Journal of Dental Sciences 20 (2025) 238–247

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

Prognostic nomogram for proliferative verrucous leukoplakia

Yanning Zhang [a,b], Xinning Zhang [a,c], Zhiming Qin [a,c], Jing Yan [a], Binbin Li [a,c*]

[a] *Department of Oral Pathology, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing, PR China*

[b] *Laboratory of Stomatology Hebei Clinical Research Center for Oral Diseases, School and Hospital of Stomatology, Hebei Medical University, Shijiazhuang, PR China*

[c] *Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Chinese Academy of Medical Sciences (2019RU034), PR China*

Received 3 July 2024; Final revision received 30 July 2024
Available online 13 August 2024

KEYWORDS
Proliferative verrucous leukoplakia;
Nomogram;
Early diagnosis;
Prognosis;
Predictive model

Abstract *Background:* Proliferative verrucous leukoplakia (PVL) is a special type of leukoplakia characterized by high rate of malignant transformation into oral squamous cell carcinoma (OSCC). This study aimed to analyze the canceration risk and prognostic factors of PVL and establish effective diagnostic and prognostic predictive models.

Materials and methods: A total of 467 patients were enrolled, including 170 cases of PVL. The independent risk and prognostic factors of PVL were analyzed by univariable and multivariable logistic regression. Nomogram models were constructed to predict the canceration risk and prognosis of PVL. The predictive power was evaluated by Hosmer–Lemeshow test, receiver operating characteristic (ROC) curve, calibration curve and decision curve analysis.

Results: Multivariable logistic regression analyses identified that canceration risk factors of PVL included sex, lesion sites, clinical presentation, non-smoker and oral epithelial dysplasia (OED). The independent prognostic factors of PVL were sex, clinical presentation, local irritants and OED. Diagnosis and prognostic nomogram models were constructed. The areas under the ROC curve were 0.945 and 0.893, respectively. The calibration plots showed strong agreement between the prediction and observation. Decision curve analysis indicated that the models provided significant clinical benefits for patients.

* Corresponding author. Department of Oral Pathology, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Chinese Academy of Medical Sciences (2019RU034), No. 22 Zhongguancun South Avenue, Haidian District, Beijing, 100081, PR China.
E-mail address: kqlibinbin@bjmu.edu.cn (B. Li).

https://doi.org/10.1016/j.jds.2024.07.037

Conclusion: Our study established and validated the diagnosis and prognostic predictive nomogram models, which were accurate to predict the canceration risk and prognostic factors of PVL, providing individualized clinical decisions for clinical work.

Introduction

Proliferative verrucous leukoplakia (PVL) is a special type of leukoplakia with high rate of malignant transformation into oral squamous cell carcinoma (OSCC). PVL is more common in elderly women and non-smokers,[1] frequently involving gingiva, alveolar ridge, buccal mucosa and tongue abdomen.[2] It tends to affect multiple sites, has a wide range, is easy to recur, and exhibits invasive proliferative features.

PVL is characterized by a progressive clinical course, constantly changing clinical and histopathological features, and has the highest risk of malignant transformation compared to other potentially malignant disorders (OPMDs). It has been reported a recurrence rate of 67.2% and a malignant transformation rate of 26.7%–72.4%.[3–5] However, compared with OSCC, PVL demonstrates a relatively favored prognosis, especially in terms of survival rates,[6] which indicates that PVL is distinct from typical oral leukoplakia.

No specific risk factors have been identified, although viral and bacterial infection have been studied, there is no clear evidence to suggest that PVL is associated with HPV infection.[7–9] There have been limited studies focus on the EB virus infection in PVL. In a study conducted by Bagan et al., the EB virus was detected positive in 40% of PVL cases (6 out of 10 patients).[10] Additionally, PVL patients have been found to have a higher abundance of *Campilobacterota* and lower *Proteobacteria*.[11] However, there is still a lack of sufficient data to establish a direct relationship between microbial infection and PVL.

Since 1985, several diagnostic criteria have been proposed,[2,12–15] but there are still no unified diagnostic criteria. Among them, the criteria proposed by Cerero-Lapiedra et al., with its quantifiable diagnostic indicators and easy calculation, are relatively easy to implement in clinical practice. The criteria included the disorder affecting more than two different oral sites and the presentation of verrucous appearance. However, it is important to note that the initial manifestation of PVL may be a flat white area or lichenoid appearance, similar to oral leukoplakia, oral lichen planus and other oral white lesions.[2,16,17] Thus, these cases could be erroneously treated as conventional oral leukoplakia (COL) or oral lichen planus (OLP), ignoring the risk factors, subsequently malignant transformation.

Due to the lack of uniform diagnostic criteria for PVL, and few specific risk factors and candidate biomarkers predictive of malignant transformation have been associated with PVL, timely and accurate diagnosis and prediction are challenging in clinical practice. Therefore, we utilized logistic regression to analyze the canceration risk and prognostic factors of PVL and visualized them by nomogram, establishing a system for accurate assessment.

Methods and materials

Patient enrollment

This study included data from patients with leukoplakia collected at Peking University School and Hospital of Stomatology from January 2013 to December 2020. The studies involving human participants were reviewed and approved by The Biomedical Ethics Committee of the Department of Peking University (No. PKUSSIRB-201948111). The inclusion criteria were as follows: (a) Histologically confirmed oral leukoplakia, (b) It is not clinically diagnosable for other diseases. Exclusion criteria were: (a) Those with previous or present OSCCs, (b) With tumors of other origins or other serious diseases; (c) Insufficient follow up data.

