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Review Article

Candida species colonization in oral lichen planus: A meta-analysis

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ABSTRACT

Objective: Oral lichen planus (OLP) is a common chronic inflammatory disease that affects 1%–2% of the population. *Candida* species superinfection can aggravate the symptoms of OLP, especially of the erosive forms, and promote malignant transformation by producing carcinogenics as nitrosamines or acetaldehyde. On the other hand, antifungal treatment of *Candida*-infected OLPs improves the clinical symptoms of the disease. The objective of this study is to assess the possible influence of *Candida* species colonization in oral lichen planus.

Methods: A search for studies on *Candida* and oral lichen planus was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Scopus. Data analysis: The estimated prevalence of *Candida* detection in OLP was calculated according to the DerSimonian and Laird random model. For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratio (OR) using Mantel-Haenszel (M-H) method with 95% confidence intervals.

Results: Twenty-four studies were included in this meta-analysis. The estimated prevalence of *Candida* species detection in oral lichen planus (OLP) lesions was 37.00% (95% CI: 30.52–43.72%). OLP patients were almost 2½ times more likely to be infected by *Candida* species compared to healthy controls (OR: 2.48, $P < 0.001$). Likewise, *Candida* species superinfection was more likely in erosive OLP forms (OR: 2.53, $P < 0.001$), and by *non-albicans Candida* species (OR: 2.33, $P = 0.02$).

Conclusions: More than one-third of OLP lesions are infected by *Candida* species, modifying their biological behavior.

Keywords: Candida, candidiasis oral, microbiology, lichen planus oral

Introduction

Oral lichen planus (OLP) is a common chronic inflammatory disease that affects 1–2% of the population, most commonly women in their fifth and sixth decades of life. OLP usually presents with recurrences and periods of clinical exacerbation and remission. OLP etiology remains unknown. An immune response presumably mediated by CD4+ and CD8+ T lymphocytes appears to develop in the oral mucosa, which produces cytokines such as interleukin-2 and tumor necrosis factor and induces a chronic inflammatory response and apoptosis of keratinocytes.[1] OLP lesions are characterized by a bilateral and symmetrical distribution, mainly affecting the buccal mucosa, the tongue, and gingiva. Anderson's clinical classification distinguishes between six clinical forms: Reticular, atrophic, erosive, papular, plaque, and bullous. A typical manifestation of all OLP clinical forms is the presence of white striae called Wickham striae. Reticular OLP is the most common clinical form. It presents as asymptomatic white striae lesions with a reticular disposition. The OLP atrophic-erosive forms are usually symptomatic and present as erythematous-ulcerated areas with peripheral white striae.[2]

Although the possible relationship between *Candida* species colonization and OLP is not sufficiently clear, antifungal treatment of *Candida*-infected OLP lesions improves the clinical symptoms of the disease. In the oral microbiota, *Candida albicans* is found in approximately 8% of the healthy population. In OLP patients, this percentage is much higher. There is a positive correlation between the presence of *Candida* species in OLP lesions and interleukin-17 levels.[3] This interleukin plays a fundamental role in many immune regulatory functions through the production of immune signaling molecules that are involved in the pathogenesis of OLP. Both high IL-17 expression in the epithelial cells and markedly elevated serum levels have been observed in these patients compared to subjects without OLP.[4]

Candida superinfection may aggravate the OLP symptoms, especially of the erosive forms. *Candida* metabolism produces various carcinogenic agents such as nitrosamine or acetaldehyde.[5] OLP lesions exposed to established risk factors for oral malignancy such as smoking and alcohol consumption or *Candida* species superinfection requires special monitoring due to their increased malignant transformation potential.[6] This study purposed to analyze the repercussion of *Candida* superinfection on oral lichen planus.

Methods

All research steps, including search, study selection, data extraction, and evaluation, were performed independently by the two authors (ARA and SFT). Later, they agreed on which articles to consider in this study.

