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Review Article

Dentistry Section

Diagnostic Accuracy of Chemiluminescence for Oral Potentially Malignant Disorders: A Systematic Review and Meta-analysis

AMAR KUMAR SHAW[1], MADHURA MAHAJAN[2], SHIVANGI VARSHNEY[3], MARLIN JENA[4], LAVANYA ROHATGI[5], SANA BASHIR[6], SUMIT TEWARI[7], JESSICA ROY[8]

ABSTRACT

Introduction: Biopsy is the gold standard for Oral Potentially Malignant Disorders (OPMD) diagnosis. Chemiluminescence provides promising complementary alternative diagnostic adjunct for its simple non invasive collection and technique and to screen large populations.

Aim: To summarise and compare the existing evidence on diagnostic accuracy of chemiluminescence in detecting OPMD.

Materials and Methods: The systematic review and meta-analysis protocol was registered at the international prospective register of systematic reviews (PROSPERO- CRD42022306061) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Diagnostic Test Accuracy (PRISMA-DTA) checklist. PubMed, Google Scholar, EBSCOhost were searched from 2000 to 2021 to identify the screening potential of chemiluminescence for OPMD. True positive, false positive, true negative, false negative, sensitivity, and specificity values were extracted or calculated if not present for each study. Quality of selected studies was evaluated based on Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Meta-analysis was performed in Meta-Disc 1.4 software and Review Manager 5.3 using a bivariate model parameter for the sensitivity and specificity and summary points. Summary Receiver Operating Curve (SROC), confidence region, and prediction region were calculated.

Results: Twenty-four studies were included for qualitative synthesis and out of that, 14 were included for meta-analysis. Sufficient data for meta-analysis was available only for leukoplakia, oral lichen planus (OLP) and oral submucous fibrosis (OSMF). Sensitivity and specificity were calculated with Area Under Curve (AUC). For leukoplakia, chemiluminescence had sensitivity and specificity of 75% and 98% with 0.74 AUC. For OLP, it was 78% and 60% with 0.70 AUC. For oral submucous fibrosis it was 89% and 76% with 0.69 AUC.

Conclusion: Chemiluminescence overall had good sensitivity and specificity values along with good AUC. This strongly supports the fact that it can be used as an alternative diagnostic adjunct to biopsy for various OPMD.

Keywords: Erythroplakia, Leukoplakia, Oral lichen planus, Oral submucous fibrosis, Sensitivity, Specificity

INTRODUCTION

Oral cancer is a rapidly growing serious life-threatening disease and is identified as sixth to eighth most common cancer worldwide [1,2]. The five year survival rate of oral cancer ranges from 30-80% [3-5]. It accounts for 5% of all cancers globally and 60,000 new cases are reported every year in India due to excessive use of tobacco and tobacco related products [6,7].

Most oral cancers develop from potentially malignant disorders. Oral Potentially Malignant Disorders (OPMD) refers to "any oral mucosal abnormality which is associated with a statistically increased risk of developing oral cancer" [8]. Leukoplakia, erythroplakia, smoker's palate, Oral Submucous Fibrosis (OSMF), Oral Lichen Planus (OLP), actinic keratosis and discoid lupus erythematosus are the presently known OPMDs. In India, overall prevalence of OPMD is 13.2-13.9%, while that of leukoplakia alone is 0.2-5.2%, OSMF is 8.06% and erythroplakia is 0.24% [9]. Approximately 1.36% OPMDs transform to oral cancers per year [1]. These lesions have greater potential for malignant transformation than other oral lesions [8].

The OPMDs are usually diagnosed when they become symptomatic or if the lesion increases to a size >1 cm in dimension. By this stage, two-third of patients develop advanced disease [10]. Early detection of these lesions would increase the survival rate along with quality of life of patients. Delayed detection is the primary reason for poor prognosis, high morbidity and mortality rates, and this strongly supports the need to perk up early detection of these OPMDs [11]. The gold standard for diagnosis is still biopsy, which is not suited for screening purposes due to its invasive nature, high cost, need for specially trained medical personnel, equipment and chances of secondary biopsy are also high [12].

There has been development of diagnostic tools both at clinical as well as molecular level for early detection from the advancements made in the field of oral cancer research [6]. A number of diagnostic methods have emerged in the past decades with manufacturers claiming to enhance oral mucosal examinations and facilitate the detection of and distinction between benign disorders and OPMD. Chemiluminescence is such an optical based test and has been used for many years as a diagnostic method in examination of oral premalignant and malignant lesions [13].

Eilhardt Weidemann first coined the term "Chemiluminescence" in 1888 [6]. Chemiluminescence refers to emission of light during a chemical reaction [5]. Blue, green, yellow-green, yellow, orange and red are various colours produced from the reaction. It helps oral physicians to detect lesions at much earlier stage as it is a painless, effective, and fast procedure. Chemiluminescence works on the mechanism that the application of acetic acid solution removes debris, damages the glycoprotein barrier on the surface epithelium and dessicates the mucosa, causing better penetration of light; due to which oral mucosal changes are better visualised due to changes in their refractive properties [14]. Its diagnostic system detects the mucosal tissues undergoing abnormal metabolic or structural changes leading to different absorbance and reflectance profiles when exposed to various forms of light sources [13].

Clinicians who use these techniques may be unaware of the status of evidences supporting their diagnostic ability [15]. Understanding the diagnostic accuracy of chemiluminescence would help clinicians to choose the most effective treatment by reaching a correct diagnosis. Diagnostic accuracy includes specificity, sensitivity, and Receiver Operating Characteristics (ROC) analysis [15].

