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Original Article

Risk factors for the development of oral precancerous lesions in a cohort of 293 oral lichen planus patients with or without chronic periodontitis in southern Taiwan

Hsun-Yu Huang^{a†}, Pei-Yu Lin^{a†}, Chien-Chin Chen^{b,c*},
Yuk-Kwan Chen^{d,e,f**}

^a Department of Stomatology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan

^b Department of Pathology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan

^c Program in Translational Medicine, Rong Hsing Research Center for Translational Medicine, National Chung Hsing University, Taichung, Taiwan

^d School of Dentistry, College of Dental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

^e Division of Oral Pathology & Maxillofacial Radiology, Department of Dentistry, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^f Oral & Maxillofacial Imaging Center, Kaohsiung Medical University, Kaohsiung, Taiwan

Received 27 August 2023; Final revision received 17 October 2023

Available online 10 November 2023

KEYWORDS

Chronic periodontitis;
Oral lichen planus;
Oral precancerous
lesions;
Risk factors

Abstract *Background/purpose:* Oral lichen planus (OLP) may contribute to the risk of chronic periodontitis, and no reports have shown whether OLP patients with periodontitis have a greater risk of oral precancerous lesions, *Candida* infection or other clinicopathological diseases. This study aimed to assess the risk factors for the development of oral precancerous lesions in a cohort of 293 OLP patients with or without chronic periodontitis in southern Taiwan. *Materials and methods:* The current study recruited 293 OLP patients without preexisting periodontitis at a tertiary institution from 1995 to 2018. The patients were divided into two groups based on the presence or absence of periodontitis. The study compared various clinical and pathological characteristics between the two groups, and also estimated the odds ratio (OR) and the 10-year cumulative risk of chronic periodontitis in OLP patients using logistic regression models and Kaplan–Meier analysis methods, respectively.

* Corresponding author. Department of Pathology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, No. 539, Zhongxiao Rd., East Dist., Chiayi City, 600, Taiwan.

** Corresponding author. Division of Oral Pathology & Maxillofacial Radiology, Department of Dentistry, Kaohsiung Medical University Hospital, No. 100, Ziyou 1st Rd., Sanmin Dist., Kaohsiung City, 807, Taiwan.

E-mail addresses: hmarkc@gmail.com (C.-C. Chen), k0285@ms22.hinet.net (Y.-K. Chen).

† These two authors contributed equally to this work.

<https://doi.org/10.1016/j.jds.2023.10.020>

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Results: After adjusting for age and gender, the significant contributors to oral precancerous lesions in OLP patients ($P < 0.05$) were periodontal disease (OR = 2.24) and the male gender (OR = 7.52). Betel nut consumption (OR = 2.61), smoking (OR = 2.46), and candidiasis infection (OR = 3.02) also showed significant associations. Older OLP patients had a lower lesion risk, while a longer OLP duration heightened the periodontal disease likelihood.

Conclusion: The present study demonstrated that coexisting periodontal disease increases the likelihood of developing precancerous lesions in patients with OLP. Periodontal management with oral hygiene care and quitting betel nut consumption and smoking can reduce the risk.

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Introduction

Periodontitis is a prevalent immunoinflammatory disease caused by gram-negative microbial biofilms triggering a host immune response, leading to periodontal attachment loss, bone destruction, and dysbiosis in periodontal pathogens, resulting in gradual and chronic tissue destruction.¹ Chronic periodontitis involves immunological and inflammatory processes that can lead to the release of inflammatory mediators such as cytokines, prostaglandins, C-reactive protein, and interleukins (ILs). Other investigations have shown that bacteria from the subgingival biofilm may enter the bloodstream and spread to distant organs and tissues, causing systemic inflammation.²

Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disease that commonly affects the buccal mucosa, dorsum of the tongue, and gingiva in the oral cavity. It has a prevalence ranging from 0.1% to 4%, varying depending on the sampled population. OLP is more frequently observed in middle-aged to older women, with a women to men ratio of approximately 3:2.³ However, in Taiwan, the ratio can be as high as 4:1 or 5:1.⁴ Histopathologically, OLP is characterized by a varying epithelial thickness, basal cell destruction, and a clustered infiltration of lymphocytes in the lamina propria.^{5,6} Moreover, OLP is generally considered to be related to the immune dysfunction of T cells against epithelial cells. Activated CD8⁺ lymphocytes, known to induce keratinocyte apoptosis, are commonly found in the affected epithelium.⁷

The coexistence of chronic periodontitis and OLP suggests a potential interaction between these two conditions. Both diseases involve chronic inflammation and immune responses, with elevated levels of proinflammatory cytokines and matrix metalloproteinases (MMPs) observed in affected tissues. In periodontitis, upregulated cytokines contribute to tissue destruction and bone loss.⁸ Similarly, OLP is characterized by T lymphocyte aggregation and the release of cytokines involved in the pathogenesis of the disease.^{9–11} Elevated levels of inflammatory markers in the serum are associated with the severity of periodontal destruction. These findings support the notion of an interplay between OLP and chronic periodontitis.^{6,12}

Previous case studies have shown significant manifestations of periodontitis in OLP patients, particularly in the presence of atrophic-erosive lesions.^{3,13} However, as these were cross-sectional studies, it was difficult to determine

the causal relationship between the two conditions, leading to a lack of consensus in the literature regarding the interrelationship between the two diseases. A direct correlation between OLP and the development of periodontitis has yet to be conclusively verified. One systematic review and meta-analysis suggested a significant relationship between the severity of periodontal disease and the presence of OLP, although further population studies with consideration of potential confounding factors are needed to confirm this association.¹⁴ Additionally, there is a lack of long-term follow-up data examining the incidence of periodontitis in OLP cases.

Despite OLP being regarded as a potential precancerous lesion by the World Health Organization (WHO), the increased risk of malignant transformation remains a contentious issue with clinical implications. The current literature does not reveal an increased incidence of oral precancerous lesions (such as leukoplakia, oral submucous fibrosis and verrucous hyperplasia) in OLP patients, nor has the association between OLP with chronic periodontitis and other oral pathological diseases been thoroughly examined.^{14,15} Hence, the present study investigated the risk factors for the development of oral precancerous lesions in a cohort of 293 OLP patients with or without chronic periodontitis in southern Taiwan.

Materials and methods

The current retrospective study, approved by the Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital (IRB-2019075), searched for cases with histopathological diagnoses of OLP, which were consistent with clinical diagnoses recorded by ICD-10 codes L43, L43.0, L43.8, and L43.9, between 1995 and 2018.

The inclusion criteria were a clinical and histopathologic diagnosis of OLP based on the criteria of the American Academy of Oral and Maxillofacial Pathology (AAOMP) in 2016.¹⁶ Initially, 318 OLP patients were confirmed to meet our study's criteria; 25 with preexisting chronic periodontitis were excluded. The final study included 293 OLP patients divided into two groups: an experimental group ($n = 59$) with subsequent chronic periodontitis and a control group ($n = 234$) without chronic periodontitis. All data were confirmed before statistical analysis. The clinical manifestations and pathological characteristics, including age at diagnosis, gender, location, systemic diseases (e.g.,

liver diseases, diabetes mellitus, cardiovascular disease, chronic kidney disease, hyperlipidemia, autoimmune diseases, and psychiatric diseases), oral precancerous lesions, alcohol consumption, betel nut consumption, cigarette smoking, candidiasis, and chronic periodontitis, were collected from the medical records and pathological reports. Diagnoses of the systemic diseases mentioned above were made by our internal medicine physicians in accordance with WHO guidelines and documented in the medical records. Among the oral precancerous lesions adapted from the medical records were leukoplakia, erythroplakia, oral submucosal fibrosis, verrucous hyperplasia, and oral epithelial dysplasia. For the diagnosis of periodontal disease, we included ICD-10 K0530 in the medical records and confirmed alveolar bone loss through panoramic radiographs taken during the patient's clinic visit. Periodontal disease was initially determined by assessing interproximal tissue loss and considering bone loss of less than 15 % on radiographs.¹⁷ Based on these criteria, 59 cases of periodontal disease were included. The date of diagnosis according to ICD-10 code K0530 was also recorded.

