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Effectiveness of adjunctive screening tools for potentially malignant oral disorders and oral cancer: A systematic review

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ABSTRACT

Background and objectives: To enhance the abilities of healthcare professionals to make informed treatment decisions and establish accurate diagnoses, it is essential to assess the diagnostic reliability of different adjunctive aids. This systematic review aimed to compare the accuracy of various adjunctive methods for diagnosing suspected oral cancer (OC) or potentially malignant oral disorders (OPMD) in adults against histopathological investigative results.

Materials and methods: The review protocol registered in the PROSPERO database (CRD42023463525) was developed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Diagnostic Test Accuracy checklist. A comprehensive electronic search was conducted to identify relevant research articles published between January 2014 and April 2023 using the PubMed and EBSCO databases. The research question was meticulously structured following the participants' index test, reference standard, target condition, and study setting framework. To evaluate methodological quality and assess the risk of bias (RoB), the Quality Assessment for Diagnostic Accuracy Studies-2 tool was used.

Results: An initial search yielded 483 publications, which were reduced to 278 after removal of duplicates. Finally, 85 publications underwent full-text review by two investigators, which lead to 29 studies that met the inclusion criteria. Among these, 7% had a low RoB, 72% had an unclear RoB, and 21% had a high RoB. Applicability concerns were expressed in 59% of the studies with low concern, 31% with unclear quality evidence of concern, and 10% with high concern.

Conclusion: The review findings support the use of these diagnostic methods as valuable adjuncts to biopsy for the early detection of various OPMD and OC. They also highlight the importance of regular screening and awareness in reducing the global burden of OC, while acknowledging that they cannot replace the gold standards of surgical biopsy and histopathological evaluation.

1. Introduction

Oral cancer (OC) is the 11th most commonly diagnosed cancer worldwide and poses a major health issue (Singh et al., 2020; Ho et al., 2019). OC may result from genetic changes or malignancies in potentially malignant oral disorders (OPMD) (Singh et al., 2020). OPMD, including conditions such as leukoplakia, erythroplakia, oral submucosal fibrosis, lichen planus, discoid lupus erythematosus, and actinic keratosis carry a high risk of developing OC (Shaw et al., 2022). Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of all intraoral cancers, with nearly half of the cases detected at advanced stages that feature larger tumors and lymph node invasion. Delayed medical attention, often exceeding three months after symptom recognition, contributes to the protracted diagnosis process. Additionally, up to 30% of individuals develop multiple tumors within 5–10 years, further complicating their prognosis (Gonzalez-Moles et al., 2022).

Managing early stage OC results in a positive prognosis, increased chances of survival, and improved quality of life (Warnakulasuriya and Kerr, 2021). Conventional oral examination (COE) relies on visual and tactile assessment under white light but may miss lesions in normal-looking mucosa. Surgical biopsy remains the gold standard for definitive diagnosis, although only 25% of leukoplakia cases have been confirmed to be premalignant or dysplastic. Supplementary chairside tools assist in OC assessment and high-risk individual evaluations

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(Hanken et al., 2013). These tools include toluidine blue (TB) staining, brush biopsy (BB) cytological investigations, and optical techniques such as VELscope, ViziLite, and restricted band imaging (Amirchaghmaghi et al., 2018). Vital staining using TB highlights cells with elevated DNA content and aberrant DNA in dysplastic or cancerous tissues (Su et al., 2021). DNA aneuploidy, a non-intrusive technique that detects malignant changes in the squamous epithelium and serves as a hallmark of malignant cell transition, is often employed alongside BB and DNA image cytometry for objective DNA aneuploidy assessment (Ma et al., 2014).

Optical biopsies, which have gained popularity in recent decades, offer a non-invasive alternative to traditional tissue excision and histological evaluation. These biopsies utilize the optical spectroscopic properties of tissues to consistently detect precancerous and cancerous tumors (Amirchaghmaghi et al., 2018). Chemiluminescence is an optical diagnostic technique that involves the application of an acetic acid solution to the surface epithelium. This process eliminates debris, breaks down the glycoprotein layer, desiccates the mucosa, and enhances light absorption, thereby improving the visibility of mucosal alterations related to refractive changes (Shaw et al., 2022). Autofluorescence utilizes natural fluorochromes in the epithelium and submucosa, with fluorochromes emitting mild green autofluorescence at wavelengths of 375–440 nm. This phenomenon was observed in normal, undamaged mucosa using a narrowband filter (Ganga et al., 2017). Understanding the diagnostic reliability of these additional tools enables healthcare professionals to select the most effective treatment based on an accurate diagnosis. Therefore, the primary objective of this systematic review was to compare the diagnostic accuracy of various supplementary methods using histopathological results in adults with suspected OC or OPMD.

2. Materials and methods

2.1. Study protocol

The review protocol was registered in the PROSPERO database (CRD42023463525) and was developed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Diagnostic Test Accuracy (PRISMA-DTA) checklist (Salameh et al., 2020).

2.2. Focused question

The focused research question, structured around the participants (P), index test (I), reference standard (R), target condition (T), study setting, and design, aimed to evaluate the accuracy of adjuvant diagnostic tests in comparison to biopsy for patients with clinically suspicious OPMD and/or OSCC lesions referred to specialized healthcare facilities. The review included studies that compared adjuvant procedures to biopsy; assessed diagnostic parameters, such as sensitivity and specificity; and their evaluation methods.

2.3. Selection criteria of eligible studies

This study included individuals with suspicious lesions related to OPMD or OSCC identified during screening programs or routine checkups. Index tests included vital staining (e.g., TB, oral cytology, and BB) and light-based methods (autofluorescence and chemiluminescence). The reference test was a surgical or punch biopsy with a histopathological examination. Participants were suspected of having OPMD and/or OC. The study design included in vivo assessments (cross-sectional, observational, and clinical trials) that compared adjuvant tests with the gold standard. Outcome measurements were used to evaluate diagnostic accuracy (sensitivity, specificity, and overall accuracy) using various techniques. Articles published in English between 2014 and 2022 with full-text access were considered.

