JBPT Journal of Biomolecules Pathogenesis and Therapeutics

AL-NAJAM INSTITUTE FOR EXCELLENCE IN ADVANCED SCIENTIFIC RESEARCH

META-ANALYSIS OPEN ACCESS

Molecular and Cytopathological Determinants of Malignant Transformations in Oral Leukoplakia: A Meta-Analytic Synthesis of AgNOR, DNA Ploidy, Cytokeratin, and Podoplanin Evidence

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Citation: Asghar K, Ashraf R, Taimoor M, Ahmed A, Khalid H. Molecular and Cytopathological Determinants of Malignant Transformations in Oral Leukoplakia: A Meta-Analytic Synthesis of AgNOR, DNA Ploidy, Cytokeratin, and Podoplanin Evidence. J Biomol Pathog Ther. 2025;1(1):33–38.

Received: 05 December, 2025 **Revised:** 28 December, 2025 **Accepted:** 29 December, 2025

ABSTRACT

Background: Oral leukoplakia is one of the cancer-causing oral diseases, which often manifest as predecessors of oral cancer. This study summarizes diagnostic characteristics and prognostic predictors of leukoplakia, a known contributor to cancer metamorphosis, by understanding dysplasia categories and lesional properties. **Methodology**: The research adopted a thorough database search in PubMed, Scopus, and Web of Science according to PRISMA protocols, from 2011 till 2024. The inclusion criteria involved studies with retrospective disease measurements coupled with leukoplakia and malignancy evaluation. Non-human research or studies lacking quantitative analysis were excluded. The Newcastle-Ottawa Scale was used for evaluating risk of bias whereas, quality of study was evaluated using GRADE approach. RevMan 5.4 was used for statistical analysis. **Results**: Total 12 studies were included in this study and results showed that the combination of epithelial dysplasia with AgNOR count and DNA ploidy analysis with biomarker expression studies, indicated positive relationships between markers of risk and malignant cell transformation. The risk of bias of most studies was measured as moderate to high through and GRADE rated certainty of evidence as moderate. A pooled odds ratio (OR) of 3.31 (95% CI: 1.69–6.46, $p < 0.05$) with high heterogeneity I^2 value of 98%, were observed. **Conclusion**: An integrated study on the analysis of tissue structure and molecular evidence might help in the better diagnosis of leukoplakia as being a marker of oral malignancy as well as better estimation of risk.

Keywords: Oral Leukoplakia, Oral Neoplasms, Epithelial Dysplasia, Biomarkers, Tumor, Disease Progression

Introduction

Leukoplakia with dysplastic changes often progress into invasive squamous cell carcinoma [1]. In diagnostic oral pathology, the assessment of the severity of the dysplasia was made using the structural and cytological criteria to determine the outcomes that might be expected in the future and possible treatments strategies [2,3]. The exact pathways involved in disease progression during oral leukoplakia remained unclear since the currently used histological grading techniques had limited capacity in predicting cancer transformation [4,5].

Risk of malignant transformation arises in different ways depending on the exact location, lesion size, how intense the condition appears under a microscope, and patient risks [6-8]. The diagnostic accuracy of leukoplakia and its prognosis is lacking due to varying interpretation by the technicians as well as limitation of sampling method and dysplasia analysis is by subjective terms [9].

An in-depth analysis of the association of leukoplakia with the development of oral cancer should be conducted since there was disparate interpretative accuracy of the physicians in decoding diagnostic data and examining clinical manifestations [10,11]. The systematic assessment with the evidence should state whether or not leukoplakia was an indicator of developing a cancer and its role in risk assessment process.

The current systematic review and meta-analysis was focused on the diagnosis and prediction potential of leukoplakia by analyzing dysplasia stages and lesion characteristics and the influence they might had on malignant outcome. The purpose of the evaluative process was to determine the predictive ability of leukoplakia in the onset of oral malignancy to enhance the clinical decision-making and early diagnosis.

Methodology

The investigation followed the PRISMA 2020 guidelines to assess oral leukoplakia as a potential oral malignancy predictor and its clinical diagnostic and prognostic characteristics [12].

Inclusion and Exclusion Criteria

The criteria for included studies were human-based studies that had either observational elements or retrospective disease measurements combined with leukoplakia and malignancy evaluation. The evaluation excluded non-human research articles and studies that failed to provide quantitative data regarding the association between oral leukoplakia and malignant transformation.

