Received: 12 February 2019 | Revised: 27 March 2019 | Accepted: 4 April 2019

DOI: 10.1111/jop.12862

ORIGINAL ARTICLE

Journal of Oral Pathology & Medicine WILEY

Development and validation of nomogram for prediction of malignant transformation in oral leukoplakia: A large-scale cohort study

Tianjiao Wang[1] | Lin Wang[1] | Huifang Yang[2] | Han Lu[1] | Jianyun Zhang[3] | Nan Li[4] | Chuan-Bin Guo[1]

[1]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China

[2]Center of Digital Dentistry, National Engineering Laboratory for Digital and Material Technology of Stomatology, Peking University School and Hospital of Stomatology, Beijing, China

[3]Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, China

[4]Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, China

Correspondence
Chuan-Bin Guo, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, 22 Zhongguancun Avenue South, Haidian District, Beijing 100081, China.
Email: guodazuo@sina.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81470707 and 81672664

Abstract

Purpose: Oral leukoplakia (OL) is the well-known disorder of oral mucosa, which has potential to be malignant and can lead to squamous cell carcinoma (OSCC). In the following study, we developed a comprehensive nomogram for predicting the malignant progression of OL, based on analysis of clinicopathological variables.

Methods: A retrospective analysis of patients diagnosed with OL was performed between 1998 and 2017 at the Peking University School and Hospital of Stomatology. OL was confirmed by pre-treatment biopsy. The candidate risk factors for OL malignant transformation were screened from clinicopathological variables using the Cox proportional hazard regression analysis. The nomogram model was generated based on the COX regression results and was validated through Harrell concordance index (c-index) and calibration plots

Results: The incidence of OL malignant transformation (MT) was 12.2% (107/875), and the mean follow-up time was 4.5 years. The risk factors (age, histologic grade, site of lesion and smoking habit) derived from Cox proportional hazard regression analysis were incorporated in a novel nomogram model for prediction of MT severity. The c-index value of the nomogram model was 0.752, which confirmed the prediction ability; and was further confirmed by calibration plots results.

Conclusion: Our data suggest that patients with OL who are over 50 years old, nonsmokers with dysplasia, and OL lesions involving the lip, the floor of mouth, and tongue have an enhanced risk of MT. The established nomogram model has the predictive value of malignant progression, which is conductive to screen high-risk patients and guide treatment strategy.

KEYWORDS

nomogram, oral leukoplakia, precancerous conditions, risk factors, tumorigenic transformation

Wang and Wang are contributed equally to this work.

1 | INTRODUCTION

Epithelial carcinogenesis is a multi-stage process regulated by genetic and environmental factors.[1] Oral squamous cell carcinoma (OSCC) is the 12th most common cancer in women and the 6th in men that comprises more than 92% of all oral cancers.[2] It has been reported that patients with early-stage OSCC have significantly higher 5-year survival rate (83.7%) compared to patients with late-stage OSCC (38.5%).[3] From the perspective of medical economics, patients with higher T stage are associated with higher treatment costs and longer hospitalization.[4] Therefore, an early detection, diagnosis, and treatment of OSCC could significantly improve the survival rate and reduce the treatment costs for patients with OSCC.[5]

Many oral squamous cell carcinomas develop from potentially malignant oral disorders of oral mucosa, such as leukoplakia, lichen planus, erythema, chronic discoid lupus erythematosus, and oral submucous fibrosis.[6] Oral leukoplakia (OL), defined as a "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" is the best-known condition of the oral mucosa that can be potentially malignant. So far, a number of studies have indicated that 15.8%-48.0% of patients with OSCC are affected with OL.[7,8]

As reported, many risk factors have been reported for prediction of the OL malignant transformation, including gender (female), long duration of OL, non-smoker status, tongue located disease, size over 200 mm^2, non-homogeneous type, presence of epithelial dysplasia, and DNA aneuploidy. Due to the diverse clinical manifestations, the presence of epithelial dysplasia is generally accepted as one of the most important and useful predictors of malignant development in OL.[9-12] Although WHO has proposed certain histological classification criteria of epithelial dysplasia, the criteria for diagnosing and grading dysplasia are still controversial and the actual pathological diagnosis cannot be performed without subjective judgement. Accordingly, biomarker profiles are of high value and they might actually ultimately supersede histopathologic staging in the future.[13]

The rates of malignant transformation of OL vary in different parts of the world, probably as a result of different lifestyle habits and environmental factors.[14] For example, chewing areca has been regarded as a strong correlative factor for OL in oral mucosa in Hunan, China.[15] Additionally, a case-control studies performed in India have shown that tobacco chewers have 66% risk for the development of oral cavity cancers. [16] Nevertheless, so far, no similar data were analyzed for China.