Sensitivity and specificity describe the intrinsic ability of diagnostic test to correctly identify diseased and non-diseased, respectively. They are independent of disease prevalence which refers to probability of disease in a specific population at a given time. A Summary Receiver Operating Characteristics (SROC) analysis is used to evaluate the predictive power of chemiluminescence for diagnosing OPMD's [15,16].

Going through evidences, till date no study has provided a comprehensive, quantitative analysis of chemiluminescence for OPMD individually, on which diagnostic reasoning can be established. Therefore, the aim of this systematic review was to assess the diagnostic accuracy of chemiluminescence in adults with OPMD through a meta-analysis.

MATERIALS AND METHODS

Protocol and Registration

The systematic review and meta-analysis protocol was registered at the International prospective register of systematic reviews (PROSPERO- CRD42022306061) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Diagnostic Test Accuracy (PRISMA-DTA) checklist [16].

Study Design

The following focused research question in the Participants (P), Index test (I), Reference standard (R) and Target condition (T) format was proposed "What are the diagnostic accuracy of chemiluminescence (I) compared to biopsy (R) in patients (P) with OPMD (T)"? Studies evaluating chemiluminescence along with their method of assessment as compared to biopsy and reporting measures of diagnostic test accuracy such as sensitivity and specificity were eligible for inclusion.

Eligibility Criteria

Inclusion criteria: The inclusion criteria were as follows:

- Study design: In-vivo studies- Observational studies or Clinical trials comparing the diagnostic accuracy of chemiluminescence
- Participant characteristics: Patients with presumptive diagnosis of OPMD
- Outcome measurements: Diagnostic accuracy including sensitivity, specificity, accuracy, determined using different methods irrespective of the methods of quantifying the outcomes
- Articles written in English language
- Articles published from 2000-2021 and available as free full text

Exclusion criteria: The exclusion criteria were as follows:

- Non-clinical studies, in-vitro studies, and animal studies
- Studies done on individuals less than 18 years of age
- Studies not fully available in the database
- Article reporting only abstracts were also excluded
- Studies not reporting primary outcomes of accuracy, sensitivity, and specificity as well as where primary outcomes are not possible to calculate from the given raw data

Search Protocol and Study Selection

A comprehensive electronic search was performed till 31st December 2021 for the studies published within the last 21 years (from 2000 to 2021) using the following databases: PubMed and EBSCOhost to retrieve articles in the English language. The searches in the clinical trials database, cross-referencing and grey literature were conducted using Google Scholar, Greylist, and OpenGrey. In addition to the electronic search, a hand search was also made, and reference lists of the selected articles were screened.

Search Strategy

Appropriate key words and Medical Subject Heading (MeSH) terms were selected and combined with Boolean operators like AND. The search strategy used was as follows: (chemiluminescence AND sensitivity AND specificity AND premalignant lesion), (chemiluminescence AND leukoplakia AND lichen planus AND sensitivity AND specificity), (chemiluminescence AND oral submucous fibrosis AND sensitivity AND specificity). The search and screening, according to the previously established protocol were conducted by two review authors.

A two-phase selection of articles was conducted. In phase one, two reviewers reviewed titles and abstracts of all articles. Articles that did not meet the inclusion criteria were excluded. In phase-two, selected full articles were independently reviewed and screened by the same reviewers. Any disagreement was resolved by discussion. When mutual agreement between the two reviewers was not reached, a third reviewer was involved to make the final decision. The final selection was based on consensus among all three authors.

Data Extraction

For all included studies, following descriptive study details were extracted by two independent reviewing authors using pilot-tested customised data extraction forms: authors, study year, mean age of participants, sample size (n), gender (male/female), disorder or lesion investigated, method of investigation, reference standard and conclusion. Quantitative data of sensitivity and specificity were compiled from each study and using these quantitative data, values like true positive, true negative, false positive and false negatives were calculated manually for the studies using the below formula's where the data was not provided by authors [17]. The corresponding author was contacted via email where further information was needed.

- False positive=(1-specificity)×(1-diseased cases/total sample)
- True negative=specificity×(1-diseased cases/total sample)
- True positive=sensitivity×diseased cases/total sample
- False negative=(1-sensitivity)×diseased cases/total sample

Assessment of Methodological Quality

The methodological quality or the risk of bias was evaluated using Quality Assessment for Diagnostic Accuracy Studies -2 (QUADAS-2) tool [18]. The QUADAS-2 is a revised tool developed to assess quality of diagnostic studies through its four domains:

- Patient selection
- Index test
- Reference standard
- Flow and timing of participants

Each domain had signalling questions with options of "Yes", "No" or "Unclear". The overall risk of bias was assessed as:

- High answered 'No' to any question

- Low: if answered 'Yes' to all questions
- Unclear: if answered 'Unclear' to all questions or accompanied by any 'Yes'

Risk of bias summary and applicability concern was graphically plotted using Review Manager (RevMan) software version 5.3.

STATISTICAL ANALYSIS AND DATA SYNTHESIS

Raw data was used to calculate sensitivity and specificity for each biomarker with their estimation method. For overall accuracy, we calculated pooled sensitivity, pooled specificity with 95% confidence interval, area under SROC. Interpretation of Area Under Curve (AUC) values were as follows: value above 80% were considered as excellent, between 70% and 80% as good, between 60% and 69% as fair and below 60% as poor outcomes for a diagnostic test [17]. To assess the impact of heterogeneity, Higgins I2 test was used. This test represents the proportion of variability due to heterogeneity rather than due to sampling error [19]. According to I2 test statistic the heterogeneity could be low (I2 <50%) or high (I2 >50%) [19]. Results were presented graphically as coupled forest plot for each salivary biomarker with their estimation method using Meta-Disc 1.4 software.

