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Review Article

Expression of Different Tumor Biomarkers in Oral Lichen Planus: A Meta-analysis

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Abstract

Background: Oral lichen planus (OLP) is a potentially malignant oral disorder that affects 0.5-2% of the general population with a malignant transformation rate of around 1.1%. Malignant transformation is characterized by the increased proliferation of basal layer cells under the influence of biomarkers released from the inflammatory infiltrate. This study was conducted to assess the expression of biomarkers in OLP and their possible predictive value for malignant transformation of these lesions.

Methods: A search for studies on tumor biomarkers in OLP was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science, and Scopus. Data were analyzed using the statistical software RevMan 5.4 (The Cochrane Collaboration, Oxford, UK). For continuous outcomes, the estimates of effects of an intervention were expressed as mean differences (MD) using the inverse variance (IV) method, and for dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (OR) using Mantel-Haenszel (M-H) method, all with 95% confidence intervals.

Results: A total of 30 studies were included in this meta-analysis. OLP patients compared to controls without the disease had a significantly higher expression of mutated p53 protein ($P<0.001$), Ki-67 antigen ($P<0.001$), p16 protein ($P<0.001$), and cell proliferation nuclear antigen (PCNA) ($P=0.04$), but not blc-2 protein. In contrast, OLP patients showed 3.71 times higher probability of bcl-2 protein detection ($P=0.01$).

Conclusions: The expression of tumor biomarkers in OLP suggests the potentially malignant nature of some of these lesions.

Keywords: Biomarkers, Tumor; Lichen planus, Oral, Mouth, Precancerous conditions

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Introduction

Oral lichen planus (OLP) is a potentially malignant oral disorder characterized by a chronic mucocutaneous inflammatory disease that affects 0.5%-2% of the general population. The age of onset is generally between 30 and 60 years, with greater involvement in the female gender (1). Clinically, OLP has multiple presentations ranging from asymptomatic white keratotic lesions to painful erosions and ulcerations with six distinctive clinical forms including white ones (reticular, papular, plaque) and red ones (erosive, atrophic, and bullous). Histopathologically, it is characterized by hydropic degeneration of basal epithelial cells and a "band" chorionic inflammatory infiltrate (2).

According to a recent study, the malignancy rate of OLP is around 1.1%, with a higher incidence in smokers, drinkers, those infected with the hepatitis C virus, and patients with erosive lesions (3). The average time of transformation of an OLP into an oral squamous cell carcinoma (OSCC) is about 5.5 years (4). OLP patients require periodic monitoring to identify early clinical and/or histopathological signs of malignant transformation to OSCC. Several biomarkers related to OLP have been studied, such as apoptosis modulators (p53 and bcl-2), cell cycle regulators (Ki-67, p16, and PCNA), tissue remodeling factors (MMPs), and inflammatory factors (TNF-α, IL-6, and COX-2). Malignant transformation is characterized by increased proliferation of basal layer cells under the influence of biomarkers released from the inflammatory infiltrate that activate different pathways and can lead to tumor development (5). This study aimed to assess the expression of tumor biomarkers in OLP and its possible predictive value for malignant transformation of these lesions.

Materials and Methods

The two authors (ARA and BHP) independently carried out all research steps (search, study selection, data extraction, and evaluation). Subsequently, they jointly agreed on the articles to include in this study.

A search for studies on tumor biomarkers and OLP up to October 2021 was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Scopus. Search strategies were developed for each database combining Medical Subjects Headings (MeSH) and free-text terms. The search terms were as follows: ("ki 67 antigen"[MeSH Terms] OR "tumor suppressor protein p53"[MeSH Terms] OR "proliferating cell nuclear antigen"[MeSH Terms] OR "genes, p16"[MeSH Terms] OR "bcl-2" OR "biomarkers, tumor"[MeSH Terms]) AND "lichen planus, oral"[MeSH Terms]; ("ki 67" OR "p53" OR "PCNA" OR "bcl-2") AND "oral lichen planus"; TITLE-ABS-KEY (("ki 67" OR "p53" OR "PCNA" OR "bcl-2") AND "oral lichen planus"). Articles with a relevant risk of bias (score <6 points based on the Newcastle-Ottawa methodological quality assessment scale) (6), articles without full-text availability, articles without a healthy control group, studies without clinical data, and studies with non-usable data were excluded from the study.