The exclusion criteria were applied to filter the selected studies and excluded in vitro studies; animal-based research; investigations involving individuals < 18 years; randomized controlled trials primarily focused on the efficacy of screening programs; studies related to mobile applications designed for OC screening; and studies that failed to report primary outcomes related to accuracy, sensitivity, and specificity. These criteria were implemented to ensure the relevance and quality of the studies included in this systematic review and *meta*-analysis, thereby contributing to the robust evaluation of adjuvant diagnostic methods for individuals with suspected OPMD and/or OC.

2.4. Search protocol

English-language studies published between January 2014 and April 2023 were systematically searched using the PubMed and EBSCO databases. Google Scholar was used to explore clinical trials, cross-references, and grey literature. Furthermore, a manual search was conducted in conjunction with an electronic search, including a review of selected publications.

2.5. Search strategy

A search for potentially relevant publications in English from 2014 to 2023 was conducted electronically in PubMed, Scopus, EMBASE, Cochrane Oral Health Group, and Dentistry and Oral Science Source databases via EBSCO. MeSH (Medical Subject Headings) phrases, including ("Toluidine Blue," "Brush Biopsy," "Chemiluminescence," "Brush Cytology," "Autofluorescence," "VELscope," "Liquid-based Cytology," "ViziLite," "Image Cytometry") AND ("Surgical Biopsy," "Scalpel Biopsy," "Incisional Biopsy," "Excisional Biopsy," "Punch Biopsy," "Histopathology," "Exfoliative Cytology") AND ("Oral Potentially Malignant Diseases," "Oral Cancer," "Oral Squamous Cell Carcinoma," "Epithelial Dysplasia," "Premalignant Lesion," "Malignant Lesions," "Intraoral Malignancies," "Lichen Planus," "Oral Submucous Fibrosis," "Leukoplakia") AND ("Diagnostic Accuracy Studies," "Sensitivity," "Specificity," "Predictive Value"), were employed. The search and screening, which were based on predefined criteria were independently performed by two reviewers.

2.6. Study selection

The titles and abstracts of all articles were independently reviewed by two authors. Articles that did not meet the inclusion criteria were also excluded. The selected full-text publications were screened independently and evaluated by the same reviewer. Additional relevant articles were obtained from the reference lists of selected studies. Disagreements were resolved through reviewer discussions; when a consensus could not be reached between the two reviewers, a third reviewer was involved in making the final decision, which was reached unanimously by all three reviewers.

2.7. Data extraction

Two independent reviewers collected the following details using custom data collection forms for all the included studies: author names, publication year, mean sample age, sample size, sex distribution, target condition, index test, reference standard, study objectives, findings, and conclusions. Each study provided quantitative data on sensitivity and specificity. When available, false-negative and true-negative rates, as well as positive and negative predictive values, were obtained. In cases where additional information was required, the corresponding author was consulted.

2.8. Assessment of methodological quality

Methodological quality and risk of bias (RoB) were assessed using the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool,

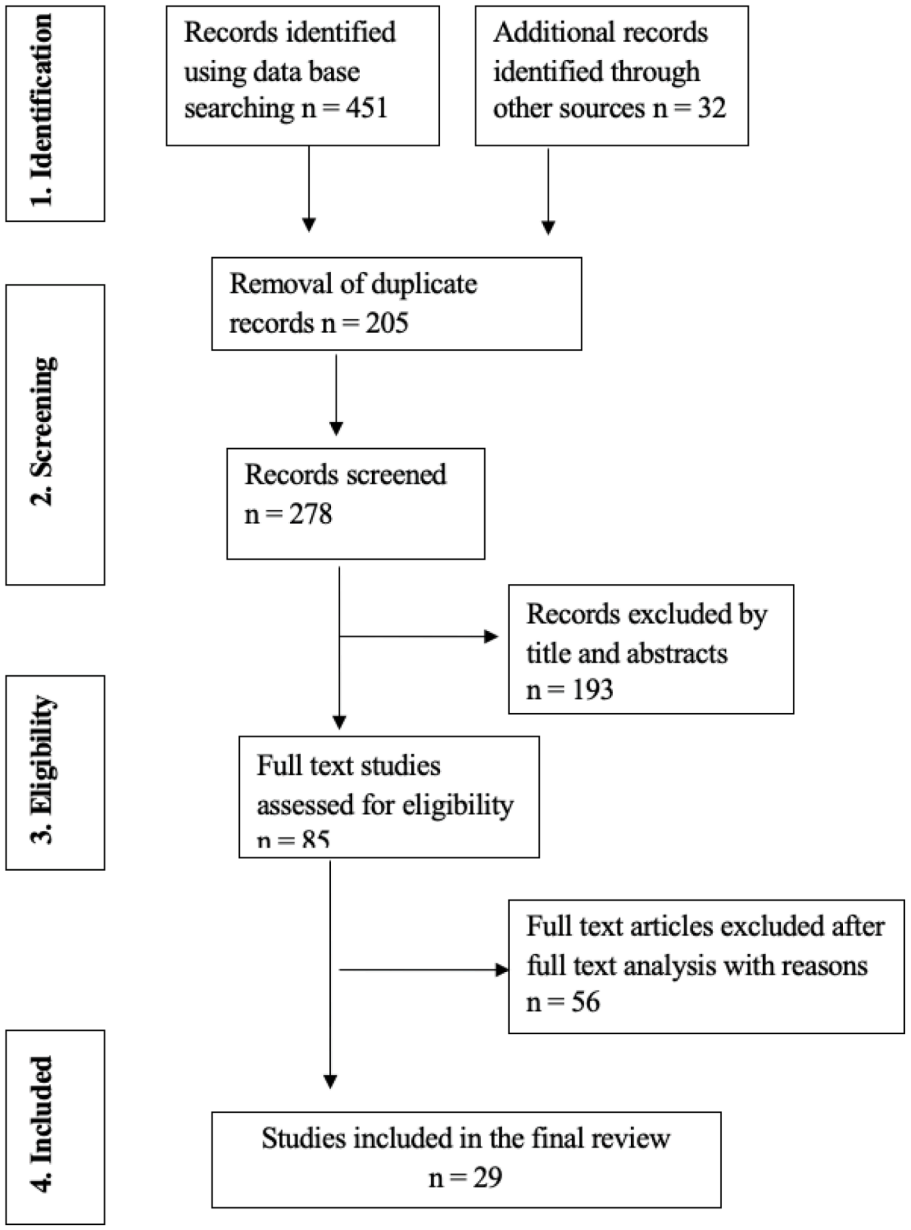

Fig. 1. PRISMA flow chart of the included studies (adapted from the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 Flow Diagram).

designed to evaluate the quality of diagnostic studies. It encompasses domains for patient selection, the index test, the reference standard, the flow, and the timing of the participants to assess RoB, and three domains (patient selection, the index test, and the reference standard) to assess applicability concerns. Each domain included 'Yes,' 'No,' or 'Unclear' response options, and the overall quality of evidence was categorized as high (if any question received a 'No' response), low (if all questions were answered with 'Yes'), or unclear (if all questions were 'Unclear' or combined with any 'Yes') (Whiting et al., 2011; Walsh et al., 2021).

