Precancerous Lesion Group												
Brindha, E.2017[49]	India	U	137	U	U	EV: Urine	PC-LDA	52	1	5	79	HW
Chundayil, M.G.2019[50]	India	U	37	290	60.9 ± 10.6	EV: Tissu (frozen)	PCA-DA	64	0	0	81	FP
Elumalai, B.2015[46]	India	121	121	U	U	EV: Urine	PC-LDA	44	5	7	65	FP
Krishna, H.2013(A)[53]	India	U	U	403	U	IV	MRDF-SMLR	136	11	4	252	FP
Krishna, H.2013(B)[54]	India	86	U	486	U	IV	MRDF-SMLR	197	6	2	281	FP
Li, Yi.2010[55]	China	75	75	75	U	EV:Tissue (fresh)	SVM	43	0	0	32	FP
Xue, L.2015[21]	China	75	75	U	U	EV: Tissu (fresh)	PCA-DFA	43	0	0	32	FP
Majumder, S. K.2010[56]	India	72	U	423	U	IV:	MRDF-SMLR	151	29	4	239	FP
Rekha, P.2015[57]	India	57	57	U	U	EV: Blood	PCA-LDA	24	6	3	24	FP
Rekha, P.2016[58]	India	51	83	U	U	EV: Saliva	PCA-LDA	26	7	2	16	FP
Sahu, A.2017[47]	India	67	80	665	U	EV:Exfoliated cells	PC-LDA	179	47	55	384	FP
Sahu, A.2015(C)[59]	India	173	173	U	U	EV: Blood	PC-LDA	37	21	10	95	FP
Sahu, A.2014[48]	India	51	72	659	U	EV:Exfoliated cells	PC-LDA	92	129	56	382	FP
Singh, S. P.2012(C)[60]	India	U	U	188	U	IV	PCA-LDA	66	1	12	109	FP
Ghosh, A.2018[52]	India	U	U	29	U	EV:Exfoliated cells	PCA-LDA	16	1	2	10	FP

TABLE 3 Quality assessment of the included studies using the QUADAS tool

(A) Oral Cancer Group																
Reference	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**	**Score**	**Rate of Y**
Barroso, E. M.2018[22]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Brindha, E.2016(a)[23]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Brindha, E.2016(b)[23]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Brindha, E.2016(c)[23]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Brindha, E.2017[49]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Cals, F. 2018[24]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Connolly, J. M.2016(a)[25]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Connolly, J. M.2016(b)[25]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Chundayil, M. G.2019[50]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Deshmukh, A.2011(a)[1]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Deshmukh, A.2011(b)[1]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Du, Z.2013(A)[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Du, Z.2013(B)[27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Elumalai, B.2014[51]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Ghosh, A.2018[52]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Hole, A.2017[28]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Hole, A.2018[29]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Knipfer, C.2014[30]	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Krishna, H.2013(A)[53]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Krishna, H.2013(B)[54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Li, Yi.2010[55]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Majumder, S. K.2010[56]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Rekha, P.2016[58]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Rekha, P.2015[57]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Pachaiappan, R.2017(A)[31]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Pachaiappan, R.2017(B)(a)[32]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Pachaiappan, R.2017(B)(b)[32]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Sahu, A.2013(a)[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2013(b)[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2013(c)[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2014(a)[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2014(b)[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2014 (c)[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2015(A)(a)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4

(Continues)

TABLE 3 (Continued)

(A) Oral Cancer Group																
Reference	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**	**Score**	**Rate of Y**
Sahu, A.2015(A)(b)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(A)(c)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(A)(d)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(A)(e)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(A)(f)[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(B)[38]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Sahu, A.2015(C)[59]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2016(a)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2016(b)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2016 (c)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2016 (d)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2019[34]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Singh, S. P.2012(B)[39]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Singh, S. P.2012(C)[60]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Xue, L.2015[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Yan, B.2015(a)[42]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yan, B.2015(b)[42]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yan, B.2015(c)[42]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yan, B.2011[43]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Yu, M.2019(a)[45]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yu, M.2019(b)[45]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yu, M.2019(c)[45]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yu, M.2019(d)[45]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Yaogai Hu.2008[44]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Tan.Y.2017(A)[40]	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Tan.Y.2017(B)(a)[41]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Tan.Y.2017(B)(b)[41]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
Tan.Y.2017(B)(c)[41]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	9	64.3
(B) Oral Precancerous Lesion Group																
Brindha, E.2017[49]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Chundayil,M. G.2019[50]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Elumalai, B.2015[51]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	U	U	10	71.4
Krishna, H.2013(A)[53]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Krishna, H.2013(B)[54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Li, Yi.2010[55]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Xue, L.2015[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	U	10	71.4
Majumder, S. K.2010[56]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Rekha, P.2016[58]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Rekha, P.2015[57]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6

