Review Article
Association between oral lichen planus and Candida albicans infection: a systematic review and meta-analysis

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Abstract: This study examines the potential association between Oral Lichen Planus (OLP) and Candida albicans infection, exploring its potential impact on the development of OLP. A meta-analysis of individual case-control studies was performed, estimating odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). A quality assessment of the literature was conducted using the Newcastle-Ottawa Scale (NOS). Due to considerable heterogeneity in the selected studies, subgroup analyses were performed based on geographical location and recruitment methods. No significant publication bias was detected. A sensitivity analysis validated the robustness of the findings when applying a random-effects model. The meta-analysis included ten studies, comprising 1,124 OLP patients and 1,063 healthy controls. Results indicated a significantly higher detection rate of Candida albicans in OLP patients compared to healthy controls (OR = 1.74, P = 0.003, 95% CI: 1.20, 2.52). Additionally, an increased risk of Candida albicans infection was observed in erosive OLP (E-OLP) patients compared to healthy controls (OR = 3.97, 95% CI: 2.31, 6.84, P < 0.00001). These findings suggest a complex interplay between OLP and Candida albicans, highlighting the need for further research to elucidate the varying susceptibilities among different clinical types of OLP. This study provides novel insights for future research directions and clinical treatment strategies in this field.

Keywords: Oral lichen planus, Candida albicans, odds ratio, confidence interval, meta-analysis

Introduction

Oral lichen planus (OLP), a chronic inflammatory mucosal disease affecting skin and mucous membranes, particularly in the oral cavity [1], is characterized by white, thread-like lesions on cheek linings, tongues, gums, and occasionally the oral roof [2]. These lesions can cause significant discomfort, particularly with spicy or acidic foods [3]. Clinically, OLP is categorized as non-erosive or erosive, based on lesion characteristics [4]. Non-erosive OLP (non-E-OLP) presents with white, reticular patterns or plaques, while E-OLP manifests as red, painful erosions or ulcers [5]. Non-E-OLP may be asymptomatic or cause minor discomfort, while erosive OLP often results in significant pain, burning sensations, and difficulties with eating and speaking [6, 7]. Despite research suggesting links between infections, immune compromise, and systemic conditions with OLP development, the

precise etiology and mechanisms remain unclear [8]. Consequently, there is a need for further etiological exploration and the development of more effective clinical treatments. Candida albicans, a common fungal species residing in the human body, particularly in the gastrointestinal tract, mouth, and vaginal region [9], is typically a harmless component of the microbiota [10]. However, under conditions such as immunocompromise, hormonal imbalances, or antibiotic use, C. albicans can proliferate unchecked, resulting in infections [11]. Recent research suggests a potential association between C. albicans presence and OLP, attributed to alterations in the oral microbiota or compromised mucosal barriers [12]. The fungus is hypothesized to exacerbate inflammatory responses in OLP lesions, worsening symptoms and discomfort. Conversely, there is evidence indicating that C. albicans in the oral cavity may not always directly trigger OLP onset or progres-

sion [13]. Some researchers posit that Candida colonization in OLP patients may be a secondary event stemming from the altered oral environment associated with the disease [14]. To draw objective conclusions that can guide future research and clinical interventions, a comprehensive analysis of domestic and international research data on the OLP-C. albicans relationship is crucial. Therefore, the present study aims to investigate this link through a meta-analysis approach.

Materials and methods

Selection criteria

The selection criteria for this study were as follows: ① Study design: We included English-language case-control studies that examined the potential correlation between OLP and Candida albicans infection. ② Study population: The study population was comprised of adult patients with a confirmed diagnosis of OLP. The control group consisted of healthy individuals, matched for age and gender, without OLP or systemic diseases. ③ Outcome indicators: The detection rate of Candida albicans in OLP lesions and oral rinse solutions was considered, with adherence to internationally recognized identification methods.

The exclusion criteria were: ① Participants with malignancies, diabetes, or systemic diseases; those who had used antibiotics or immunosuppressive agents in the past three months; and OLP patients with concurrent oral infectious diseases. ② Studies with repetitive publications or incomplete data. ③ Quantitative meta-analyses, abstracts, reviews, and commentaries.

This meta-analysis was registered with IN-PLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols, ID: 202460006).