PVL was diagnosed according to the criteria proposed by Cerero-Lapiedra et al..[13] Major criteria: (a) Leukoplakia lesion with more than two different oral sites; (b) Verrucous appearance; (c) Spreading or engrossing during the disease development; (d) Presence of recurrence in a previously treated area; (e) Histopathological test: oral epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma, or squamous cell carcinoma, whether in situ or infiltrating. Minor criteria: (a) Oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas; (b) Female patient; (c) Non-smoker regardless of gender; (d) More than 5 years evolution. Diagnostic criteria: Three major criteria (one of which must include the evolution of the histopathological lesions) or two major criteria (one of which must include the evolution of the histopathological lesions) + two minor criteria.

The rest patients except those diagnosed with PVL were classified as conventional oral leukoplakia (COL). A minimum of 9-year clinical follow-up was required for COL patients, and 5-year clinical follow up for PVL patients.

Data collection and processing

Baseline characteristics of PVL patients were collected, including sex, age, local irritants, tobacco and alcohol habits, clinical presentation, primary site, malignant transformation, and oral epithelial dysplasia (OED). Local irritants, such as faulty restorations, residual roots, sharp tooth cusps, dental appliances, silver amalgam, were included in the possible influencing factors accessed in this analysis. The primary lesion sites included oral subsites:

dorsum and ventrum of the tongue, buccal mucosa, floor of the mouth, gingiva, lip, soft palate, hard palate. Furthermore, based on the number of subsites involved, the lesion sites were categorized into those affecting more than two subsites and those affecting two or fewer subsites. The involvement of the ventral tongue and floor of the mouth as primary sites was also considered as potential risk factors and prognostic factors. Clinical presentation was considered homogeneous in the presence of predominantly white, flat, thin or wrinkled lesions; and non-homogeneous in the presence of mixed white-and-red, erosion, nodular, granular, and verrucous lesions.

Model construction and evaluation

All variables underwent univariable logistic analysis, and those with a *P*-value <0.05 were included in the multivariable logistic analysis to identify the risk and prognostic factors for PVL. Subsequently, diagnostic and prognostic nomogram models were developed based on the factors identified through multivariate logistic regression analysis. The accuracy of the model was assessed using ROC analysis. The calibration curve was employed to assess the agreement between the predicted and actual probability. A closer alignment between the two lines indicates a higher consistency between the predicted and actual incidence rates, suggesting better performance of the nomogram prediction model. Lastly, decision curve analysis (DCA) was employed to evaluate the net benefit and clinical utility for patients by quantifying the net benefit at different threshold probabilities.

Statistical analysis

Statistical analyses were performed using SPSS software (version 22.0, IBM Corp., Armonk, NY, USA) and R 4.4.0. Continuous variables were expressed as the mean ± SD or median (interquartile range). Categorical variables are presented as numbers (percentages). Independent t-tests or Mann–Whitney U tests were used for analyzing continuous variables, depending on their distribution. For categorical variables, the chi-squared test or Fisher's exact test was employed. A two-sided *P*-value <0.05 was considered statistically significant.

Results

Clinical and pathological characteristics

A total of 467 patients were enrolled in this study with oral leukoplakia (OLK) confirmed by two pathologists, including 207 males and 260 females. The age ranged from 13 to 88 years, with a mean of 55 years. In these OLK patients, 170 cases were diagnosed with PVL according the criteria. As shown in Table 1, patients with PVL were predominantly

Table 1 Descriptive clinicopathological characteristics of proliferative verrucous leukoplakia (PVL) cases and conventional oral leukoplakia (COL) Controls.

Participants Characteristics	COL (n = 297)	PVL (n = 170)	*P*-Value
Age (years)	54.00 [46.00; 63.00]	57.00 [49.00; 64.00]	0.042*
Sex:			<0.001
Female	121 (40.74%)	139 (81.76%)	
Male	176 (59.26%)	31 (18.24%)	
Lesion sites:			<0.001
< =2	242 (81.48%)	45 (26.47%)	
>2	55 (18.52%)	125 (73.53%)	
Clinical presentation:			<0.001
homogeneous	241 (81.14%)	101 (59.41%)	
non-homogeneous	56 (18.86%)	69 (40.59%)	
Local irritants:			>0.99
No	176 (59.26%)	101 (59.41%)	
Yes	121 (40.74%)	69 (40.59%)	
Smoker:			<0.001
No	188 (63.30%)	162 (95.29%)	
Yes	109 (36.70%)	8 (4.71%)	
Alcohol use:			<0.001
No	238 (80.13%)	161 (94.71%)	
Yes	59 (19.87%)	9 (5.29%)	
OED:			<0.001
Non-OED	218 (73.40%)	79 (46.47%)	
OED	79 (26.60%)	91 (53.53%)	
VT or FOM involved:			<0.001
No	246 (82.83%)	112 (65.88%)	
Yes	51 (17.17%)	58 (34.12%)	

*Mann–Whitney U test.
OED, oral epithelial dysplasia; Non-OED, without oral epithelial dysplasia; VT or FOM involved, ventral tongue or floor of mouth involved.