TABLE 3 (Continued)

(A) Oral Cancer Group																
Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score	Rate of Y
Singh, S. P.2012(C)[60]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2017[47]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2014[48]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Sahu, A.2015(C)[59]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6
Ghosh, A.2018[52]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	U	11	78.6

Note. Q1. Was the spectrum of patient's representative of the patients who will receive the test in practice? Q2. Were selection criteria clearly described? Q3. Is the reference standard likely to correctly classify the target condition? Q4. Is the time period between reference standard and index test short enough to be reasonable? Q5. Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis? Q6. Did patients receive the same reference standard regardless of the index test result? Q7. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)? Q8. Was the execution of the index test described in sufficient detail to permit replication of the test? Q9. Was the execution of the reference standard described in sufficient detail to permit its replication? Q10. Were the index test results interpreted without knowledge of the results of the reference test? Q11. Were the reference standard results interpreted without knowledge of the results of the index test? Q12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Q13. Were interpretable/intermediate test results reported? Q14. Were withdrawals from the study explained? Y yes, N no, U unclear, QUADAS Quality assessment of diagnostic accuracy studied.

1,628.93]), which demonstrates very high accuracy. The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9937.

Oral precancerous lesion group

Three studies[21,50,55] examined tissues ex vivo. The pooled sensitivity and specificity for RS were 1.00 (95% CI [0.98, 1.00], $p = 1.0000$, $I^2 = 0.0\%$) and 1.00 (95% CI [0.97, 1.00], $p = 1.0000$, $I^2 = 0.0\%$), respectively (Figure S2). The pooled PLR and NLR were 88.33 (95% CI [18.00, 433.40]) and 0.01 (95% CI [0.00, 0.05]), respectively. The DOR was 8777.35 (95% CI [901.48, 85,461.36]), revealing that the accuracy is very high. The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9990.

3.4.3 | Fresh tissue/ex vivo group

Oral cancer group

Five[21,22,30,45,55] studies examined fresh tissues in vitro. The coalescent sensibility and specificity for RS were 0.96 (95% CI [0.95, 0.97], $p = .0000$, $I^2 = 81.9\%$) and 0.89 (95% CI [0.88, 0.91], $p = .0001$, $I^2 = 77.1\%$), respectively (Figure S2). The pooled PLR and NLR were 11.12 (95% CI [7.73, 16.01] and 0.04 (95% CI [0.02, 0.08]), respectively. The DOR was 315.63 (95% CI [137.23, 725.97]), which also revealed high accuracy. The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9750.

3.4.4 | Frozen tissue/vitro group

3.4.5 | Oral cancer group

Seven[1,24,26,27,39,44,50]studies examined frozen tissues in vitro. The coalescent sensibility and specificity for RS were 0.97 (95% CI [0.96, 0.98], $p = .0000$, $I^2 = 90.9\%$) and 0.96 (95% CI [0.95, 0.97], $p = 0.0000$, $I^2 = 92.9\%$), respectively (Figure S2). The pooled PLR and NLR were 49.89 (95% CI [11.96, 208.07]) and 0.04 (95% CI [0.01, 0.11]), respectively. The DOR was 2,130.33 (95% CI [220.12, 20,617.21]), which also revealed high accuracy. The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9968.

3.4.6 | Dehydrated tissue/vitro group

Oral cancer group

Only one[43] study examined dehydrated tissue in vitro to assess the discriminative ability of RS. Therefore, a meta-analysis could not be performed.