A search for studies on the *Candida* species detection and oral lichen planus up to November 2021 was conducted in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Scopus. Search strategies included the combination of Medical Subjects Headings (MeSH) and free-text terms. The search terms were the following: "lichen planus, oral" [MeSH Terms] AND "Candida" [MeSH Terms]; "oral lichen planus" AND "Candida;" TITLE-ABS-KEY ("oral lichen planus" AND "Candida"). Articles without date or language of publication restrictions were initially included. The exclusion criteria were as follows: (a) Articles with relevant risk of bias (<6 points) according to the Newcastle-Ottawa methodological quality assessment scale,[7] (b) articles without full-text availability, (c) studies without clinical data, and (d) studies with non-usable data.

Statistical analysis

The MedCalc Statistical Software version 20.019 (MedCalc Software Ltd. Ostend, Belgium) program was used to calculate the estimated prevalence according to the DerSimonian and Laird random model. In addition, the RevMan 5.4 meta-analysis program (The Cochrane Collaboration, Oxford, UK) was applied for the dichotomous variables using the odds ratio (OR) with the Mantel-Haenszel Chi-square (MH) formula, all with 95% confidence intervals (95% CI). Heterogeneity was determined according to the Higgins statistic (I^2) values. In cases of high heterogeneity ($I^2 > 50\%$), the random-effects model was performed. The minimum level of significance was set at $P < 0.05$. Publication bias was estimated using the funnel plot and the Egger test, with $P < 0.1$ as statistically significant.

Results

After the initial search, 232 articles were recorded (31 in PubMed, 118 in WoS, and 83 in Scopus) from 1974 to 2020, 30 of them duplicates, leaving 202 eligible articles. The exclusion criteria were as follows: (a) Articles with a relevant risk of bias (<6 points) according to the Newcastle-Ottawa methodological quality assessment scale[7] ($n = 41$), (b) articles without full-text availability ($n = 45$), (c) studies without clinical data ($n = 32$), and (d) studies with non-usable data ($n = 60$). After applying these criteria, 24 studies were included in this meta-analysis [Figure 1].

Table 1 presents the prevalence of *Candida* species detection in 1303 patients with oral lichen planus (OLP) considered in 22 studies[8-29] carried out in 13 different countries. The estimated global prevalence was 37.00% (95% CI: 30.52–43.72%). The variability by studies ranged from the maximum prevalence of 76.66% (95% CI: 57.71–90.06%) found in the study by Jainkittivong (Thailand, 2007)[12] to the minimum of 10.00% (95% CI: 2.11–26.52%) observed in the study by Sumanth (India, 2003).[11]

Fifteen studies[9,12-20,22,23,27-29] examined *Candida* species detection in oral lichen planus (OLP) patients and controls without the disease [Figure 2]. OLP patients were 2.48 times more likely to be infected by *Candida* species, with a highly statistically significant relationship (OR = 2.48; 95% CI: 1.94–3.18; $P < 0.001$).

The funnel plot for *Candida* species detection showed some asymmetry, suggesting that there may be publication bias, as presented in Figure 3. Egger's test results (t = 1.54, $P = 0.02$) indicated evidence of publication bias.

The odds ratios and 95% confidence intervals for oral lichen planus (OLP) clinical forms (non-erosive/erosive) and different *Candida* species detection (*C. albicans/C. non-albicans*) in OLP patients are shown in Table 2.

Ten studies[11,16,17,21,24,25,27,29-31] assessed *Candida* species superinfection according to the OLP clinical form, observing that erosive OLP patients increased 2.53-fold the probability of *Candida* superinfection in their lesions. After the statistical analysis, highly significant differences were found between *Candida* species detection and OLP clinical form (OR = 2.43; 95% CI: 1.92–3.33; $P < 0.001$).

Five studies[12,14,20,22,23] investigated the different *Candida* species (*C. albicans*/*C. non-albicans*) in OLP patients, finding that *Candida non-albicans* species were 2.33 times more frequent in OLP lesions. Statistical analysis showed a significant association (OR = 2.33; 95% CI: 1.13–4.81; $P = 0.02$).

Discussion

Data from 24 studies on *Candida* species superinfection of lesions from oral lichen planus (OLP) patients have been included in the present meta-analysis.

