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BIOMARKERS FOR DIFFERENTIATION BETWEEN ORAL LICHEN PLANUS AND EARLY ORAL CANCER LESIONS

Campos LAF
Student at the School of Dentistry, Federal University of Juiz de Fora

Dantas MCFRD
Student in the Graduate Program in Dentistry at the Federal University of Juiz de Fora

Fabri GMC
Professor at the School of Dentistry, Federal University of Juiz de Fora

Fernandes GOM
Student at the School of Dentistry, Federal University of Juiz de Fora

Gomes IT
Student in the Graduate Program in Dentistry at the Federal University of Juiz de Fora

Matos MB
Student at the School of Dentistry, Federal University of Juiz de Fora

Oliveira CB
Student in the Graduate Program in Dentistry at the Federal University of Juiz de Fora

Ribeiro LWR
Student at the School of Dentistry, Federal University of Juiz de Fora

Rocha CMSAR
Student at the School of Dentistry, Federal University of Juiz de Fora

Vital ABL
Student at the School of Dentistry, Federal University of Juiz de Fora

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Abstract: Introduction: Oral lichen planus (OLP) is a potentially malignant oral disorder whose distinction from early neoplastic transformation lesions is hampered by the overlap between chronic inflammation, mild dysplasia, and early epithelial changes. **Objective:** To synthesize evidence on tissue, salivary, and serum biomarkers capable of assisting in the differential diagnosis between OLP and potentially malignant lesions, based on a review conducted in October 2025. **Results:** Among the most studied biomarkers are p53, Ki-67, and PCNA, related to cell proliferation; Bcl-2, Bax, and caspase-3, associated with apoptosis regulation; and proinflammatory cytokines, immunological markers, and angiogenic mediators such as COX-2 and VEGF. Emerging approaches include salivary microRNAs, metabolomics, liquid biopsy, and evaluation of mutations in genes linked to oral carcinoma. Although these strategies broaden the understanding of the mechanisms involved in the progression of OPC, important limitations remain, such as methodological heterogeneity, small sample sizes, and lack of standardization between studies, which restricts clinical application. **Conclusion:** No single biomarker is accurate enough to replace clinical-histopathological evaluation. The integration of clinical, morphological, and molecular findings remains the most effective approach for monitoring and risk stratification in patients with OPL.

Introduction

Potentially malignant oral disorders (PMOD) represent a set of conditions characterized by epithelial and inflammatory changes that increase the risk of developing oral squamous cell carcinoma.

From a clinical and epidemiological point of view, these disorders are particularly relevant because they lie in a borderline zone between persistent benign lesions and initial changes in the carcinogenic process, requiring careful monitoring and accurate diagnosis. The heterogeneity of their manifestations, histopathological overlap with initial malignant lesions, and variability in diagnostic criteria hinder clinical management and reinforce the need for complementary tools for risk assessment and early detection.

In this scenario, oral lichen planus (OLP) stands out as one of the most prevalent conditions, characterized by chronic T-cell-mediated inflammation, basal layer degeneration, and reactive epithelial changes. Although classically considered stable, OL has a documented risk of malignant transformation, estimated between 0.4% and 2%, especially in the erosive and atrophic variants (Keim-Del Pino et al., 2024). This possibility of progression justifies its current classification as DOPM by the World Health Organization and reinforces the need for continuous monitoring.

The diagnostic difficulty arises mainly from the morphological similarities between LPO, discrete degrees of epithelial dysplasia, and the early stages of oral squamous cell carcinoma. At the same time, advances in the understanding of pathobiological mechanisms demonstrate that the persistent inflammatory microenvironment persistent inflammatory microenvironment, associated with sustained cytokine release and cellular stress, creates favorable conditions for the progressive accumulation of molecular changes. In this context, biomarkers emerge as tools capable of reflecting, with greater precision, the different stages of this process, helping to distinguish between stable chronic inflammation and epithelial changes with malignant potential (Singh et al., 2022).

Recent research has explored markers in tissue, blood, and saliva, highlighting the latter due to its non-invasive nature and ability to represent local changes in the oral mucosa. Studies indicate that inflammatory proteins, epithelial structural fragments, and regulatory microRNAs may exhibit distinct expression patterns between OHL and early malignant lesions, suggesting their usefulness in supporting differential diagnosis (Rezaei et al., 2023). Although there are still methodological discrepancies between studies, the current trend indicates that combinations of markers, rather than isolated molecules, have greater potential for clinical use.

Given this scenario, it is essential to understand how oral lichen planus ranks among potentially malignant oral disorders and which biological markers can contribute to identifying epithelial changes related to neoplastic progression. This chapter takes an integrated approach, bringing together current evidence on the main cellular and molecular mechanisms involved in the evolution of OLP, as well as the tissue, salivary, and serum biomarkers with the greatest potential to differentiate stable inflammatory conditions from early stages of malignant transformation. By systematizing these elements, we seek to offer the reader a critical analysis of the most consistent parameters for diagnostic refinement and risk stratification in potentially malignant lesions of the oral mucosa.