The distributions of age, gender, and clinical parameters were analyzed descriptively, and independent *t*-test and chi-squared test were used to identify the differences between groups. All results adjusted for confounders and interactions were estimated with the odds ratio (OR) and 95 % confidence interval (CI) by conducting a logistic regression model. The 10-year cumulative risk in OLP patients from different perspectives of age and periodontitis was measured using the Kaplan–Meier analysis method. All statistical analyses were performed using SAS 9.4 for

Windows (SAS Institute, Inc., Cary, NC, USA). The significant value was defined as two-tailed $P < 0.05$.

Results

Over the duration of 23 years, a total of 293 cases were clinically and histopathologically diagnosed as OLP, among which 59 cases (20.1 %) had generalized chronic periodontitis. The demographic characteristics and clinical parameters of the two groups are presented in Table 1. The study included 179 males (61.09 %) and 114 females (38.91 %) with a mean age of 53.33 years at OLP diagnosis. There was no significant difference between genders. Periodontal disease was more prevalent in OLP patients younger than 50 years (57.63 %) than in those older than 50 years (42.37 %). Additionally, OLP patients with periodontal disease showed higher rates of precancerous lesions, betel nut consumption, and candidiasis infections than those without periodontal disease.

The factors influencing oral precancerous lesions in patients with OLP are presented in Table 2. After adjusting for age and sex, patients with periodontal disease had a 2.24-fold (adjusted OR = 2.24, $P = 0.016$) higher likelihood of developing oral precancerous lesions than those without periodontal disease. Similarly, being male increased the likelihood of developing precancerous lesions by 7.52 times (adjusted OR = 7.52, $P < 0.001$) compared to females. Patients below 50 years of age with OLP also had a higher risk of precancerous lesions than those above 50 years. The crude OR revealed higher risks of precancerous lesions in

Table 1 Baseline characteristics of oral lichen planus in the current study.

	Total	Periodontitis	Nonperiodontitis	<i>P</i> value
Number	293	59	234	
Age, mean ± standard deviation	53.33 ± 14.61	48.02 ± 14.03	54.66 ± 14.48	0.002 ^a
Age grouping (years)				
<50	119 (40.61)	34 (57.63)	85 (36.32)	0.003 ^a
≥50	174 (59.39)	25 (42.37)	149 (63.66)	
Male	179 (61.09)	42 (71.19)	137 (58.55)	0.075
Location				
Buccal	218 (74.40)	45 (76.27)	173 (73.93)	0.713
Nonbuccal	75 (25.60)	14 (23.73)	61 (26.07)	
Liver diseases	51 (17.41)	9 (15.25)	42 (17.95)	0.626
Diabetes mellitus	55 (18.77)	12 (20.14)	43 (18.38)	0.730
Cardiovascular disease	84 (28.67)	13 (22.03)	71 (30.34)	0.207
Peptic ulcer	49 (16.72)	13 (22.03)	36 (15.38)	0.221
Chronic kidney disease	11 (3.75)	1 (1.69)	10 (4.27)	0.700
Hyperlipidemia	22 (7.51)	5 (8.47)	17 (7.26)	0.783
Autoimmune diseases	25 (8.53)	6 (10.17)	19 (8.12)	0.615
Psychiatric diseases	22 (7.51)	5 (8.47)	17 (7.26)	0.873
Oral precancerous lesions	114 (38.91)	34 (57.63)	80 (34.19)	0.001 ^a
Cancer (other than oral cancer)	26 (8.87)	5 (8.47)	21 (8.97)	0.904
Alcohol drinking	19 (6.48)	4 (6.78)	15 (6.41)	>0.999
Betel nut chewing	65 (22.18)	21 (35.59)	44 (18.80)	0.006 ^a
Cigarette smoking	74 (25.26)	17 (28.81)	57 (24.36)	0.482
Candidiasis	35 (11.95)	17 (28.81)	18 (7.69)	<0.001 ^a
Oral cancer	32 (10.92)	9 (15.25)	23 (9.83)	0.233

^a $P < 0.05$, statistically significant; $P > 0.05$, statistically insignificant. Categorical variables are presented as numbers (%).