In this study, in 1303 OLP patients considered in 22 studies,[8-29] the estimated prevalence of *Candida* species was 37%, with an

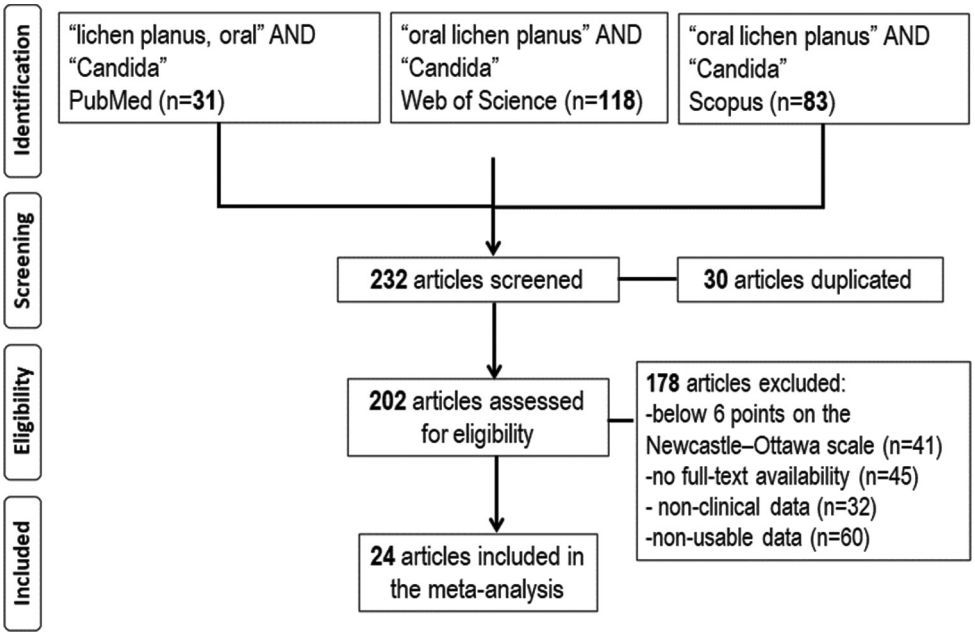

Figure 1: Flow diagram of study selection

Table 1: Prevalence (and 95% CI) of *Candida* species detection in oral lichen planus (OLP) patients

Study	Year	Country	n	Prevalence%	(IC95%)
Simon[8]	1980	Germany	28	50.00	(30.64−69.35)
Lundstrom[9]	1984	Sweden	41	43.90	(28.46−60.25)
Krogh[10]	1987	Denmark	19	47.36	(24.44−71.13)
Hatchuel[11]	1990	South Africa/Canada	145	16.55	(10.90−23.62)
Lipperheide[12]	1996	Spain	34	23.52	(10.74−41.17)
Sumanth[13]	2003	India	30	10.00	(2.11−26.52)
Jainkittivong[14]	2007	Thailand	30	76.66	(57.71−90.06)
Nakazawa[15]	2007	Japan	49	48.98	(34.42−63.66)
Zeng[16]	2008	China	86	24.42	(15.79−34.87)
Zeng[17]	2009	China	300	28.67	(23.61−34.14)
Bhavasar[18]	2010	India	6	16.67	(0.42−64.12)
Mehdipour[19]	2010	Iran	21	33.33	(14.58−56.96)
Masaki[20]	2011	Japan	15	53.33	(26.58−78.73)
Shivanandappa[21]	2012	India	34	44.12	(27.18−62.11)
Bokor-Bratic[22]	2013	Serbia	90	48.89	(38.19−59.65)
Artico[23]	2014	Brazil	38	28.95	(15.42−45.90)
Ebrahimi[24]	2014	Iran	37	48.65	(31.92−65.60)
Meru[25]	2014	India	30	56.67	(37.42−74.53)
Werneck[26]	2015	Brazil	21	38.09	(18.11−61.56)
Arora[27]	2016	India	80	32.50	(22.44−43.89)
Samatha[28]	2019	India	20	40.00	(19.11−63.94)
He[29]	2020	China	149	18.79	(12.86−26.00)
Total (*random-effects*)			1303	37.00	(30.52 − 43.72)

Test for heterogeneity. Q=115.79; df: 21 (P<0.0001); I^2=81.86%; 95%IC: (73.49−87.59). *n*: Sample size; (95% CI): 95% confidence interval

interval that ranged between 10.0% and 76.6%. An increase in *Candida* species superinfection has been observed in subjects with other predisposing factors such as immunodeficiencies, diabetes mellitus, corticosteroids or antibiotics treatment, xerostomia, or poor oral hygiene. Oral lichen planus, especially the erosive clinical forms in which there is a loss of mucosal integrity, favors candidal colonization. *Candida* species may produce endogenous N-nitrosobenzylmethylamine, a

