# Risk Factors for Malignant Transformation of Oral Lichen Planus

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## Abstract

We aimed to identify factors for malignant transformation of oral lichen planus to oral cancer in order to inform the different specialists undertaking their clinical management. A retrospective cohort of biopsy-confirmed oral lichen planus consecutively diagnosed in 1995–2014 and followed-up until 2017 was selected. Demographic, clinical and follow-up information was collected. Multivariate Cox proportional-hazards models were performed to evaluate clinical and pathological factors associated with progression to oral cancer. The study included 257 oral lichen planus of which 5.4% progressed to oral cancer. Men and women differed in tobacco and alcohol consumption, and patients with and without described clinical aspect differed in diagnostic period, alcohol consumption and treatment. Alcohol consumption, tongue site, oldest diagnostic period and surgery as a type of treatment were independent prognostic factors for progression.

This large non-selected retrospective cohort of oral lichen planus underscores the existing limitations of the current standard-of-care of such lesions. Well-designed, robust prospective studies and multidisciplinary treatment guidelines are warranted.


## Introduction

Lichen planus (LP) is a mucocutaneous inflammatory disorder potentially affecting skin and/or mucous membranes. The disease has a broad spectrum of clinical manifestations,[1] such as its oral subtype, oral lichen planus (OLP). OLP affects from 1–4% of the worldwide population and is more common among older women.[2] The disease is characterized by a T-cell mediated response against epithelial basal cells, leading to basal cell degeneration and subepithelial band like infiltration by T-lymphocytes.[3] There have been described six clinical forms of OLP: three white forms (reticular, papular, plaque-like), and three red forms (erosive (ulcerated), atrophic (erythematous) and bullous). The most common OLP type is the reticular pattern presenting as fine white striae known as ‘Wickham’s striae’, typically symmetrical and bilateral.[4]

The etiology of OLP is still unknown, but microbiological agents, psychological stress, local and systemic cell-mediated hypersensitivity, and immune response are considered etiopathogenic factors for OLP, among others.[3]

The World Health Organization (WHO) developed in 1978 a OLP diagnostic criteria based on clinical and histopathological standards.[5] These criteria were modified in 2003 with the recommendation that both clinical and histological features should be considered for the diagnosis of an OLP.[6] Later, at a workshop in 2005, WHO suggested the term ‘potentially malignant oral disorders’ (PMOD) for any lesion or condition of the oral mucosa with potential for malignant transformation, including OLP.[7]

Oral squamous cell carcinoma (OSCC) accounts for 90% of all oral cancers and is the most common head and neck cancer. Since the first report of OLP malignant transformation to OSCC was published in 1910,[8] several studies have showed different rates of OLP malignant transformation, spanning from 0–14.3%.[9] This variability is largely due to the use of heterogeneous inclusion and exclusion criteria.[10,11,12] Some studies also found patients with OLP to be at greater risk of developing OSCC, but more precise and internationally agreed-upon criteria for OLP diagnosis need to be established. Risk factors associated with a significantly greater rate of malignant transformation of OLPs are smoking, alcoholism, hepatitis C virus infection,[9,10] erosive lesions[13] at tongue site[14] and female gender.[1]

This study aimed to identify predictive factors for the malignant transformation of OLP to OSCC in a large, unselected sample of Spanish OLP cases, in order to inform the heterogeneous spectrum of specialists undertaking the clinical management of such lesions.

## Material And Methods

# Study design and samples

The protocols have been described elsewhere.[15] Briefly, a retrospective cohort study of patients consecutively diagnosed with OLP at Bellvitge University Hospital and Odontological University Hospital of Barcelona (Spain) at 1995–2014 with available sociodemographic, clinical and follow-up data was conducted. Patients were treated at dermatology, odontology,maxillofacial

surgery and otolaryngology/plastic surgery departments, and processed, analyzed and reported by the pathology department. The cases were identified and included in the study on the basis of the histopathological instead of the clinical diagnosis because clinical lesions were diagnosed by different medical specialists while the histopathological study was performed centrally in the same pathology department, according to the current guidelines.[5,16] The inclusion criteria included: to have a histopathological diagnosis of OLP located at the tongue, gingiva, floor of the mouth, palate, cheek mucosa or oral cavity not specified and to do not have a previous diagnosis of OSCC or oropharyngeal cancer. External lip lesions were excluded since are more related to chronic sun exposure. Medical records were reviewed for all eligible cases and information on demographics, smoking and alcohol consumption, comorbidities, treatment, and follow-up data was collected up to 2017.

Comorbidities (excluding malignancies) were grouped as follows: cardiovascular diseases; blood, immunological and endocrine disorders; skin disorders; diseases of the respiratory, digestive and genitourinary system; others. OLP's patients Hepatitis C virus (HCV) infection status was not ascertained as it was not indicated in most of the medical records.

Data about topical treatment, surgery, $CO_2$ laser and oral retinoids was collected. When excisional biopsies of the whole lesion were taken and no further treatment was performed, the patients were considered as surgically treated.