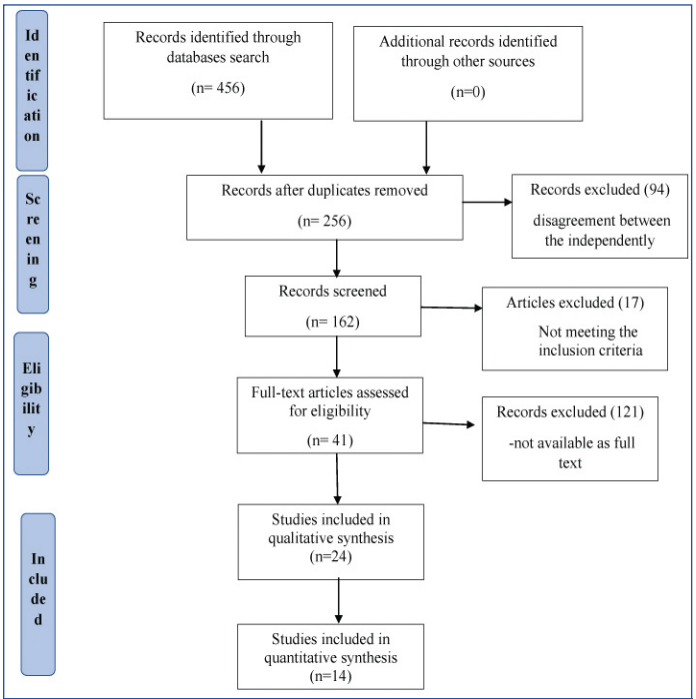
Additional Analysis

Additional analysis was performed with Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) using DerSimonian-Laird's estimator considering random effect model. Positive likelihood ratio in range of 2-5, 5-10 and >10 represents small, moderate and large increase in probability of disease when the test is positive while NLR in range of 0.2-0.5, 0.1-0.2 and <0.1 represents small, moderate and large decrease in probability of disease when the test is negative [20].

RESULTS

Study Selection

A flowchart of identification, inclusion and exclusion of studies is shown in [Table/Fig-1]. After duplicates removal, reference list of all included studies was screened, of which 121 studies were excluded. After this full text articles were assessed for eligibility and articles that did not meet inclusion criteria were excluded. Only 24 studies [4-6,13-15,21-38] fulfilled the eligibility criteria and were included in qualitative synthesis. Of those, only 14 studies were adequate to use for meta-analysis.



[Table/Fig-1]: Showing PRISMA flowchart of literature search and selection criteria.

Study Characteristics

A summary of descriptive characteristics of all included 24 studies [4,6,13-15,21,22,29-33,35,36] is provided in [Table/Fig-2]. Data was evaluated from an aggregate of 1833 patients with mean age of 50.2 years with male and female proportion being 56% and 44% respectively of total sample size. The articles were published between 2000 to 2021 and conducted in 10 countries: 10 studies [4,5,14,21,22,26,30,33,35,37] in India, three studies [23,27,38] in United States, three studies [24,25,29] in Australia, two studies [6,36] in Malaysia, one study [13] in United Kingdom, one study [15] in Saudi Arabia, one study [28] in China, one study [31] in Poland, one study [32] in South Korea, and one study [34] in Romania. Diagnostic accuracy of chemiluminescence for leukoplakia was evaluated in 11 studies [4,13,14,15,21,22,29,30,31,33,36], for OLP it was evaluated in seven studies [6,13,30,31,32,35,36], for OSMF it was evaluated in five studies [4,13,21,33,36], and for erythroplakia it was evaluated in two studies [14,38]. As only two studies [14,38] evaluated for erythroplakia, not sufficient studies and data were present due to which calculating the diagnostic accuracy or doing meta-analysis of chemiluminescene for erythroplakia was not possible.

Risk of Bias within Studies

Almost all of the included studies were classified as low risk of bias for all four domains. Patient selection was considered as high risk of bias in seven studies [6,15,22,29,33,34,37] and unclear in one study [13], which was mainly due to method of patient enrollment, nature of study design and implementing inappropriate exclusion.

The index test was considered to be at high risk of bias only in one study [15]. High risk of bias was reported with respect to index test domain due to insufficient details reported as to whether results of index test was interpreted without prior knowledge of reference standard results, lack of pre-specification of a test-positive threshold and statement of conflict of interest.

Similarly, three studies [22,31,34] reported high risk of bias regarding reference standard and three studies [22,29,31] for flow and timing domain.

Regarding the applicability concern, only one study [34] reported high risk for patient selection and one study [26] for index test while all studies reported low risk for reference standard.

The risk of bias and applicability concern summary and graph is depicted in [Table/Fig-3,4].