Database Search

Researchers conducted a detailed literature search in PubMed, Scopus, Web of Science, and the Cochrane Library.

Search String Used

The research employed the terms “oral leukoplakia,” “oral malignancy,” “oral cancer,” “dysplasia,” “malignant transformation,” and “oral pathology,” Boolean operators “AND” and “OR.” were also applied to refine the search.

Study Selection

The title and abstract of were reviewed independently by two researchers until proper inclusion requirement met. The reviewers settled their selection differences either through group agreement or expert consultation.

Data Extraction

Two reviewers extracted data in separate sessions using a pre-developed data extraction form. The investigators extracted information based on study design, sample size, confounders, outcomes measured and key findings. The reviewers used discussion and third-reviewer adjudication to solve discrepancies during the data extraction process.

Primary Outcome

Transformation of oral leukoplakia to oral squamous cell carcinoma (OSCC) had been evaluated based on molecular, cytopathological, and genetic endpoints i.e., number of AgNOR, the state of DNA ploidy, the pattern of cytokeratin expression, podoplanin expression, and select genomic changes.

Quality Assessment

An assessment of selection factors, outcome parameters and comparison of quality in selected observational studies was evaluated using Newcastle-Ottawa Scale (NOS) [13]. The authors applied the GRADE framework to perform quality assessment on available evidence.

Statistical Assessment

RevMan 5.4 was used for statistical analysis. An inverse variance random effects model was used to derive pooled odds ratios (ORs) together with 95% confidence intervals (CIs) [14]. Heterogeneity was measured through the I^2 statistic, and forest plots were generated to visualize effect sizes. Sensitivity analysis was applied to eliminate studies with a potential high risk of to verify the stability of the obtained data.o

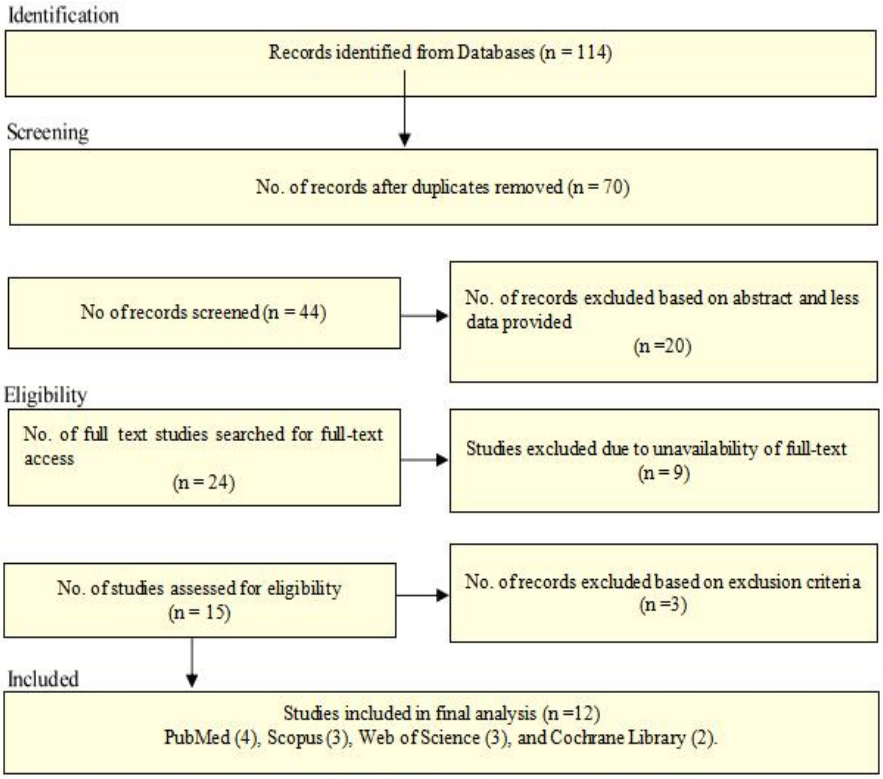

Figure 1: PRISMA Flow Diagram for the Selection of Studies

Results

The study analyzed the use of leukoplakia and associated dysplastic lesions to predict oral malignancies through retrospective and observational research approaches. A total of 114 records were retrieved after database search and 70 of them were duplicates. Among the 44