Assessment of Methodological Quality

The methodological quality of the studies included in this manuscript was determined using the Newcastle-Ottawa methodological quality assessment scale consisting of eight items that evaluate three dimensions (selection, comparability, and exposure) (6). According to the score obtained, the studies are classified as high quality (≥7 points), moderate quality (4-6 points), and low quality (1-3 points).

Statistical Analysis

For the meta-analysis, the data were processed using RevMan 5.4 software (The Cochrane Collaboration, Oxford, UK). For continuous outcomes, the inverse of the variance (IV) for the mean difference (MD) was used, and for dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel chi-square formula (M-H) was used, both with 95% confidence intervals (95% CI). Heterogeneity was determined according to the Higgins statistic (I^2). In case of high heterogeneity (I^2>50%), the random-effects model was applied. P<0.05 was considered the minimum level of significance. In addition, the MedCalc Statistical Software version 20.019 (MedCalc Software Ltd. Ostend, Belgium) was used to estimate publication bias through funnel plots and the Egger test, with a significance value of P<0.1.

Results

In the initial search, 408 articles were found (125 in PubMed, 166 in WoS, and 117 in Scopus), 122 of which were duplicates, leaving 286 articles for eligibility. There were no restrictions on language or publication date. The exclusion criteria were: (a) articles with a relevant risk of bias (<6 points) according to the Newcastle-Ottawa methodological quality assessment scale (6) (n=82), (b) articles without full-text availability (n=61), (c) articles without a healthy control group (n=46), (d) studies without clinical data (n=14), and (e) studies with non-usable data (n=53). Finally, 30 articles were included in this meta-analysis (Figure 1).

Table 1 presents the main reporting characteristics and the methodological quality of the 30 studies included in this meta-analysis according to the NOS scale (7-36). A total of 1247 individuals, 831 patients (66.6%) with OLP, and 416 (33.4%) healthy controls were included in these articles. Among OLP patients, 62.8% were female and 37.2% were male, and among controls without the disease, 52.2% were female and 47.8% were male. Considering the Newcastle-Ottawa (NOS) quality scale (6), 20 articles (66.7%) had 6 points, 9 articles (30.0%) got 7 points, and 1 article (3.3%) reached 8 points.

The analysis of various tumor biomarkers concentrations in OLP patients versus. controls without the disease is shown in Table 2.

Nine studies (11,12,17,19-21,26,28,35) analyzed the

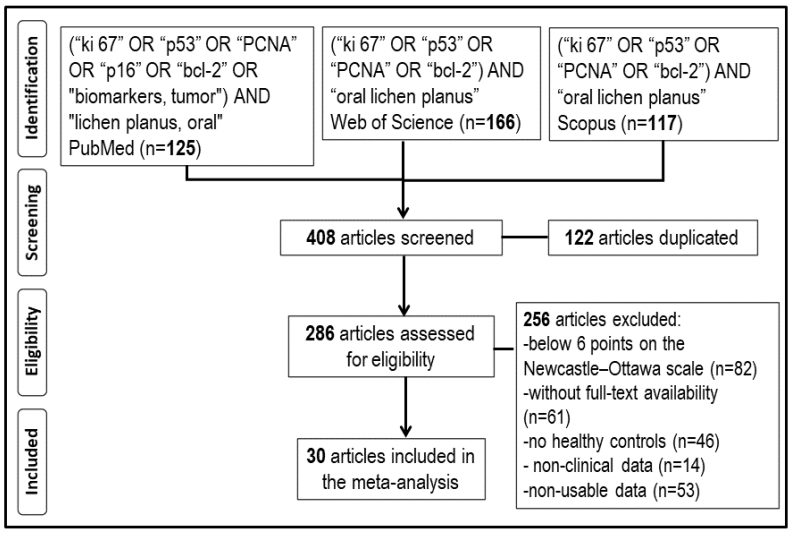

Figure 1. Study Selection Flowchart.