3. Results

3.1. Study selection

Following the PRISMA-DTA guidelines (Fig. 1), the initial electronic search yielded 451 articles. An additional 32 papers were identified through manual searches, resulting in 483 publications for the initial examination. After the elimination of duplicates, 278 studies were identified. Among these, 193 were evaluated based on their titles and abstracts, which lead to an independent full-text review of 85 publications by two investigators. Following further screening based on predefined criteria, 56 publications were excluded, leaving 29 studies for qualitative synthesis (Ma et al., 2014; Ganga et al., 2017; Sharma et al., 2022; Neumann et al., 2022; Nazir and Monalisa, 2020; Morikawa et al., 2020; Jayasinghe et al., 2020; Bayad et al., 2019; Johnson et al., 2019; Chiang et al., 2019; Deuerling et al., 2019; Shi et al., 2019; Bagga et al., 2017; Popa et al., 2017; Baeten et al., 2017; Yamamoto et al., 2017; Lalla et al., 2016; Kaur and Handa, 2016; Nanayakkara et al., 2016; Sawan and Mashlah, 2015; Trakroo et al., 2015; Awan et al., 2015; Singh and Shukla, 2015; Petruzzi et al., 2014; Gupta et al., 2014; Casparis et al., 2014; Vashisht et al., 2014; Suyambukesan et al., 2014). Inter-examiner reliability assessments for title/abstract screening and full-text evaluation resulted in kappa scores of 0.84 and 0.90, respectively, and any discrepancies were resolved with the involvement of a third reviewer. However, heterogeneity among studies driven by differences in geography, study settings, index tests, and reference standards precluded the possibility of conducting a *meta*-analysis.

Table 1
A summary of the characteristics of the reviewed studies.

Author-year	Study design/ sampling	Study setting	Study participants	Target condition and intraoral lesion site	Index test	Reference standard
Sharma et al., 2022	Cross-sectional study employing systematic random sampling	Community based	Exactly 950 subjects were selected from the screening of 3800 high risk individuals and 250 subjects were included	OPMD	Autofluorescence examination(Velscope)	**Incisional biopsy**
Neumann et al., 2022	Cross-sectional study	Clinical	There were 814 (47% men and 53% women), with suspicious lesions from 670 patients	OSCC and OPMD	Oral BB using liquid-based cytology	**Histopathology**
Nazir and Monalisa, 2020	Cross-sectional study	Academic	There were 100 patients	OPMD and OSCC	Chemiluminescence and TB	**Histopathology**
Morikawa et al., 2020	Cross-sectional	Academic	There were 502 patients (M/F = 276/226)	OSCC and OPMD on tongue and buccal mucosa	Fluorescence visualization with optical instruments	**Histopathology**
Jayasinghe et al., 2020	Cross-sectional	Academic	There were 65 patients	OPMD	TB	**Incisional biopsy**
Bayad et al., 2019	Cross-sectional	Academic	There were 50 patients with OPMD (M/F = 1.4/1) and OC (5.2/1)	OPMD and OC	TB	**Histopathology**
Johnson et al., 2019	Multicentric trial	Academic	There were 100 lesions (86 patients and 11 controls)	Intraoral malignancies and dysplasia	WGA-FITC	**Biopsy**
Chiang et al., 2019	Cross-sectional	Clinical	There were 126 patients	OPMD	Autofluorescence	**Biopsy**
Deuerling et al., 2019	Retrospective	Academic	A total of 1352 (M/F = 608/744) samples from 992 patients	OSCC and OPMD	Liquid-based oral brush	**Histopathology**
Shi et al., 2019	Prospective study employing consecutive sampling	Academic	There were 517 patients (M/F = 238/279)	OPMD	Autofluorescence (VELscope)	**Biopsy**
Bagga et al., 2017	Cross-sectional	Academic	There were 100 subjects	OPMD (50 each of oral leukoplakia and oral submucous fibrosis)	Chemiluminescence and TB	**Punch biopsy**
Popa et al., 2017	Cross-sectional	Clinical	A total of 186 subjects (M/F = 62/124) were diagnosed with OPMD	OPMD	Chemiluminescence (ViziLite Plus)	**Histopathology**
Baeten et al., 2017	Cross-sectional	Academic	Group 1 had normal mucosal lesions (11 subjects) and group 2 had clinically suspicious oral lesions (44 subjects)	Intraoral malignancies and dysplasia	WGA-FITC	**Scalpel or punch biopsy**
Adil et al., 2017	Cross-sectional	Academic	There were 90 patients (M/F = 75/15) exhibiting tobacco related hyperkeratotic red and white lesions/ulcerative lesions and intraoral cancer	Intraoral malignancies and OPMD	VELscope and TB	**Histopathology**
Ganga et al., 2017	Cross-sectional	Academic	There were 200 patients	Intraoral malignancies and OPMD	VELscope	**Histopathology**
Yamamoto et al., 2017	Cross-sectional	Academic	There were 79 specimens obtained from 62 patients (M/F = 31/31)	OPMD and OSCC	VELscope and the iodine-staining method	**Biopsy**
Lalla et al., 2016	Cross-sectional	Clinical	There were 88 patients (with 231 oral lesions by COE)	OPMD on the tongue, buccal mucosa, hard palate, lip, and floor of the mouth	Autofluorescence imaging and reflectance spectroscopy	**Incisional biopsy**
Kaur and Handa, 2016	Cross-sectional study with consecutive sample	Academic	100 (M/F = 78/22) patients	Intraoral malignancies	BB with DNA-IC	**Incisional biopsy**
Nanayakkara et al., 2016	Cross-sectional	Academic	There were 76 suspicious OC and 116 leukoplakia (M/F = 149/43)	Intraoral malignancies and OPMD	Spatula and cytobrush cytology	**Incisional or excisional biopsy**
Sawan and Mashlah, 2015	Cross-sectional using a random sample	Academic	There were 748 (M/F = 414/334) subjects	Intraoral malignancies and OPMD	VELscope	**Incisional and excisional biopsy**
Trakroo et al., 2015	Cross-sectional	Academic	There were 50 (M/F = 43/7) subjects	Intraoral malignancies and OPMD	BB	**Scalpel biopsy**
Awan et al., 2015	Cross-sectional	Academic	There were a total of 126 patients, exhibiting red, white, and heterogeneous patches	OPMD	Autofluorescence, chemiluminescence, and TB	**Histopathology**
Singh and Shukla, 2015	Cross-sectional	Academic	There were 50 patients with suspicion of malignancy	Intraoral malignancies	TB	**Punch biopsy**
Petruzzi et al., 2014	Double center, cross-sectional study	Academic	There were 56 subjects	OSCC and dysplasia	Autofluorescence and TB	**Surgical biopsy**
Ma et al., 2014	Cross-sectional	Academic	There were 22 patients with malignant epithelial lesions and 30 subjects as controls	OPMD	BB	**Scalpel biopsy**