Synthesis of Results

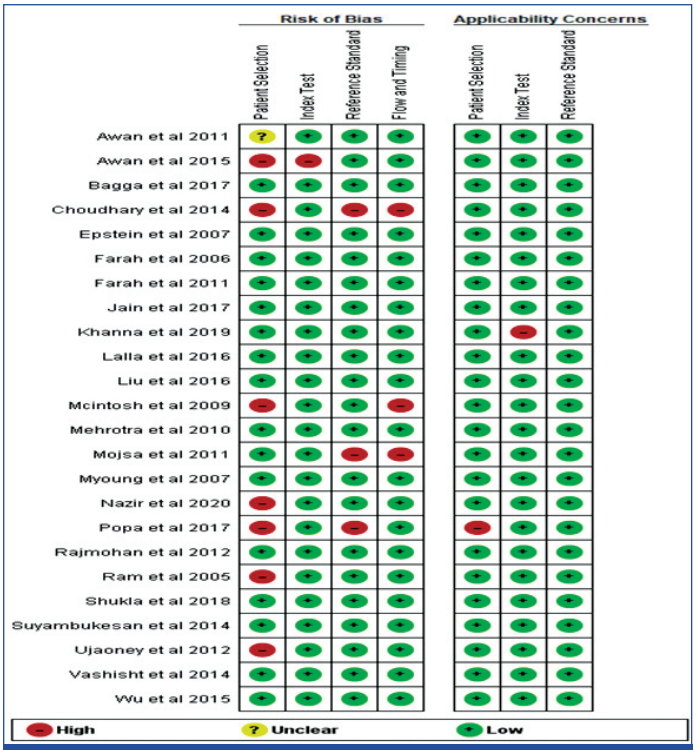
Diagnostic accuracy of chemiluminescence for leukoplakia: A total of 906 patients from 11 studies investigated the accuracy of chemiluminescence for leukoplakia [4,13,14,15,21,22,29,30,31,33,36]. The pooled sensitivity was 0.75 (CI: 0.29-0.98) and pooled specificity was 0.98 (CI: 0.91-1.00) as shown in [Table/Fig-5].

Diagnostic accuracy of chemiluminescence for oral lichen planus: A total of 439 patients from seven studies [6,13,30-32,35,36] investigated the accuracy of chemiluminescence for OLP. The pooled sensitivity was 0.78 (CI 0.18-1.0) and the pooled specificity was 0.60 (CI 0.11-0.96) as shown in [Table/Fig-6].

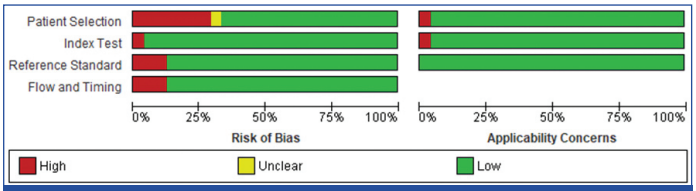
Diagnostic accuracy of chemiluminescence for oral submucous fibrosis: A total of 438 patients from five studies [4,13,21,33,36] investigated the accuracy of chemiluminescence for OSMF. The pooled sensitivity was 0.89 (CI 0.13-1.0) and the pooled specificity was 0.76 (CI 0.12-1.0) as shown in [Table/Fig-7].