Table 1. Reporting Characteristics and Methodological Quality Evaluation of the 30 Studies Included in this Meta-analysis

Study	Year	Country	Study Population	Detection Method	Tumor Biomarker	NOS
Schifter (7)	1998	Australia	46 OLP (12M, 34F, 56y) 18 Cont (9M, 9F, 59y)	IMH	p53	7
Bloor (8)	1999	UK	36 OLP (na, na, na) 8 Cont (na, na, na)	IMH	Ki-67, bcl-2	6
da Silva Fonseca (9)	2001	Brazil	20 OLP (7M, 13F, 43y) 20 Cont (7M, 13F, 43y)	IMH	PCNA	6
Garcia-Pola (10)	2001	Spain	10 OLP (4M, 6F, 58y) 10 Cont (5M, 5F, 56y)	IMH	Ki-67	6
Valente (11)	2001	Italy	15 OLP (10M, 5F, 57y) 7 Cont (na, na, na)	IMH	p53	6
Hirota (12)	2002	Japan	19 OLP (6M, 13F, 57y) 10 Cont (na, na, na)	IMH	Ki-67, p53, p21	6
Ogmundsdottir (13)	2002	Iceland	48 OLP (na, na, na) 10 Cont (na, na, na)	IMH	p53	7
Sklavounou-Andrikopoulou (14)	2004	Greece	26 OLP (8M, 18F, 57y) 26 Cont (11M, 15F, 47y)	ELISA	bcl-2	7
Lee (15)	2005	Taiwan	56 OLP (26M, 30F, 48y) 20 Cont (na, na, na)	IMH	PCNA, p53	7
González-Moles (16)	2006	Spain	51 OLP (18M, 33F, 55y) 26 Cont (13M, 13F, 55y)	IMH	Ki-67, p53, p21, bcl-2	7
Montebugnoli (17)	2006	Italy	30 OLP (13M, 17F, 53y) 9 Cont (4M, 5F, 53y)	IMH	Ki-67, p53	6
Abdel-Latif (18)	2009	Egypt	25 OLP (16M, 9F, 45y) 10 Cont (na, na, na)	IMH	bcl-2	6
Agha-Hosseini (19)	2009	Iran	44 OLP (17M, 27F, 46y) 30 Cont (12M, 18F, 44y)	IMH	Ki-67, p53	7
Freitas (20)	2010	Brazil	7 OLP (na, na, na) 7 Cont (na, na, na)	IMH	PCNA, p53, bcl-2	6
Safadi (21)	2010	Jordan	18 OLP (8M, 10F, 48y) 10 Cont (5M, 5F, 47y)	IMH	p53, p21	7
Poomsawat (22)	2011	Thailand	23 OLP (6M, 17F, na) 10 Cont (4M, 6F, na)	IMH	p16	6
Leyva-Huerta (23)	2012	Mexico	21 OLP (5M, 16F, 56y) 4 Cont (na, na, na)	IMH	p53, bcl-2	6
Dang (24)	2013	China	20 OLP (8M, 12F, 49y) 10 Cont (5M, 5F, 28y)	PCR	p16	6
Zargaran (25)	2013	Iran	16 OLP (1M, 15F, 38y) 17 Cont (13M, 4F, 46y)	IMH	Ki-67	6
Al-Azzawi (26)	2014	Iraq	21 OLP (na, na, na) 10 Cont (na, na, na)	IMH	PCNA, p53	6
Salehinejad (27)	2014	Iran	15 OLP (na, na, na) 8 Cont (na, na, na)	IMH	p16	6
Agha-Hosseini (28)	2015	Iran	34 OLP (15M, 19F, na) 41 Cont (19M, 22F, na)	ELISA	p53	7
Kumar (29)	2015	India	20 OLP (na, na, na) 20 Cont (na, na, na)	IMH	Ki-67	6
Pigatti (30)	2015	Brazil	14 OLP (na, na, na) 9 Cont (na, na, na)	IMH	Ki-67, bcl-2	6
Basheer (31)	2017	India	10 OLP (na, na, na) 10 Cont (na, na, na)	IMH	p53	6
Hadzi-Mihailovic (32)	2017	Serbia	40 OLP (12M, 28F, 58y) 13 Cont (6M, 7F, na)	IMH	p53	7
Danielsson (33)	2018	Sweden	79 OLP (26M, 54F, 57y) 15 Cont (9M, 6F, 46y)	IMH	p16	8
Shimada (34)	2018	Japan	20 OLP (na, na, 50y) 5 Cont (na, na, 60y)	IMH	Ki-67	6
Shiva (35)	2018	Iran	32 OLP (15M, 17F, 46y) 8 Cont (na, na, na)	IMH	p53	6
Beevi (36)	2019	India	15 OLP (na, na, na) 15 Cont (na, na, na)	IMH	Ki-67	6