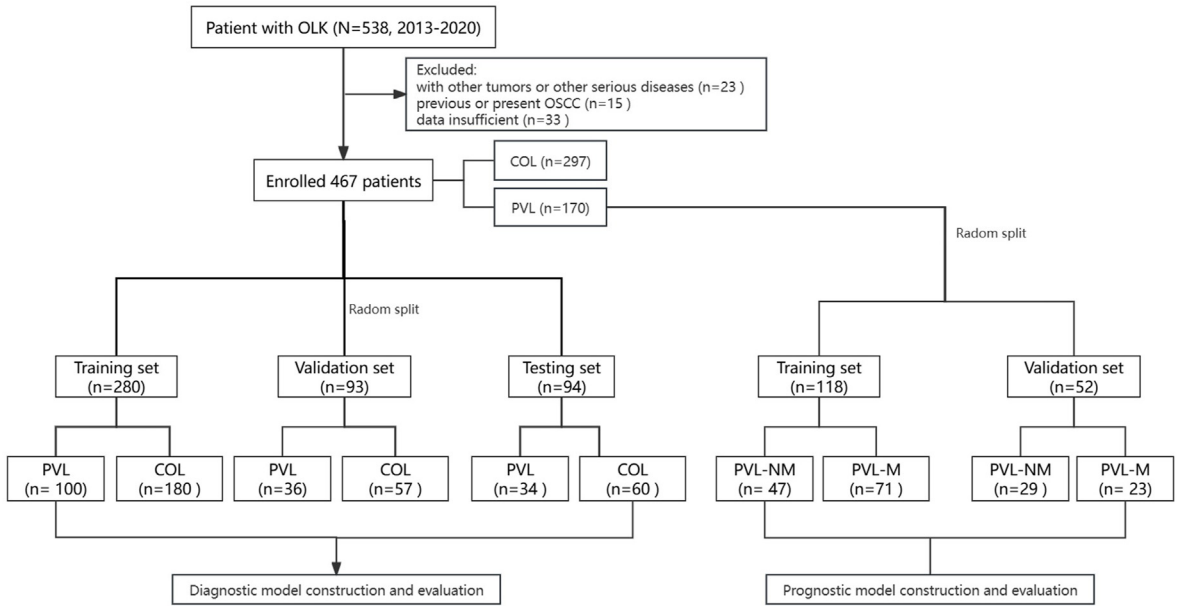

Figure 1 Flow chart of patient enrollment. OLK, oral leukoplakia; COL, conventional oral leukoplakia; PVL, proliferative verrucous leukoplakia; PVL-NM, PVL without malignant transformation; PVL-M, PVL with malignant transformation.

Table 2 Univariable and multivariable logistic regression of risk factor of proliferative verrucous leukoplakia (PVL).

variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.013(0.994–1.033)	0.172		
Sex	0.112(0.06–0.21)	<0.001	0.111(0.036–0.342)	<0.001
Lesion sites	11.893(6.658–21.244)	<0.001	103.956(31.962–338.12)	<0.001
Clinical presentation	2.312(1.327–4.028)	0.003	2.993(1.144–7.828)	0.025
Local irritants	0.933(0.567–1.536)	0.786		
Smoker	0.052(0.016–0.171)	<0.001	0.068(0.013–0.36)	0.002
Alcohol use	0.079(0.019–0.335)	0.001	0.216(0.026–1.796)	0.156
OED	3.285(1.961–5.504)	<0.001	7.374(2.658–20.455)	<0.001
VT or FOM involved	2.546(1.413–4.588)	0.002	2.079(0.82–5.271)	0.123

OED, oral epithelial dysplasia; VT or FOM involved, ventral tongue or floor of mouth involved.

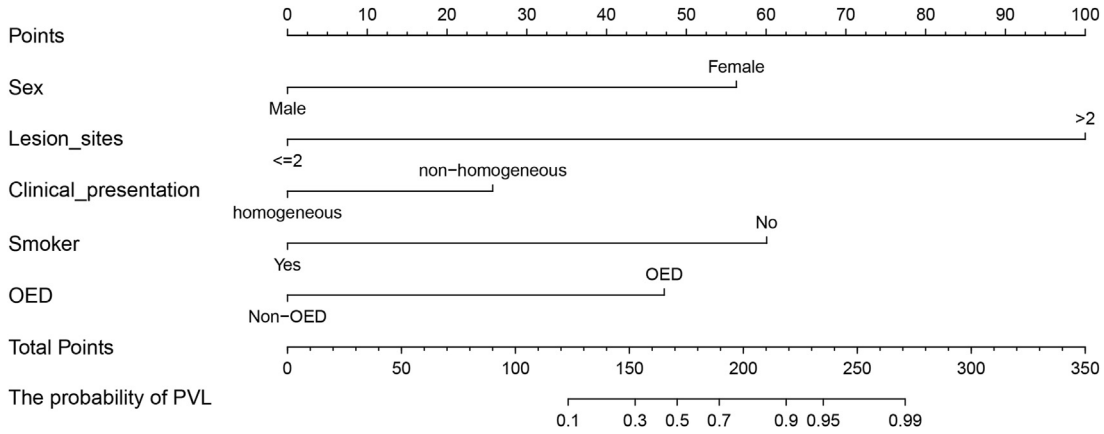

Figure 2 Nomogram for predicting risk of proliferative verrucous leukoplakia (PVL). Five factors were calculated into the PVL prediction nomogram. OED, oral epithelial dysplasia.

female (81.76%), non-smokers (95.29%), and non-alcohol users (94.71%). They also had a higher likelihood of presenting with multifocal lesions initially (73.53%). Additionally, OED was observed in 53.53% of patients with PVL. Lesions located on the ventral tongue or floor of the mouth were more commonly observed in this patient population (Table 1).

In the diagnostic nomogram model, all samples were divided into training set (n = 280), validation set (n = 93) and testing set (n = 94) according to the 6:2:2 random allocation principle. And in the prognostic nomogram model, PVL samples were divided into a training set (n = 118), and validation set (n = 52). The details of cohort inclusion were shown in Fig. 1.

Diagnostic nomogram model for PVL

Univariable logistic analysis on 9 potential factors, and the result determined PVL-related risk factors, including sex, number of lesion sites, clinical presentation, smoker, alcohol use, OED and ventral tongue or floor of mouth involved. Additionally, the multivariable logistic regression analysis revealed that independent risk factor of PVL were sex, number of lesion sites, clinical presentation, smoker, and OED (Table 2).