S. No.	Author/Year	Place of study	Sample size	Mean age of participants	Gender M/F (cases)	Type of OPMD diagnosed	Method of detection	Conclusion
1.	Awan KH et al., (2011) [13]	United Kingdom	126	58.5 years	70/56	Leukoplakia, erythroplakia, OLP, OSMF	Chemiluminescence	Chemiluminescence has ability to detect OPMD but do not accurately delineate dysplastic changes.
2.	Awan KH et al., (2015) [15]	Saudi Arabia	126	57.5 years	70/56	Leukoplakia, erythroplakia, OLP, OSMF	Chemiluminescence, Autofluorescence, Toluidine blue	While all tests were useful in detecting oral mucosal changes, their accuracy in identifying OPMD is questionable. However, in combination, tests yielded better results, with improved specificity.
3.	Bagga M et al., (2017) [21]	India	100	34.95 years	50/50	Leukoplakia, OSMF	Clinical examination, Chemiluminescence, Toluidine blue	Chemiluminescence and toluidine blue cannot be compared with histopathology as these are adjunctive aids in early diagnosis of oral pre-cancer and cancer.
4.	Chaudhry A et al., (2016) [22]	India	100	30.5 years	74/26	Leukoplakia	Chemiluminescence, Toluidine blue	Chemiluminescence and toluidine blue have adjunctive utility in diagnosis of dysplasia in leukoplakia, but toluidine blue was more effective in identifying severe grades of dysplasia, and it effectively discriminated high-risk from low-risk.
5.	Epstein JB et al., (2008) [23]	United States	84	59.7 years	44/40	Leukoplakia, OLP	Visual examination, Chemiluminescence, Toluidine blue	Chemiluminescence enhances visual characteristics of oral lesions and may improve visual identification of oral mucosal lesions.
6.	Farah CS and McCullough MJ, (2007) [24]	Australia	55	57.4 years	26/29	Leukoplakia, OLP, OSMF	Chemiluminescence	Chemiluminescence appears as useful general visualisation tool for examining oral cavity, but do not aid in identification of malignant and potentially malignant lesions of oral mucosa.
7.	Farah CS et al., (2012) [25]	Australia	112	58.8 years	46/66	Leukoplakia	Autofluorescence, Chemiluminescence	Tissue fluorescence and luminescence cannot provide definitive diagnosis regarding epithelial dysplasia.
8.	Jain N et al., (2018) [5]	India	40	47.25 years	38/2	Leukoplakia	Chemiluminescence	Chemiluminescence has potential to revolutionise diagnostic protocol for OPMDs.
9.	Khanna V et al., (2019) [26]	India	30	Not mentioned	Not mentioned	Leukoplakia	Chemiluminescence, Toluidine blue	Chemiluminescence is definitely a screening test but its diagnostic properties are questionable.
10.	Lalla Y et al., (2016) [27]	United States	88	60.5 years	39/49	OSMF	Light luminescence and spectroscopy	Clinicians should use light features of identification in sequential and differential manner.
11.	Liu D et al., (2016) [28]	China	123	54.7 years	Not mentioned	Oral premalignant lesions	Clinical examination, Chemiluminescence, Toluidine blue, autofluorescence	Most of the non-invasive detection techniques showed great potential for screening and monitoring OPMDs.
12.	McIntosh L et al., (2009) [29]	Australia	50	57.3 years	23/27	Leukoplakia, OLP	Chemiluminescence	Chemiluminescence improves visualisation of oral mucosal lesions.
13.	Mehrotra R et al., (2010) [30]	India	102	39.6 years	39/63	Leukoplakia, OLP	Chemiluminescence, autofluorescence	Chemiluminescence and autofluorescence can be used as screening tests and wasn't beneficial in identifying dysplasia.
14.	Mojsa I et al., (2012) [31]	Poland	30	50.3 years	21/9	Leukoplakia, OLP, OSMF	Chemiluminescence, visual examination	Chemiluminescence system may help practitioners to visualise oral pathologies that are not readily detectable with conventional incandescent lighting.
15.	Myoung H et al., (2007) [32]	South Korea	41	Not mentioned	Not mentioned	OLP	Chemiluminescence	Chemiluminescence light may not be proper for screen test of oral cancer or premalignant lesion but showed some possibility for additional diagnostic tool for definitively diagnosed patient in determination of lesion margin and scope.
16.	Nazir H et al., (2020) [33]	India	100	41.5 years	Not mentioned	Leukoplakia, OSMF, OLP	Clinical examination, Chemiluminescence, Toluidine blue	Chemiluminescence was relatively reliable in screening premalignant epithelial lesions compared to toluidine blue
17.	Popa C et al., (2017) [34]	Romania	186	66.8 years	62/124	Leukoplakia	Chemiluminescence	Chemiluminescence has 100% accuracy in screening OPMD
18.	Rajmohan M et al., (2012) [35]	India	30	Not mentioned	Not mentioned	Pre-cancerous lesions	Chemiluminescence, Toluidine blue	Chemiluminescence test was sensitive for precancerous lesions. It is relatively stable and accurate and useful chair side diagnostic test.
19.	Ram S and Siar CH, (2005) [6]	Malaysia	40	35.5 years	17/23	Leukoplakia, OLP	Chemiluminescence, Toluidine blue	Chemiluminescence is more reliable diagnostic tool than toluidine blue in detection of OPMDs.
20.	Shukla A et al., (2018) [4]	India	42	Not mentioned	37/5	Leukoplakia, OSMF	Chemiluminescence, Toluidine blue	Chemiluminescence has high sensitivity but low specificity
21.	Suyambukesan S et al., (2014) [36]	Malaysia	70	45.60 years	40/30	Leukoplakia, OSMF, OLP	Chemiluminescence	Chemiluminescence has potential to diagnose OPMDs.
22.	Ujaoney S et al., (2012) [37]	India	55	45.4 years	51/4	Leukoplakia	Chemiluminescence, Toluidine blue	Toluidine blue retention test may be better than chemiluminescence to detect high-risk OPMDs
23.	Vashisht N et al., (2014) [14]	India	60	Not mentioned	Not mentioned	Leukoplakia	Chemiluminescence, Toluidine blue	Chemiluminescence was relatively reliable in screening OPMDs.
24.	Chainani WN et al., (2015) [38]	United States	43	53.5 years	13/30	Leukoplakia, Erythroplakia	Visual examination, Chemiluminescence, Toluidine blue	Chemiluminescence is a potential screening tool for OPMDs

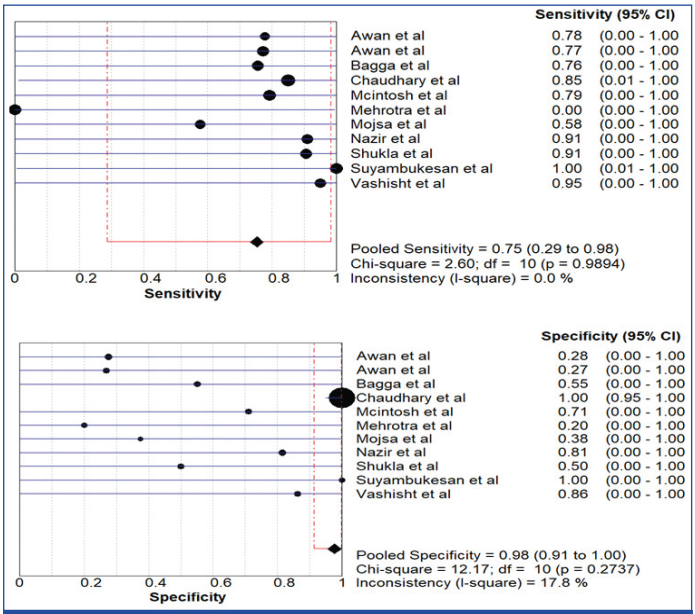
[Table/Fig-2]: Showing descriptive study characteristics of included studies [4-6,13-15,21-38].
*Only the data for chemiluminescence were extracted from relevant study and included in the analysis; OSMF: Oral submucous fibrosis; OLP: Oral lichen planus; OPMD: Oral potentially malignant disorders



[Table/Fig-3]: Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study [4-6,13-15,21-38].