OLP: oral lichen planus patients; Cont: healthy controls; M: male; F: female; y: mean age in years; na: not available; IMH: immunohistochemistry; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; PCNA: proliferating cell nuclear antigen; NOS: Newcastle-Ottawa methodological quality scale

Table 2. Analysis of Various Tumor Biomarkers Concentrations in Oral Lichen Planus Patients vs. Controls Without the Disease

Tumor Biomarker	References	Value	MD	(95% CI)	I^2(%)	*P* Value
p53	(11,12,17,19-21,26,28,35)	OLP	14.17	(7.96 to 20.39)	96%	<0.001*
Ki-67	(8,10-12,17,19,25,29,36)	OLP	17.32	(11.37 to 23.27)	95%	<0.001*
PCNA	(9,15,20,26)	OLP	13.98	(0.75 to 27.22)	98%	0.040*
bcl-2	(14,18,20)	OLP	0.02	(-0.04 to 0.07)	0%	0.560

PCNA: proliferating cell nuclear antigen; MD: mean difference; CI: confidence interval; I^2(%): Higgins statistic for heterogeneity (percentage); *Statistically significant.

percentage of positivity for p53, indicating that OLP patients had 14.17% higher positivity, with a highly statistically significant relationship (MD=14.17; 95% CI: 7.96 to 20.39; *P*<0.001).

Nine studies (8,10-12,17,19,25,29,36) examined the percentage of Ki-67 antigen-positive cells. Positivity for Ki-67 increased by 17.32% in OLP patients, with highly statistically significant differences (MD=17.32; 95% CI: 11.37 to 23.27; *P*<0.001).

Four studies (9,15,20,26) quantified the percentage of proliferating cell nuclear antigen (PCNA) positivity, with 13.98% higher PCNA positivity in OLP patients and a statistically significant relationship (MD=13.98; 95% CI%: 0.75 to 27.22; *P*=0.040).

Three studies (14,18,20) determined the bcl-2 protein levels, without observing variations between the two population groups. The statistical analysis did not show significant differences (MD=0.02; 95% CI: -0.04 to 0.07; *P*=0.560).

Table 3 exhibits the odds ratios for several tumor biomarkers expression in subjects with and without OLP.

Eight studies (7,13,15,16,23,31,32,35) evaluated the p53 protein expression in 2 groups, finding that OLP patients were 5.73 times more likely to express p53 compared to controls, with a highly statistically significant association (OR=5.73; 95% CI: 3.44 to 9.54; *P*<0.001).

Three other studies (15,30,34) investigated the Ki-67 antigen expression, showing that OLP patients were 10.59 times more likely to express Ki-67 in their lesions. In the statistical analysis, a significant relationship was found (OR=10.59; 95% CI: 1.23 to 91.33; *P*=0.030).

Four studies (22,24,27,33) estimated the p16 protein expression, indicating an increase of 18.48-fold in the likelihood of p16 expression in OLP patients compared to controls. Based on statistical analysis, highly significant differences were found (OR=18.48; 95% CI: 4.87 to 70.03; *P*<0.001).

Three other studies (16,18,30) assessed the bcl-2 protein expression, verifying a 3.71-fold increase in the probability of blc-2 expression in OLP patients, with a highly statistically significant association (OR=3.71; 95% CI: 1.29 to 10.65; *P*=0.010).

The evaluation of publication bias for p53 protein, Ki-67 antigen, bcl-2 protein, and PCNA is shown in Figure 2. The visual inspection of funnel plots displays some asymmetry for p53 and PCNA with probable publication bias, but not for Ki-67 and bcl-2. At the same time, based on the results of Egger's test, there was some publication bias for p53 (t=7.80, *P*=0.04) and PCNA (t=-8.24, *P*=0.02); however, no publication bias was detected for Ki-67 (t=5.96, *P*=0.13) and bcl-2 (t=-1.59, *P*=0.34).

Discussion

In the present meta-analysis on the expression of tumor biomarkers in OLP, data from 30 studies were included.

The TP53 gene, called the "genome guardian", encodes the tumor suppressor protein p53. This protein performs important functions such as the arrest of cell division (senescence), the induction of programmed cell death (apoptosis), or the DNA repair in mutated cells. Protein p53 activation after DNA damage or oncogenic signaling is an important protective mechanism, facilitating DNA repair and stimulating the apoptosis of damaged cells. Functional loss and altered expression of the p53 protein are the most common genetic changes (mutations) found in human cancers (28).