The study was performed in agreement with the Declaration of Helsinki and had formal approval on January 23th, 2014 (ref. PR351/13) by the Ethical Committee for Clinical and Epidemiological research of the Hospital of Bellvitge, Catalan Institute of Oncology (ICO), Odontological University Hospital of Barcelona and Hospital of University of Barcelona (*Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge*, L'Hospitalet de Llobregat, Spain). Adequate measures to ensure data protection, patients' privacy and anonymization were taken into account in compliance with European and Spanish current laws and regulations.

## Statistical analyses

Descriptive analyses were performed and differences between OLPs with and without described clinical aspect and between males and females were assessed. Cancer-Free Survival (CFS) was calculated from the date of OLP diagnosis to the date of OSCC diagnosis. Cumulative probability of survival was estimated with Kaplan–Meier analysis. The log-rank test was used to compare different survival curves, and crude (cHR) and adjusted hazard ratios (aHR) and their 95%CI were estimated using proportional hazard regression (Cox) models for CFS. All significant covariates in the univariate analysis were considered in the multivariate analysis. Forward selection of the covariates was used, adding at each step the covariate that best improves the model (significant log-likelihood ratio test and AIC criteria). Statistical significance for all analyses was set at the 2-sided 0.05 level. Data analyses were performed with STATA software v.15.1 (Stata Corp., College Station, TX, USA) and R software.

## Results

A total of 257 OLPs consecutive patients diagnosed from July 21st, 1995 to May 21st, 2014 were included in the study. Baseline demographic and clinical characteristics of the cases, overall and by gender and clinical aspect availability, are presented in Table 1. More than half of the patients (150, 58.4%) were women with a mean age at diagnosis of 59.1 (Standard deviation (SD) = 11.7) years. Most patients were non-drinkers (220 patients, 85.6%) and non-smokers (161 patients, 62.6%). Clinical aspect of the OLP was described for 165 (64.2%) patients and was mostly leukoplakia (144, 56%). Previous neoplasia different from head and neck cancer or non-melanoma skin cancer was diagnosed for 11 patients (4.3%). The most common comorbidities were respiratory, digestive and/or genitourinary disorders (79 patients, 30.7%) and buccal mucosa was the most common site of the lesion (58.8%). The most performed treatment was topical treatment (102 patients, 32.7%) followed by clinical control (89 patients, 34.6%) and surgery and/or excisional biopsy (52 patients, 20.2%).

Table 1
Sociodemographic and clinical characteristics of OLP patients by gender and by clinical aspect availability

| Characteristic | All OLP | | Gender | | | | | Clinical aspect | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | | Female | | *P*-value[1] | Unknown | | Known | | *P*-value[1] |
| | N | (%) [a] | N | (%) [b] | N | (%) [b] | | N | (%) [b] | N | (%) [b] | |
| **Age at diagnosis** | | | | | | | 0.315[2] | | | | | 0.310[2] |
| Mean (SD) | 59.1 | (11.7) | 58.2 | (11.6) | 59.7 | (11.8) | | 58.0 | (13.2) | 59.7 | (10.7) | |
| Median (Min-Max) | 59.7 | (24.0-86.3) | 59.3 | (25.9–82.8) | 59.9 | (24.0-86.3) | | 58.4 | (24.0-82.8) | 60.1 | (26.4–86.3) | |
| **Gender** | | | | | | | - | | | | | 0.731 |
| Male | 107 | (41.6) | 107 | (100.0) | 0 | (0.0) | | 37 | (34.6) | 70 | (65.4) | |
| Female | 150 | (58.4) | 0 | (0.0) | 150 | (100.0) | | 55 | (36.7) | 95 | (63.3) | |
| **OLP diagnostic date** | | | | | | | 0.322 | | | | | **< 0.001** |
| 1995–1999 | 24 | (9.3) | 11 | (45.8) | 13 | (54.2) | | 17 | (70.8) | 7 | (29.2) | |
| 2000–2004 | 43 | (16.7) | 23 | (53.5) | 20 | (46.5) | | 25 | (58.1) | 18 | (41.9) | |
| 2005–2009 | 108 | (42.0) | 41 | (38.0) | 67 | (62.0) | | 35 | (32.4) | 73 | (67.6) | |
| 2010–2014 | 82 | (31.9) | 32 | (39.0) | 50 | (61.0) | | 15 | (18.3) | 67 | (81.7) | |
| **Alcohol consumption** | | | | | | | **< 0.001** | | | | | **0.033** |
| Never | 220 | (85.6) | 76 | (34.5) | 144 | (65.5) | | 73 | (33.2) | 147 | (66.8) | |
| Ever | 37 | (14.4) | 31 | (83.8) | 6 | (16.2) | | 19 | (51.4) | 18 | (48.6) | |
| **Tobacco consumption** | | | | | | | **< 0.001** | | | | | 0.328 |
| Never | 161 | (62.6) | 44 | (27.3) | 117 | (72.7) | | 54 | (33.5) | 107 | (66.5) | |
| Ever | 96 | (37.4) | 63 | (65.6) | 33 | (34.4) | | 38 | (39.6) | 58 | (60.4) | |
| **Previous Neoplasia** | | | | | | | 0.717 | | | | | 0.968 |
| No | 246 | (95.7) | 103 | (41.9) | 143 | (58.1) | | 88 | (35.8) | 158 | (64.2) | |
| Yes | 11 | (4.3) | 4 | (36.4) | 7 | (63.6) | | 4 | (36.4) | 7 | (63.6) | |
| **Clinical aspect** | | | | | | | 0.362 | | | | | - |
| Erythroplakia | 1 | (0.4) | 1 | (100.0) | 0 | (0.0) | | 0 | (0.0) | 1 | (100.0) | |
| Leukoplakia | 144 | (56.0) | 60 | (41.7) | 84 | (58.3) | | 0 | (0.0) | 144 | (100.0) | |
| Ulcer ± Leukoplakia | 18 | (7.0) | 7 | (38.9) | 11 | (61.1) | | 0 | (0.0) | 18 | (100.0) | |
| Verrucous lesion | 2 | (0.8) | 2 | (100.0) | 0 | (0.0) | | 0 | (0.0) | 2 | (100.0) | |