3.4.7 | Bio fluids/ex vivo group

Oral cancer group

Fifteen[23,25,31,32,35–37,40–42,49,51,57–59] studies examined in vitro bio fluid samples, such as urine, blood plasma, and saliva. The coalescent sensibility and specificity for

RS were 0.80 (95% CI 0.[79, 0.82], $P = .0000$, $I^2 = 79.6\%$) and 0.86 (95% CI [0.84, 0.88], $p = 0.0000$, $I^2 = 87.2\%$), respectively (Figure S3). The pooled PLR and NLR were 4.67 (95% CI [3.35, 6.50]) and 0.24 (95% CI [0.20, 0.29]), respectively. The DOR was 22.74 (95% CI [13.90, 37.22]. The overall diagnostic accuracy was estimated by generating an SROC curve, according to which the AUC was 0.8972.

Oral precancerous lesion group

Five[36,49,51,57,58] studies examined bio fluid samples in vitro, and their coalescent sensibility and specificity for RS were 0.77 (95% CI [0.74, 0.80], $p = .0000$, $I^2 = 80.8\%$) and 0.83 (95% CI [0.81, 0.85], $p = .0000$, $I^2 = 89.4\%$), respectively (Figure S3). The pooled PLR and NLR were 5.67 (95% CI [3.24, 9.93]) and 0.20 (95% CI [0.13, 0.32]), respectively. The DOR was 33.41 (95% CI [12.88, 86.66]). The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9121.

3.4.8 | Exfoliated cells/vitro group

Oral cancer group

Six[25,28,29,34,38,52] studies examined exfoliated cell samples in vitro. The coalescent sensibility and specificity for RS were 0.84 (95% CI [0.80, 0.86], $p = .0000$, $I^2 = 92.6\%$) and 0.85 (95% CI [0.82, 0.88], $p = .0000$, $I^2 = 91.7\%$), respectively (Figure S3). The coalescent PLR and NLR were 6.30 (95% CI [2.24, 17.69]) and 0.17 (95% CI [0.08, 0.39]), respectively. The DOR was 38.26 (95% CI [7.93, 184.60]). The overall diagnostic accuracy was estimated by generating an SROC curve, and the AUC was 0.9254.

Oral precancerous lesion group

Three[47,48,52] studies examined exfoliated cell samples in vitro. The coalescent sensibility and specificity for RS were 0.72 (95% CI [0.67, 0.76], $p = .0023$, $I^2 = 83.5\%$) and 0.81 (95% CI [0.79, 0.84], $p = .0000$, $I^2 = 94.1\%$), respectively (Figure S3). The pooled PLR and NLR were 4.78 (95% CI [1.78, 12.83]) and 0.31 (95% CI [0.17, 0.58]), respectively. The DOR was 16.48 (95% CI [3.67, 73.98]). The overall diagnostic accuracy was estimated by generating an SROC curve, and its AUC was 0.9275.

3.5 | Publication bias

No significant publication bias was found in this meta-analysis by Deeks' funnel plot asymmetry test. The outcomes of the estimation of publication bias and heterogeneity for each group are shown in Table 4. The funnel plots are shown in Figure 2.

3.6 | Heterogeneity

The forest plot of the sensitivity and specificity for each study (Figure 3) reveals that the heterogeneity of sensitivity and specificity is obvious. In addition, the Q test value and I^2 index of the sensitivity and specificity were 1,079.00 ($p = 0.00$) and $I^2 = 94.35$ (95% CI [94.45, 95.24]) and 932.09 ($p = .00$) and $I^2 = 93.46$ (95% CI [92.37, 94.54]), respectively.

Meta-regression was conducted to investigate the source of heterogeneity, and the sample type, spectral range, diagnostic algorithm, and sample size were included as covariates. The results are shown in Table 5.

In the oral cancer group, for sensitivity, the p value of the sample type and diagnostic algorithm was less than .05, which was statistically significant. In addition, for specificity, only the diagnostic algorithm was statistically significant. In addition, when we performed a subgroup analysis of the sample type once more, we found that the p values in the in vivo group and the biofluids/in vitro group were statistically significant, which means that they can be a heterogeneous source of sensitivity and specificity. In addition, the exfoliated cell/in vitro group was significantly different from the other groups, which means that it may be a source of heterogeneity as well.

For the oral precancerous lesion group, only the diagnostic algorithm had a slice value of less than 0.05, which was statistically significant.