Clinical and Histopathological Foundations of Oral Lichen Planus

Oral lichen planus (OLP) is a chronic mucocutaneous disorder of an immune-mediated nature, whose presentation clinical is marked by significant heterogeneity. Manifestations include reticular, papular, plaque, atrophic, erosive, and bullous (Sousa; Rosa, 2008; Mutafchieva; Tashkova, 2025). The reticular and plaque variants, which are more frequently observed, are usually asymptomatic and present the classic Wickham striae, which are fine white lace-like lines, usually bilateral and symmetrical, surrounded by a discrete erythematous halo. The buccal mucosa is the most commonly affected site, although lesions may also occur on the tongue, gums, and palate (Fernández-González et al., 2011; Nukaly et al., 2024). In contrast, the atrophic and erosive forms are clinically more severe, characterized by erythematous, ulcerated, and painful areas that can make chewing and speaking difficult (Anitua et al., 2019; Esquivel-Pedraza et al., 2016). The less common bullous form manifests as vesicles and blisters that rupture easily, resulting in painful ulcerations (Kumari, et al., 2022). In general, LPO has a chronic course, with periods of remission and exacerbation (Anitua et al., 2019; Nukaly et al., 2024).

The diagnosis of LPO is based on the integration of clinical and histopathological findings, since other conditions, such as lichenoid contact or drug reactions, may present similar characteristics (Fernández-González et al., 2011; Nukaly et al., 2024). A biopsy is essential for a definitive diagnosis, allowing observation of epithelial changes and the characteristic inflammatory pattern. Histologically, LPO presents hyperkeratosis, acanthosis, hypergranulosis, and hydropic degeneration of the basal layer, associated with a predominantly lymphocytic inflammatory infiltrate arranged in a continuous band below the epithelium (Mutafchieva; Tashkova, 2025; Anitua et al., 2019). The presence of Civatte bodies, apoptotic remnants of keratinocytes, and the serrated pattern of the epithelial ridges are frequent findings and considered characteristic (Sousa; Rosa, 2008; Kumari et al., 2022). In some cases, eosinophilic deposits are observed in the basement membrane and the presence of plasma cells and eosinophils in the infiltrate, suggestive of lichenoid reactionary processes (Fernández-González et al., 2011; Anitua et al., 2019; Nukaly et al., 2024).

From a pathophysiological point of view, LPO is an autoimmune disorder mediated mainly by CD8+ T lymphocytes, which promote the destruction of basal layer cells, perpetuating inflammation and epithelial degeneration. This process triggers chronic and sustained tissue injury over time (Fernández-González et al., 2011; Kumari et al., 2022). The continuous immune activation and oxidative stress associated with the inflammatory process justify its classification by the World Health Organization (WHO) as an oral potentially malignant lesion (OPMD) (Nukaly et al., 2024; Tan et al., 2023). The rate of malignant transformation to oral squamous cell carcinoma (OSCC) varies between 1% and 2%, being higher in the atrophic and erosive variants (Esquivel-Pedraza et al., 2016; Kumari et al., 2022).

OPMDs encompass several other oral mucosal changes with an increased risk of progression to cancer, including leukoplakia, erythroplasia, and oral submucosal fibrosis (Torabi et al., 2021; Tan et al., 2023). Leukoplakia is characterized by non-removable white plaque, whose risk of malignancy varies between 1% and 30%, especially in non-homogeneous and verrucous forms. Erythroplasia, in turn, has a reddish color and an even higher risk, and can progress to carcinoma in situ in up to half of cases (Tan et al., 2023). Early identification of these lesions is essential, as patients with OPMDs have a considerably higher risk of developing OSCC when compared to individuals without mucosal changes (Khan et al., 2023).

Oral squamous cell carcinoma is the most common malignant neoplasm of the oral cavity and represents the final stage of progression of several OPMDs, including LPO (Tan et al., 2023; Rivera; Venegas, 2014). Clinically, it may begin as white, red, or mixed areas with defined edges and an irregular surface, progressing to hardened and usually painless ulcerations. The most affected regions include the lateral edge of the tongue, the floor of the mouth, and the gums (Pires et al., 2013). Histologically, it is characterized by the proliferation of atypical squamous cells that infiltrate the lamina propria, forming epithelial islands and cords, accompanied by classic keratin pearls in well-differentiated tumors (Rivera; Venegas, 2014). Changes such as hyperkeratosis, acanthosis, and epithelial dysplasia are often observed in the early stages of carcinogenesis (Kumari et al., 2022; Tan et al., 2023).

In summary, LPO is a chronic and potentially malignant inflammatory condition that requires systematic follow-up

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and rigorous clinical-histopathological correlation. The literature reinforces that the variability of clinical findings, the composition of the inflammatory infiltrate, and the susceptibility to malignant transformation make continuous monitoring of patients with LPO and other OPMDs indispensable (Nukaly et al., 2024; Souza; Rosa, 2008; Tan et al., 2023; Rivera; Venegas, 2014).

Biomarkers for Diagnostic Differentiation

Biomarkers are detectable biological elements in tissues, blood, or other bodily fluids that reflect physiological or pathological changes in the body. In general, a biomarker is considered to be any measurable substance that serves as an indicator of normal biological processes, conditions associated with diseases, or the body's responses to therapeutic interventions (Ravindran et al., 2025; Ahmad et al., 2023; Desmurget et al., 2024).

In this context, there is growing interest in biological indicators capable of providing more consistent and measurable data, reducing the exclusive dependence on subjective analyses. Research into markers applicable to the diagnosis and monitoring of potentially malignant lesions (PML) and oral squamous cell carcinoma seeks not only to identify lesions with a higher risk of transformation, but also to predict therapeutic response and the possibility of regional or distant metastases (Bastías et al., 2024).

These markers can be classified according to their biological origin, being divided into molecular, cellular, and tissue markers. Molecular markers are substances identified in body fluids or tissues; cellular markers correspond to changes observed in cells; and tissue markers encompass morphological and structural changes, usually assessed by biopsies (Ahmad et al., 2023).