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Table 1 (*continued*)

Author-year	Study design/ sampling	Study setting	Study participants	Target condition and intraoral lesion site	Index test	Reference standard
Gupta et al., 2014	Histopathological study; random sampling	Academic	There were 225 clinically diagnosed lesions from among 1099 lesions in 877 patients	OPMD with chronic non-healing ulcer/lesions without any hyperplastic growth, associated with or without a suspicious precancerous lesion in the buccal mucosa and tongue	Modified oral BB.	**Scalpel and punch biopsy; exfoliative cytology**
Casparis et al., 2014	Convenience sampling	Academic	There were 263 oral biopsies from 200 patients	OPMD on tongue, buccal mucosa, retromolar triangle, attached gingiva, mucosa of the alveolar process, and floor of the mouth, lips, and palate	Transepithelial BB	**Scalpel biopsy**
Vashisht et al., 2014	Cross-sectional	Academic	Study group I had 25 patients with leukoplakia. Study group II had 10 patients with clinically diagnosed OSCC. The control group had 25 high-risk patients with no clinically visible lesions	OPMD and OSCC	Chemiluminescence and TB	**Histopathology**
Suyambukesan et al., 2014	Cross-sectional	Academic	There were 70 patients (50 were identified with OPMD and 20 had no apparent lesions) (M/F = 59/11)	OPMD	Chemiluminescence	**Incisional biopsy**

OPMD, oral potentially malignant disease; OSCC, oral squamous cell carcinoma; DNA-IC, DNA image cytometry; TB, toluidine blue; BB, brush biopsy; OC, oral cancer; COE, conventional oral examination; WGA-FITC, wheat germ agglutinin–fluorescein isothiocyanate.

3.2. Characteristics of included studies

Most of the reviewed studies (n = 12, 41%) were conducted in India (Ganga et al., 2017; Sharma et al., 2022; Nazir and Monalisa, 2020; Bayad et al., 2019; Bagga et al., 2017; Baeten et al., 2017; Adil et al., 2017; Kaur and Handa, 2016; Singh and Shukla, 2015; Gupta et al., 2014; Vashisht et al., 2014). Two studies were conducted in Germany (Neumann et al., 2022; Chiang et al., 2019), China (Ma et al., 2014; Shi et al., 2019), Japan (Morikawa et al., 2020; Yamamoto et al., 2017), and Sri Lanka (Jayasinghe et al., 2020; Nanayakkara et al., 2016). There was one study each from Switzerland (Casparis et al., 2014), Romania (Popa et al., 2017), Italy (Petruzzi et al., 2014), Pakistan (Awan et al., 2015), Syria (Sawan and Mashlah, 2015), Australia (Lalla et al., 2016), Taiwan (Chiang et al., 2019), and Malaysia (Suyambukesan et al., 2014). The first was a multicenter study conducted at three universities (two in the United States and one in India). Jayasinghe et al. (2020) conducted a multicenter study at three universities in Sri Lanka (Jayasinghe et al., 2020). Another was a double-center study conducted at two dental clinics at the University of Italy. Hence, the results can be applied to a broader demographic population considering the diverse geographical locations of the studies that involved individuals with suspicious oral lesions, including OPMD or intraoral malignancies. The reviewed studies focused on assessing the diagnostic accuracy of vital staining with TB, oral cytology, and light-based detection methods such as, VELscope, ViziLite, and wheat germ agglutinin-fluorescein isothiocyanate (WGA-FITC). One of the community-based investigations was conducted by Sharma et al (Sharma et al., 2022). Four of the included studies (Neumann et al., 2022; Chiang et al., 2019; Lalla et al., 2016) were conducted in a clinical setting, while the remaining studies were performed in an institutional or university setting. An overwhelming majority of the studies examined one supplementary test using one sample. Seven of the remaining studies evaluated two tests using the same sample (Nazir and Monalisa, 2020; Bagga et al., 2017; Yamamoto et al., 2017; Kaur and Handa, 2016; Vashisht et al., 2014). Moreover, one study evaluated three tests that were conducted using the same sample (Awan et al., 2015).