screened articles, 20 were removed after the abstract evaluation. Due to unavailability of full text, 9 studies were further removed and remaining 15 studies were assessed for eligibility. After excluding 3 studies on the basis of exclusion criteria, 12 studies were included in this study to establish the synthesis. The 12 included studies ranging from small focused cohort studies up to large population-based studies with a single nationwide observational study of more than 3 million participants. The analysis results involved cross-sectional, retrospective cohort, prospective observational, and observational studies. The main confounders that were usually manipulated in the studies were age, sex, smoking status, alcohol intake, nature of lesions, and histological grade. An overview of the features and key findings of the included works are displayed in Table 1.

Table 1. Summary of Included Studies and their Key Findings

Author & Year	Sample Size (n)	Study Design	Confounders	Outcomes Measured	Key Findings
Dogenski et al., 2021 [15]	107	Cross-sectional, observational study	Smoking, alcohol use, age, and sex	Mean AgNOR count, lesion characteristics, symptoms, and histopathological traits	AgNOR count significantly linked with lesion characteristics.
Nomura et al., 2018 [16]	114	Retrospective Observational Study	Age, smoking, and drinking habits	Prevalence of oral leukoplakia; association with cumulative PLD dose	High PLD dose is significantly associated with leukoplakia.
Pentenero et al., 2023 [17]	153	Prospective Observational	Clinical presentation, lesion site, DNA ploidy, OED	Malignant transformation (MT)	OED and DNA ploidy predicted malignancy transformation.
Arora, K. S. et al., 2018 [18]	60	Observational study	Age, Gender, Pre-existing conditions	Efficacy of diode laser in managing oral leukoplakia and oral lichen planus	Diode laser is effective in reducing leukoplakia recurrence.
Chiu, S.-F. et al., 2021 [19]	3,362,232	Observational study	Age, Habit, Gender	Malignant transformation rates	Malignant transformation rates are higher for OVH and OSF, with female patients at higher risk.
Wei Cao et al., 2011 [20]	76	Observational study	Age, Habit, Gender	EZH2 expression, OSCC development	Higher EZH2 expression levels correlate with dysplasia and OSCC development.
Moreira et al., 2024 [21]	67	Cross-sectional observational study	Age, Habit (smoking, alcohol consumption), Gender	Sociodemographic and clinicopathological features	Dysplasia is common in proliferative verrucous leukoplakia.
Wils et al., 2023 [22]	176	Retrospective cohort	Presence of classic epithelial dysplasia; cytokeratin 13/17 expression	Malignant transformation to oral squamous cell carcinoma (OSCC) during follow-up	Epithelial dysplasia increases cancer risk, with differentiated dysplasia showing the highest risk.
Wils et al., 2020 [23]	84	Retrospective cohort	Histological grade, CK13/CK17 status	Malignant progression to oral SCC; expression of CK13/17; presence of differentiated vs classic dysplasia	30% of cases developed SCC; differentiated dysplasia and CK13 loss were strongly associated with progression.
Wils et al., 2023 [24]	89	Retrospective cohort	Age, Habit, Gender	Genomic copy-number alterations, mutations (TP53, FAT1, NOTCH1), development of OSCC	28% developed OSCC; genetic alterations and dysplasia combined in risk model.
Monteiro et al., 2022 [25]	52 OL (41 LG, 11 HG) + 12 NT	Observational	Dysplasia grade, biomarker expression	Malignant transformation (MT), biomarker expression levels	High podoplanin expression increases malignant transformation, combined with dysplasia grade.
Costa et al., 2019 [26]	57	Retrospective study	Dysplasia grade, biomarker expression	ALDH1A1 and ALDH2 expression in OLP and OSCC	ALDH1A1 expression decreases in OSCC, while ALDH2 increases.