OLP: Oral Lichen Planus. N: Number of patients; SD: Standard Deviation; aColumn percentage; bRow percentage; cIncludes mental and nervous system illnesses, ear and eye diseases and musculoskeletal disorders; dIncludes gums, other regions of oral cavity and oral cavity not specified; eIncludes oral retinoid, CO2 laser and unspecified; 1: Chi2 test P-value; 2: ANOVA test P-value.

| Characteristic | All OLP | | Gender | | | | | Clinical aspect | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | | Female | | *P*-value[1] | Unknown | | Known | | *P*-value[1] |
| | N | (%) [a] | N | (%) [b] | N | (%) [b] | | N | (%) [b] | N | (%) [b] | |
| Without clinical aspect | 92 | (35.8) | 37 | (40.2) | 55 | (59.8) | | 92 | (100.0) | 0 | (0.0) | |
| **Associated diseases** | | | | | | | 0.156 | | | | | 0.163 |
| No disease | 32 | (12.5) | 15 | (46.9) | 17 | (53.1) | | 16 | (50.0) | 16 | (50.0) | |
| Cardiovascular diseases | 34 | (13.2) | 18 | (52.9) | 16 | (47.1) | | 12 | (35.3) | 22 | (64.7) | |
| Skin diseases | 30 | (11.7) | 6 | (20.0) | 24 | (80.0) | | 15 | (50.0) | 15 | (50.0) | |
| Respiratory /digestive/ genitourinary disorders | 79 | (30.7) | 34 | (43.0) | 45 | (57.0) | | 26 | (32.9) | 53 | (67.1) | |
| Blood / immunological / endocrine disorders | 43 | (16.7) | 18 | (41.9) | 25 | (58.1) | | 12 | (27.9) | 31 | (72.1) | |
| Others[c] | 39 | (15.2) | 16 | (41.0) | 23 | (59.0) | | 11 | (28.2) | 28 | (71.8) | |
| **Location of the lesion** | | | | | | | 0.759 | | | | | 0.082 |
| Tongue | 47 | (18.3) | 20 | (42.55) | 27 | (57.45) | | 46 | (30.5) | 105 | (69.5) | |
| Buccal mucosa | 151 | (58.8) | 62 | (41.1) | 89 | (58.9) | | 23 | (48.9) | 24 | (51.1) | |
| Floor of the mouth | 5 | (1.9) | 1 | (20.0) | 4 | (80.0) | | 3 | (60.0) | 2 | (40.0) | |
| Others[d] | 54 | (21.0) | 24 | (44.4) | 30 | (55.6) | | 20 | (37.0) | 34 | (63.0) | |
| **Treatment** | | | | | | | 0.125 | | | | | **0.001** |
| No treatment (clinical control) | 89 | (34.6) | 32 | (36.0) | 57 | (64.0) | | 43 | (48.3) | 46 | (51.7) | |
| Topical treatment | 102 | (39.7) | 41 | (40.2) | 61 | (59.8) | | 25 | (24.5) | 77 | (75.5) | |
| Surgery | 52 | (20.2) | 29 | (55.8) | 23 | (44.2) | | 22 | (42.3) | 30 | (57.7) | |
| Others[e] | 14 | (5.45) | 5 | (35.7) | 9 | (64.3) | | 2 | (14.3) | 12 | (85.7) | |
| **Total** | **257** | **(100.0)** | **107** | **(41.6)** | **150** | **(58.4)** | | **92** | **(35.8)** | **165** | **(64.2)** | |

OLP: Oral Lichen Planus. N: Number of patients; SD: Standard Deviation; aColumn percentage; bRow percentage; cIncludes mental and nervous system illnesses, ear and eye diseases and musculoskeletal disorders; dIncludes gums, other regions of oral cavity and oral cavity not specified; eIncludes oral retinoid, CO2 laser and unspecified; 1: Chi2 test P-value; 2: ANOVA test P-value.