Due to various clinical manifestations and regional differences, nomogram risk model has been introduced to predict malignant progression in patients with OL. The accuracy of this model depends on its sample number and risk factors enrolled. The aim of this study was to validate the prediction value of a novel nomogram model during the malignant progression among patients with OL, based on the large cohort with long-time follow-up observation. This model could serve as an objective guideline for evaluation of the OL malignant transformation in China. In addition, based on this model, clinicians could select high-risk individuals and implement early interventions to reduce the incidence of OSCC.

2 | MATERIAL AND METHODS

2.1 | Patients

A retrospective analysis was performed in a representative sample of the Chinese population diagnosed with OL between 1998 and 2017 at the Peking University School and Hospital of Stomatology. When possible etiological factors were observed, a definitive diagnosis of OL was identified due to suspected etiological factors with no regression within 2-4 weeks and histopathological support.[17] Pathological review was done by two experienced pathologists to confirm the type of dysplasia in each tissue.

Inclusion criteria were the following: (a) clinical examination and histopathological observations were used to confirm OL in all patients; (b) the follow-up time for all patients was at least 1 year. The exclusion criteria were the following: (a) patients who developed OSCC at the other sites before the occurrence of OL lesion; (b) patients with oral cancer at the time of OL lesion; and (c) patients unable to provide all required information.

The ethics committee of Peking University School and Hospital of Stomatology (PKUSSIRB-201839129) approved this study. Clinical trial was registered on Chinese Clinical Trial Registry (ChiCTR1800017545).

2.2 | Data collection

For each case, the following data were collected: personal characteristics (age, gender), smoking and drinking habits, clinical manifestation (the site/size/diameter of the lesion), histopathological details, and type of treatment method.

The pathological classification of OL was classified into four types: dysplasia, low and moderate dysplasia, severe dysplasia, and proliferative verrucous leukoplakia (PVL). PVL is a multifocal, recurrent, and exophytic variant of leukoplakia with a relative high rate of malignant progression.[18] In addition, all patients were encouraged to quit smoking and drinking; meanwhile, the drug therapies such as carotenoids and vitamins were also recommended. Patients with mild and severe epithelial dysplasia were strongly encouraged to undergo surgery. Every patient underwent a clinical routine follow-up at an interval of 3-6 months.

2.3 | Statistical analysis

All statistical analyses were conducted using SPSS18.0 statistical package. The chi-square test was used for categorical variables to compare the differences among various groups. Univariable and multivariable Cox proportional hazard regression models were used to estimate the prediction effect of OL malignant transformation among various variables. Nomogram risk prediction model was constructed based on the results of the multivariate COX regression

analyses using the statistical software R package R 3.5.1 (http://www.R-project.org, The R Foundation). To validate the nomogram, 500 bootstrap resamples were used to calculate the estimated Harrell concordance index (C-index) values and to evaluate the discriminative ability between patients who got malignant transformation (MT) versus those who did not. The C-index ranged between 0.5 and 1.0, with 0.5 indicating a random chance and 1 indicating a perfect discrimination of the model.[19] To assess the accuracy of the nomogram, we used calibration plots to visualize the consistency between the predicted and actual 3-year and 5-year event-free possibility. Moreover, all these groups were stratified into subgroups according to the cutoff value based on the survival Receiver operating characteristic curve. Kaplan-Meier method and log-rank test were used to compare the risk of MT between two groups with different total scores, which were calculated by the nomogram.

3 | RESULTS

3.1 | Patient characteristics and risk factors of malignant transformation

A total of 875 patients were included in this study. The incidence of OL malignant transformation was 12.2% (107/875), and the average follow-up time was 4.5 years (Data S1). According to the chi-square test, parameters such as gender, age, site, size, diameter, dysplasia, smoking history, and treatment therapy were all associated with malignant progression of OL ($P < 0.05$; Table 1).