Based on the combined model, we developed an intuitive, simple-to-use nomogram for individual risk prediction of PVL (Fig. 2). Hosmer–Lemeshow test indicated a great calibration performance ($P = 0.628$). ROC analysis revealed

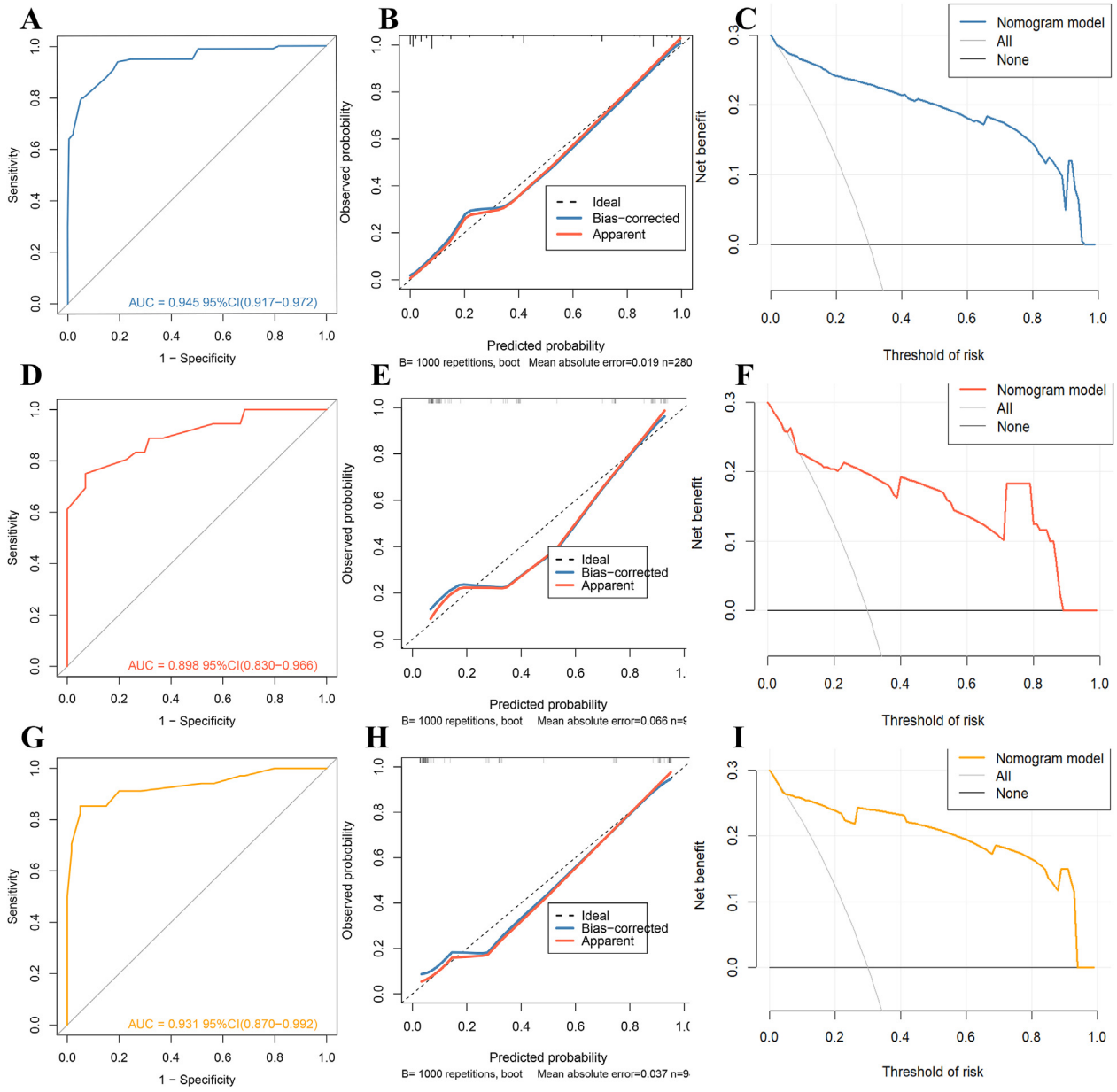

Figure 3 Receiver operating characteristic (ROC) curves, calibration plots and decision curve analysis (DCA) of the nomogram for the risk factor of proliferative verrucous leukoplakia (PVL). ROC for nomogram in training set (A), validation set (D) and testing set (G); Calibration plot for the diagnostic nomogram in training set (B), validation set (E) and testing set (H); Decision curve analysis for the diagnostic nomogram in training set (C), validation set (F) and testing set (I).

that AUC value of the nomogram reached 0.945, indicating that this model has excellent discriminant ability (Fig. 3A). The calibration plot revealed good predictive accuracy between the actual probability and predicted probability (Fig. 3B). In addition, DCA showed that the nomogram model is effective in clinical practice (Fig. 3C).

To further validate the model, ROC analysis of the nomogram revealed that AUC reached 0.898 and 0.931 in the validation set and testing set respectively, suggesting that the nomogram has excellent accuracy. Calibration curve and DCA were employed to verify the effectiveness of nomogram model (Fig. 3D–I).

Prognostic nomogram model for PVL

As shown in Table 3, a total of 170 PVL patients was utilized to analyze the prognostic factor. univariable logistic analysis on 9 potential factors, and the result determined PVL malignant transformation related variables, including sex, clinical presentation, local irritants and OED. Additionally, the multivariable logistic regression analysis revealed that independent predictors of PVL were sex, clinical presentation, local irritants and OED (Table 4).

Based on the independent predictors in the training cohort, we constructed a predictive nomogram model of PVL (Fig. 4). Hosmer–Lemeshow test indicated a great calibration performance ($P = 0.796$). ROC analysis revealed that AUC value of the nomogram reached 0.893, indicating that this model has preferable discriminant ability (Fig. 5A). The calibration plot revealed good predictive accuracy between the actual probability and predicted probability (Fig. 5B). In addition, DCA showed that the nomogram model was effective in clinical practice (Fig. 5C). To further validate the model, ROC analysis of the nomogram revealed that AUC reached 0.723 in the validation cohort. Calibration curve and DCA were employed to verify the effectiveness of nomogram model training cohort (Fig. 5D–F).