The proportion of ever-smokers and ever-drinkers was higher among male than female patients ($p < 0.001$). Patients diagnosed at the most recent periods (2010–2014) had more clinical aspect availability than those diagnosed at older periods (1995–1999) ($p < 0.001$). Never-drinkers had also more commonly described clinical aspect of their lesion than ever-drinkers ($p = 0.003$) whereas treatment also differed by clinical aspect availability ($p < 0.001$).

After 11 years of follow-up, OLP patients' CFS was 92% and no more progressions to cancer were observed up to the end of the 21 years of follow-up.

Figure 1 and Fig. 2 show Kaplan–Meier curves and log-rank tests for 5-year CFS of all OLPs by gender, age, alcohol and tobacco consumption, OLP location, associated diseases, clinical aspect and treatment. Cox proportional Hazard multivariate models for CFS showed that alcohol consumption (aHR = 5.29, 95%CI 1.41–19.85), tongue site (aHR = 5.51, 95%CI 1.30-23.37), surgery as type of treatment (aHR = 9.34, 95%CI 1.86–46.84) and oldest diagnostic periods were prognostic factors for progression to OSCC during follow-up (Table 2). Tobacco use and unknown clinical aspect were also found to increase the risk of progression to OSCC, although the result did not reach statistical significance (p = 0.107 and p = 0.149, Table 2). Other variables such as gender, comorbidities and previous neoplasia did not show any independent prognostic value.

Table 2
OLP patients progressing to invasive cancer during follow-up for each sociodemographic and clinical characteristic and crude and adjusted hazard ratios for progression

| Characteristics | OLP patients | | | Crude HR | | | Adjusted* HR | | |
|---|---|---|---|---|---|---|---|---|---|
| | n/N | (%)[a] | P-value[$] | cHR | [95%CI] | P-value[#] | aHR | [95%CI] | P-value[#] |
| **Age at diagnosis** | | | 0.357[&] | | | 0.263 | | | |
| Mean (SD) | 61.9 (10.5) / 59.1 (11.7) | | | 1.03 | [0.98–1.08] | | | | |
| Range | 42–81 / 24–86 | | | | | | | | |
| **Age at diagnosis (in quartiles)** | | | 0.607 | | | 0.562 | | | |
| < 51 | 2/62 | (3.2) | | 0.33 | [0.06–1.70] | | | | |
| 51–60 | 4/71 | (5.6) | | 0.59 | [0.16–2.18] | | | | |
| 60–69 | 3/66 | (4.5) | | 0.52 | [0.12–2.18] | | | | |
| 69+ | 5/58 | (8.6) | | Ref. | | | | | |
| **Gender** | | | **0.020** | | | **0.025** | | | |
| Male | 10/107 | (9.3) | | 3.48 | [1.09–11.09] | | | | |
| Female | 4/150 | (2.7) | | Ref. | | | | | |
| **OPMDs diagnostic date** | | | **0.045** | | | 0.055 | | | **0.037** |
| 1995–1999 | 3/24 | (12.5) | | Ref. | | | Ref. | | |
| 2000–2004 | 3/43 | (7.0) | | 0.60 | [0.12–2.97] | | 0.18 | [0.03–1.23] | |
| 2005–2009 | 8/108 | (7.4) | | 0.78 | [0.20–3.01] | | 0.56 | [0.10–3.04] | |
| 2010–2014 | 0/82 | (0.0) | | _[$] | - | | _[$] | - | |
| **Alcohol consumption** | | | **< 0.001** | | | **0.001** | | | **0.011** |
| Never | 7/220 | (3.2) | | Ref. | | | Ref. | | |
| Ever | 7/37 | (18.9) | | **6.25** | **[2.19–17.88]** | | **5.29** | **[1.41–19.85]** | |
| **Tobacco consumption** | | | 0.115 | | | 0.107 | | | |
| Never | 6/161 | (3.7) | | Ref. | | | | | |
| Ever | 8/96 | (8.3) | | 2.38 | [0.82–6.85] | | | | |

n: Number of patients progressing to invasive cancer during follow-up; N: Number of patients; SD: Standard Deviation; SCC: Squamous Cell Carcinoma; HR: Hazard ratio; [a]Percentage of cases progressing to invasive cancer during follow-up; [b]Others: includes mental and nervous system illnesses, ear and eye diseases and musculoskeletal disorders; [c]Others: includes gums, other regions of oral cavity and oral cavity not specified; [d]Others: Includes oral retinoid and CO2 laser; $: Chi2 test *P*-value; &: ANOVA test *P*-value; #: Log-likelihood ratio test *P*-value; *: Adjusted by alcohol consumption, period of diagnosis and treatment.