Although the presence of oral epithelial dysplasia remains the most widely used parameter for estimating the risk of malignant transformation, its practical application has limitations. The histopathological changes observed in Oral Lichen Planus (OLP) can be confused with those found in lichenoid reactions of dysplastic conditions, making it difficult to accurately distinguish between these conditions. In addition, microscopic evaluation is influenced by the individual interpretation of the examiner, resulting in inter- and intra-observer variability (Al-Jamaei et al., 2022).

The use of biomarkers, although relevant, is not sufficient to be used as an exclusive diagnostic method. Their interpretation acquires greater value when performed in an integrated manner, combining clinical data, imaging exams, and histopathological analysis of the tissue, whose convergence favors a more reliable assessment and the obtaining of a truly reliable diagnosis (Premnath; Zubair, 2025).

Biomarkers associated with cell proliferation and instability

p53 is a tumor suppressor protein that is essential for maintaining genomic integrity, acting to arrest the cell cycle, repair DNA, and induce apoptosis in response to cellular damage. Approximately 67% of LPO cases show increased p53 expression, which may reflect the activation of wild-type protein in response to the inflammatory stress typical of chronic diseases, albeit with a pattern distinct from that observed in invasive oral carcinomas (Keim-Del Pino et al., 2024). In

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LPO, this overexpression tends to be predominantly associated with inflammatory mechanisms and oxidative stress resulting from the lymphocytic infiltration characteristic of the disease, indicating that most cases do not have profiles compatible with TP53 mutations (Bahramian et al., 2024).

Ki-67, in turn, is a marker of cell proliferation expressed in the active phases of the cell cycle and widely used to assess the epithelial proliferation rate. In cases of LPO, its expression remains mostly restricted to the basal layer, consistent with a moderate and reactive proliferation moderate and reactive proliferation, typical of chronic inflammatory processes and without evidence of epithelial disorganization, reinforcing the non-dysplastic nature of the lesion (Suwasini et al., 2018). In addition, recent analyses show that Ki-67 levels are significantly higher in dysplastic epithelia compared to LPO without dysplasia, highlighting its value as a differential marker between reactive proliferation and pre-neoplastic changes (Bahramian et al., 2024).

In LPMs, such as leukoplakia with dysplasia, both p53 and Ki-67 tend to show more intense and disorganized expression patterns, reflecting greater genomic instability and risk of neoplastic progression. In particular, the increase in p53 in these lesions often indicates the accumulation of mutant proteins, which correlates with more severe degrees of epithelial dysplasia (Humayun; Prasad, 2011). Similarly, Ki-67 demonstrates expansion of labeling to suprabasal layers, indicating loss of proliferative hierarchy, a finding strongly associated with increased risk of malignant transformation (Sundberg et al., 2021).

Biomarkers associated with apoptosis

The regulation of the intrinsic apoptosis pathway in the oral mucosa depends on the balance between proteins of the Bcl-2 family and the effectors of the caspase cascade. While Bcl-2 acts to preserve mitochondrial integrity, Bax promotes its permeabilization and the subsequent release of pro-apoptotic factors, culminating in the activation of caspase-3, responsible for the execution of programmed cell death (Al-Jamaei et al., 2022).

In LPO, several studies demonstrate that caspase-3 is active in areas of keratinocyte degeneration, reinforcing the central role of apoptosis in the elimination of target cells by cytotoxic T lymphocytes (Ibrahim et al., 2023; Jana et al., 2022).

On the other hand, in LPMs, the literature shows a tendency to evade apoptosis. It is common to observe increased expression of Bcl-2, changes in the Bcl-2/Bax ratio, and reduced caspase-3 activation, resulting in the survival of cells with genomic instability, a behavior compatible with neoplastic progression (Lingam et al., 2021; Escobar et al., 2023).

When evaluated in conjunction with proliferation markers, such as PCNA, these findings are intensified: lesions with an anti-apoptotic profile (elevated Bcl-2, reduced Bax, and low caspase-3 activity) generally exhibit higher proliferation rates, reflecting a higher risk of biological progression (Mutafchieva et al., 2025; Lalitha et al., 2022).

Biomarkers associated with inflammation and immune response

The pathophysiology of LPO involves a persistently activated immunoinflammatory microenvironment, in which proinflammatory cytokines play a decisive role in maintaining the immune response. TNF-α, IL-1β, IL-6, and IL-8 appear significantly increased in the saliva of patients, especially in erosive forms, reflecting greater inflammatory activity and correlation with clinical severity. In addition to these molecules, cell recruitment mediators such as MIP-1α, MIP-1β, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are also elevated, favoring the continuous migration of inflammatory cells to the lamina propria and sustaining the chronic course of the disease (Zhu et al., 2022).

The subepithelial infiltrate is characterized by a predominance of T lymphocytes, with emphasis on CD8+ cells distributed at the epithelium-connective tissue interface, a finding repeatedly described in immunohistochemical studies. The significant presence of these cytotoxic lymphocytes reinforces their direct participation in the observed epithelial damage (Rassol; Zaidan, 2023).

Several studies demonstrate increased local production of IFN-γ by CD4+ and CD8+ T cells, especially in erosive manifestations, evidencing a predominantly Th1/cytotoxic immune response (Sun et al., 2021; Mozaffari et al., 2019). In parallel, tissue, salivary, and serum studies show elevated levels of IL-17, in addition to markers associated with the Th17 axis, suggesting an additional contribution of this pathway to mucosal inflammation, again with a greater impact on erosive forms (Husein-ElAhmed; Steinhoff; 2022; Abboud et al.,2023).