Search strategy

A comprehensive search was conducted in PubMed, Embase, Medline, Cochrane Library, and Web of Science from their inception through January 31, 2024, to identify relevant case-control studies examining the association between OLP and Candida albicans infection. The search strategy incorporated both free text

and Medical Subject Headings (MeSH), utilizing terms such as "Candida albicans", "Monilia albicans", "Dematium albicans", "Oral Lichen Planus", "Mucosal Lichen Planus", "Lichen planopilaris", and "Lichen Planus". The search queries were formulated as (((Candida albicans [MeSH]) OR Dematium albicans [MeSH] OR Monilia albicans [MeSH]) AND (Oral Lichen Planus [MeSH] OR "Oral Lichen Planus" [All Fields] OR Lichen Planus [MeSH] OR Mucosal Lichen Planus [MeSH] OR "Lichen planopilaris" [All Fields])).

Literature screening and data extraction

Data from eligible studies were independently extracted by two researchers (DHM and YX) based on predefined inclusion and exclusion criteria. The primary data extracted included the first author's name, publication year, country of origin, number of cases and controls, source of participants for both case and control groups, age, gender, method of Candida albicans identification, and outcome measures. Any discrepancies in data extraction were resolved through discussion.

Quality assessment

The methodological quality of the included studies was rigorously assessed by two researchers using the Newcastle-Ottawa Scale (NOS) scoring criteria. The NOS scoring ranges from 0 to 9, with scores of 0-5 indicating low quality, 6-7 indicating moderate quality, and 8-9 indicating high quality. Any discrepancies in the quality ratings were resolved through discussion between the researchers.

Statistical analysis

The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed for each case-control study using Review Manager 5.3 software. Heterogeneity across the studies was evaluated using the Cochrane's Q test and the I^2 statistic, with I^2 values between 25% and 50% considered low, 50% to 75% moderate, and over 75% indicating high heterogeneity. Meta-analyses were conducted using a random-effects model to obtain pooled ORs and 95% CIs, which were presented in a forest plot. To further investigate potential sources of heterogeneity, subgroup analyses were performed considering clinical types,
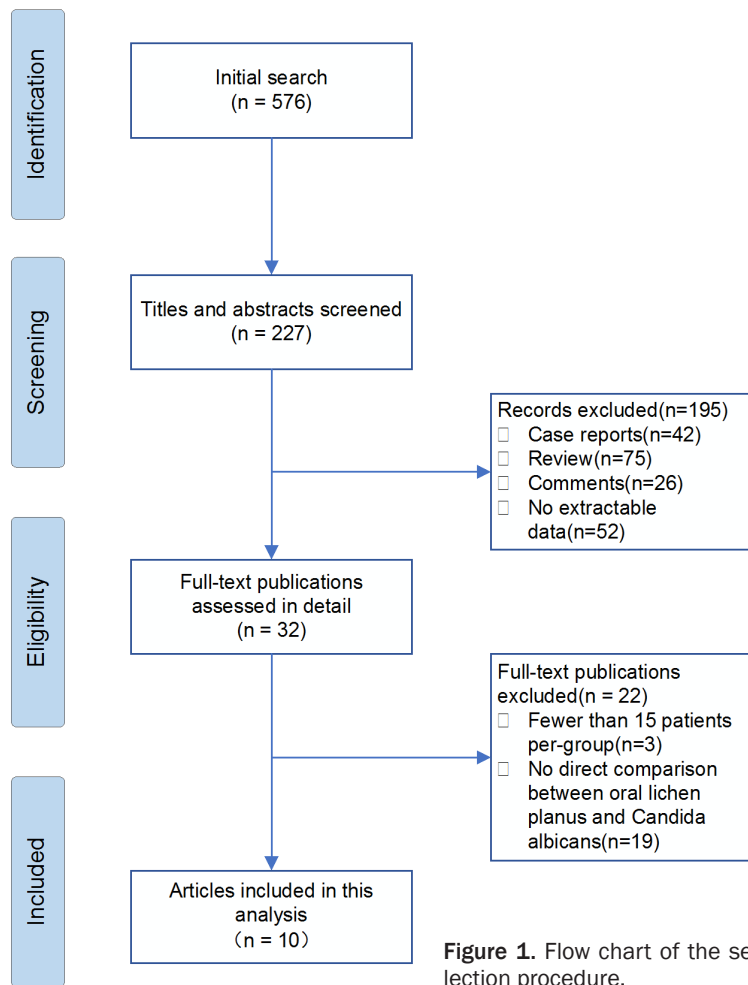
Figure 1. Flow chart of the selection procedure.