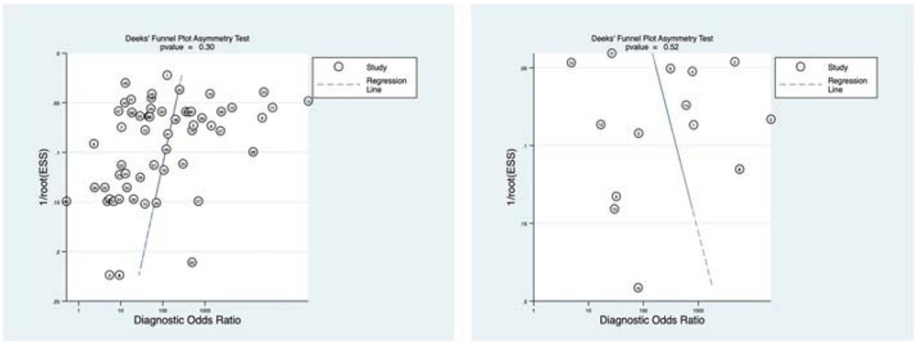
4 | DISCUSSION

This meta-analysis was the first article to evaluate the accuracy of RS in identifying oral cancer tissue and healthy tissue. Of the 955 records identified through our search, 41 unique studies were determined to be eligible for our meta-analysis. One of these studies was published in Chinese, and the remaining studies were published in English. In addition, the relevant research teams were mostly from India and China, which is reasonable and understandable because the Raman spectrum was discovered by Indian scientist Raman, and the incidence of oral cancer tends to be concentrated in South Asia.[61] Bangladesh is the country with the highest incidence and mortality of oral and oropharyngeal cancer in South Asia.[62] Therefore, most studies are conducted by teams in these developing countries. Therefore, relevant research in these developing countries must be performed to obtain comprehensive epidemiologic information, which is the reason why we carried out this meta-analysis.

According to the results in Table 4, both the RS analyses of oral cancer tissue in vivo (AUC = 0.9284) and

TABLE 4 Coalescent estimation of sensitivity, positive likelihood ratio, negative likelihood ratio, specificity, diagnostic odds ratio, and area under the curve for Raman spectroscopy (RS)

(A). Oral Cancer Group							
Groups (*N*)	**SEN (95% CI *p*, I^2)**	**SPE (95% CI *p*, I^2)**	**PLR (95% CI *p*, I^2)**	**NLR (95% CI *p*, I^2)**	**DOR (95% CI *p*, I^2)**	**AUC**	**Publication bias(p^*)**
In vivo (8)	0.91(0.89–0.92), 0.0000, 96.9%	0.85(0.84–0.86), 0.0000, 94.7%	8.01(4.65–13.81), 0.0000,96.6%	0.10(0.05–0.20), 0.0000, 95.3%	85.72(28.65–256.47), 0.0000,96.1%	0.9284	0.94
Ex vivo (54)							
EV tissue (17)	0.96(0.96–0.97), 0.0000, 87.1%	0.92(0.92–0.93), 0.0000,91.6%	17.35(11.19–26.90), 0.0000, 83.6%	0.04(0.02–0.07), 0.0000,78.5%	693.59(295.33–1628.93), 0.0000,81.6%	0.9937	0.22
EV tissue fresh Tissue (8)	0.96(0.95–0.97), 0.0000,81.9%	0.89(0.88–0.91), 0.0001, 77.1%	11.12(7.73–16.01), 0.0085, 63.0%	0.04(0.02–0.08), 0.0011,71.1%	315.63(137.23–725.97), 0.0007, 72.3%	0,9,750	0.06
EV tissue frozen Tissue (8)	0.97(0.96–0.98), 0.0000, 90.9%	0.96(0.95–0.97), 0.0000, 92.9%	49.89(11.96–208.07), 0.0000, 94.0%	0.04(0.01–0.11), 0.0000,85.5%	2130.33(220.12–20617.21), 0.0000,87.6%	0.9968	0.10
EV tissue Dehydrated tissue (1)	-	-	-	-	-	-	-
Ex bio fluids (31)	0.80(0.79–0.82), 0.0000, 79.6%	0.86(0.84–0.88), 0.0000, 87.2%	4.67(3.35–6.50), 0.0000, 88.9%	0.24(0.20–0.29), 0.0000, 78.1%	22.74(13.90–37.22), 0.0000, 84.5%	0.8972	0.10
EV exfoliated Cells (6)	0.84(0.80–0.86), 0.0000, 92.6%	0.85(0.82–0.88), 0.0000, 91.7%	6.30(2.24–17.69), 0.0000, 94.9%	0.17(0.08–0.39), 0.0000, 94.1%	38.26(7.93–184.60), 0.0000, 94.1%	0.9254	0.87
(B) Oral Precancerous Lesion Group							
In vivo(4)	0.96(0.94–0.98), 0.0000,87.3%	0.95(0.93–0.96), 0.0000,89.0%	25.85(9.18–72.78), 0.0000,88.9%	0.04(0.01–0.15), 0.0000,90.2%	839.25(274.50–2565.92), 0.0560,60.3%	0.9932	0.58
Ex vivo (14)							
EV tissue(3)	1.00(0.98–1.00), 1.0000,0.0%	1.00(0.97–1.00), 1.0000,0.0%	88.33(18.00–433.40), 0.8676,0.0%	0.01(0.00–0.05), 0.9721,0.0%	8777.35(901.48–85461.36), 0.8672,0.0%	0.9990	-
Ex bio fluids (5)	0.77(0.74–0.80), 0.0000,80.8%	0.83(0.81–0.85), 0.0000,89.4%	5.67(3.24–9.93), 0.0000,89.8%	0.20(0.13–0.32), 0.0000,84.3%	33.41(12.88–86.66), 0.0000,88.9%	0.9121	0.29
EV exfoliated Cells (3)	0.72(0.67–0.76), 0.0023,83.5%	0.81(0.79–0.84), 0.0000,94.1%	4.78(1.78–12.83), 0.0000,95.3%	0.31(0.17–0.58), 0.0001,89.8%	16.48(3.67–73.98), 0.0000,94.4%	0.9275	0.87