Abbreviations: *AgNOR, Argyrophilic Nucleolar Organizer Regions. ALDH1A1, Aldehyde Dehydrogenase 1 Family Member A1. ALDH2, Aldehyde Dehydrogenase 2. CK13, Cytokeratin 13. CK17, Cytokeratin 17. DNA, Deoxyribonucleic Acid. EZH2, Enhancer of Zeste Homolog 2. HG, High Grade. LG, Low Grade. MT, Malignant Transformation. NT, Normal Tissue. OED, Oral Epithelial Dysplasia. OL, Oral Leukoplakia. OLP, Oral Lichen Planus. OSCC, Oral Squamous Cell Carcinoma. OSF, Oral Submucous Fibrosis. OVH, Oral Verrucous Hyperplasia. PLD, Pegylated Liposomal Doxorubicin. SCC, Squamous Cell Carcinoma. TP53, Tumor Protein p53. FAT1, FAT Atypical Cadherin 1. NOTCH1, Notch Receptor 1.*

Malignant transformation OSCC and the expression or change of molecular and cytopathological biomarkers (AgNOR count, DNA ploidy status, cytokeratin (CK13/CK17) expression, podoplanin, EZH2, and ALDH isoenzymes) were the main outcomes that were evaluated. A number of

studies proved that the severity of epithelial dysplasia, its aneuploidy, CK13 destruction, CK17 acquisition, and high podoplanin level correlated with the risk of malignant transformation significantly.

Newcastle-Ottawa Scale (NOS) was used to determine the risk of bias in observational studies. The overall quality of the studies was moderate to high with the total scores being between 5-9 out of possible 9 points. Four articles had the best score (NOS = 9) of good selection criteria, decent comparability, and good outcome measure. Most of the studies (n=7) had a low or moderately low risk of bias whereas one study had a relatively high risk of bias because of poor comparability and outcome measuring. Table 2 presents the risk of bias scoring in detail.

Table 2: Risk of Bias Assessment of Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Dogenski et al., 2021 [15]	★★★	★★	★★	7
Nomura et al., 2018 [16]	★★	★★	★★	6
Pentenero et al., 2023 [17]	★★★★	★★	★★★	9
Arora, K. S. et al., 2018 [18]	★★★	★★	★★★	8
Chiu, S.-F. et al., 2021 [19]	★★★★	★★	★★★	9
Wei Cao et al., 2011 [20]	★★★	★★	★★★	8
Moreira et al., 2024 [21]	★★★	★★	★★★	8
Wils et al., 2023 [22]	★★★	★★	★★★	8
Wils et al., 2020 [23]	★★★	★★	★★★	8
Wils et al., 2023 [24]	★★	★★	★★	6
Monteiro et al., 2022 [25]	★★★	★★	★★★	8
Costa et al., 2019 [26]	★★	★	★★	5

Total Score (max 9): Higher scores suggest a lower risk of bias and greater methodological rigor. 7–9 stars: Low risk of bias, 4–6: Moderate risk of bias, <4: High risk of bias.

The GRADE evidence showed consistent reliability through a combination of studies showing either moderate or high scores, although some studies experienced slight limitations in their comparability and selection methods.

RevMan version 5.4 was used to perform quantitative synthesis, with an inverse variance random-effects model used to explain clinical and methodological heterogeneity by the studies. The pooled analysis showed statistically significant association between the malignant transformation and the molecular/cytopathological abnormalities of the oral leukoplakia with the overall odds ratio (OR) of 3.31 (95% CI: 1.69-6.46, p <0.05), as shown in Figure 2. The result shows that, patients who had high-risk molecular or cytopathological features (compared to the patients who lacked such features) were three times more likely to develop malignant.