Table 2 The influencing factors of oral precancerous lesion obtained after oral lichen planus in the current study.

	Crude OR (95 % CI)	P value	Adjusted OR ^b (95 % CI)	P value
Periodontitis	2.62 (1.46, 4.69)	0.001 ^a	2.24 (1.16, 4.31)	0.016 ^a
Age				
<50	Ref. ^c		Ref. ^c	
≥50	0.44 (0.27, 0.72)	<0.001 ^a	0.60 (0.35, 1.02)	0.058
Male	8.17 (4.40, 15.15)	<0.001 ^a	7.52 (4.01, 14.11)	<0.001 ^a
Location				
Buccal	Ref. ^c		Ref. ^c	
Nonbuccal	0.57 (0.32, 1.00)	0.050	0.58 (0.31, 1.09)	0.092
Liver diseases	1.02 (0.55, 1.89)	0.960	0.85 (0.43, 1.68)	0.630
Diabetes mellitus	1.40 (0.77, 2.52)	0.270	1.53 (0.78, 2.99)	0.215
Cardiovascular disease	0.57 (0.33, 0.98)	0.043 ^a	0.59 (0.32, 1.08)	0.086
Peptic ulcer	0.58 (0.30, 1.13)	0.107	0.78 (0.37, 1.63)	0.505
Chronic kidney disease	2.86 (0.82, 10.01)	0.100	2.85 (0.72, 11.27)	0.136
Hyperlipidemia	1.63 (0.68, 3.90)	0.271	2.10 (0.78, 5.65)	0.141
Autoimmune diseases	1.79 (0.79, 4.08)	0.165	2.25 (0.89, 5.72)	0.088
Psychiatric diseases	1.34 (0.56, 3.21)	0.514	1.61 (0.60, 4.36)	0.345
Cancer (other than oral cancer)	0.68 (0.28, 1.61)	0.375	0.52 (0.21, 1.31)	0.166
Alcohol drinking	3.71 (1.37, 10.07)	0.010 ^a	2.06 (0.73, 5.82)	0.172
Betel nut drinking	5.70 (3.11, 10.43)	<0.001 ^a	2.61 (1.35, 5.04)	0.004 ^a
Cigarette smoking	5.49 (3.10, 9.73)	<0.001 ^a	2.46 (1.31, 4.63)	0.005 ^a
Candidiasis	3.05 (1.47, 6.35)	0.003 ^a	3.02 (1.33, 6.87)	0.008 ^a

OR: odds ratio; CI: confidence interval; Ref.: reference.

^a $P < 0.05$, statistically significant; $P > 0.05$, statistically insignificant.

^b All variables were adjusted for age and sex.

^c Reference as a control group within the group.

OLP patients consuming alcohol (OR = 3.71, $P = 0.01$), betel nut (OR = 5.70, $P < 0.001$), and cigarettes (OR = 5.49, $P < 0.001$) than in nonconsumers. After age and gender adjustment, the significance of alcohol consumption was diminished, but betel nut consumption and cigarette smoking retained significant associations (adjusted OR = 2.61 and 2.46, respectively). Additionally, candidiasis infection emerged as a significant factor for precancerous lesions (adjusted OR = 3.02, $P = 0.008$) in the present study.

The study also observed the 10-year cumulative incidence of OLP from different perspectives. The cumulative incidence was significantly higher in individuals younger than 50 years of age than in those older than 50 years (log-rank test = 0.01) (Fig. 1). Additionally, an increased cumulative incidence in the development of chronic periodontitis was observed in OLP patients (Fig. 2).