Table 2: Odds ratios and 95% confidence intervals for OLP clinical forms and different *Candida* species detection in OLP patients

Variable	References	Value	OR	(95% CI)	*I2*(%)	*P*-value
OLP clinical form (nef/ef)	[11,16,17,21,24,25,27,29-31]	ef	2.53	(1.92–3.33)	36	<0.001*
Candida species (ca/cna)	[12,14,20,22,23]	cna	2.33	(1.13–4.81)	28	0.02*

OLP: Oral lichen planus, ef: Erosive OLP clinical form, nef: Non-erosive OLP clinical form, ca: *Candida albicans* species, cna: *Candida non-albicans* species: Ref.: Reference numbers, OR: Odds ratio, (95% CI): 95% confidence interval, I^2(%): Higgins statistic for heterogeneity (percentage); *statistically significant

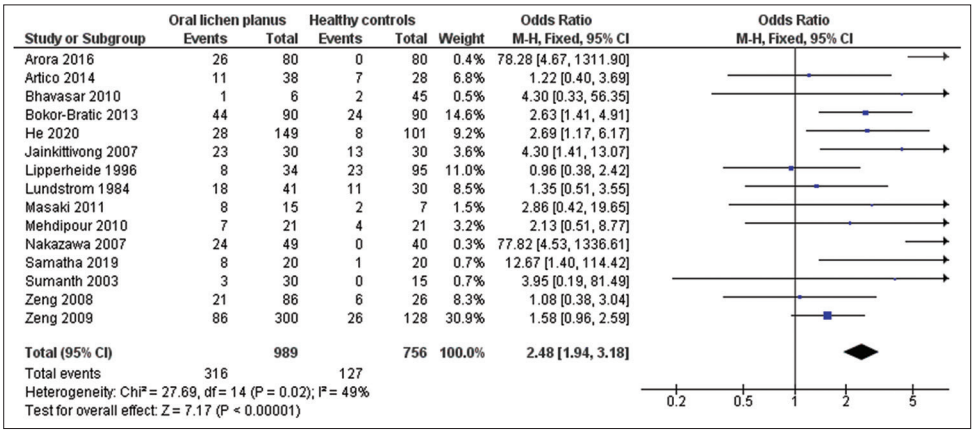

Figure 2: Study data and forest plot graph on the *Candida* species detection in patients with oral lichen planus (OLP) and controls without the disease

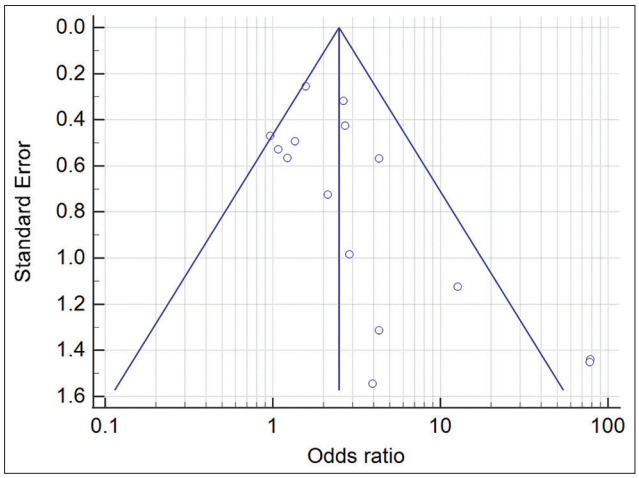

Figure 3: Funnel plot for publication bias

carcinogen that could play a role in the potential malignant transformation of oral lichen planus.[27]