| Characteristics | OLP patients | | | Crude HR | | | Adjusted* HR | | |
|---|---|---|---|---|---|---|---|---|---|
| | n/N | (%)[a] | P-value[$] | cHR | [95%CI] | P-value[#] | aHR | [95%CI] | P-value[#] |
| **Previous Neoplasia** | | | 0.416 | | | - | | | |
| No | 14/246 | (5.7) | | Ref. | | | | | |
| Yes | 0/11 | (0.0) | | _$ | - | | | | |
| **Clinical aspect** | | | 0.076 | | | 0.149 | | | |
| Erythroplakia | 0/1 | (0.0) | | _$ | - | | | | |
| Leukoplakia | 4/144 | (2.8) | | 0.31 | **[0.10–0.99]** | | | | |
| Ulcer ± Leukoplakia | 0/18 | (0.0) | | _$ | - | | | | |
| Verrucous lesion | 0/2 | (0.0) | | _$ | - | | | | |
| Without clinical aspect | 10/92 | (10.9) | | Ref. | | | | | |
| **Associated diseases** | | | 0.465 | | | **0.005** | | | |
| No disease | 4/32 | (12.5) | | Ref. | | | | | |
| Cardiovascular diseases | 0/34 | (0.0) | | _$ | - | | | | |
| Skin diseases | 1/30 | (3.3) | | 0.24 | [0.03–2.12] | | | | |
| Respiratory /digestive/ genitourinary disorders | 5/79 | (6.3) | | 0.51 | [0.14–1.91] | | | | |
| Blood / immunological / endocrine disorders | 4/43 | (9.3) | | 0.86 | [0.21–3.46] | | | | |
| Others[b] | 0/39 | (0.0) | | _$ | - | | | | |
| **Location of the lesion** | | | **0.017** | | | **0.022** | | | 0.065 |
| Buccal mucosa | 3/151 | (2.0) | | Ref. | | | Ref. | | |
| Tongue | 6/47 | (12.8) | | **6.39** | **[1.60-25.58]** | | **5.51** | **[1.30-23.37]** | |
| Floor of the mouth | 0/5 | (0.0) | | _$ | - | | _$ | - | |
| Others[c] | 5/54 | (9.3) | | **4.79** | **[1.14–20.06]** | | 3.28 | [0.72–14.96] | |
| **Treatment** | | | **< 0.001** | | | **< 0.001** | | | **< 0.001** |
| No treatment (clinical control) | 0/89 | (0.0) | | _$ | - | | _$ | - | |
| Topical treatment | 2/102 | (2.0) | | Ref. | | | Ref. | | |

n: Number of patients progressing to invasive cancer during follow-up; N: Number of patients; SD: Standard Deviation; SCC: Squamous Cell Carcinoma; HR: Hazard ratio; [a]Percentage of cases progressing to invasive cancer during follow-up; [b]Others: includes mental and nervous system illnesses, ear and eye diseases and musculoskeletal disorders; [c]Others: includes gums, other regions of oral cavity and oral cavity not specified; [d]Others: Includes oral retinoid and CO2 laser; $: Chi2 test *P*-value; &: ANOVA test *P*-value; #: Log-likelihood ratio test *P*-value; *: Adjusted by alcohol consumption, period of diagnosis and treatment.

| Characteristics | OLP patients | | | Crude HR | | | Adjusted* HR | | |
|---|---|---|---|---|---|---|---|---|---|
| | n/N | (%)[a] | P-value[$] | cHR | [95%CI] | P-value[#] | aHR | [95%CI] | P-value[#] |
| Surgery | 11/52 | (21.2) | | **11.24** | **[2.49–50.71]** | | **9.34** | **[1.86–46.84]** | |
| Others[d] | 1/14 | (7.1) | | 3.66 | [0.33–40.34] | | 2.58 | [0.19–35.04] | |
| **Total** | **14/257** | **(5.4)** | | | | | | | |

n: Number of patients progressing to invasive cancer during follow-up; N: Number of patients; SD: Standard Deviation; SCC: Squamous Cell Carcinoma; HR: Hazard ratio; [a]Percentage of cases progressing to invasive cancer during follow-up; [b]Others: includes mental and nervous system illnesses, ear and eye diseases and musculoskeletal disorders; [c]Others: includes gums, other regions of oral cavity and oral cavity not specified; [d]Others: Includes oral retinoid and CO2 laser; $: Chi2 test *P*-value; &: ANOVA test *P*-value; #: Log-likelihood ratio test *P*-value; *: Adjusted by alcohol consumption, period of diagnosis and treatment.

## Discussion

The malignant transformation of OLP is still a controversial health topic and there are yet considerable gaps in knowledge on the most effective treatment for such lesions, as well as on factors related to their progression to OSCC. Moreover, in the clinical practice, OLP - as well other OPMDs - are managed by a broad range of specialists but there are not consensus guidelines for classification and treatment of OLP.