[Table/Fig-4]: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

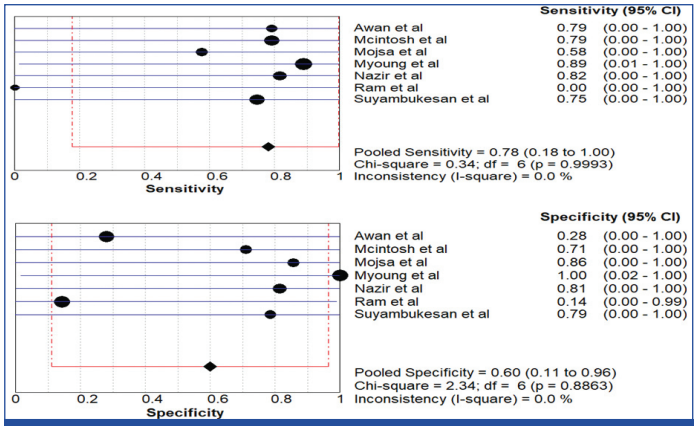


[Table/Fig-5]: Pooled sensitivity and specificity of chemiluminescence for leukoplakia.

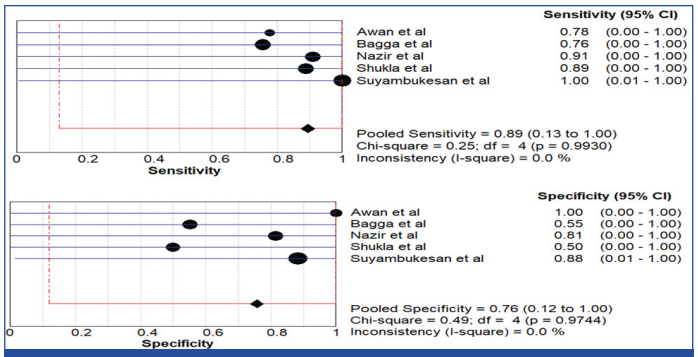
The AUC was calculated through SROC analysis as shown in [Table/Fig-8]. The highest AUC was seen for leukoplakia of 0.74, followed by OLP of 0.70 and OSMF of 0.69. AUC was considered as good both for leukoplakia and OLP and fair for OSMF.

Additional Analysis

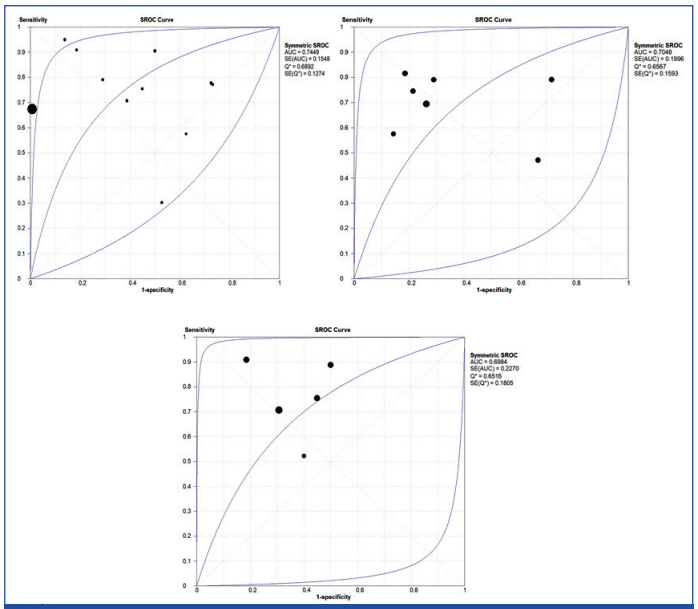
The likelihood ratio (positive and negative) was calculated along with diagnostic odds ratio of chemiluminescence for leukoplakia, OLP and OSMF is shown in [Table/Fig-9,10,11]. Likelihood Ratio (LR) analysis shows that chemiluminescence had small likelihood of



[Table/Fig-6]: Pooled sensitivity and specificity of chemiluminescence for OLP.



[Table/Fig-7]: Pooled sensitivity and specificity of chemiluminescence for OSMF.