(a) Oral Cancer Group (b) Oral Precancerous Lesion Group

FIGURE 2 Deeks' funnel plots indicating no publication bias

ex vivo (AUC = 0.9937) are better than those of bio fluids (AUC = 0.8972) and exfoliated cells (AUC = 0.9254), and the RS analysis of tissue ex vivo is superior to that of tissue in vivo. In the in vitro RS analysis of tissue, the effect of frozen tissue is higher than that of fresh tissue, with AUC values of 0.9968 and 0.9750, respectively. However, it is unfortunate that the dehydrated tissue group cannot be assessed due to an insufficient sample size. The oral precancerous lesion group and the oral cancer group showed the same results. The AUC values of the RS analysis of tissue in vivo and ex vivo were 0.9932 and 0.9990, respectively, whereas the AUC values of the RS analysis of biofluids and exfoliated cells were 0.9121 and 0.9275, respectively. The reason for these results may be that the fiber-optic probes used in in vivo RS are disturbed by the intense fused-silica background signal when the spectrum information in the FP region is collected. However, the spectral ranges used in the in vivo tissue RS analysis that we included in this study were those in the FP region.

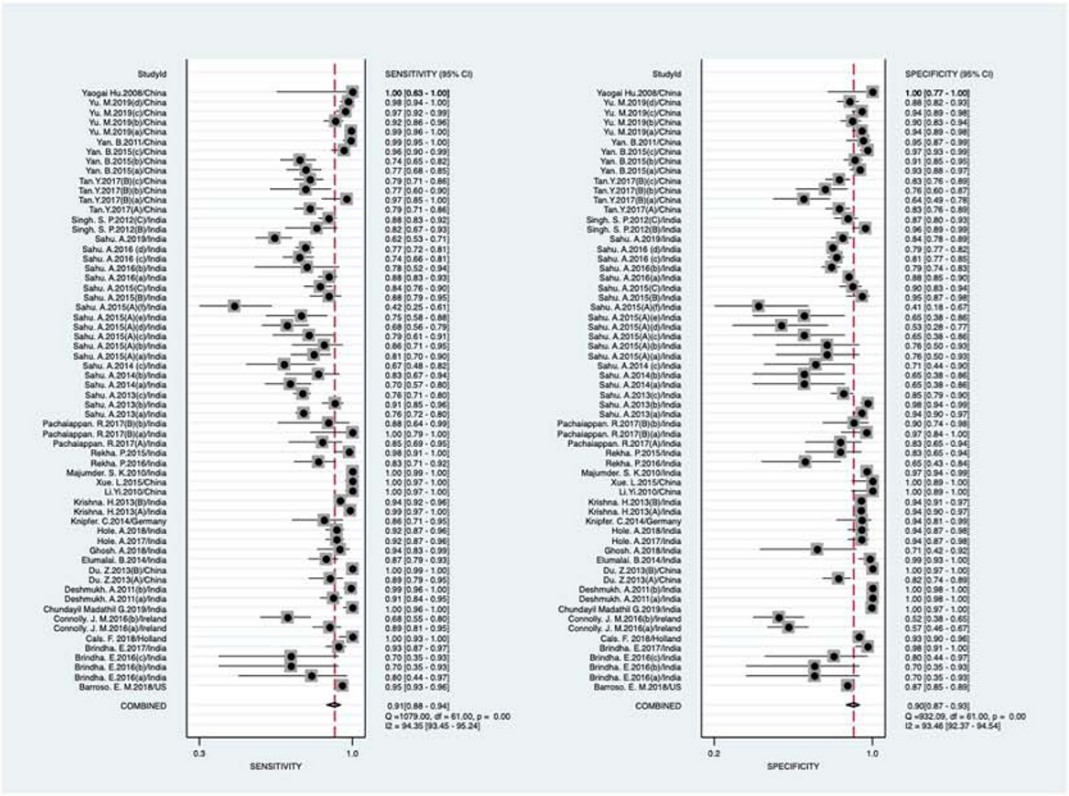
As shown in Table 4, the diagnostic accuracy of the biofluid group was obviously lower than that of the other groups. Raman spectra of biological samples are often superimposed on a strong fluorescent background, which may be overwhelming, as Raman signals are weak and susceptible to background fluorescence interference, making it difficult to extract Raman signals.[63] Therefore, its application in the detection of biological samples with complex components is limited. The enhanced local electromagnetic field greatly increases the probability of the Raman scattering of molecules adsorbed on the surface of the nanoscale probe, thus enhancing the Raman intensity of the sample and even exponentially amplifying the weak Raman signal. In addition, nanoscale probes do not interfere with the sample signals because the material does not have obvious Raman signals.[41,64–66] Therefore, studies using SERS have shown higher diagnostic accuracy than studies with unknown RS have, with AUCs of 0.9183 and 0.8872, respectively (as shown in Figure S4).