Discussion

Based on the literature review, there is a significant relationship between periodontal disease severity and OLP; however, further studies are needed to consider potential confounding factors.¹⁴ By carefully analyzing medical and dental histories, as well as personal oral habits, the relationships between periodontal disease, OLP, and other systemic diseases were successfully identified. In the present study, younger patients with OLP (below 50 years) had

a higher proportion of periodontal disease than older patients (Table 1). This suggested that the occurrence of OLP at a younger age may be more likely to be accompanied by periodontal disease. Difficulties in maintaining good oral hygiene due to uncomfortable oral lesions could be a contributing factor, as mentioned in previous studies.³

From an immunological perspective, OLP is a chronic inflammatory disorder characterized by oral mucous membrane destruction involving T-cell-mediated autoimmune processes.⁸ The inflammatory response in OLP includes the presence of T lymphocytes and various cytokines, such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, tumor growth factor (TGF)- β , interferon (IFN)- γ , and tumor necrosis factor (TNF)- α .^{9–11} These cytokines indicate immunological dysregulation and play a significant role in the development of OLP.¹⁸ Chronic periodontitis is another inflammatory disease caused by microorganisms and immune-inflammatory responses, involving several cytokines, such as IL-1 α , IL-1 β , IL-6, IL-17, and TNF- α .⁸ Although limited studies have shown the interaction of cytokines in OLP and chronic periodontitis, patients with both conditions exhibit significantly higher levels of proinflammatory cytokines (such as IL-17 and IL-23) in their serum than healthy individuals.⁶ In other words, long-term exposure to inflammatory cytokines in OLP patients, especially at a younger age, may contribute to periodontal tissue instability and worsen the disease. Our study further investigated this using the 10-year cumulative incidence, showing that the longer OLP is present, the higher the prevalence of

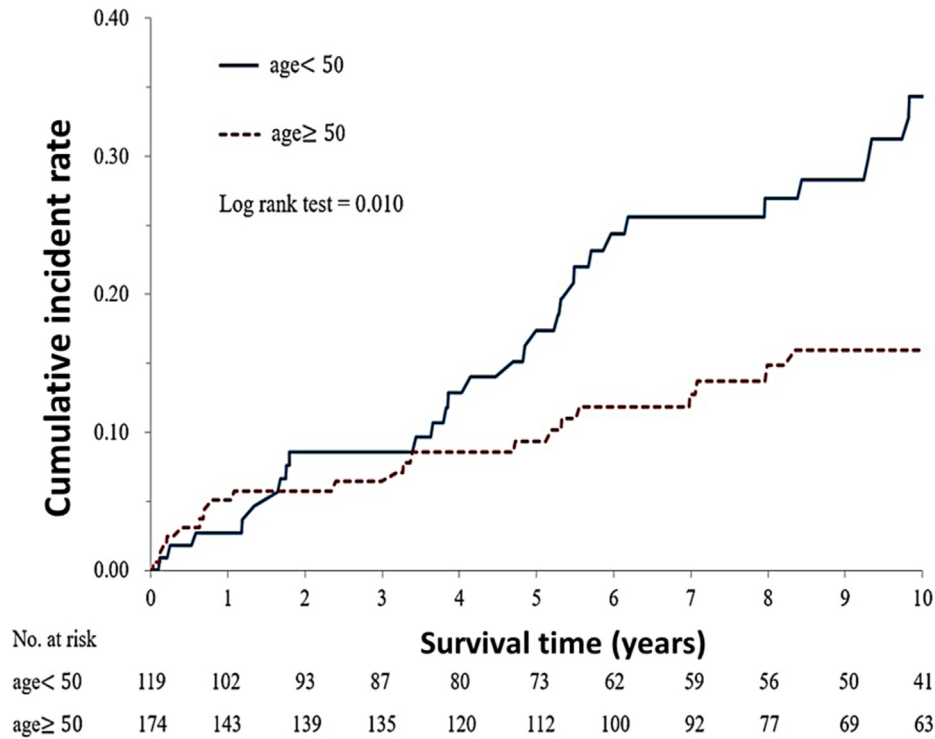


Fig. 1 10-year cumulative incidence rate of oral lichen planus (OLP) by age.