Basic characteristics of included studies

Table 1 summarizes the baseline characteristics of the ten included studies in this meta-analysis. These studies, published between 1996 and 2022, encompass a total of 1,124 patients with OLP and 1,063 healthy controls. With two exceptions, the majority employed the concentrated oral rinse method for detection. The studies originate from various countries, including Romania, Germany, Iran, China, Serbia, Malaysia, Thailand, Brazil, and Spain.

Quality assessment

The quality assessment conducted according to the Cochrane bias risk criteria indicated that all included studies exhibited a high level of methodological rigor and quality (**Figure 2**).

Meta-analysis results

The pooled data from ten studies encompassing 1,124 patients with OLP and 1,063 healthy controls revealed significant differences in the detection rate of Candida albicans. Among OLP patients, 353 cases tested positive for Candida albicans, yielding a detection rate of 31.41%. In contrast, the healthy control group exhibited a lower detection rate of 24.13% (187 positive cases). The meta-analysis showed a statistically significant increase in the detection rate of Candida albicans among OLP patients compared to healthy controls (OR = 1.74, P = 0.003, 95% CI: 1.20, 2.52; see **Figure 3**).

Of the ten studies, five performed a clinical classification of OLP patients. These studies revealed a significantly higher risk of Candida albicans infection in patients with e E-OLP compared to healthy controls (OR = 3.97, 95% CI: 2.31, 6.84, P < 0.00001; see **Figure 4**). However, no significant difference was observed in

regional distributions, and detection methods of OLP patients. Sensitivity analysis was performed by sequentially excluding each study to assess the robustness of the findings. Finally, a funnel plot was used to evaluate potential publication bias.

Results

Literature search results

The initial search of electronic databases resulted in 576 publications, as shown in **Figure 1**. After eliminating duplicates and screening titles and abstracts, 227 unique publications remained for detailed evaluation. Following a thorough full-text review, 32 articles were assessed for eligibility, with 22 ultimately excluded. Consequently, the current meta-analysis incorporates data from ten eligible articles. See in **Figure 1**.

Table 1. Characteristics of included publications

Authors	Year	Country	OLP (n)	Controls	Oral candidiasis (n)	Clinical Type of OLP	Detection method	Detection indicators
Parlatescu et al. [25]	2021	Romania	203	94	75	E-OLP:17; NE-OLP:58	Mucus swab method	Culture positive number
Molkenthin et al. [14]	2022	Germany	160	97	117	E-OLP:56; NE-OLP:61	Mucus swab method	Culture positive number
Rezazadeh et al. [26]	2022	Iran	40	32	32	NA	Mucus swab method	Culture positive number
He et al. [27]	2020	China	149	101	28	E-OLP:53; NE-OLP:96	Mucus swab method	Culture positive number
Zeng et al. [28]	2008	China	300	128	86	E-OLP:140; NE-OLP:160	Concentrated oral rinse method	Culture positive number
Bokor et al. [29]	2013	Serbia	90	90	36	NA	Mucus swab method	Culture positive number
Arora et al. [30]	2016	Malaysia	80	80	26	E-OLP:16; NE-OLP:64	Mucus swab method	Culture positive number
Jainkittivong et al. [31]	2007	Thailand	30	30	21	NA	Mucus swab method	Culture positive number
Artico et al. [32]	2014	Brazil	38	28	11	NA	Mucus swab method	Culture positive number
Lipperheide et al. [33]	1996	Spain	34	95	17	NA	Concentrated oral rinse method	Culture positive number