Ten studies explored vital staining or rinsing (Singh et al., 2020; Nazir and Monalisa, 2020; Jayasinghe et al., 2020; Bayad et al., 2019; Bagga et al., 2017; Adil et al., 2017; Yamamoto et al., 2017; Awan et al., 2015; Vashisht et al., 2014). Oral cytology was studied in eight investigations (Ma et al., 2014; Neumann et al., 2022; Deuerling et al., 2019; Kaur and Handa, 2016; Nanayakkara et al., 2016; Trakroo et al., 2015; Gupta et al., 2014; Vashisht et al., 2014). Sixteen studies investigated the efficacy of light-based technologies (Ganga et al., 2017; Sharma et al., 2022; Nazir and Monalisa, 2020; Morikawa et al., 2020; Chiang et al., 2019; Shi et al., 2019; Bagga et al., 2017; Popa et al., 2017; Adil et al., 2017; Yamamoto et al., 2017; Lalla et al., 2016; Sawan and Mashlah, 2015; Awan et al., 2015; Petruzzi et al., 2014; Vashisht et al., 2014; Suyambukesan et al., 2014). Ten studies addressed the diagnostic utility of autofluorescence (Ganga et al., 2017; Sharma et al., 2022; Morikawa et al., 2020; Chiang et al., 2019; Shi et al., 2019; Adil et al., 2017; Yamamoto et al., 2017; Sawan and Mashlah, 2015; Awan et al., 2015; Petruzzi et al., 2014), whereas six used chemiluminescence (Nazir and Monalisa, 2020; Bagga et al., 2017; Popa et al., 2017; Awan et al., 2015; Vashisht et al., 2014; Suyambukesan et al., 2014). Autofluorescence imaging and tissue reflectance spectroscopy were investigated in one study (Lalla et al., 2016). Ganga et al. demonstrated that the high negative predictive value of VELscope is useful for ruling out the existence of malignant transformations and can help reduce the anxiety of the patient and concerns of practitioners over clinically suspicious oral lesions (Ganga et al., 2017). Two studies investigated the utility of the imaging technique by employing WGA-FITC (Johnson et al., 2019; Baeten et al., 2017). All investigations used biopsy and histopathological evaluation as reference tests (Table 1).

The estimates for sensitivity and specificity varied from 12.5% (Lalla et al., 2016) to 100% (Johnson et al., 2019; Suyambukesan et al., 2014) and 44.1% (Casparis et al., 2014) to 100% (Suyambukesan et al., 2014), respectively (Table 2). Popa et al. calculated the diagnostic accuracy of chemiluminescence using the ViziLite Plus instrument as 100% (Popa et al., 2017). Bayad et al. (2019) found that the diagnostic accuracies of TB as an additional technique for the early diagnosis of OPMD and OC were 88.88% and 93.75%, respectively (Bayad et al., 2019). Trakroo et al. used BB to assess dysplasia in OPMD and OC and found an accuracy rate of 86% (Trakroo et al., 2015). The efficacy of TB in the diagnosis of intraoral cancer lesions revealed an accuracy of 90% in one of the reviewed studies (Singh and Shukla, 2015).

Table 2
Summary of the diagnostic utility of the index test employed in the reviewed studies.

Author-Year	Country	Study objective	Mean age	Study result	Study conclusion
Sharma et al., 2022	India	To determine the effectiveness of the tissue autofluorescence (VELscope) in identifying the dysplastic or neoplastic changes in oral mucosa followed by biopsy	18–75	The VELscope examination showed 75% sensitivity and 61.39% specificity. PPV was 31.58% and NPV was 91.18%.	**The combined strategies of VELscope and COE illustrate a promising diagnostic aid for prompt identification of OPMD and intraoral malignancies**
Neumann et al., 2022	Germany	To examine if the BB is an effective tool for early diagnosis of oral cancer in routine practice	20–96	The sensitivity of BB was 100% for identifying cancer cells. The specificity for detecting non-cancer cells was 86.5%, with a 43.1% PPV and 100% NPV	**BB serves as a useful tool for prompt detection of OSCC in routine practice**
Nazir and Monalisa, 2020	India	To compare and validate the clinical examination, chemiluminescence, and 1% TB in assessing the OPMD	NR	Sensitivity and specificity of chemiluminescence were reported to be 91.32% and 80.5%, respectively, and for TB, 84.66% and 72.7%, respectively.	**Chemiluminescence serves as a diagnostic tool and was more reliable in screening OPMD compared to TB**
Morikawa et al., 2020	Japan	To determine the applicability of subjective and objective analysis of fluorescence visualization for OC screening and to enhance the accuracy by combining both of these	62.3	For subjective analysis of OC detection, the sensitivity and specificity were 96.8% and 48.4%, respectively. While that of the objective evaluation were 43.7% and 84.6%, respectively.	**The subjective and objective analysis was beneficial for screening of OC.**
Jayasinghe et al., 2020	Sri Lanka	To evaluate the diagnostic effectiveness of TB staining to identify dysplasia or high-risk regions of OPMD	>18 years	The sensitivity was 68.3% and the specificity was 63.1%. PPV, FP, and FN rates of 80%, 36.8%, and 31.7% were observed, respectively.	**TB staining served as an adjunct aid in identifying high-risk OPMD**
Bayad et al., 2019	India	To evaluate the use of TB as an adjunct tool in the identification of OPMD and OC at the incipient stage.	20–80	Sensitivity and specificity of TB for OPMD were 92.30% and 80%, respectively, with a PPV and NPV of 92.30%, and 80%, respectively. The accuracy was 88.88%. The sensitivity, specificity, accuracy, PPV, and NPV of OC were 96.30%, 80%, 93.75%, 96.30%, and 80%, respectively	**TB serves as an adjunct tool for identifying OPMD and OC at an early stage.**
Johnson et al., 2019	USA, India	To determine the accuracy of OC screening by evaluating aberrant glycosylation through employment of a fluorescent-labelled lectin WGA- FITC	18–40	The identification system showed 100%, 100%, and 74% sensitivity for OC, high- and low-grade dysplasia, respectively. The reported specificity was 80%.	**WGA- FITC improved the visualization of lesions with respect to dimension and margins.**
Chiang et al., 2019	Taiwan	To evaluate the efficacy of autofluorescence imaging and histopathological evaluation of OPMD	NR	The sensitivity, specificity, PPV, NPV, and accuracy for OPMD were found to be 77.94%, 35.42%, 63.10%, 53.13%, and 60.34%, respectively. While that of the epithelial dysplasia were 88.89%, 43.86%, 63.64%, 78.13%, and 67.50%, respectively.	**Autofluorescence imaging serves as a beneficial tool in assessing OPMD with high-group without compromising patient comfort**
Deuerling et al., 2019	Germany	To evaluate the accuracy of the screening of liquid-based BB cytology with that of histopathology	61.6	The sensitivity and specificity of the liquid-based BB were 95.6% and 84.9%, respectively.	**BB is a highly sensitive method for cytological diagnosis of OC.**
Shi et al., 2019	China	To evaluate the diagnostic accuracy of VELscope in OPMD.	51.9	The NPV of the high-risk lesion diagnosis and OSCC were 98.2% and 100%, respectively.	**VELscope investigation could detect high-risk lesions but cannot discriminate low-risk lesions from malignant lesions.**
Bagga et al., 2017	India	To compare the usefulness and validity of clinical examination, chemiluminescence, and TB in assessing OPMD	34.92	The sensitivity and specificity for chemiluminescence were 75% and 54.7%, respectively, and for TB they were 57.4% and 44.1%, respectively.	**The adjunctive value of the index tests is of great importance for mass screening of OC**
Popa et al., 2017	Romania	To assess the efficiency of the complementary examination using the ViziLite Plus device	50–79	Accuracy of 100%	**ViziLite Plus serves as the most predictive complementary test in the diagnosis of high risk OPMD**
Baeten et al., 2017	India	To investigate fluorescently labelled WGA-FITC as a point-of-care aid for identifying OC and dysplasia.	51–60	WGA-FITC had a sensitivity and specificity of 89% and 82%, respectively	**The results showed that WGA-FITC has the propensity to differentiate malignancy from dysplasia, and benign from normal mucosa**
Adil et al., 2017	India	To compare the reliability of VELscope and TB in the diagnosis of OC and OPMD in comparison to histopathological evaluation	22–70	VELscope showed a sensitivity and specificity of 85.36% and 75%, respectively, in comparison to TB at 87.5% and 83.13%, respectively.	**VELscope served as a reliable aid for the detection of intraoral malignancies at an early stage compared to TB**
Ganga et al., 2017	India	The evaluate the efficacy of VELscope in the detection of dysplastic or neoplastic oral lesions	NR	The sensitivity, specificity, PPV, and NPV were 76%, 66.29%, 24.36%, and 95.08%, respectively.	**VELscope failed to arrive at a definitive diagnosis of dysplastic changes. Yet, a high NPV served to reduce the patient's anxiety of suspicious oral lesions.**
Yamamoto et al., 2017	Japan	To evaluate the diagnostic accuracy of epithelial dysplasia by utilizing the objective AVM and its clinical utility	59.6	The luminance ratio of 1.62 was significantly higher in the epithelial dysplasia. The objective AVM showed much higher consistency between histopathological results than the other two methods.	**The objective AVM has a propensity to be used as an auxiliary method for diagnosis of epithelial dysplasia.**