As for resident T cells (Trm), there is evidence of their presence in the oral mucosa, identified mainly by CD8+CD103+ and CD8+CD69+ phenotypes, recognized as markers of tissue retention and rapid response to antigen re-exposure. Although reviews of skin and other mucous membranes confirm the functional role of CD69 and CD103, specific studies quantifying these populations in oral lesions are still scarce and heterogeneous (Stolley et al., 2023; Emmanuel et al., 2021).

In general, the evidence points to an infiltrate predominantly composed of T lymphocytes with a Th1/cytotoxic profile, marked by IFN-γ, associated with the relevant participation of the Th17 axis. The possible role of Trm in maintaining chronicity is plausible but requires further investigation (Rassol; Zaidan, 2023; Sun et al., 2021; Husein-ElAhmed; Steinhoff; 2022; Stolley et al., 2023).

Biomarkers associated with malignant progression

Markers of malignant transformation help identify oral leukoplakia with a higher risk of progressing to carcinoma. Among the most evaluated are p53, Ki-67, p16, COX-2, and E-cadherin, which are associated with changes in the cell cycle, proliferation, and adhesion between cells. Although they do not define the diagnosis in isolation, these biomarkers complement clinical and histopathological evaluation, helping to estimate the potential for malignancy of OLP. An in-depth discussion of the mechanisms, interpretations, and individual relevance of each marker will be presented in the specific chapter dedicated to biomarkers.

Table 2 presents a summary of the main biomarkers for differentiating LPO from LPM. It organizes each marker according to its diagnostic function and highlights findings related to proliferation, apoptosis,

Biomarker	Type	Function in Cell Control	Expression Pattern in OLP	Expression Pattern in PML
p53	Tumor suppressor / cell cycle regulator	DNA repair, apoptosis induction, genomic damage control	Increase in ~67% of cases, usually reactive to inflammatory stress and associated with lymphocytic infiltration, without mutation in **TP53**	Greater intensity and disorganization; accumulation of mutant protein, correlated with severe degrees of dysplasia
Ki-67	Proliferative	Marker of cell proliferation, expressed in the active phases of the cell cycle	Restricted to the basal layer, reflecting moderate and reactive proliferation	Expansion to suprabasal layers, indicating loss of proliferative hierarchy and increased risk of malignancy
Bcl-2 / Bax / Caspase-3	Apoptosis	Regulation of apoptosis by the intrinsic pathway (anti--apoptotic Bcl-2, Bax pro-apoptotic, Caspase-3 executor)	Caspase-3 active in areas of keratinocyte degeneration, suggesting functional apoptosis	Elevated Bcl-2, reduced Bax, and low Caspase-3 activity, reflecting apoptosis evasion and genomic instability
PCNA	Proliferative	Assessment of cell proliferation rate	Moderate expression, predominantly in basal layers	Elevated, especially when associated with an anti-apoptotic profile
Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8)	Inflammation	Indicate active inflammatory microenvironment	Elevated, especially in erosive forms, associated with inflammatory activity	May be present, but are not specific for malignant transformation
IFN-γ / IL-17	Immune response	Activation of Th1 and Th17 axes	Increased, related to chronicity of inflammation	May contribute to maintenance of inflammatory infiltrate, but less directly associated with dysplasia
Resident memory T cells (Trm) (CD8+-CD103+, CD8+CD69+)	Tissue immune response	Tissue retention and rapid response to antigen re-exposure	Present in the infiltrate; role still under study	Presence observed, but relevance in malignant progression still uncertain

Table 1: Summary of the main biomarkers for differentiation between Oral Lichen Planus (OLP) and Potentially Malignant Lesions (PML)

Source: *author*

inflammation, as well as methodological limitations identified in the studies.

Despite growing interest in biomarkers to differentiate early oral cancer lesions from oral lichen planus, available studies have important limitations. Most research is based on small series with heterogeneous samples in terms of age, sex, extent, and subtype of lesions, which makes it difficult to generalize the findings and reduces the statistical robustness of the conclusions (Ravindran et al., 2025; Ahmad et al., 2023). In addition, the evaluation methodology varies widely between studies: different immunohistochemistry protocols, antibodies, scoring systems, and interpretation criteria make direct comparisons and meta-analyses difficult (Desmurget et al., 2024; Al-Jamaei et al., 2022).

Another limitation relates to the intrinsic nature of the biomarkers studied. Markers such as p53, Ki-67, p16, COX-2, and E-cadherin may show overlapping patterns between LPO and leukoplakia with dysplasia, especially in cases of erosive LPO or intense inflammation, leading to potentially ambiguous interpretations (Bahramian et al., 2024; Humayun; Prasad, 2011). Thus, no single marker is capable of definitively differentiating potentially ambiguous lesions (Bahramian et al., 2024; Humayun; Prasad, 2011). potentially ambiguous interpretations (Bahramian et al., 2024; Humayun; Prasad, 2011). Thus, no single marker is capable of definitively differentiating reactive inflammatory lesions from potentially malignant lesions, requiring combined analysis of multiple indicators.

Additionally, the presence of chronic inflammation and lymphocytic infiltration in the LPO can alter the expression of biomarkers associated with proliferation or apoptosis, such as Ki-67, Bcl-2, and caspase-3, leading to misinterpretations about the risk of malignancy (Mutafchieva et al., 2025; Ibrahim et al., 2023). Inter- and intra-observer variability in histopathological and immunohistochemical evaluation also contributes to inconsistencies between studies (Premnath; Zubair, 2025).