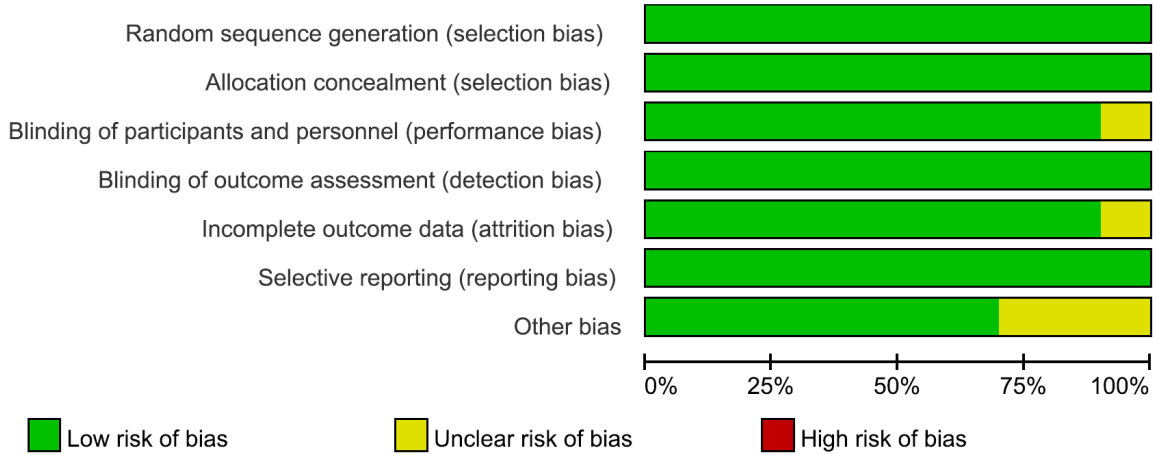OLP: oral lichen planus; NE-OLP: non-erosive OLP; E-OLP: erosive OLP; NA: Not Available.
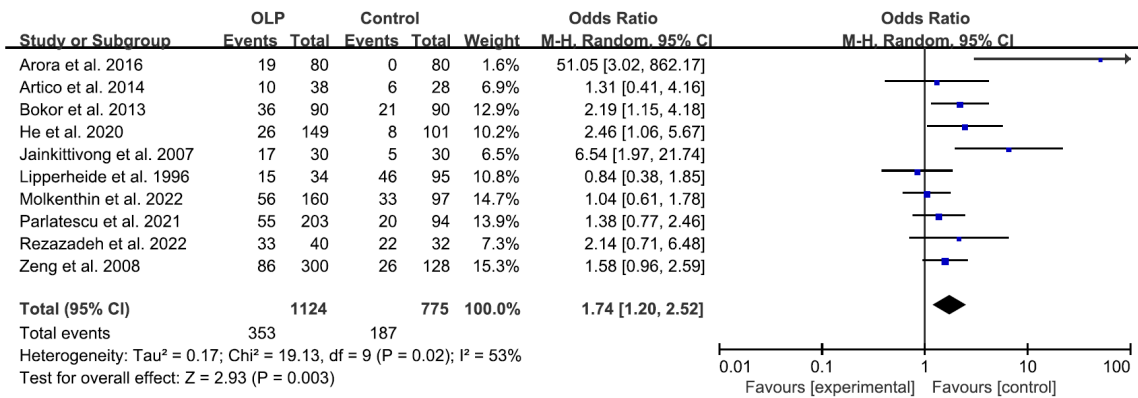
Figure 2. Bias risk assessment.

Figure 3. The forest plot of the association between OLP and Candida albicans infection. OLP: oral lichen planus.

the detection rate of Candida albicans between non-erosive OLP patients and normal controls (P = 0.06, **Figure 4**).

Subgroup analysis

Given the substantial heterogeneity observed among studies (I^2 = 53%, P = 0.02), a subgroup analysis was undertaken to identify the underlying causes. The geographical distribution of the study populations revealed a significantly elevated risk of Candida albicans infection in OLP patients in both Asian (OR = 2.96, 95% CI: 1.43, 6.13, P = 0.004) and non-Asian regions (OR = 1.29, 95% CI: 0.94, 1.77, P = 0.11; **Figure 5**). Additionally, the subgroup analysis based on sample collection methods demonstrated a significant association between Candida albicans infection and OLP, regardless of whether mucosal swab culture (OR = 2.03, 95% CI 0.68, 2.26, P = 0.003) or rinse culture (OR =

1.24, 95% CI 1.46-2.58, P = 0.047) was used (**Figure 6**).

Publication bias analysis

A funnel plot analysis was performed to assess potential publication bias among the included studies. As depicted in **Figure 7**, the studies exhibited symmetry, indicating no significant publication bias across the ten studies.