Discussion

PVL typically exhibits a slow and persistent progression over an extended period, followed by sudden rapid growth or malignant transformation. Hyperkeratosis without dysplasia is the most common histopathological diagnosis during the initial visit.[2] These making it challenging to provide an accurate diagnosis during the first clinical visit. However, PVL is acknowledged as an aggressive lesion with frequent recurrences, and nearly 50% of cases undergo malignant transformation, primarily towards OSCC.[18] Therefore, early diagnosis and prognosis assessment are critical challenges that need to be addressed.

According to the existing diagnostic criteria, we adopted the criteria proposed by Cerero-Lapiedra et al. as the

Table 3 Descriptive clinicopathological characteristics of proliferative verrucous leukoplakia (PVL) patients.

Variable	PVL without malignant transformation (n = 76)	PVL with malignant transformation (n = 94)	*P*-value
Age	57.00 [48.00; 63.00]	57.50 [50.25; 64.75]	0.204*
Sex:			0.032
Female	68 (89.47%)	71 (75.53%)	
Male	8 (10.53%)	23 (24.47%)	
Lesion sites:			<0.001
<=2	0 (0.00%)	45 (47.87%)	
>2	76 (100.00%)	49 (52.13%)	
Clinical presentation:			<0.001
homogeneous	65 (85.53%)	36 (38.30%)	
non-homogeneous	11 (14.47%)	58 (61.70%)	
Local irritants:			0.172
No	50 (65.79%)	51 (54.26%)	
Yes	26 (34.21%)	43 (45.74%)	
Smoker:			0.076
No	75 (98.68%)	87 (92.55%)	
Yes	1 (1.32%)	7 (7.45%)	
Alcohol use:			0.043
No	75 (98.68%)	86 (91.49%)	
Yes	1 (1.32%)	8 (8.51%)	
OED:			<0.001
Non-OED	55 (72.37%)	24 (25.53%)	
OED	21 (27.63%)	70 (74.47%)	
VT or FOM involved:			0.150
No	55 (72.37%)	57 (60.64%)	
Yes	21 (27.63%)	37 (39.36%)	

*Mann–Whitney U test.
OED, oral epithelial dysplasia; Non-OED, without oral epithelial dysplasia; VT or FOM involved, ventral tongue or floor of mouth involved.

Table 4 Univariate and multivariate logistic regression of prognostic factor of proliferative verrucous leukoplakia (PVL).

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.015(0.984−1.047)	0.344		
Sex	3.651(1.149−11.596)	0.028	5.224(1.211−22.538)	0.027
Lesion sites	0(0-Inf)	0.987		
Clinical presentation	17.53(6.123−50.194)	<0.001	20.596(6.01−70.581)	<0.001
Local irritants	2.292(1.051−4.996)	0.037	3.03(1.022−8.983)	0.046
Smoker	31243846.563(0-Inf)	0.991		
Alchole use	5.031(0.598−42.308)	0.137		
OED	7.982(3.445−18.494)	<0.001	5.875(2.093−16.492)	<0.001
VT or FOM involved	1.309(0.601−2.851)	0.498		

OED, oral epithelial dysplasia; VT or FOM involved, ventral tongue or floor of mouth involved.

inclusion criteria for this study.[13] More than two different oral sites involved and the existence of a verrucous area were included in the criteria. As shown in this study, 101 cases of PVL (59.41%) presented as homogeneous leukoplakia without a verrucous area during the initial visit. This highlights the complexity of the clinical presentation of PVL, emphasizing the need to consider multiple factors in the diagnostic and predictive models for this condition.

Unlike COL, PVL appears to have no clear association with factors such as smoking or alcohol consumption.[18] The analysis conducted in this study revealed no specific relationship between tobacco or alcohol consumption and PVL. Among the PVL patients, 162 cases (95.29%) were nonsmokers, and there were 87 cases (92.55%) of nonsmokers among the PVL malignant transformation cases. However, local irritants, such as faulty restorations, residual roots, sharp tooth cusps, dental appliances, silver amalgam, were identified as prognostic factors for malignant transformation in PVL ($P < 0.05$).

Previous case reports have shown that PVL is more commonly observed in elderly female.[18] Initially, PVL lesions manifest unifocal, homogeneous, slowly and persistent growth lesion, these lesions tend to become multifocal and may exhibit an exophytic, verrucous, or erythematous area.[2,19] In this study, according to the incidence population, elderly female (median age was 57 years) is a risk factor for the diagnosis of PVL, but the male patients are more likely to suffer malignant transformation ($P < 0.05$). The lesion presented nonhomogeneous clinical manifestation was independent risk factor and prognostic factor for malignant transformation of PVL. In addition, multifocal lesion was a risk factor for the diagnosis of PVL, but was not associated with its malignant outcome.