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Table 2 (*continued*)

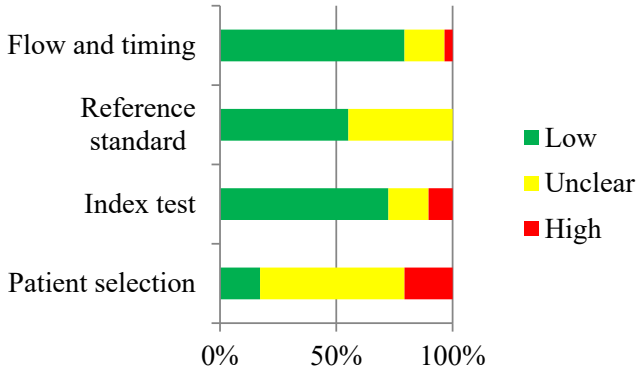
Author-Year	Country	Study objective	Mean age	Study result	Study conclusion
Lalla et al., 2016	Australia	To evaluate the efficacy of autofluorescence imaging and tissue reflectance spectroscopy in OPMD screening	NR	The violet light exhibited a sensitivity of 12.5% and a specificity of 85.4% for dysplasia screening. The visible vasculature was observed in 40.9% of lesions using the green light.	**The intraoral white light enabled comprehensive visualization compared to using an external white-light source combined with magnification.**
Kaur and Handa, 2016	India	The efficacy of BB as an adjunct in DNA-IC in the early diagnosis of OC was determined.	50.4	For OC detection, the sensitivity and specificity were 83.3% and 95.8%, respectively. The PPV, NPV and accuracy were 95.2%, 85.2%, and 86%, respectively.	**DNA-IC served as an adjunct to BB in diagnosing OC.**
Nanayakkara et al., 2016	Sri Lanka	To evaluate the diagnostic effectiveness of the spatula and the cytobrush methods in comparison to that of the histological findings	21–95	For the cytobrush and spatula technique, the sensitivity was 89.58% and 60.42% for diagnosing intraoral malignancies, respectively. While it was 88.89% and 55.56% for diagnosing leukoplakia, respectively.	**Cytobrush was considered as a beneficial screening technique for the detection of suspicious OPMD at an early stage**
Sawan and Mashlah, 2015	Syria	To determine the detection of OPMD using autofluorescence (VELscope).	37	A sensitivity and specificity of 74.1% and 96.3% were observed, respectively	**VELscope served as a diagnostic tool in identifying the borders for surgical biopsy and surgical excision**
Trakroo et al., 2015	India	To evaluate the accuracy of oral BB in identifying dysplasia in OPMD and OC	20–70	The sensitivity was 84.37% and the specificity was 88.89% for BB. The diagnostic accuracy, PPV and NPV were 86%, 93.10%, and 76.19%, respectively.	**BB is a non-invasive population screening program for the detection of OPMD and OC incapacitated regions**
Awan et al., 2015	Pakistan	The accuracy of autofluorescence, chemiluminescence, and TB employed in combination against COE and scalpel biopsy for estimating the risk level of OPMD	>16 years	The autofluorescence, chemiluminescence, and TB had a sensitivity of 87.1%, 77.1% and 52.9%, respectively. The corresponding specificity was 21.4%, 26.8%, and 67.9% for leukoplakia/erythroplakia, respectively. Similarly, the corresponding sensitivities and specificities were 84.1%, 77.3%, and 56.8%, and 15.3%, 27.8%, and 65.8% for dysplasia, respectively	**The evaluated tests were effective in the detection of mucosal alterations. However, the accuracy in detecting OPMD is controversial, though a combination of the investigations was observed to give a higher specificity**
Singh and Shukla, 2015	India	To determine the utility of TB in detecting lesions of OC	49.2	The sensitivity of TB in detecting OPMD was 97.8%. The overall specificity was 100%. The PPV, NPV, and diagnostic accuracy were 100%, 80%, and 90%, respectively	**TB staining was cost-effective, non-invasive, and a reliable adjunct for detecting in situ and invasive OC**
Petruzzi et al., 2014	Italy	To compare TB and autofluorescence for evaluating oral dysplasia and OSCC in suspicious lesions	>18 years	The sensitivity and specificity were 70% and 57.7% for autofluorescence, respectively. TB displayed 80% sensitivity and 61.5% specificity.	**Autofluorescence and TB were sensitive and not specific in the diagnosis of OSCC and dysplasia**
Ma et al., 2014	China	The diagnostic effectiveness of exfoliative cytology and DNA-IC in OPMD was investigated	NR	The sensitivity, specificity, PPV, NPV, FP, and FN were 86.36%, 90%, 86.36%, 90%, 13.64%, and 10%, respectively.	**BB with DNA-IC is useful for the screening of OPMD but cannot substitute the role of histopathological examination**
Gupta et al., 2014	India	The clinical effectiveness of exfoliative cytology, modified BB, and biopsy in the detection of OPMD and OC.	31–60	Modified oral BB revealed a higher sensitivity of 81.69%, and a specificity of 68.42% in comparison to exfoliative cytology, which had a sensitivity of 48.57% and a specificity of 86.48%	**Modified oral BB was effective in screening for OPMD. Biopsy is mandatory to confirm the diagnosis**
Casparis et al., 2014	Switzerland	To examine whether the BB and subsequent computer-assisted analysis can serve as a screening tool in private practice	51–60	A sensitivity of 90% and specificity of 44.1% was found for the detection of abnormal cells. The PPV and NPV was 47.2% and 88.2%. respectively.	**OPMD can be detected using the BB in routine dental practice. DNA-IC enhances the results of the BB**
Vashisht et al., 2014	India	The diagnostic ability of chemiluminescence and 1% TB was evaluated with that of the histopathological analysis.	NR	Sensitivity and specificity of ViziLite was 95.45% and 84.6%, respectively. Sensitivity and specificity of TB was found to be 86.36% and 76.9%, respectively	**ViziLite was more reliable in screening epithelial dysplasia than TB and was a useful diagnostic tool.**
Suyambukesan et al., 2014	Malaysia	The effectiveness of ViziLite in detecting OPMD was evaluated.	NR	The sensitivity and specificity were 100% for leukoplakia. But the sensitivity for lichen planus and oral submucous fibrosis was not detected	**COE and scalpel biopsy were effective in the diagnosis of oral lesions compared to VizLiite.**