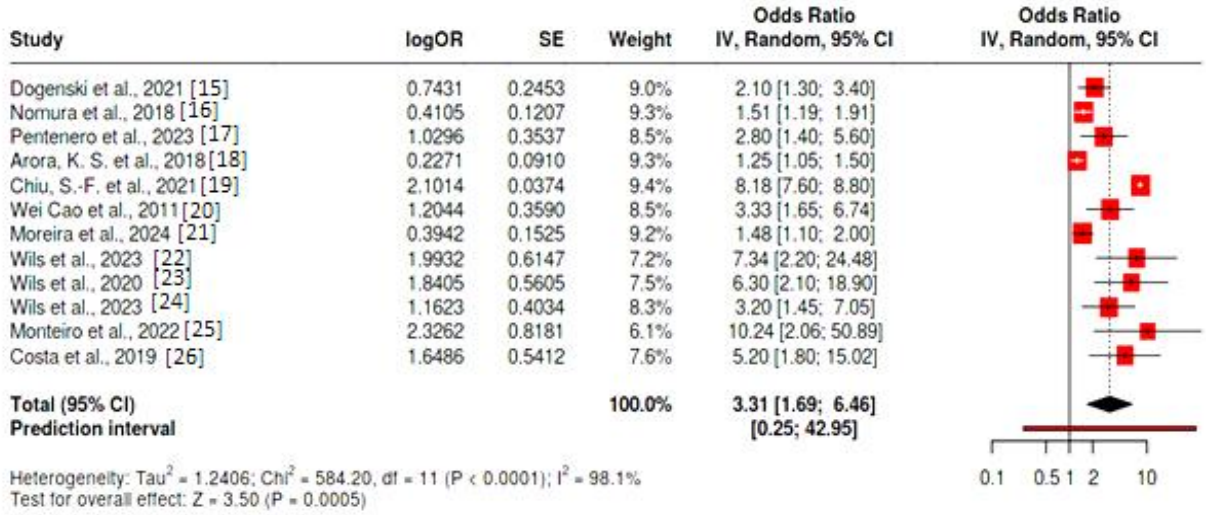

Figure 2. Meta-analytic forest plot of studies examining the association between leukoplakia and oral malignant transformation

There was a significant heterogeneity among the included studies (I^2 = 98, p < 0.01) that was observed because lesion site, lesion size, histopathological grading, methods used in the assessment of biomarkers and duration of follow-ups varied greatly. Although significant heterogeneity was observed, the direction and magnitude of effect remained constant, confirming the strength of the observed association. The pooled effect estimate was stable and was performed by sensitivity analysis by sequentially dropping out studies until all studies dropped out of the overall conclusions. The results indicated that no single dataset had an overbearing impact in the meta-analytic results.

Discussion

Oral leukoplakia's capability to predict oral malignancies is a hot topic among scientists, since multiple academic investigations analyzed its diagnostic and prognostic value [27]. This comprehensive systematic review, together with meta-analysis, demonstrated strong proof regarding the critical predictive value of leukoplakia in oral tissue transformation toward malignancy [28]. The analysis revealed that oral cancer development had a higher chance with dysplastic leukoplakia than with other types of leukoplakia. The literature further confirmed that epithelial dysplasia served as a critical element to determine future cancer development risks in patients [29].

The probability of oral cancer development from leukoplakia depended on which location of lesion in the mouth and what stage of dysplasia it displayed, together with AgNOR numbers and DNA ploidy measurements [30]. Combining different factors enhanced the accuracy of prediction regarding cancerous potential. The aggressive nature of leukoplakia and its risk of becoming malignant could be better assessed through p53 and Ki-67 biomarker expression levels [31,32]. The results showed substantial variation because different procedures had been used for biomarker measurements, as well as limitations of retrospective research designs [33-34].

The results showed smoking and alcohol usage as secondary risk factors that created substantial effects on the cancer-forming potential of leukoplakia tissue [35,36]. Various research papers indicated that cigarette smoking, along with alcohol consumption, contributed to increase the chances of malignant changes [37,38]. Additional research was needed on how environmental risk elements interact with molecular pathways of leukoplakia to cause malignancy because studies show inconsistent findings about how these risk elements influence [39,40].

This study had several limitations. The variable study findings derived from multiple methodological reasons, including sample size differences alongside varied study designs, follow-up protocols, and assessment methods. Research methods that use different protocols for histopathological and molecular analysis contributed to these inconsistent results. Studies with negative or inconclusive results face decreased chances of being published in this field, thus indicating potential biases in overall conclusions. Further research by using standard protocol was needed for better study comparisons. The requirement for extensive multicenter randomized controlled trials (RCTs) was required because they would deliver stronger evidence about oral malignancy prediction linked to leukoplakia.

Conclusion

This meta-analysis based systematic study endorsed oral leukoplakia as a predictory factor in the development of oral tumors. Dysplasia, key molecular pointers and evident clinical signs contribute to the elevation of risk of emergence of malignant development in the future. Across research studies, there was heterogeneity in the research designs and this gap should be bridged by employing the standardized clinical protocols as well as longitudinal studies to ensure the derivation of a conclusive risk assessment model.

Acknowledgment: None

Grant Support & Funding Source: None

Conflict of Interest : None

Authors' Contribution: Study is Meta-Analysis and all Authors Contributed equally as per ICMJE roles.

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