In the clinical context, the use of biomarkers remains limited. They do not replace clinical examination, histopathological evaluation, and, when indicated, imaging tests, but act as complementary tools for risk stratification and follow-up (Premnath; Zubair, 2025). Interpretation should be done in an integrated manner, considering the clinical profile of the lesion, the patient's history, and other risk factors for malignant transformation (Premnath; Zubair, 2025).

In summary, biomarkers offer the potential to support the differentiation between LPO and leukoplakia with dysplasia, but methodological limitations, overlapping expressions, and variability in interpretation reduce their applicability as a standalone diagnostic tool. Future studies with larger samples, standardized protocols, and simultaneous analysis of multiple markers are needed to consolidate their role in clinical practice.

Monitoring Malignant Potential Using Biomarkers

Oral lichen planus (OLP) is a chronic disease with a predominantly benign behavior, but it is widely recognized as a potentially malignant oral lesion (González-Moles and Ramos-García, 2024). The classical literature reports a malignant transformation rate of around 1–2% of cases over time. More recent studies, however, point to variations in these values, attributed to methodological differences, the diagnostic criteria used, and the duration of patient follow-up. Despite these discrepancies, there is consensus that LPO requires continuous clinical surveillance due to the risk, albeit low, of progression to oral squamous cell carcinoma (OSCC) (Keim-Del Pino, Ramos-García, González-Moles, 2024; Tampa *et al.,* 2018).

The clinical concern is not only the overall probability, but the early identification of lesions with a higher probability of malignancy (González-Ruiz *et al*., 2025; Rossi, 2025). Lesions with an erosive pattern, topography in high-risk sites, especially lateral and ventral to the tongue, persistence despite treatment, and changes in morphology are clinical signs that raise suspicion and indicate the need for diagnostic biopsy and more intensive follow-up (González-Ruiz *et al*., 2025; Rossi, 2025; Maciel *et al.,* 2025).

In histological analysis, the presence of epithelial dysplasia represents the most consistent finding associated with an increased risk of malignant transformation (Keim--Del Pino, Ramos-García, González-Moles, 2024; Maciel *et al.,* 2025). In addition, cytological changes, such as nuclear atypia, suprabasal mitoses, and architectural changes in the parabasal layers, reinforce this concern. However, the chronic inflammation characteristic of LPO can generate reactive changes that mimic true dysplasia, making interpretation more complex and requiring careful evaluation by experienced pathologists (Keim-Del Pino, Ramos-García, González-Moles, 2024; Maciel *et al.,* 2025; Li *et al*., 2023; Holbrook and Ögmundsdóttir, 2022).

The use of molecular biomarkers adds layers of information that can improve the risk stratification of oral lichen planus malignancy. The p53 protein, a product of the TP53 tumor suppressor gene, plays a central role in regulating the cell cycle and maintaining genomic stability. The detection of its accumulation by immunohistochemistry (IHC) and, more conclusively, the identification of mutations in the TP53 gene in certain series suggest the occurrence of genomic instability that may precede malignant transformation (Aziz, Hamad, and Qasim, 2023; Ögmundsdóttir *et al*., 2009). It is important to note, however, that a simple overexpression of p53 by IHC does not imply necessarily in gene mutation or absolutely predicts malignancy (Aziz, Hamad, & Qasim, 2023; Ögmundsdóttir *et al*., 2009; Sanketh *et al*., 2019).

However, when evaluated in conjunction with histological and clinical findings, the presence of p53 increases the suspicion of neoplastic progression. Cohort studies and case series analyses have demonstrated a correlation between elevated p53 expression and lesions that progress to oral squamous cell carcinoma (OSCC), reinforcing the value of this protein as a complementary marker in the surveillance of oral lichen planus (Holbrook and Ögmundsdóttir, 2022; Sanketh *et al*., 2019; Kojima *et al*., 2025; Gupta *et al*., 2023; Lysitsa *et al*., 2008).

The cell proliferation index measured by Ki-67 is another marker with practical utility in OLP. Increased Ki-67 levels have been consistently reported in lesions with dysplasia and in cases that subsequently progressed to carcinoma, when compared to normal oral mucosa or reticular forms without significant changes (Sanketh *et al*., 2019; Gupta *et al*., 2023; Farah, 2021). Thus, Ki-67 represents a quantitative parameter of proliferative activity that, when elevated in association with histological dysplasia, can support clinical decisions for more rigorous follow-up or even early intervention. However, reference values vary between laboratories, and reactive inflammation can interfere with the interpretation of results, reinforcing the need for contextual analysis and methodological standardization (Sanketh *et al.*, 2019; Kojima *et al.*, 2025; Gupta *et al.*, 2023; Farah, 2021; Polizzi *et al.*, 2025).

Investigation of the inflammatory and angiogenic microenvironment also provides relevant information. Increased expression of COX-2 (cyclooxygenase-2) has been associated with erosive forms of LPO and, in some series, with cases that progressed to malignancy, suggesting that chronic inflammatory processes mediated by prostaglandins may promote carcinogenesis (Sanketh *et al.*, 2019; Marabi *et al.*, 2024; Aziz, Hamad, and Qasim, 2023). Similarly, VEGF (vascular endothelial growth factor) indicates angiogenic activation and has been found at higher levels in more severe lesions and in areas with dysplasia, raising the hypothesis that early angiogenesis may create an environment conducive to neoplastic progression. Both COX-2 and VEGF act primarily as indicators of the pro-tumor microenvironment, rather than as direct markers of transformation, and are therefore complementary to proliferation markers and genetic alterations (Sanketh *et al.*, 2019; Marabi *et al.*, 2024; Aziz, Hamad, & Qasim, 2023).