AVM, autofluorescence visualization method; OPMD, potentially oral malignant disease; OSCC, oral squamous cell carcinoma; DNA-IC, DNA image cytometry; TB, toluidine blue; BB, brush biopsy; PPV, positive predictive value; NPV, negative predictive value; FP, false positive; FN, false negative; OC, oral cancer; COE, conventional oral examination; WGA-FITC, wheat germ agglutinin-fluorescein isothiocyanate; NR, not reported.

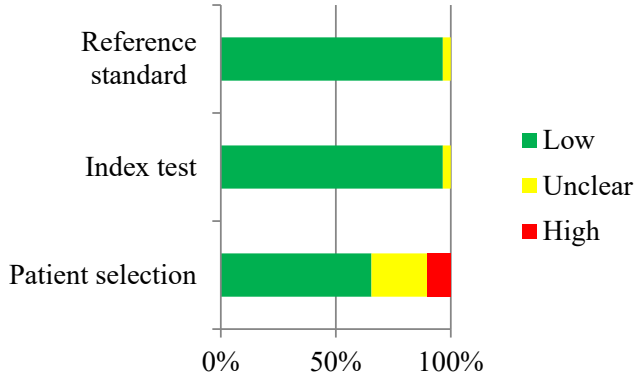
3.3. Quality assessment of the reviewed studies

Graphs 1 and 2 summarize the QUADAS-2 tool's RoB and applicability concerns. Table 3 presents the individual study assessments. Two studies (7%) had a low RoB, 21 (72%) had an unclear RoB, and six (21%) had a high RoB. Concerns about applicability were noted in 17 studies (59%) as low concern, nine (31%) as unclear concern, and three (10%) as high concern. However, concerns arose when selecting populations of entirely high- or low-risk patients. Insufficiently clear descriptions of index and reference tests led to uncertain ratings.

For patient selection, five studies (17%) had a low RoB, 18 (62%) had an unclear RoB, and six (21%) exhibited a high RoB. Patient recruitment



Graph 1. Risk of Bias of QUADAS-2 across the reviewed studies.



Graph 2. Applicability concerns of QUADAS-2 across the reviewed studies.

was generally poorly described, with only five studies (17%) reporting random or sequential patient sampling. Most studies (19 out of 29) showed few concerns regarding patient selection. The index test domain in 21 studies (72%) had a low RoB, while in five studies (17%) it remained unclear, often due to insufficient details about clinician training or standardization. Nearly all the studies (28 out of 29) were deemed to have low concerns regarding the index tests.

The reference standard in 16 studies (55%) was evaluated as having a low RoB, whereas in 13 studies (45%) it remained unclear. All included studies utilized an appropriate reference standard involving a biopsy conducted by an expert oral pathologist, followed by histopathological assessment. However, many studies lacked sufficient details regarding biopsy techniques and histopathological standards. Most studies (28) raised concerns about the reference standards. The flow and timing domains had a low RoB in 23 studies (79%) and were uncertain in five studies (17%). Most studies showed a short time gap between the index test and the reference standard or derived it from the procedural technique.

4. Discussion

This systematic review assessed the accuracy of adjunct diagnostic methods for detecting OPMD in adults using tissue biopsy as the reference standard. The World Health Organization recommends OC screening that typically relies on visual inspection and palpation by professionals. Distinguishing between the various mucosal conditions in the oral cavity is challenging. The symptoms of OPMD, such as lichen planus, leukoplakia, erythroplakia, and chronic candidiasis, can potentially lead to OSCC. Timely identification and treatment of epithelial dysplasia in OPMD is crucial to prevent malignant transformation and detect subtle changes (Morikawa et al., 2020; Morikawa et al., 2021). Given the prospective advantages of OC screening, a few nations with significant OC frequency have developed nationwide or pilot OC screening programs aimed at high-risk populations (Parak et al., 2022).