In our study, 5.4% of the patients diagnosed with OLP developed OSCC during follow-up, while selective pooling of studies using the WHO 2003 diagnostic criteria showed a pooled malignant transformation rate considerably lower, 1.1%.[8] Nevertheless, most included studies were heterogeneous in terms of design, inclusion criteria and lengths of follow up and malignant transformation rates ranged from 0.0 to 14.3%.

Both active treatment and surveillance are the current standards-of-care of OLPs although those approaches may not prevent their malignant transformation to OSCC. The rationale behind remains uncertain but possible explanations like the field of cancerization or genetic changes have been discussed.[17] Although some molecular studies assessing the risk of progression of OLP have been performed, the biomarkers evaluated in these studies are not currently being used in the clinical practice.[18]

We found that alcohol consumption was the most important prognostic factor for progression of OLP to OSCC, which is supported by the results of a recent systematic review.[8] The review also pointed out the significant increase of malignant transformation risk among smokers and HCV-infected patients, but these results were not observed in our study. We also found higher aHRs for progression to OSCC in OLP located at the tongue, as previously observed.[1]

Oldest diagnostic periods were also found to be a prognostic factor for progression to OSCC during follow-up, which may be due to the improvement over time in the accuracy of the clinical diagnosis of the lesions.

Surgery as a type of treatment was also an independent prognostic factor for progression to OSCC in our cohort. Of note, many medical records did not make distinction between complete surgical excision, or biopsy excision with the intention to remove all the lesion, and incisional biopsy. Moreover, international guidelines do not recommend surgical excision of OPL lesions. Other authors have also found higher rates of malignant transformation among patients treated with surgery,[19] but these results must be interpreted with caution and could be explained by the fact that apparently most severe or widespread lesions will more likely be surgically treated. Clinicians decide the most appropriate treatment according to their own experience given the lack of general recommendations or treatment guidelines, which should be developed from a multidisciplinary approach.

Gender and age were not prognostic factors of malignant transformation in our cohort, but female gender seemed to slightly increase the transformation risk of OLP in a recent systematic review.[1]

Our study has several limitations. The retrospective nature of our cohort limited the thorough characterization of the patients in terms of risk factors such as tobacco-alcohol use since this information could only be partially obtained from medical records. The histopathological diagnosis of each case was not reconfirmed after the initial diagnosis of the lesion. Yet, this is consistent with the real-world practice. Aspect and size of the lesions have not been herein evaluated as those were not reported at most clinical records. Last, as this study involves different medical specialists, decision making about treatment and interventions are not homogeneous and depend on clinical management or experience and knowledge of each physician. On the other hand, the main strengths of our study were the non-selected consecutive inclusion of cases and the large sample size herein evaluated. Moreover, our analyses were based on the original interpretation of histologic findings by pathologists at the time of diagnosis, reflecting thus a real-world clinical practice. Although randomized clinical trials would be the best model to analyze if surgical management and other factors are predictive for malignant transformation of OLPs, those would be somehow unethical and thus unfeasible.

In conclusion, our results have clinical implications and underscore the need to homogenize the diagnosis and treatment of OLP across the different medical specialties undertaking the management of these lesions, beside well-designed, robust prospective studies to corroborate our findings.

# Declarations

### DISCLOSURE

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# References

1. Giuliani M, Troiano G, Cordaro M, Corsalini M, Gioco G, Lo Muzio L, Pignatelli P, Lajolo C. Rate of malignant transformation of oral lichen planus: A systematic review. Oral Dis 2019;25(3):693–709.
2. McCartan BE, Healy CM. The reported prevalence of oral lichen planus: a review and critique. J Oral Pathol Med 2008;37(8):447–53.
3. Roopashree MR, Gondhalekar RV, Shashikanth MC, George J, Thippeswamy SH, Shukla A. Pathogenesis of oral lichen planus–a review. J Oral Pathol Med 2010;39(10):729–34.
4. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Sci 2007 Jun;49(2):89–106.
5. Kramer IR, Lucas RB, Pindborg JJ, Sobin LH. Definition of leukoplakia and related lesions: An aid to studies on oral precancer. Oral Surg Oral Med Oral Pathol 1978;46(4), 518–539.
6. Rad M, Hashemipoor MA, Mojtahedi A, Zarei MR, Chamani G, Kakoei S, Izadi N. Correlation between clinical and histopathologic diagnoses of oral lichen planus based on modified WHO diagnostic criteria. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107(6):796–800.
7. Ghazi N, Khorasanchi M. Markers associated with malignant transformation of oral lichen planus: A review article. Arch Oral Biol 2021;127:105158.
8. Hallopeau H. Sur un cas de lichen de Wilson gingival avec neoplasie voisine dans la region maxillaire. Bulletin de La Societe Francaise de Dermatologie et de Syphiligraphie 1910;17:32.
9. Aghbari SMH, Abushouk AI, Attia A, Elmaraezy A, Menshawy A, Ahmed MS, Elsaadany BA, Ahmed EM. Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. Oral Oncol 2017;68:92–102.
10. Landini G, Mylonas P, Shah IS and Hamburger J. The reported rates of transformation of oral lichen planus. J Oral Maxil Surg 2014;26:213–220.