In this study, OLP patients showed 14.17% higher positivity for p53 than controls, with a highly statistically significant relationship (*P*<0.001). Nine studies (11,12,17,19-21,26,28,35) that evaluated the percentage of p53 positivity indicated the highest percentage of expression of this protein in OLP patients. Likewise, these patients were 5.73 times more likely to express p53 compared to controls, with a highly statistically significant association (*P*<0.001). All the studies (7,13,15,16,23,31,32,35) that analyzed this protein confirmed this higher detection of p53 in cases of OLP. This increased p53 expression may be due to the cellular immune response that develops in OLP, inducing epithelial dysplastic changes (28). González-Moles et al (16) suggested that, in OLP, p53 overexpression

Table 3. Odds Ratios and 95% Confidence Intervals for Several Tumor Biomarkers Expression in Subjects With and Without Oral Lichen Planus

Tumor biomarker	References	Value	OR	(95% CI)	I^2(%)	*P* Value
p53	(7,13,15,16,23,31,32,35)	OLP	5.73	(3.44 to 9.54)	0%	<0.001*
Ki-67	(15,30,34)	OLP	10.59	(1.23 to 91.33)	70%	0.030*
p16	(22,24,27,33)	OLP	18.48	(4.87 to 70.03)	0%	<0.001*
bcl-2	(16,18,30)	OLP	3.71	(1.29 to 10.65)	0%	0.010*

PCNA: proliferating cell nuclear antigen; OR: odds ratio; CI: Confidence interval; I^2(%): Higgins statistic for heterogeneity (percentage); *Statistically significant.

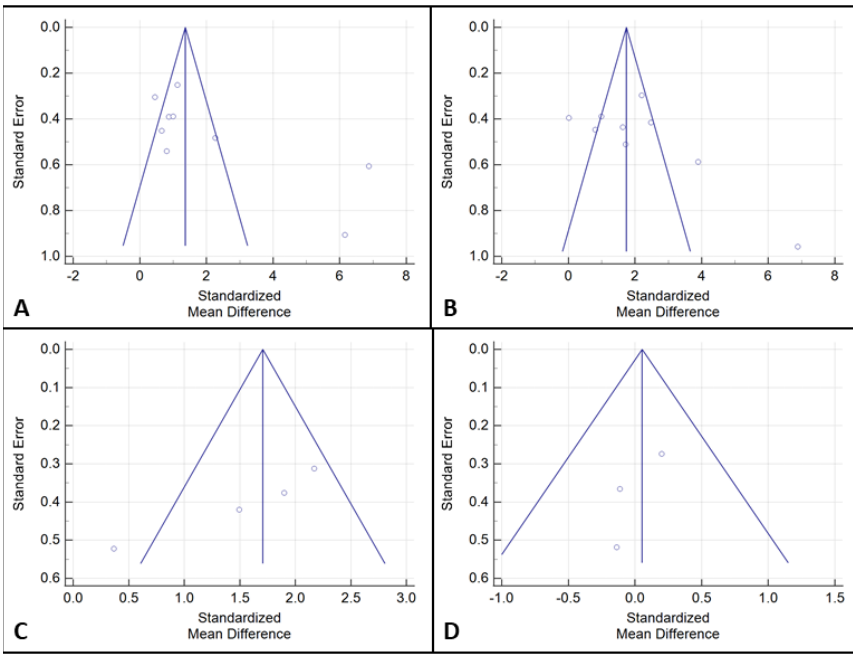

Figure 2. Funnel Plots for Publication Bias Assessment of the Levels of p53 Protein (A), Ki-67 Antigen (B), bcl-2 Protein (C), and PCNA (D) in OLP Patients

would act mainly by arresting the cell cycle to induce DNA repair in cells mutated in these lesions.

The Ki-67 antigen is an immunohistochemical marker of cell proliferation expressed in the G2 and M phases of cell division, being a biological marker of mitotic activity. The positivity for the Ki-67 antigen is correlated with the clinical course of the disease, providing relevant information on the worst biological behavior and the higher probability of malignancy for the lesions (36). In the present study, OLP patients presented 17.32% higher positivity for the Ki-67 antigen compared to controls. Based on statistical analysis, highly significant differences were found (P<0.001). Nine studies (8,10-12,17,19,25,29,36) that assessed positivity for Ki-67 are in agreement with this finding. It was also observed that OLP patients were 10.59 times more likely to express Ki-67 in their lesions, with a statistically significant association (P=0.030). All the studies (15,30,34) that examined the Ki-67 antigen expression confirmed this increased risk of Ki-67 detection in OLP lesions. The increase in the expression of Ki-67 antigen in OLP patients would be correlated with the proliferative activity and the degree of dysplasia of the epithelial cells, suggesting a more active biological behavior of these lesions (29).