In this study, OLP patients were 2.48 times more likely to present *Candida* species superinfection, with highly statistically significant differences ($P < 0.001$). Of the 15 studies that analyzed *Candida* detection in OLP lesions, 14 of them[9,13-20,22,23,26-28] agreed in pointing out this higher detection of *Candida* species in OLP patients, and only one[12] did not observe it. The possible relationship between *Candida* species infection and the etiology of OLP has disconcerted many researchers for a long time and is not yet fully clarified. Nevertheless, *Candida* species infection is common in OLP patients. *Candida albicans* stimulation could cause leukocyte dysfunction, inhibiting both lymphocyte proliferation and cytokine production, modulating the immune response in oral lichen planus. All these changes modify the biological behavior of OLP lesions.[29] In addition, the use of antifungals together with other drugs in the OLP treatment induces a significant improvement in the lesions and, on some occasions, changes from erosive OLP clinical forms to asymptomatic OLP reticular forms.[27] On the other hand, the use of corticosteroids for the OLP treatment leads to immunosuppression, decreases salivary flow, and creates an ideal microenvironment for the proliferation and growth of *Candida* species, which makes OLP patients, especially susceptible to this fungal infection.[14]

OLP patients with erosive clinical forms were 2.53 times more likely to have *Candida* superinfection, with a highly statistically significant association ($P < 0.001$). The 10 studies[11,16,17,21,24,25,27,29-31] that examined this parameter confirmed this finding of a greater presence of *Candida* species in erosive lesions.

The different clinical forms of OLP can be classified into two main groups: Non-erosive (predominantly white) and erosive (predominantly red) clinical forms. Non-erosive OLP forms are usually asymptomatic and do not require medical treatment, only regular follow-up of the lesions. However, the erosive OLP forms, which present as superficial ulcerations, often cause significant symptoms. Erosive OLP patients require treatment and frequent follow-up due to the greater potential for malignant transformation of these OLP clinical forms.[2] *Candida* species detection rates in OLP patients are higher in erosive than in non-erosive forms. Several reasons could justify this

finding: (1) Lesions from erosive OLP show superficial ulceration with the breakdown of mucosal integrity, facilitating the invasion and *Candida* species colonization of oral mucosa and (2) erosive OLP lesions modify the oral microenvironment, allowing some *Candida* species to better adapt to this situation, influencing the pathogenesis and progression of oral lichen planus.[17]

In the present meta-analysis, *Candida non-albicans* infection was 2.33 times more frequent in OLP lesions with a statistically significant relationship ($P = 0.02$). All the studies[12,14,20,22,23] about the different species of the genus *Candida* that infected the OLP lesions indicated this higher prevalence of the *non-albicans Candida* species in the OLP cases.

The frequency of *Candida* species detection is significantly higher in OLP patients compared to healthy controls. Of all *Candida* species, *C. albicans* is the most frequently detected species in the normal oral microbiota as a harmless commensal microorganism. In some oral lesions, it becomes an opportunistic pathogenic microorganism, favoring candidal infection. However, in OLP patients, other *non-albicans Candida* species such as *C. glabrata* or *C. parapsilosis* are identified, which are rarely found in the oral microbiota of the healthy population. Specifically, *C. glabrata* is less susceptible to the antifungal action of beta-defensins, histatins, or salivary mucins. It also has phospholipase activity that induces the destruction of cell membranes, promoting tissue invasion of the microorganism. This action is increased in the case of OLP patients who, moreover, present tissue alterations and disturbances in the immune response.[20]

This study has some limitations. Publication bias requires a careful interpretation of the results about *Candida* species detection in OLP patients versus healthy controls. The different methods for *Candida* species detection performed could influence the results. The number of *Candida* species infected cells in the OLP lesions was not quantified either. Similarly, the extension and severity of the OLP lesions could not be adequately assessed. Some possible confounding factors such as tobacco and/or alcohol consumption could not be considered.

New studies are required to establish the real role of *Candida* species infection in the etiopathogenesis of oral lichen planus (OLP). This infection seems to affect the biological behavior of these lesions and their potential for malignant transformation.

Conclusions

In this meta-analysis, the estimated prevalence of *Candida* species detection in oral lichen planus (OLP) lesions was 37.00%. OLP patients were almost 2½ times more likely to be infected by *Candida* species compared to healthy controls (OR: 2.48). Likewise, *Candida* species superinfection was more likely in erosive OLP forms (OR: 2.53) and by *non-albicans Candida* species (OR: 2.33).

Authors' Declaration Statements

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing interests

None.

Funding

None.

Authors' Contributions

The two authors contributed equally to the study design, data collection, analysis, and manuscript preparation. Both approved the final version.

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None.

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