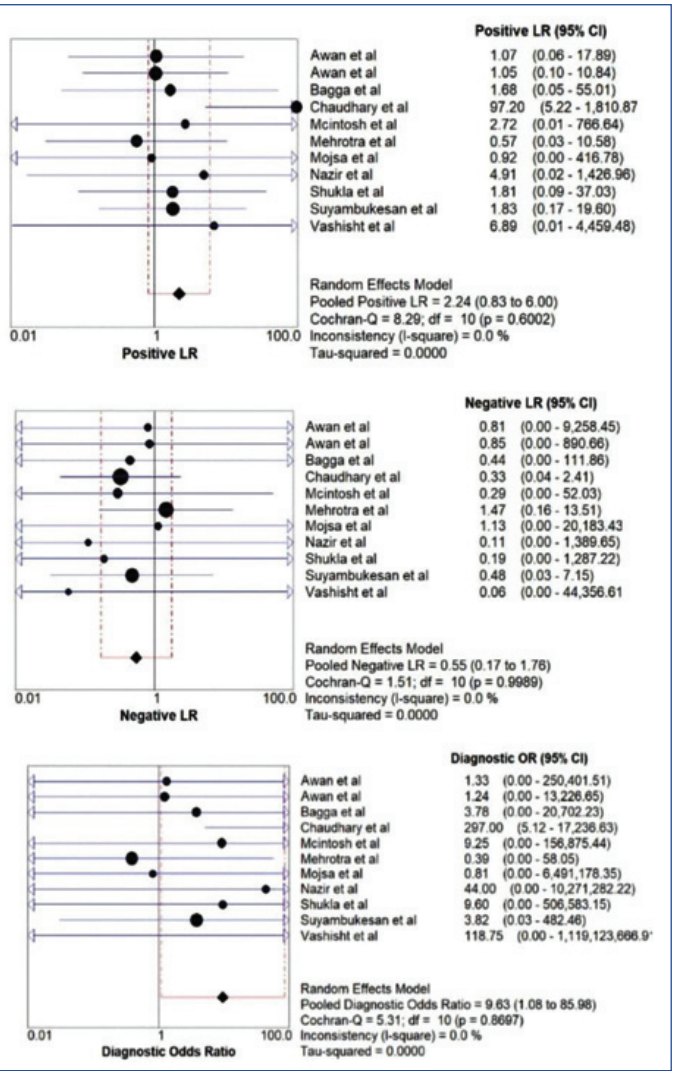


[Table/Fig-8]: The Area Under the Curve (AUC) with Summary Receiver Operating Characteristics (SROC) curve for: a) Leukoplakia, b) OLP and c) OSMF.

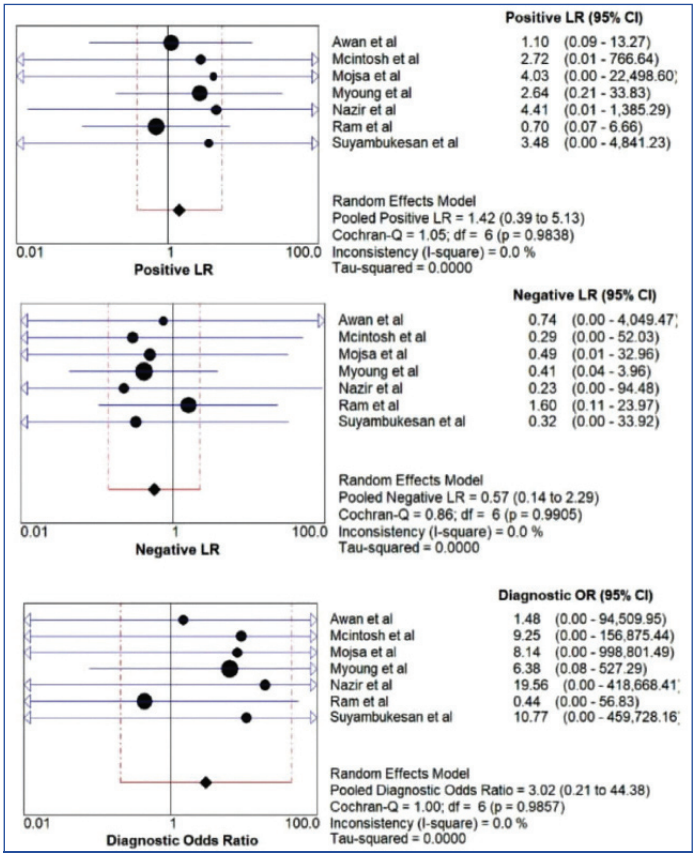
positively saying disease is positive when the disease is actually present and moderately negative likelihood of saying disease is negative when the disease is actually not present or when the subject tests negative for disease.

DISCUSSION

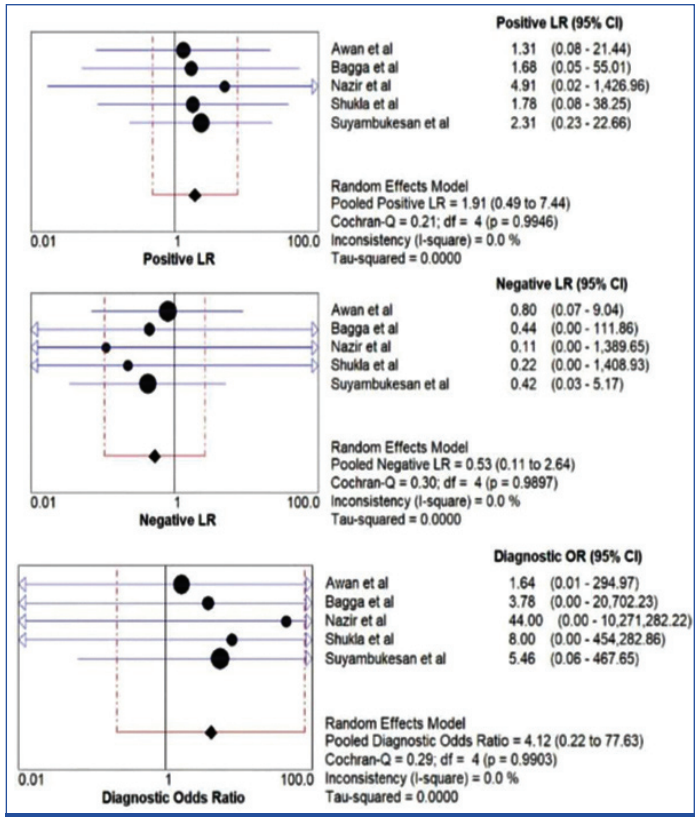
The aim of this systematic review and meta-analysis was to summarise existing evidence on diagnostic accuracy of chemiluminescence and to compare their accuracy in diagnosing oral potentially malignant disorders in adults against biopsy as reference standard. To the best of the authors' knowledge, this is the first systematic review and meta-analysis which provides a comprehensive quantitative analysis of chemiluminescence for various OPMDs on which diagnostic reasoning can be established. A total of 1833 patients with mean age of 50.2 years from 24 eligible studies were included in review and analysis. Chemiluminescence



[Table/Fig-9]: Likelihood Ratio (LR) and Diagnostic Odds Ratio (DOR) of chemiluminescence for leukoplakia.