PCNA is a cofactor of DNA polymerase-delta that participates in DNA synthesis during the S phase of the cell cycle and its detection is used to evaluate the degree of cell proliferation (26). In this study, OLP patients showed 13.98% more positivity for PCNA, indicating statistically significant differences (P=0.040). Four studies (9,15,20,26) that investigated this antigen confirmed this higher expression in OLP lesions. The increase in PCNA positivity is suggestive of an alteration in the cell differentiation mechanism and may also be related to the presence of growth factors in OLP induced by the chronic inflammation seen in this disease (26).

The p16 protein is the product of the CDKN2 gene located on chromosome 9p21 and plays a crucial role in cell cycle regulation. This protein prevents the association of CDK4/CDK6 with cyclin D which, in turn, prevents the phosphorylation of important substrates in the G1 phase of the cell cycle, resulting in the inhibition of cell proliferation. Overexpression of p16 is a common occurrence in potentially malignant and malignant oral lesions (33). In the present meta-analysis, OLP patients had 18.48 times higher risk of p16 protein detection, with a highly statistically significant relationship (P<0.001). All studies (22,24,27,33) that analyzed this protein indicated a higher detection rate of p16 in OLP lesions. The increase in the p16 protein expression could be explained by the increase in the release of pro-inflammatory cytokines such as IFN-γ or TNF-α in OLP patients since these mediators are related to increased p16 expression (33).

Several proteins of the Bcl gene family are involved in the regulation of programmed cell death either by preventing apoptosis (Bcl-2, Bcl-xL, Bcl-w, Mcl-I) or promoting apoptosis (Bax, Bik, Bak, Bad, Bcl-xs). Because many of these proteins are co-expressed in the same cells, the ratio of anti-apoptotic to pro-apoptotic proteins determines the inherent susceptibility of a given cell to respond to apoptotic signals. The absence or low rate of apoptosis observed in OLP could be the consequence of antiapoptotic actions exerted by the bcl-2 protein on basal cells (18).

OLP patients had slightly higher levels of bcl-2 protein expression than controls, although statistical significance was not reached (P=0.560). Three studies (14,18,20) that focused on bcl-2 found no conclusive results. In contrast, OLP patients had 3.71 times higher probability of expressing this protein compared to controls, with a statistically significant association (P=0.010). Three

studies (16,18,30) that investigated the bcl-2 expression in OLP patients showed a higher probability of detection in these patients. The bcl-2 protein seems not to be directly involved in the epithelial changes that occur in OLP, since keratinocytes do not show immunoreactivity for this protein (14). On other occasions, bcl-2 could be conjugated with other proteins such as bax, bad, or bcl-xL, making its detection difficult (20). On the contrary, overexpression of p16 protein has been observed in the inflammatory infiltrates, inhibiting the apoptosis of the lymphocytes and promoting the band-like inflammatory cells infiltrate, distinctive of OLP (22).

This study presents some limitations. First, the results of this meta-analysis should be interpreted with caution due to the high heterogeneity observed in some comparisons. Second, some studies did not allow an adequate assessment of the clinical type of OLP or its severity. In others, there was a lack of data on the population characteristics (age and gender) or the time of disease evolution. Third, the use of different detection methods for biomarkers could have influenced the results.

New studies are required to delve into the degree of implication of these tumor biomarkers in the biological behavior and prognosis of OLP, a common potentially malignant oral disorder.

Conclusion

In this meta-analysis, OLP patients compared to controls without the disease had a significantly higher expression of the mutated p53 protein (P<0.001), Ki-67 antigen (P<0.001), p16 protein (P<0.001), and cell proliferation nuclear antigen (PCNA) (P=0.040), but not blc-2 protein. In contrast, OLP patients had 3.71 times higher probability of bcl-2 protein detection (P=0.010).

Authors' Contribution

ARA and BHP contributed equally to the study design, data collection, data analysis, and manuscript preparation. Both approved the final version.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

Not applicable.

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