The histological morphological appearances of PVL are varied, ranging from simple hyperplasia, hyperkeratosis, epithelial dysplasia, verrucous carcinoma, carcinoma in situ, to squamous cell carcinoma, but lacking specific

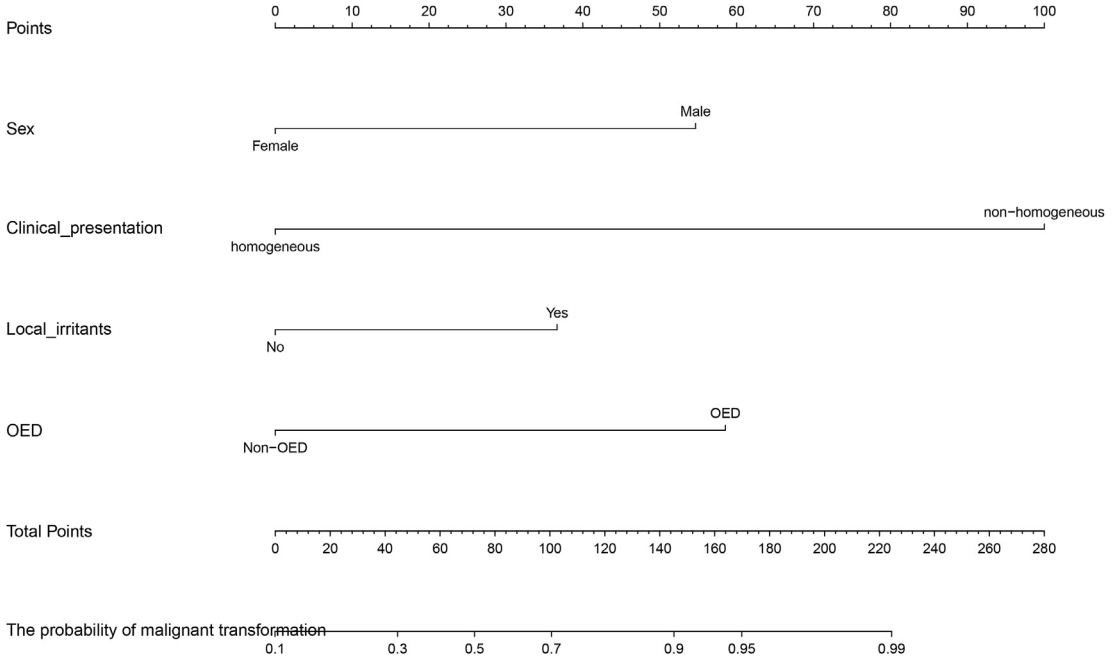

Figure 4 Nomogram for predicting the malignant transformation of patients with proliferative verrucous leukoplakia (PVL). Four factors were calculated into the PVL prognostic prediction nomogram. OED, oral epithelial dysplasia.

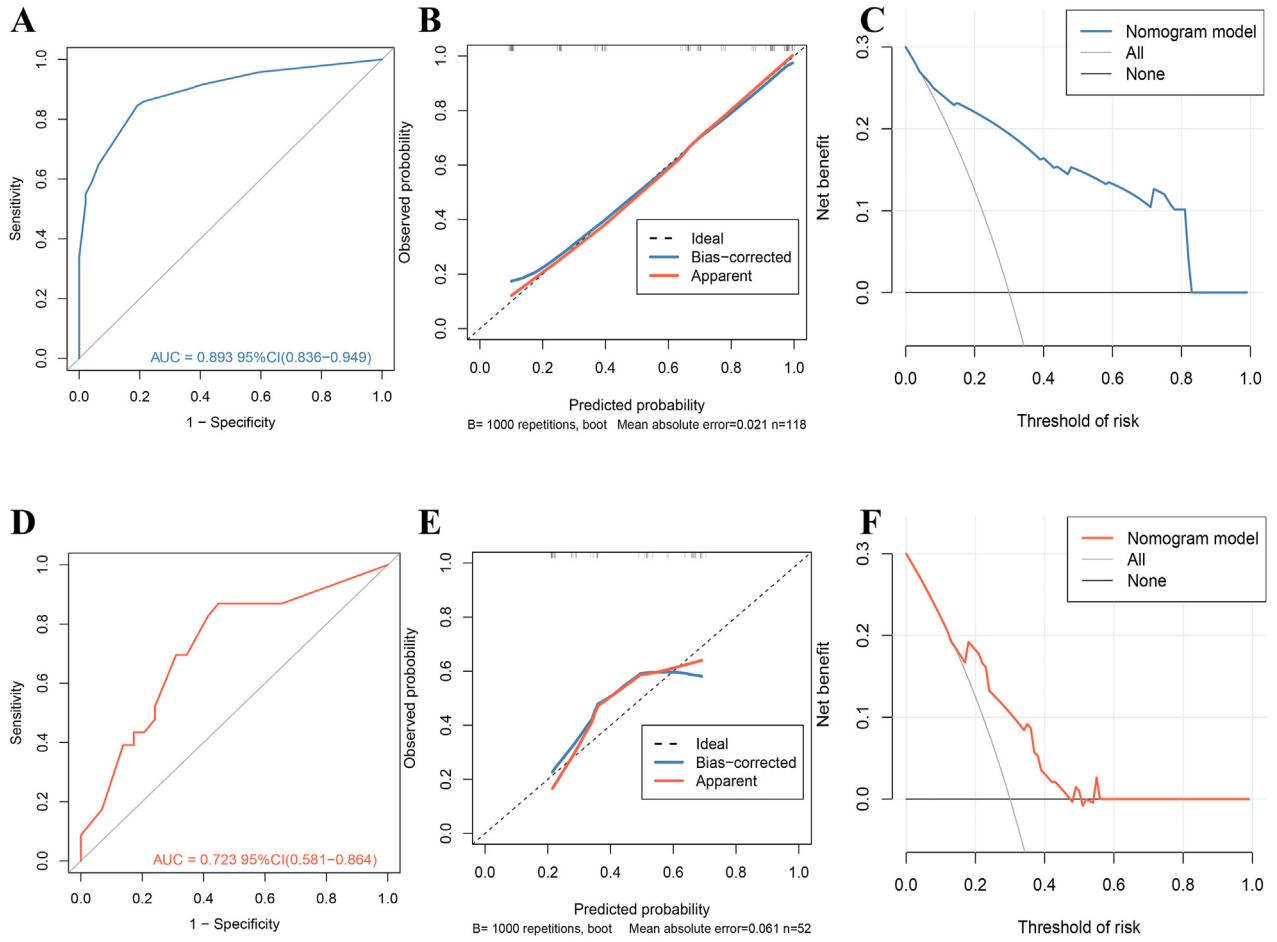

Figure 5 Receiver operating characteristic (ROC) curves, calibration plots and decision curve analysis (DCA) of the nomogram for the prognostic factor of proliferative verrucous leukoplakia (PVL). ROC for nomogram in training set (A) and validation set (D); Calibration plot for nomogram in training set (B) and validation set (E); Decision curve analysis for the nomogram in training set (C) and validation set (F).