[Table/Fig-10]: Likelihood Ratio (LR) and diagnostic odds ratio (DOR) of chemiluminescence for oral lichen planus.



[Table/Fig-11]: Likelihood Ratio (LR) and Diagnostic Odds Ratio (DOR) of chemiluminescence for oral submucous fibrosis.

overall had good diagnostic accuracy with pooled sensitivity and specificity. To further evaluate their diagnostic accuracy, we calculated pooled positive and negative likelihood ratio along with their diagnostic odds ratio.

In this study, most of the included studies were at low risk of selection bias arising from use of a case-control study design [4-6,14,21,23,24-28,30,32,33,35,37,38]. In addition, patient sampling and/or recruitment into studies were insufficiently reported. All studies used biopsy as reference standard and chemiluminescence as index test. However, insufficient detail and lack of clarity in reporting studies made it difficult to assess risk of bias. Therefore, use of Statement for Reporting Studies of Diagnostic (STARD) checklist in reporting primary studies could have facilitated the quality appraisal [39]. Reporting guidelines for primary diagnostic studies should be followed strictly and studies should address all potential source of bias and applicability concern as indicated in QUADAS-2 tool [17].

Among the included studies for analysis, 10 studies were from India [4,5,14,21,22,26,30,33,35,38]. It is important to keep in mind that India itself accounts for fifth of all oral cancer cases worldwide, and all oral cancer cases developed from potentially malignant disorders are seen in patients, including betel quid users [40]. Studies have shown that chemicals in betel quid have cytotoxic and genotoxic effects on mucosal epithelial cells due to the generation of Reactive Oxygen Species (ROS), genetic damage, and micronuclei formation [8]. Consequently, similar studies should be performed in other ethnic populations. To overcome these challenges, research efforts should be addressed in validating chemiluminescence for proper OPMD's diagnosis, characterisation, and monitoring [1].

This study provided information on the accuracy and applicability of chemiluminescence in improving OPMD's detection through dynamic and non invasive methods. Sufficient data for meta-analysis was available only for leukoplakia, OLP and OSMF. Among the included studies, sensitivity ranged from 0-100% while specificity ranged from 20-100%. For leukoplakia, chemiluminescence had sensitivity and specificity of 75% and 98% with 0.74 AUC. For OLP it was 78% and 60% with 0.70 AUC. For OSMF it was 89% and

76% with 0.69 AUC. Also, the pooled positive likelihood showed smaller increase in probability of a disease when the test is actually positive. By contrast the pooled Negative Likelihood Ratio (NLR) even showed smaller decrease in probability of disease when the test is actually negative.

On comparison of the present study findings with systematic review and meta-analysis conducted by Buenahora MR et al., where comparison of diagnostic accuracy of clinical visual examinations and light-based tests in precancerous lesions of head and neck was carried [1]. The study was limited by the fact that pooled result was calculated taking all studies as a whole rather than going for individual lesions, also inability to evaluate the performance of chemiluminescence was their limitation. In the current study, the overall pooled sensitivity and specificity of chemiluminescence for individual disorders/lesions makes it a better diagnostic adjunct, while an overall good holistic AUC value highlights chemiluminescence as more accurate overall. The higher AUC value of chemiluminescence for various OPMD's suggests a more easily interpretable and meaningful measure of performance in correctly diagnosing the target condition.

Limitation(s)

This study was limited by overall quality of included studies. Further studies on other standardised diagnostic test with minimal potential sources of bias through rigorous design, conduct and reporting are needed.

CONCLUSION(S)

Chemiluminescence overall had good sensitivity and specificity values along with good AUC. The study findings provide evidence and this strongly supports the fact that chemiluminescence can be used as an alternative diagnostic adjunct to biopsy for early screening and diagnosis of various OPMDs. Thus, it can be concluded that, chemiluminescence can be useful for secondary level of prevention for early oral squamous cell carcinoma under early diagnosis and prompt treatment. Future research must focus on the accuracy of chemiluminescence in detection of OPMDs with clear and robust methodology. Also, further studies must be performed on other OPMDs like erythroplakia, actinic keratosis and discoid lupus erythematosus.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Public Health Dentistry, Sinhgad Dental College and Hospital, Pune, Maharashtra, India.
2. Postgraduate Student, Department of Oral Medicine and Radiology, Sinhgad Dental College and Hospital, Pune, Maharashtra, India.
3. Postgraduate Student, Department of Public Health Dentistry, ITS Dental College, Muradnagar, Uttar Pradesh, India.
4. Postgraduate Student, Department of Public Health Dentistry, Institute of Dental Sciences, Bhubaneshwar, Orissa, India.
5. Postgraduate Student, Department of Public Health Dentistry, ITS Dental College, Muradnagar, Uttar Pradesh, India.
6. Postgraduate Student, Department of Public Health Dentistry, ITS Dental College, Muradnagar, Uttar Pradesh, India.
7. Postgraduate Student, Department of Public Health Dentistry, ITS Dental College, Muradnagar, Uttar Pradesh, India.
8. Postgraduate Student, Department of Public Health Dentistry, ITS Dental College, Muradnagar, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Amar Kumar Shaw,
Maple Tower, C-20, Divya Nagar Society, Jambhulkar Chowk, Wanowarie,
Pune-411040, Maharashtra, India.
E-mail: shawamar96@gmail.com

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