Sensitivity analysis

The stability of the random-effects model selection was confirmed through sensitivity analysis. The results demonstrated low sensitivity and robust stability, with the data from all publications distributed evenly away from the center line, indicating no significant devia-
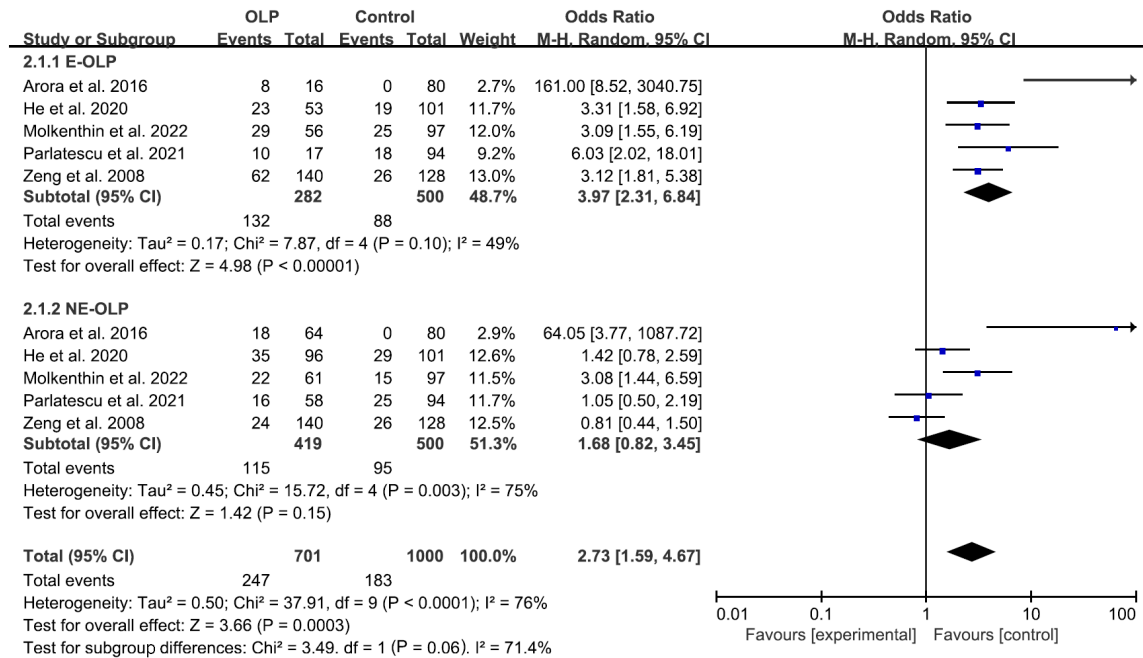
Figure 4. The forest plot of the correlation between clinical OLP and Candida albicans infection subtypes. OLP: oral lichen planus.
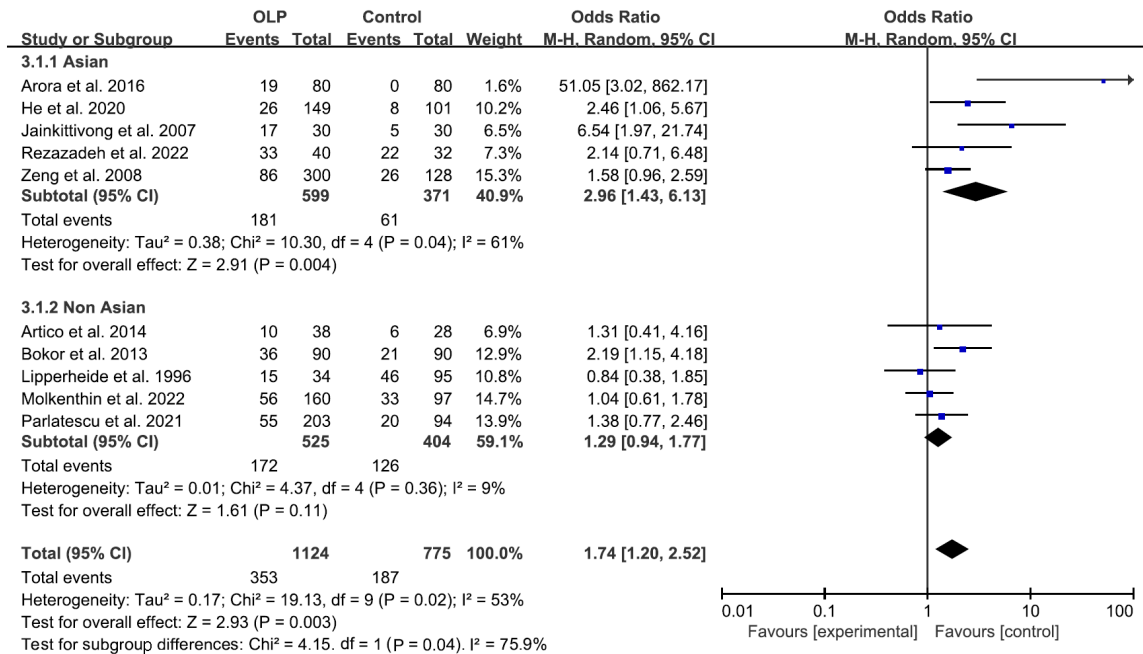