manifestations. In 2021, American Academy of Oral and Maxillofacial Pathology and the North American Society of Head and Neck Pathologists published consensus guidelines on the histological characteristics of PVL, including three categories of lesions within PVL for standardized reporting as following: (1) 'corrugated ortho(para)hyperkeratotic lesion, not reactive; ' (2) 'bulky hyperkeratotic epithelial proliferation, not reactive; ' and (3) 'suspicious for,' or 'squamous cell carcinoma'.[20] In the 5th edition of the WHO Classification of Head and Neck tumors, the newly added architectural and cytological features of OED, such as premature keratinization, sharp lateral margins, skip keratoses, and increased keratin, were demonstrated in the early lesions of PVL.[21] However, due to the limited number of cases, no feature as independent risk factor associated with PVL has been found. Moreover, there is considerable interobserver variation among pathologists in the grading of epithelial dysplasia of OPMD,[22,23] especially inter-observer variability in the diagnosis of PVL.[24] In this study, cases were classified according to the presence or absence of epithelial dysplasia, and multivariate regression analysis was performed. The results revealed that the presence of OED, regardless of the degree of dysplasia, was a risk factor for early diagnosis of PVL. Additionally, it was identified as an independent prognostic factor for its malignant transformation ($P < 0.05$).

The etiology of PVL remains unknown. Single-cell RNA sequencing of a histopathological continuum of PVL progression reveals that cellular and microenvironment remodeling, including immunosuppressive phenotypes, angiogenesis, and stromal fibrosis, are involved in the process of malignant transformation.[25] Furthermore, DNA methylation could potentially serve as a regulatory mechanism in the PVL progression.[26] Researchers have focused on investigating molecular markers as potential predictive biomarker in early stages of PVL. Studies have explored the relationship between P53, Ki-67, Mcm-2, and Mcm-5 and PVL. It has been suggested that high expression of Mcm-2 and Mcm-5 in cases of mild and moderate dysplasia could potentially serve as helpful indicators to predict the malignant transformation of PVL.[27] Aberrations in p16INK4a and p14ARF have been observed in 45% of PVL patients,[28] while aneuploidy and TERT promoter mutations have shown promise as new biomarkers for PVL,[29–31] However,

further validation is needed, as no biomarkers have been fully validated for PVL currently.

In this study, independent risk factors and prognostic factors of PVL were analyzed by multivariate logistic regression, and a visualization prediction model was established by nomogram. And some limitations should be considered. Firstly, owing to the low incidence of PVL, the study included a limited sample size, however, this is the largest sample size compared to previous studies. Secondly, the study included a demographic group from only one institution. Due to the unclearly histological definition and unified diagnostic criteria, it is difficult to conduct multicenter studies because of the heterogeneity among different investigators. Thirdly, nomograms were constructed in a retrospective manner, uncertainty might arise when the models are being applied clinically.[32] Thus, we adopted DCA to help evaluate the model effectiveness and determine whether the model is applicable in the situation. In spite of the limitations, the nomogram models showed satisfactory predictive value not only in training and validation cohort but also in test cohort, which is more helpful for early diagnosis and precise treatment. In addition, Due to the complex etiology and variable course of PVL, it is still necessary for clinicians and pathologists' collaboration to enhance understanding and management of the disease.

In summary, we identified the risk and prognostic factors of PVL based on univariate and multivariate logistic regression analysis, and establishing early diagnosis and prognosis prediction models. As diagnostic decision support tools, they are expected to provide support to clinicians and patients, improve the accuracy of diagnosis and medical outcomes for patients.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve readability and make the language expression more in line with the native English expression habits. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

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

Acknowledgements

This work was supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (2019-I2M-5—038).