The advent of sequencing techniques has enabled the detection of mutations typical of oral tumors already in pre-neoplastic stages. Genes frequently implicated in OCEC, such as TP53, NOTCH1, CDKN2A, PIK3CA, and HRAS, may exhibit variants in mucosal tissues considered potentially malignant; the detection of these molecular findings in OLP indicates that driver alterations may precede clinically evident transformation (Holbrook and Ögmundsdóttir, 2022; Farah, 2021; Ögmundsdóttir *et al.*, 2009). Thus, genetic analysis by targeted panels may be particularly useful in lesions with persistent dysplasia, clinical change, or recurrence after treatment, as the presence of mutations lowers the safety threshold and may guide approaches such as wider excision or intensified follow-up (Holbrook and Ögmundsdóttir, 2022; Farah, 2021; Ögmundsdóttir *et al.*, 2009). Despite this, the presence of a mutation does not irrevocably determine progression to cancer; interpretation requires consideration of the mutational burden, mutation type, and clinical-histological context (Holbrook and Ögmundsdóttir, 2022; Farah, 2021; Ögmundsdóttir *et al.*, 2009).

In parallel with somatic mutations, post-transcriptional regulators have also been highlighted.Genetic alterations that confer a proliferative advantage to cells, allowing them to escape normal cell cycle control mechanisms, are common in tumor suppressor genes (e.g., TP53 and CDKN2A) and proto-oncogenes (such as PIK3CA, HRAS, NOTCH1) (Polizzi *et al.*, 2025). In recent decades, microRNAs (miRNAs) have emerged as potential non-invasive biomarkers and relevant regulatory mechanisms in oral carcinogenesis (Polizzi *et al.*, 2025). Altered profiles of miR-21, miR-125b, and miR-203 have been described in both OPL and oral carcinoma, with associations between altered levels and markers of proliferation (Polizzi *et al.*, 2025; Ögmundsdóttir *et al.*, 2009). The great potential advantage of miRNAs is the possibility of detection in non-invasive fluids, especially saliva, which facilitates longitudinal monitoring (Polizzi *et al.*, 2025). However, methodological heterogeneity and the absence of large validated prospective cohorts currently limit the routine use of miRNAs in clinical practice; for now, they remain a promising tool in translational research (Polizzi *et al.*, 2025; Ögmundsdóttir *et al.*, 2009).

In centers with access to molecular testing, gene mutation testing may be considered in cases of persistent dysplasia or progressive clinical changes, helping to define therapeutic approaches (Rossi, 2025; Polizzi *et al.*, 2025; Ögmundsdóttir *et al.*, 2009; Aziz, Hamad, and Qasim, 2023). Salivary microRNA (miRNA) assessment

Biomarker	Current Evidence	What It Suggests Clinically	Main Limitations	Where It Fits Today
p53 (IHC – Immunohistochemistry)	Moderate	Possible genomic instability	Increased expression does not always indicate mutation	Complement to histological evaluation
Ki-67	Moderate	Increased cell proliferation	No universal *cut-off*	Useful in LPO with dysplasia
COX-2 (Cyclooxygenase-2)	Low–moderate	Pro-inflammatory/pro-tumor microenvironment	Inflammation may generate false positives	Complementary in erosive lesions
VEGF (Vascular Endothelial Growth Factor)	Low–moderate	Angiogenic activation associated with severity	Methodological heterogeneity between studies	Additional support in selected cases
TP53 / NOTCH1 / CDKN2A / PIK3CA / HRAS mutations	Moderate (mainly in a research context)	Presence of *driver* mutations may reduce the safety threshold for malignant transformation	Limited availability and high cost	Reference centers / translational research
salivary miRNAs (e.g., miR-21, miR--125b, miR-203)	Low	Possible non-invasive monitoring	Lack of prospective validation and standardization	Promising, but not yet clinically applicable

Table 2: Main Biomarkers

Source: author

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is emerging as a promising tool for non-invasive surveillance; however, its use should be restricted to research protocols for the time being, until validated analytical standards and clinical thresholds are established (Rossi, 2025; Polizzi *et al.*, 2025; Ögmundsdóttir *et al.*, 2009; Aziz, Hamad, & Qasim, 2023).

There is also a need for diagnostic standardization between LPO and reactive lichenoid lesions, as well as prospective cohorts with serial collection of tissue and salivary samples, in addition to multicenter validation of integrated molecular panels (González-Moles and Ramos-García, 2024; Keim-Del Pino, Ramos-García, González--Moles, 2024; Tampa et al., 2018; Sanketh et al., 2019; Polizzi et al., 2025; Mitbander *et al.*, 2025). These efforts are essential for the transition from associative observations to robust predictive models capable of guiding surveillance and clinical decision-making. Until this scenario materializes, the practical recommendation is to use biomarkers as complementary tools within a well-founded clinical and histopathological strategy, avoiding radical therapeutic decisions based on isolated markers (González-Moles and Ramos-García, 2024; Keim-Del Pino, Ramos-García, González-Moles, 2024; Tampa et al., 2018; Sanketh et al., 2019; Polizzi et al., 2025; Mitbander *et al.*, 2025).

In this context, and with the aim of objectively organizing the current state of knowledge, Table 2 presents a summary of the main biomarkers investigated at the LPO for their potential for malignant transformation. It brings together the level of evidence available for each marker, its main scientific contributions, the methodological limitations that still restrict its clinical applicability, and the positioning of each one within the translational spectrum.