The diagnostic performance of the group with PCA-LDA and PC-LDA was worse than that of the group with other diagnostic algorithms, with AUC of 0.9115 and 0.9878, respectively (as shown in Figure S5). PCA and LDA are two common diagnostic algorithms. Although these two algorithms are complex, they are not comparable with other methods. Therefore, regrettably, some important data may be lost, as other diagnostic algorithms may have more accurate diagnostic performance. The SVM maps input to high-dimensional feature spaces, reducing the amount of data lost. MRDF is a feature extraction process whose purpose is to identify a set of nonlinear transformations on the input data that can optimally distinguish different classes in the dimensionality reduction space.[56] SMLR is a probabilistic multiclass classification model based on a sparse Bayesian machine learning framework of statistical pattern recognition.[67]

The heterogeneity test results showed that all subgroup analyses were highly heterogeneous. This result may be due to the data from the study. Although most of the studies were conducted in developing countries, selectivity bias cannot be completely avoided. The type of samples, the number of samples, the diagnostic algorithm, the spectral range of the Raman spectrum, the type of RS, the country of the research team, and the utilization of the cross-validation method may be sources of heterogeneity. Thus, the variables are difficult to quantify. In addition, some information cannot be evaluated because of a lack of essential elements, such as the type of RS used. For most of the studies, all of these aspects cannot be determined. These variables deserve to be studied further. The meta-regression analysis results are shown in Table 5. The sample type (especially bio fluids or tissues), diagnostic algorithm, and sample size all increase the heterogeneity of the results.

RS is a diagnostic tool with a wide range of potential applications. It can be used to detect changes at the molecular level before morphological changes occur in the cells, so it has an advantage over traditional