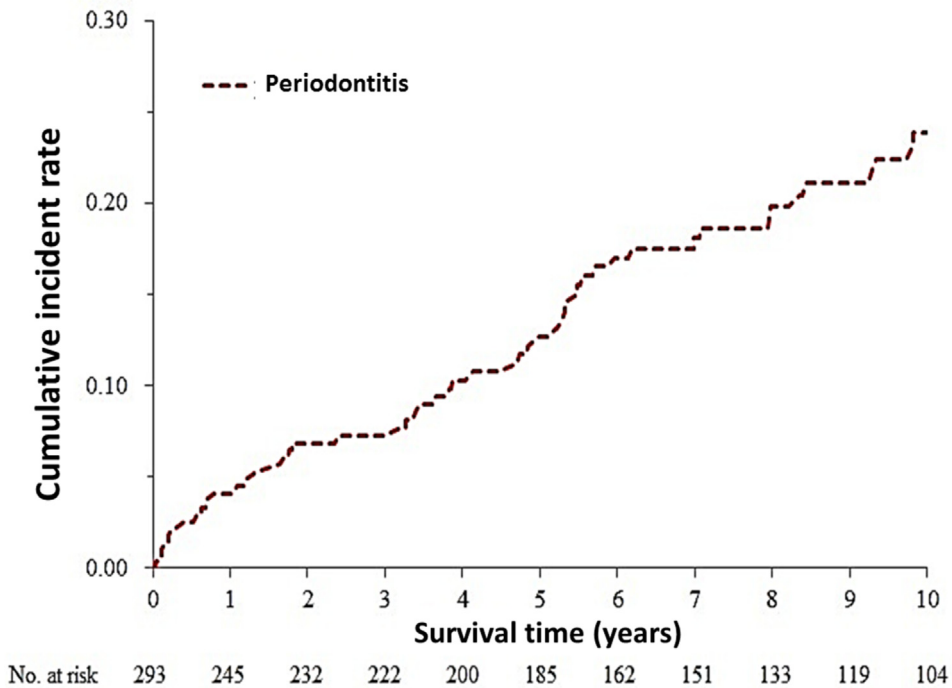


Fig. 2 10-year cumulative incidence rate of periodontitis in oral lichen planus (OLP) patients.

periodontal disease (Fig. 2). The current study was the first to demonstrate the incidence of periodontitis in OLP patients.

Additionally, the present study found a significantly high proportion of OLP patients with chronic periodontitis

presenting with oral precancerous lesions, including leukoplakia, erythroplakia, verrucous hyperplasia, oral submucous fibrosis, and oral epithelial dysplasia, based on pathological manifestations (Table 1). OLP patients with periodontitis showed elevated MMP-1 and MMP-9 levels in

gingival crevicular fluid and gingival tissue compared to those with periodontitis alone. MMPs are enzymes involved in tissue turnover and destruction, and their dysregulation can disrupt physiological processes. Increased MMP-1 levels may contribute to tissue destruction in mucosal inflammatory diseases and periodontal diseases,¹⁹ while elevated MMP-9 levels have been linked to the development of carcinogenesis in OLP.²⁰

Taken together, chronic periodontitis in OLP patients may accelerate tissue breakdown due to difficulties in maintaining oral hygiene and increased levels of inflammatory cytokines. Elevated MMPs in the mucosa of OLP and periodontitis patients contribute to soft tissue destruction, increasing susceptibility to precancerous lesions.²¹ The results of our study provided further evidence of the impact of periodontal status on OLP patients, indicating that chronic periodontitis is associated with a 2.24 times higher likelihood of oral precancerous lesions in OLP patients.