References

1. Alabdulaaly L, Villa A, Chen T, et al. Characterization of initial/early histologic features of proliferative leukoplakia and correlation with malignant transformation: a multicenter study. *Mod Pathol* 2022;35:1034—44.
2. Villa A, Menon RS, Kerr AR, et al. Proliferative leukoplakia: proposed new clinical diagnostic criteria. *Oral Dis* 2018;24:749—60.
3. Ramos-Garcia P, Gonzalez-Moles MA, Mello FW, Bagan JV, Warnakulasuriya S. Malignant transformation of oral proliferative verrucous leukoplakia: a systematic review and meta-analysis. *Oral Dis* 2021;27:1896—907.
4. Iocca O, Sollecito TP, Alawi F, et al. Potentially malignant disorders of the oral cavity and oral dysplasia: a systematic review and meta-analysis of malignant transformation rate by subtype. *Head Neck* 2020;42:539—55.
5. Proano-Haro A, Bagan L, Bagan JV. Recurrences following treatment of proliferative verrucous leukoplakia: a systematic review and meta-analysis. *J Oral Pathol Med* 2021;50:820—8.
6. Gonzalez-Moles MA, Warnakulasuriya S, Ramos-Garcia P. Prognosis parameters of oral carcinomas developed in proliferative verrucous leukoplakia: a systematic review and meta-analysis. *Cancers* 2021;13:4843.
7. Borgna SC, Clarke PT, Schache AG, et al. Management of proliferative verrucous leukoplakia: justification for a conservative approach. *Head Neck* 2017;39:1997—2003.
8. Campisi G, Giovannelli L, Ammatuna P, et al. Proliferative verrucous vs conventional leukoplakia: no significantly increased risk of HPV infection. *Oral Oncol* 2004;40:835—40.
9. Upadhyaya JD, Fitzpatrick SG, Islam MN, Bhattacharyya I, Cohen DM. A retrospective 20-year analysis of proliferative verrucous leukoplakia and its progression to malignancy and association with high-risk human papillomavirus. *Head Neck Pathol* 2018;12:500—10.
10. Bagan JV, Jimenez Y, Murillo J, et al. Epstein-Barr virus in oral proliferative verrucous leukoplakia and squamous cell carcinoma: a preliminary study. *Med Oral Patol Oral Cir Bucal* 2008;13:E110—3.
11. Herreros-Pomares A, Hervas D, Bagan-Debon L, Jantus-Lewintre E, Gimeno-Cardona C, Bagan J. On the oral microbiome of oral potentially malignant and malignant disorders: dysbiosis, loss of diversity, and pathogens enrichment. *Int J Mol Sci* 2023;24:3466.
12. Hansen LS, Olson JA, Silverman SJ. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol* 1985;60:285—98.
13. Cerero-Lapiedra R, Balade-Martinez D, Moreno-Lopez LA, Esparza-Gomez G, Bagan JV. Proliferative verrucous leukoplakia: a proposal for diagnostic criteria. *Med Oral Patol Oral Cir Bucal* 2010;15:e839—45.
14. Carrard VC, Brouns ER, van der Waal I. Proliferative verrucous leukoplakia; a critical appraisal of the diagnostic criteria. *Med Oral Patol Oral Cir Bucal* 2013;18:e411—3.
15. Gonzalez-Moles MA, Ramos-Garcia P, Warnakulasuriya S. A scoping review on gaps in the diagnostic criteria for proliferative verrucous leukoplakia: a conceptual proposal and diagnostic evidence-based criteria. *Cancers* 2021;13:3669.
16. Lopes MA, Feio P, Santos-Silva AR, Vargas PA. Proliferative verrucous leukoplakia may initially mimic lichenoid reactions. *World J Clin Cases* 2015;3:861—3.
17. McParland H, Warnakulasuriya S. Lichenoid morphology could be an early feature of oral proliferative verrucous leukoplakia. *J Oral Pathol Med* 2021;50:229—35.
18. Palaia G, Bellisario A, Pampena R, Pippi R, Romeo U. Oral proliferative verrucous leukoplakia: progression to malignancy and clinical implications. Systematic review and meta-analysis. *Cancers* 2021;13:4085.
19. Bagan J, Scully C, Jimenez Y, Martorell M. Proliferative verrucous leukoplakia: a concise update. *Oral Dis* 2010;16:328—32.
20. Thompson L, Fitzpatrick SG, Muller S, et al. Proliferative verrucous leukoplakia: an expert consensus guideline for

standardized assessment and reporting. *Head Neck Pathol* 2021;15:572—87.
21. Muller S, Tilakaratne WM. Update from the 5th edition of the World Health Organization classification of head and neck tumors: tumours of the oral cavity and mobile tongue. *Head Neck Pathol* 2022;16:54—62.
22. R SA, B NP, Hegde U, et al. Inter- and intra-observer variability in diagnosis of oral dysplasia. *Asian Pac J Cancer Prev APJCP* 2017;18:3251—4.
23. Peng JK, Dan HX, Xu H, Zeng X, Chen Q. Agreement evaluation of the severity of oral epithelial dysplasia in oral leukoplakia. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2022;57:921—6.
24. Upadhyaya JD, Fitzpatrick SG, Cohen DM, et al. Inter-observer variability in the diagnosis of proliferative verrucous leukoplakia: clinical implications for oral and maxillofacial surgeon understanding: a collaborative pilot study. *Head Neck Pathol* 2020;14:156—65.
25. Zhong L, Wang F, Liu D, et al. Single-cell transcriptomics dissects premalignant progression in proliferative verrucous leukoplakia. *Oral Dis* 2024;30:172—86.
26. Herreros-Pomares A, Hervas D, Bagan-Debon L, et al. Oral cancers preceded by proliferative verrucous leukoplakia exhibit distinctive molecular features. *Oral Dis* 2024;30:1072—83.
27. Gouvea AF, Vargas PA, Coletta RD, Jorge J, Lopes MA. Clinicopathological features and immunohistochemical expression of p53, Ki-67, Mcm-2 and Mcm-5 in proliferative verrucous leukoplakia. *J Oral Pathol Med* 2010;39:447—52.
28. Kresty LA, Mallery SR, Knobloch TJ, et al. Frequent alterations of p16INK4a and p14ARF in oral proliferative verrucous leukoplakia. *Cancer Epidemiol Biomarkers Prev* 2008;17:3179—87.
29. Rintala M, Vahlberg T, Salo T, Rautava J. Proliferative verrucous leukoplakia and its tumor markers: systematic review and meta-analysis. *Head Neck* 2019;41:1499—507.
30. Pentenero M, Castagnola P, Castillo FV, Isaevska E, Sutera S, Gandolfo S. Predictors of malignant transformation in oral leukoplakia and proliferative verrucous leukoplakia: an observational prospective study including the DNA ploidy status. *Head Neck* 2023;45:2589—604.
31. Afkhami M, Maghami E, Gernon TJ, Villaflor V, Bell D. Wolf in sheep's clothing - oral proliferative verrucous leukoplakia: progression with longitudinal molecular insights. *Ann Diagn Pathol* 2023;63:152104.
32. Lee W, Lam S, Zhang Y, Yang R, Cai J. Review of methodological workflow, interpretation and limitations of nomogram application in cancer study. *Radiat Med and Prot* 2022;3:200—7.