(a)Oral Cancer Group



(b) Oral Precancerous Lesion Group

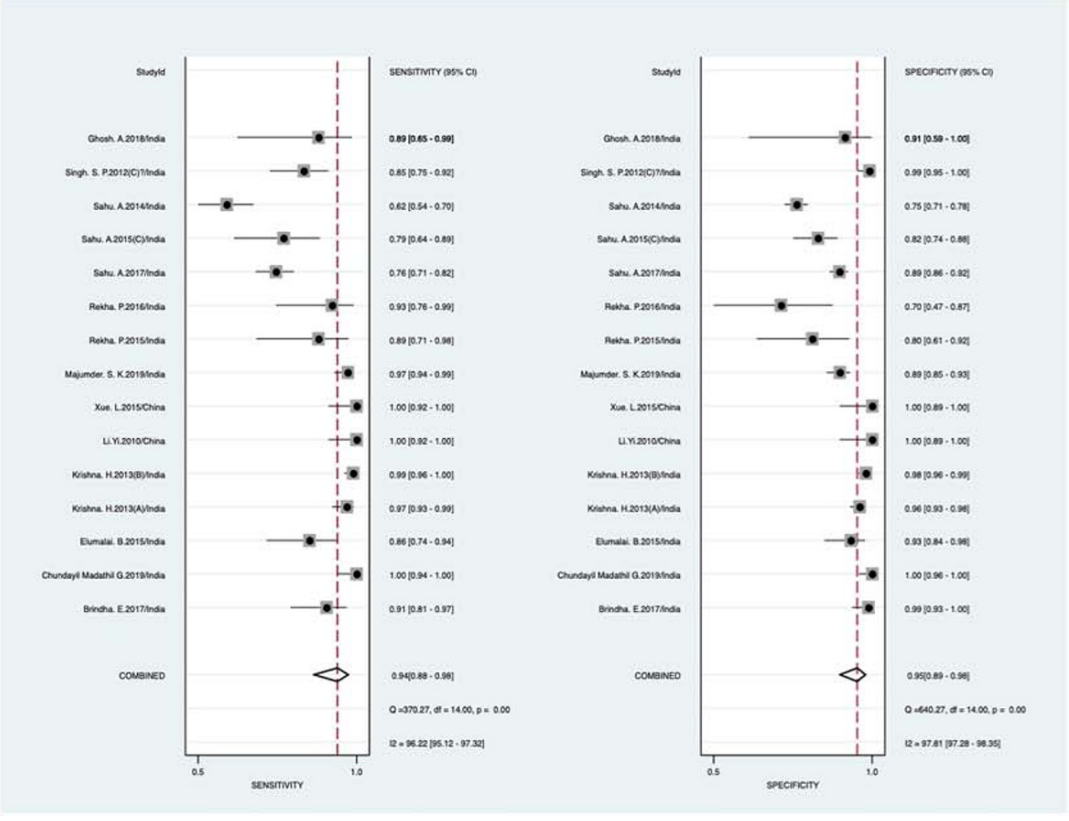


FIGURE 3 The forest plot of sensitivity and specificity of all study

TABLE 5 Results of meta-regression analysis

(A) Oral Cancer Group					
(a) all studies					
Parameter	***N***	**Sensitivity**	**p1**	**Specificity**	**p2**
Sample type					
Sample	62	0.84 [0.75–0.90]	0.03	0.85 [0.77–0.91]	0.13
In/ex					
In vivo	8	0.93 [0.86–1.00]	0.12	0.90 [0.81–0.98]	0.03
Ex vivo	54	0.91 [0.88–0.94]		0.91 [0.87–0.94]	
Bio fluids/others					
Bio fluids	31	0.83 [0.77–0.90]	0.00	0.84 [0.78–0.90]	0.00
Others	31	0.96 [0.94–0.98]		0.94 [0.92–0.97]	
Ex tissue/others					
Ex tissue	17	0.98 [0.97–0.99]	0.40	0.97 [0.95–0.99]	0.20
Others	45	0.86 [0.82–0.90]		0.85 [0.81–0.90]	
Exfoliated cells/others					
Exfoliated cells	6	0.86 [0.72–1.00]	0.04	0.87 [0.75–1.00]	0.07
Others	56	0.92 [0.89–0.95]		0.91 [0.87–0.94]	
Diagnostic algorithm					
PCA-LDA and PC-LDA	41	0.85 [0.80–0.89]	0.00	0.85 [0.80–0.90]	0.00
Others	21	0.98 [0.96–0.99]		0.96 [0.94–0.98]	
Spectral range					
FP	56	0.92 [0.89–0.95]	0.98	0.91 [0.88–0.94]	0.81
HW	6	0.82 [0.65–0.99]		0.78 [0.58–0.97]	
Sample number					
(TP + FP + FN + TN) ≥ 100	40	0.94 [0.91–0.96]	0.08	0.94 [0.91–0.96]	0.31
(TP + FP + FN + TN) < 100	22	0.85 [0.78–0.93]		0.77 [0.68–0.86]	
(b) Ex tissue					
Sample type					
Sample	17	0.99 [0.93–1.00]	0.75	0.99 [0.94–1.00]	0.42
Fresh tissue/others					
Fresh tissue	8	0.98 [0.96–1.00]	0.91	0.95 [0.90–1.00]	0.06
Others	9	0.99 [0.97–1.00]		0.99 [0.97–1.00]	
Frozen tissue/others					
Frozen tissue	8	0.99 [0.96–1.00]	0.72	0.99 [0.97–1.00]	0.23
Others	9	0.98 [0.96–1.00]		0.95 [0.91–1.00]	
Dehydrated tissue/others					
Dehydrated tissue	1	0.99 [0.97–1.00]	0.00	0.96 [0.81–1.00]	0.27
Others	16	0.98 [0.97–1.00]		0.98 [0.96–1.00]	
Diagnostic algorithm					
PCA-LDA and PC-LDA	6	0.94 [0.88–1.00]	0.01	0.95 [0.89–1.00]	0.15
Others	11	0.99 [0.98–1.00]		0.99 [0.97–1.00]	
Spectral range					
FP	16	0.99 [0.97–1.00]	0.01	0.98 [0.96–1.00]	0.01