From Table 1, we observed a higher proportion of betel nut chewing in OLP patients with chronic periodontitis than in those without. Previous research has linked betel nut chewing to negative effects on periodontal health, such as a higher prevalence of bleeding on probing, greater clinical attachment loss, and significant alveolar bone loss.^{22,23} The major alkaloid of the areca nut, arecoline, directly influences the periodontium by inhibiting cell functions and collagen synthesis.²⁴ Moreover, betel nut chewing induces an inflammatory response characterized by the production of prostaglandin E2 (PGE2),²⁵ contributing to periodontal tissue and oral mucosa damage. Heavy deposition of calculus around teeth in betel nut consumers results from hypersalivation and increased calcium salt levels, making oral hygiene practices more challenging.

Our study also found a significant odds ratio indicating an increased risk of oral precancerous lesions in OLP patients who chewed betel nut (Table 2). It is well known that arecoline in betel nut generates carcinogenic compounds through nitrication, and its polyphenolic compounds can inhibit collagenase, releasing oxygen-containing free radicals that may lead to DNA damage, cell mutation, and cancer.²⁶ Therefore, it is crucial for OLP patients to be fully aware of the negative consequences of betel nut chewing and to quit this habit promptly to prevent the onset and progression of periodontitis and precancerous lesions.

Some studies have revealed no significant difference in candidiasis infection between healthy individuals and patients with lichen planus.^{27,28} However, a meta-analysis revealed that more than one-third of OLP lesions are infected by *Candida* species.²⁹ In the present study, we found a higher proportion of candidiasis infection in OLP patients with chronic periodontitis than in those without periodontitis, consistent with previous research highlighting the strong association between *Candida* species and periodontal diseases.³⁰ *Candida* may act directly or in collaboration with other subgingival bacterial pathogens, leading to an increased risk of periodontal attachment loss and subsequent disease. Additionally, *Candida* superinfection can exacerbate OLP symptoms and contribute to oral precancerous lesions, possibly due to the production of

carcinogenic agents, such as nitrosamine or acetaldehyde.²⁹ This may explain why *Candida* infection was also identified as a significant contributor to oral precancerous lesions in our study.

In recent years, there has been growing interest in exploring the relationship between OLP and systemic diseases. Studies have investigated potential associations with liver diseases,³¹ dyslipidemia, hypertension, diabetes mellitus, chronic kidney disease,³² and autoimmune disorders.^{33,34} However, the present study found no significant association with systemic disease in OLP patients, regardless of periodontal disease.

This lack of correlation may be influenced by the sample size used in the study. Considering the complexity of systemic diseases, which are influenced by multiple factors, the absence of significant correlations in this study does not rule out the possibility of underlying connections between OLP and systemic diseases. Further research with a larger and more diverse population is needed to explore these associations and gain a better understanding.

OLP usually affects middle-aged women,^{35,36} but in our study, we found a higher proportion of men (M: F ratio = 1.57: 1) and a mean age of 53.3 years in OLP patients, with the youngest patient being 16-years-old. The unexpected male predominance in the study can be attributed to our focus on patients visiting the Oral and Maxillofacial Surgery Department, where oral mucosal diseases are more common in males. This trend is primarily due to higher rates of smoking, drinking, and betel nut consumption among men in Taiwan. Consequently, the collected population predominantly consisted of males. However, there was no significant difference in gender among OLP patients, regardless of whether they had periodontal disease (Table 1).

In conclusion, the study revealed that OLP is associated with higher risks of chronic periodontitis and precancerous lesions. Coexisting periodontal disease in OLP patients significantly increases the likelihood of developing oral precancerous lesions. Other risk factors include the male, betel nut consumption, smoking, and candidiasis infection. Proper management of periodontal disease and improved oral hygiene, along with advice on betel nut and smoking cessation, are crucial in reducing the risk of precancerous lesions in OLP patients. To the best of our knowledge, this was the first study to assess the risk factors for the development of oral precancerous lesions in OLP patients with or without chronic periodontitis and the incidence of periodontitis in OLP patients.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

There was no funding related to this study.

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