Figure 5. The forest plot shows the correlation between regional OLP and Candida albicans infection. OLP: oral lichen planus.

tion. This suggests that no single publication significantly influenced the collective findings. A *p*-value < 0.05 indicated statistical significance.

Discussion

OLP, an idiopathic chronic inflammatory condition affecting the oral mucosa [15], has recent-
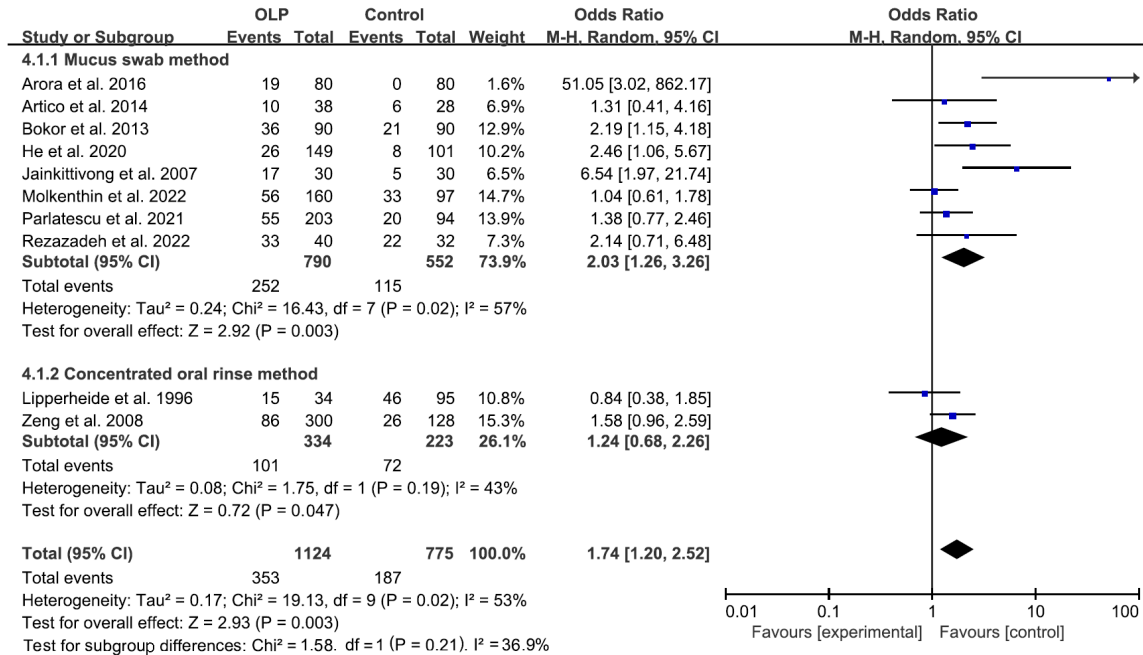
Figure 6. The forest plot shows the correlation between different collection methods for OLP and Candida albicans infection. OLP: oral lichen planus.
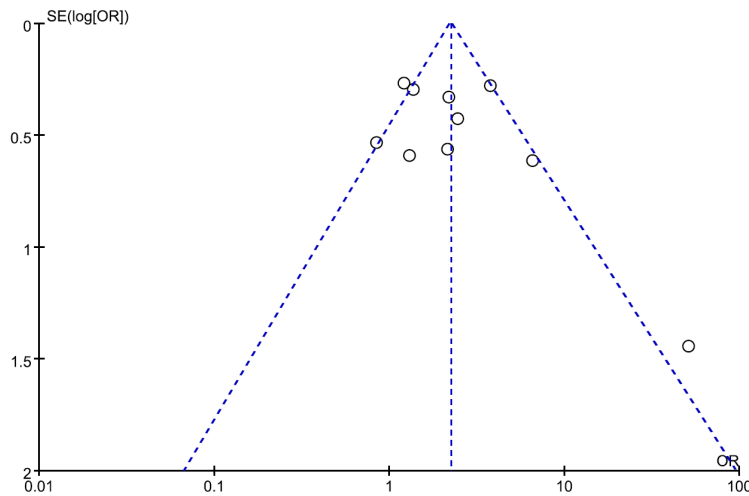

Figure 7. Publication bias analysis among the ten included studies.

py has been reported to alleviate symptoms in OLP patients, particularly in refractory cases [19]. This meta-analysis's findings support the hypothesis of an association between OLP and Candida albicans infection, further substantiated by the subgroup analysis results [20].