TABLE 5 (Continued)

(A) Oral Cancer Group					
(a) all studies					
Parameter	***N***	**Sensitivity**	**p1**	**Specificity**	**p2**
HW	1	0.95 [0.78–1.00]		0.87 [0.52–1.00]	
Sample number					
(TP + FP + FN + TN) ≥ 100	15	0.99 [0.97–1.00]	0.01	0.98 [0.95–1.00]	0.19
(TP + FP + FN + TN) < 100	2	0.96 [0.83–1.00]		0.98 [0.94–1.00]	
(B) Oral Precancerous Lesion Group					
Sample type					
Sample	15	0.86 [0.75–0.93]	0.08	0.90 [0.80–0.96]	0.24
Diagnostic algorithm					
PCA-LDA and PC-LDA	9	0.82 [0.75–0.89]	0.00	0.91 [0.84–0.97]	0.00
Others	6	0.99 [0.98–1.00]		0.98 [0.96–1.00]	
Spectral range					
FP	14	0.95 [0.90–0.99]	0.15	0.94 [0.90–0.99]	0.88
HW	1	0.92 [0.68–1.00]		0.99 [0.96–1.00]	
Sample number					
(TP + FP + FN + TN) ≥ 100	12	0.95 [0.91–1.00]	0.47	0.96 [0.93–0.99]	0.12
(TP + FP + FN + TN) < 100	3	0.92 [0.77–1.00]		0.81 [0.57–1.00]	

pathological diagnosis methods. First, spectroscopy is noninvasive. RS does not physically harm humans when it is used. In addition, RS has the advantage of real-time and in situ identification. No special treatment of the sample is required for RS. In this meta-analysis, RS was found to have high accuracy in the identification of healthy and pathological tissues. Real-time detection with RS in vivo is important for the judgment of tumor margins during surgery. Barroso et al. studied the use of high-wavenumber (2,400–3,800 cm^{-1}) regions in the Raman spectrum (HWNRS).[22,68,69] Because the fiber-optic probes used in in vivo RS are disturbed by the intense fused-silica background signal when the spectrum information in the FP region is collected, it is possible to obtain better accuracy using HW. Furthermore, Malik et al. studied the performance of RS in predicting recurrence.[70] In addition, although the data analysis for RS is relatively complicated, the time required for training is short.

However, we acknowledge that this study has some limitations. First, we cannot guarantee that all articles were searched, which means that we may have missed some research studies. Second, the heterogeneity in this study is high, which may be caused by a variety of factors. Third, some studies have small sample sizes, which may affect the results of the analysis. Therefore, more research studies with a large number of patients need to be conducted. Fourth, because of a lack of data, we were unable to perform a subgroup analysis of all variables.

5 | CONCLUSION

According to the results of this meta-analysis, RS has high precision in the diagnosis of oral cancer and oral precancerous lesions. It has the advantages of being non-invasive and allowing real-time and in situ identification, so it has a wide range of potential applications. However, at the same time, there are still some shortcomings that require further improvement. In conclusion, RS deserves to be studied and improved further to better serve clinical work.

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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