11. Idrees M, Kujan O, Shearston K, Farah CS. Oral lichen planus has a very low malignant transformation rate: A systematic review and meta-analysis using strict diagnostic and inclusion criteria. J Oral Pathol Med 2021;50(3):287–298.
12. Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. J Am Dent Assoc.2014;145(1):45–56.
13. Gonzalez-Moles MA, Scully C, Gil-Montoya JA. Oral lichen planus: controversies surrounding malignant transformation. Oral Dis 2008;14(3):229–43.
14. Bombeccari GP, Guzzi G, Tettamanti M, Giannì AB, Baj A, Pallotti F, Spadari F. Oral lichen planus and malignant transformation: a longitudinal cohort study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112(3):328–34.
15. Gomez-Armayones S, Chimenos-Küstner E, Arranz C, Tous S, Marquez S, Penin R, Quiros B, Taberna M, Alemany L, Servitje O, Mena M. Risk factors for oral epithelial dysplasias to become malignant: clinical implications. Int J Oral Maxillofac Surg 2022;51(4):473–480.
16. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol 2007;43(8):742–8.
17. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev 2011;11(1):9–22.
18. Tampa M, Caruntu C, Mitran M, Mitran C, Sarbu I, Rusu LC, Matei C, Constantin C, Neagu M, Georgescu SR. Markers of Oral Lichen Planus Malignant Transformation. Dis Markers 2018; 26;2018:1959506.
19. Balasundaram I, Payne KFB, Alibhai M, Thomas S, Bhandari R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity ? J Oral Pathol Med 2014:239–244.