While the five-year survival rate with early detection and treatment of OC stages I and II surpasses 80%, it declines to less than 20% in advanced clinical stages III and IV (Sankaranarayanan et al., 2013). Numerous innocuous-appearing early stage OC were noted clinically but were undetected. In contrast, a few other lesions warranted a biopsy after they exhibited symptoms or clinical manifestations that were diagnostic of malignancy (Hanken et al., 2013). With expertise, healthcare professionals in general practice can employ fluorescence visualization instruments to promptly identify OSCC and OPMD. This method is non-invasive, and patient discomfort can be considerably reduced (Shi et al., 2019; Kozakai et al., 2020).

Tissue autofluorescence uses light to detect deviations from the typical absorption and emission spectra of natural fluorophores in the epithelium and connective tissues. When exposed to blue light, the reduction in native fluorescence, known as “fluorescence visualization loss,” isn’t exclusive to the molecular disruptions observed in dysplasia and OSCC. Other benign conditions, particularly inflammatory mucosal disorders that clinically mimic OPMD, can yield false-positive results on light-based tests. Similarly, the underlying mechanisms of vital staining, which remain largely unknown, are not specific to dysplasia or OSCC. Standardized outcome measures for both light-based and vital staining assays have not yet been established (Walsh et al., 2021).

To reduce sampling bias, it is crucial to clearly define and implement the population and participant selection, preferably through consecutive sampling. The study context is vital because research conducted in a tertiary referral center may not directly apply to primary care settings. Comprehensive insights into the diagnostic accuracy of various testing methods across different scenarios can only be obtained by conducting research in diverse settings with various evaluators. The index test was performed by experienced and calibrated evaluators with a predefined consensus threshold (Walsh et al., 2021). Visual examination of lesions is essential for both vital staining and light-based investigations. Cytological evaluation requires expertise in conducting a transepithelial biopsy to extract basal cells from which crucial diagnostic information is derived; suprabasal cells are also relevant (Walsh et al., 2021).

Screening for OPMD and OSCC presents significant clinical and methodological challenges. These challenges include reluctance among screen-positive individuals to undergo follow-ups, lack of clear progression from premalignant to malignant states, variability in treatment options, and differences in the affordability of mass and random screening programs. Unlike cancer registries, the absence of a structured registry for documenting OPMD may hinder the accurate estimation of mortality rates, which result from screening programs that focus on premalignant lesions (Walsh et al., 2021). Consequently, the effectiveness of the targeted programs could be compromised.

5. Conclusion

The results of this review add to the growing body of evidence supporting the use of these supplementary diagnostic methods as adjuncts to biopsy for early diagnosis of various OPMD and OC cases. Screening for OC is a crucial component of preventive healthcare that enables early detection and enhances the chances of successful treatment. Early detection not only improves survival rates, but also enhances the overall quality of life. Emphasizing the importance of regular screening and raising awareness may contribute to a reduction in the global burden of OC. However, it is important to note that these supplementary tests cannot replace the current gold standard of surgical or scalpel biopsies followed by histopathological evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 3
Summary of risk of bias and applicability concerns according to the QUADAS-2 tool.

Author-Year	Risk of bias				Overall quality	Applicability concerns			Overall quality
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test	Reference standard	
Sharma et al., 2022	Y	Y	Y	Y	Low	Y	Y	Y	**Low**
Neumann et al., 2022	UC	Y	UC	UC	UC	Y	Y	Y	**Low**
Nazir and Monalisa, 2020	UC	Y	UC	UC	UC	Y	Y	Y	**Low**
Morikawa et al., 2020	UC	Y	UC	UC	UC	Y	Y	UC	**UC**
Jayasinghe et al., 2020	N	Y	Y	Y	High	Y	Y	Y	**Low**
Bayad et al., 2019	UC	Y	UC	Y	UC	Y	Y	Y	**Low**
Johnson et al., 2019	UC	N	UC	N	UC	Y	Y	Y	**Low**
Chiang et al., 2019	Y	Y	UC	Y	UC	Y	Y	Y	**Low**
Deuerling et al., 2019	UC	Y	UC	Y	UC	Y	Y	Y	**Low**
Shi et al., 2019	N	Y	Y	Y	High	Y	Y	Y	**Low**
Bagga et al., 2017	Y	Y	Y	Y	Low	Y	Y	Y	**Low**
Popa et al., 2017	UC	Y	UC	UC	UC	UC	Y	Y	**UC**
Baeten et al., 2017	UC	N	Y	Y	UC	Y	Y	Y	**Low**
Adil et al., 2017	UC	UC	UC	Y	UC	Y	Y	Y	**Low**
Ganga et al., 2017	UC	UC	Y	Y	UC	UC	Y	Y	**UC**
Yamamoto et al., 2017	UC	UC	UC	Y	UC	Y	Y	Y	**Low**
Lalla et al., 2016	UC	Y	Y	Y	UC	UC	Y	Y	**UC**
Kaur and Handa, 2016	Y	UC	Y	Y	UC	Y	UC	Y	**UC**
Nanayakkara et al., 2016	N	Y	Y	Y	High	N	Y	Y	**High**
Sawan and Mashlah, 2015	N	Y	Y	Y	High	UC	Y	Y	**UC**
Trakroo et al., 2015	UC	UC	UC	Y	UC	Y	Y	Y	**Low**
Awan et al., 2015	Y	Y	UC	Y	UC	Y	Y	Y	**Low**
Singh and Shukla, 2015	UC	Y	Y	Y	UC	UC	Y	Y	**UC**
Petruzzi et al., 2014	UC	Y	Y	UC	UC	Yes	Y	Y	**Low**
Ma et al., 2014	UC	Y	Y	Y	UC	Yes	Y	Y	**Low**
Gupta et al., 2014	UC	Y	Y	Y	UC	No	Y	Y	**High**
Casparis et al., 2014	UC	Y	Y	Y	UC	No	Y	Y	**High**
Vashisht et al., 2014	N	Y	UC	Y	High	UC	Y	Y	**UC**
Suyambukesan et al., 2014	N	Y	Y	Y	High	UC	Y	Y	**UC**

Y, Yes; N, No; UC, Unclear.

the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2023.10.011.

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