Given this set of evidence, the most appropriate clinical approach involves a multimodal and individualized approach. Patients with oral lichen planus (OLP) should undergo detailed clinical evaluation, including photographic documentation and accurate mapping of lesions. Biopsy is indicated in cases of suspicious clinical changes, persistent lesions, or lack of response to treatment. In addition to conventional histopathological examination, the application of an immunohistochemical panel covering Ki-67 and p53 can add value to risk stratification, while COX-2 and VEGF analysis can be useful for understanding the inflammatory microenvironment, especially in research contexts.

Advanced Approaches to Biomolecular Diagnosis and Monitoring

Advances in biomedical technologies have driven the development of non-invasive diagnostic techniques and the discovery of biomarkers capable of detecting diseases in their early stages with high accuracy. Clinical diagnosis is usually based on invasive methods, such as tissue biopsies, which involve risks and discomfort for the patient. In this sense, it brings to light the concept of non-invasive biomarkers, detected in simple biological samples (blood, saliva, urine, or even exhaled air) that are capable of reflecting specific pathophysiological states (Dongiovanni et al., 2023). These advances are promoted by sectors such as genomics, proteomics, metabolomics, and Artificial Intelligence (AI), with the ability to integra-

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te large amounts of data and increase diagnostic accuracy (Khalifa et al., 2024).

Saliva stands out as a biological fluid with high diagnostic potential, reflecting systemic metabolic processes and can be collected simply and painlessly (Dongiovanni et al., 2023). Recent studies have found proteins, metabolites, microRNA, and DNA fragments in saliva associated with diseases such as head and neck cancer, diabetes, and neurodegenerative diseases (Zhao et al., 2025).

Metabolomic studies indicate that the profile of salivary metabolites may be indicative of the concentration and oxidative stress in the patient's mouth and thus serve as a tool for early diagnosis and therapy monitoring (Zhao et al., 2025). Similarly, urinary biomarkers have been used for renal, hepatic, and neoplastic diseases, given the higher concentration of metabolites and RNA present in them (Zakari et al., 2024).

Liquid biopsy is one of the most promising non-invasive diagnostic methodologies and has the ability to detect circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), as well as exosomes in plasma (Ma et al., 2024). According to Parums (2025), ctDNA provides information on somatic mutations and treatment resistance, which are detected by sensitive techniques such as digital PCR and next-generation sequencing (NGS). Methylation of ctDNA is especially interesting as a biomarker, since it does not require prior sample preparation and has high specificity and stability in plasma (Li et al., 2024). This approach has proven effective in population growth, colon, and breast cancer, allowing for the tracking and monitoring of treatment response (Ma et al., 2024; Li et al., 2024).

The incorporation of such biomarkers into portable platforms and point-of-care (POC) devices should revolutionize population screening by reducing costs and increasing access to diagnosis (Celec, 2025). In medicine, Khalifa et al., 2024, claim that the set of AIs studied improved the sensitivity of medical imaging in detecting anomalies and also made it possible to correlate imaging findings with molecular profiles. In addition, AI is being used to discover new biomarkers from data generated from omics studies (genomic, proteomic, and metabolomic data), enabling a precision medicine approach (Alum et al., 2025). With this multiomics, it is possible to correlate various biological levels, such as DNA and metabolites, with clinical phenotypes, increasing diagnostic and prognostic power (Cai et al., 2025).

Despite significant advances, technical obstacles remain, such as the low concentration of ctDNA in the early stages of the disease and the need for standardization of analyses, although the development of ultra-sensitive platforms ultrasensitive tests and the use of AI are increasing the reliability and reducing the costs of these tests (Cai et al., 2025). In addition, ethical and regulatory challenges continue to limit their clinical application, especially with regard to the reproducibility and practical validation of the algorithms used (Alum et al., 2025).

Operational Limitations and Implementation Difficulties

The molecular overlap between chronic inflammatory processes and pre-neoplastic changes makes it difficult to identify biomarkers capable of differentiating LPO from precursor lesions or malignant transformations into oral squamous cell carcinomas, which represents a challenge of great clinical relevance. Recent studies have shown that both LPO and early neoplastic lesions have similar cell proliferation pathways, keratinization changes, and immune responses, which reduces the specificity of numerous proposed targets. This similarity makes it difficult to detect unique characteristics that can differentiate active chronic inflammation of LPO from initial malignant transformations (De Lanna et al., 2022).

Other critical obstacles are the lack of standardization in the procedures for collecting materials to be examined (biopsy, saliva, gingival crevicular fluid, and plasma), packaging, and analytical platforms (immunoassays, digital PCR, sequencing, proteomics). Disparate protocols generate technical variability that translates into inconsistent results between groups and makes it impossible to define validated diagnostic cutoff values for differentiating LPO vs. initiated malignant lesions. In addition, the use of different clinical-pathological criteria to classify LPO and lesions suggested or confirmed as dysplastic intensifies this variability, increasing the heterogeneity of findings (Li et al., 2024).

The high costs and specialized infrastructure required to perform highly sensitive tests, such as sequencing, high-resolution proteomics, or multiomic panels, limit their application in clinical practice, especially in primary care services or centers with resource constraints. Despite technological advances in point-of-care devices based on oral fluid, their ability to distinguish chronic inflammatory processes from malignant transformation is still incipient and often dependent on complementary histology and imaging analyses. Translation into clinical practice requires validation oral fluid, their ability to distinguish chronic inflammatory processes from malignant transformation is still incipient and often dependent on complementary histology and imaging analyses. Translation to the office setting requires regulatory validation, quality control, and costs that are currently significant barriers (Balapure et al., 2024).