## Figures

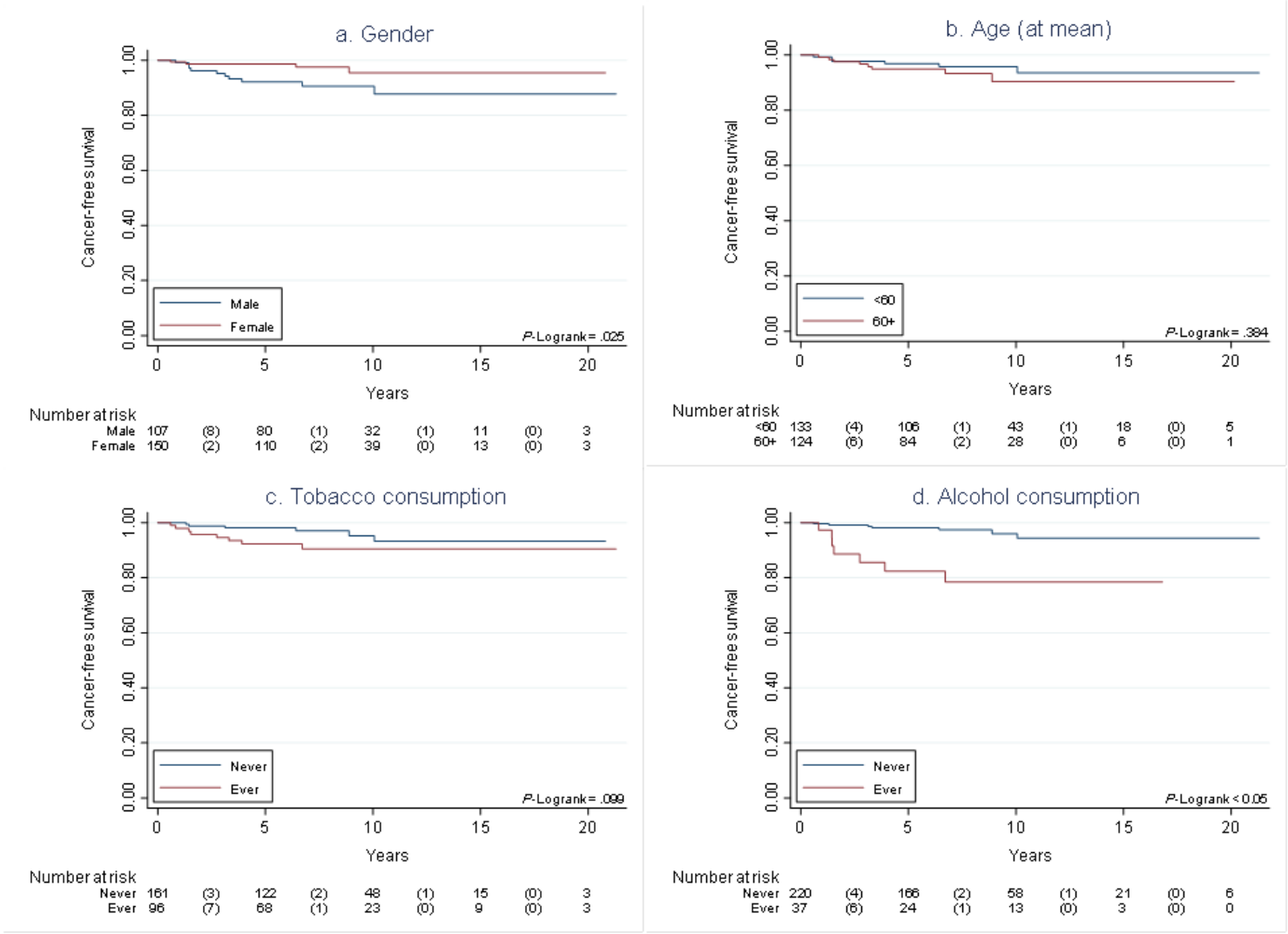


**Figure 1**

Kaplan–Meier curves and log-rank tests for 5-year cancer free-survival of OLPs by gender, age, alcohol and tobacco consumption.

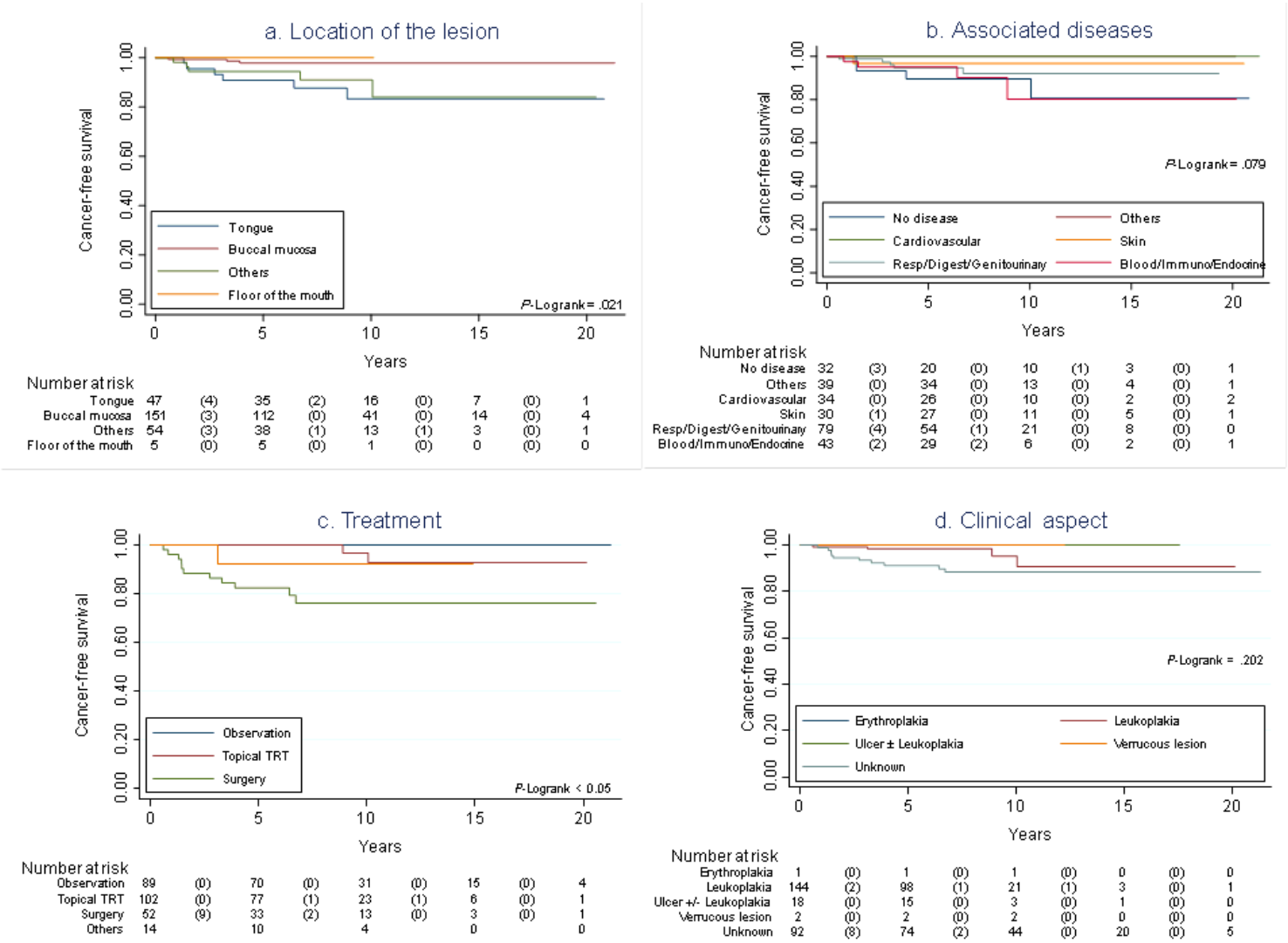


**Figure 2**

Kaplan–Meier curves and log-rank tests for 5-year cancer free-survival of OLPs by location, associated diseases, clinical aspect and treatment.