This study integrates data from ten published case-control studies to assess the correlation between OLP and Candida albicans infection. It examines how various OLP clinical manifestations impact the risk of Candida albicans infection. The results reveal a substantial association between OLP and Candida albicans infection, particularly among patients with erosive OLP. However, this correlation was not significant in non-erosive OLP patients. These findings imply that different OLP types exhibit distinct susceptibility to Candida albicans, a crucial factor contributing to clinical heterogeneity. Previous studies suggest that erosive OLP has significantly higher apoptosis levels and thinner oral epithelium compared to non-

ly garnered attention due to the high detection rate of Candida albicans in these patients [16]. The clinical manifestations of OLP and oral Candida albicans infection overlap, presenting as mucosal atrophy, erosion, and pain [17]. Research has shown that OLP patients exhibit epithelial defects in the oral mucosa, which compromise cell integrity, increase tissue fluid exudation, and decrease resistance to Candida albicans, predisposing them to opportunistic infections [18]. Furthermore, antifungal thera-

erosive OLP, facilitating Candida albicans' transition from a commensal to a pathogenic fungus. Furthermore, molecular alterations in OLP patients' oral mucosa, including aberrant gene expression of toll-like receptors and defensins, may contribute to their varying susceptibility to Candida albicans [21-24].

In this meta-analysis, heterogeneity tests indicated significant variability among the studies. To elucidate the underlying sources of heterogeneity, a subgroup analysis was conducted, focusing on geographical distribution and sampling methods. However, neither geographical distribution nor sampling methods fully accounted for the observed heterogeneity.

Notably, the subgroup analysis based on geographical distribution revealed a notable disparity in the risk of candidiasis infection among OLP patients. Specifically, the Asian group exhibited a significantly increased risk compared to the non-Asian group (Asia: OR 2.96, 95% CI: 1.43-6.13, P = 0.004 vs. non-Asia: OR 1.29, 95% CI: 0.94-1.77, P = 0.11). This finding indicates that OLP patients in Asian regions may be more susceptible to candidiasis infection than those in non-Asian regions, who appear to have a relatively lower risk.

Importantly, the *P*-value for the non-Asian group is corrected to 0.11, as the originally reported *P*-value of 0.011 does not align with the given 95% confidence interval, which suggests a non-significant trend. This correction ensures consistency in the interpretation of the statistical results.

Our sensitivity analysis and assessment for publication bias indicate that the study's results are highly reliable and robust. However, this meta-analysis has limitations stemming from variations in diagnostic criteria and research methodologies reported in the literature. Notably, foreign studies primarily adhere to the World Health Organization's diagnostic criteria, while domestic studies follow the standards set by the Chinese Society of Oral Medicine's Oral Mucosal Diseases Committee. These criteria exhibit nuanced differences, such as variations in lesion symmetry and abnormal epithelial hyperplasia, which could introduce selective bias.

Furthermore, variations in OLP patient conditions, disease stages, Candida albicans infec-

tion status, and diverse culture media sources for testing may contribute to inconsistent results. Therefore, it is recommended that more large-scale, high-quality, long-term follow-up studies be conducted to validate these findings and provide stronger evidence to support the conclusions of this study.

This study reveals the intricate relationship between OLP and Candida albicans infection, highlighting the diverse susceptibility to the latter among different clinical types of OLP. It offers novel insights and avenues for future research and clinical management. Our findings suggest a significant correlation between OLP and Candida albicans infection, implying that accurate laboratory markers should guide the administration of antifungal therapy. In cases of substantial fungal infection, antifungal treatment should be considered a primary treatment option. Consequently, Candida albicans infection should be viewed as a crucial factor in OLP treatment, indicating that fungal culture should be an essential diagnostic tool for both diagnosing and managing OLP.

Disclosure of conflict of interest

None.

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