Large-scale validation remains incomplete. There are many studies related to markers of malignant transformation of LPO (e.g., p53, Ki-67, MMPs, miRNAs, circRNAs), which are based on smaller samples, without any clinical standardization or sufficient longitudinal follow-up to calculate sensitivity/specificity and predictive values in different populations. In the absence of multicenter, prospective studies evaluating biomolecular signatures in patients with LPO over time, it is not yet possible to establish reliable clinical rules for decision-making, such as indicating biopsy, defining follow-up, or instituting treatment (Ghazi; Khorasanchi, 2021).

Specific confounding factors:

An important set of confounders are medications and comorbidities. The use of systemic or topical corticosteroids, used in the management of autoimmune diseases, and systemic therapies for other conditions can attenuate or modulate the inflammatory response of the local immune system, modifying the levels of cytokines, chemokines, and metabolites used as biomarkers. Systemic inflammatory or metabolic diseases, such as diabetes and autoimmune conditions, can modify the inflammatory and oxidative background of the oral cavity. As a result, some biomarkers become less speci-

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fic in indicating malignant transformation in OHL, since their molecular signals overlap with underlying systemic inflammation (Manchanda et al., 2024).

Smoking, alcohol consumption, poor oral hygiene, co-infections (HPV virus, Epstein-Barr virus), and oral microbiome, which are local factors, strongly influence specific proteomic and metabolomic profiles. Smoking, for example, modifies the expression of MMPs and cytokines; viral co-infections can elevate markers associated with cell proliferation; and changes in the microbiome alter detectable metabolites in saliva/plasma. These elements introduce variability that needs to be controlled in validation protocols, under penalty of false positives/negatives in the distinction between LPO and malignant lesions (Vats et al., 2024).

Demographic variations (age, sex, ethnicity) and differences in the clinical-pathological criteria used to define "transformation" or dysplasia are additional confounders that impact the generalizability of biomarkers. Studies that do not adequately stratify for these variables or that do not apply standardized diagnostic criteria present results that are difficult to replicate. Thus, analyses that combine multiple markers, integrated panels with clinical and imaging data, seem to be the most promi-

Biomarker/ Technology	TRL (Maturity Level)	Predominant Evidence	Current Status
Salivary miRNAs (e.g., miR-21, miR-203, miR-125b)	3–4	Exploratory and case-control studies, without large cohorts	Initial translational proof of concept
Salivary metabolomics	4–5	Observational studies comparing healthy controls	In transition to clinical validation
ctDNA methylation	5–6	Prospective studies in other neoplasms; initial extrapolation to LPO	Promising potential for serial monitoring
Integrated multiomic panels	3–4	Heterogeneous literature, low methodological standardization	Application still predominantly experimental
AI-based predictive models	2–3	Preliminary models, without external validation, low applicability	Preclinical phase, not implementable in clinical routine

TRL legend:

TRL 1–3 = exploratory preclinical phase

TRL 4–6 = initial validation with potential for transition to applied use

TRL ≥7 = consolidated application (no non-invasive biomarker has reached this level in the context of LPO)

Table 3: Translational readiness levels (TRL) of the main noninvasive biomarkers evaluated for risk stratification in LPO.

Source: author

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sing approach to mitigate these effects, although they require much more data and validation (Pomella et al., 2024).

Technological, ethical, and implementation limitations:

From a technological standpoint, the integration of multiomics (genomics, transcriptomics, proteomics, metabolomics) requires robust and standardized bioinformatics pipelines, which are still lacking in many centers, and creates challenges for clinical interpretation. Ethically, the use of biomarkers with low specificity can lead to unnecessary biopsies, patient anxiety, and healthcare system overload; on the other hand, sensitivity failures delay diagnosis. Such issues need to be considered when defining clinical thresholds and decision algorithms (Hu *et al.*, 2025).

Finally, translation into clinical practice requires interdisciplinary guidelines (oral dermatology, oral pathology, oncology, dentistry) and regulatory efforts that define when and how biomarkers should influence decisions (e.g., biopsy indication, follow-up frequency). Without such a framework, there is a risk of fragmented adoption of tests that do not improve, and possibly complicate, patient care. The construction of large prospective cohorts, national registries, and multicenter studies is essential to overcome this bottleneck (Balapure *et al.*, 2024).

Similar to what was observed for tissue markers, non-invasive biomarkers remain concentrated in early or intermediate TRLs. The literature consists mainly of exploratory, heterogeneous studies with little external validation, which limits the extrapolation of findings. None of the approaches evaluated are sufficiently mature for clinical application, indicating that their use should remain restricted to research. These results reinforce the need for large cohorts, standardized methodologies, and multicenter validation for such tools to advance toward clinical practice.

Conclusion

Oral lichen planus stands out among potentially malignant disorders because it represents a chronic inflammatory condition in which persistent immune response, cellular stress, and molecular changes can, in certain contexts, favor carcinogenesis. The difficulty in distinguishing inflammatory changes from early signs of dysplasia still limits diagnostic certainty based solely on morphology.

To date, no single biomarker has demonstrated sufficient capacity to reliably predict malignant transformation. On the other hand, the joint analysis of markers of proliferation, genomic instability, and inflammatory microenvironment, integrated with histopathological findings, may contribute to a more consistent risk stratification. Recent molecular evidence indicates that changes associated with neoplastic transformation pathways may be present in subgroups of patients, even when dysplasia is not evident under the microscope.

Noninvasive methods, especially those based on saliva, broaden the prospects for monitoring, but still lack standardization and clinical validation. Thus, the management of OHL should remain based on a multimodal approach, combining careful clinical evaluation, thorough histological analysis, and judicious use of biomarkers, with a focus on continuous surveillance and early identification of cases at higher risk of malignant transformation.

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