Females were more likely to have lesions (the male: female ratio of incidence of OL was 1:2), and the transformation rate in females (14.4%) was greater than in males (9.4%). OL was more common among older people (65.7% patients were over 50 years), and the highest rate of transformation was observed in patients aged 50-59 (27.8%), followed by those aged 60-69 (25%). The most common sites of OL were the tongue (340/875, 38.9%) and buccal mucosa (314/875, 35.9%). The lesions in lip (18/875, 2.1%) and floor of the mouth (6/875, 3.7%) were relatively rare, while they had the highest rate of MT (33.3%, 27.8%), followed by tongue (16.8%). The majority of lesions were <2 cm^2 in size (598/875, 68.3%), while their diameter was <2 cm (665/875, 76%); however, lesions that exceed 5 cm^2 in size had the highest rate of MT (24.4%). Pathological testing revealed no dysplasia in 56% patients (490/875), followed by mild and moderate dysplasia (31.5%), severe dysplasia (7.9%), and proliferative verrucous leukoplakia (4.6%). The MT rates for no dysplasia, mild and moderate dysplasia, severe dysplasia, and proliferative verrucous leukoplakia were 3.7%, 19.2%, 44.9%, and 12.5%, respectively. In addition, 73.1% (640/875) patients received drug therapy, 17.8% (157/875) underwent surgical resection, and 4.6% (40/875) received photodynamic treatment. Among all patients, 165 (18.9%) were smokers and 113 (12.9%) were accustomed drinkers. Nevertheless, the MT rate in non-smoking patients or in former smokers was higher (14.4%) compared to current smokers (3%).

To further identify the risk factors for malignant progression of OL, Cox regression analysis was performed. In univariate cox regression, the statistically significant risk factors included variables of age, OL site, dysplasia type, smoking habits, and treatment type, while no significant differences were found for gender, lesion size, and diameter.

The variables with the higher risk of MT included age over 50 (HR, 1.848, P = 0,009), lesions involving the tongue (HR, 3.801, P = 0.005), lips (HR, 5.943, P = 0.005), or floor of the mouth (HR, 3.988, P = 0.008); mild and moderate dysplasia (HR, 5.338, $P < 0.001$), severe dysplasia (HR,11.666, $P < 0.001$), PVL dysplasia (HR, 3.212, P = 0.022), and non-smoking patients (HR, 3.392, P = 0.008). Patients who did not undergo treatment had a significant risk of MT (HR, 5.086, $P < 0.001$), whereas a photodynamic therapy (PDT) decreased the risk of MT (HR, 0.498 95%, P = 0.001). Surgery was not significantly associated with better prognosis (HR, 1.988, P = 0.332). The treatment method was not a predictive factor, and all the above significant variables, except treatment, were entered into multivariate Cox proportional hazard regression analysis.

According to multivariate Cox proportional hazards analysis, we found that the variables of lesion involving the tongue (HR, 2.528, P = 0.050), lip (HR, 3.747, P = 0.045), as well as mild and moderate dysplasia (HR, 4.320, $P < 0.001$), severe dysplasia (HR, 9.282, $P < 0.001$) were all independent risk factors for malignant transformation of OL. The detailed results of the COX analysis are shown in Table 2.

3.2 | Nomogram construction and validation

The nomogram was used to calculate a total score for each patient by adding the score obtained from individual characteristics. Based on the above analysis, the final nomogram included age, the histologic grade, smoking habit, and lesion site (Figure 1). The calculated scores could identify the probabilities of 3-year and 5-year periods for event-free survival rate (Table S1). The c-index of the generated nomogram for the MT prediction was 0.752, indicating a high level of predictive value. Moreover, calibration plots (Figure 2) suggested that the nomogram was well calibrated (predicted probability in agreement with the actual probability) for 3-year and 5-year event-free possibility in these cohorts. These data showed that the constructed nomograms were sufficiently predictive in this cohort.

Furthermore, in addition to nomogram-derived individualized predictions, we divided the patients into two groups based on the scores obtained from the nomogram according to the cutoff value (low-risk group, score <150; high-risk group, score ≥150). Cutoff values were determined as the 3-year MT rate ≥11% in the high-risk group and <11% in the low-risk group. The P value from the comparison of the Kaplan-Meier survival curves using the log-rank test was 2e-16 ($P < 0.05$; Figure 3).

4 | DISCUSSION

The previous studies have shown that oral squamous cell cancer could originate from OL, and thus the early detection of its MT could

TABLE 1 Clinicopathological characteristics of patients enrolled in this study

Characteristics	Total n = 875	Patients with MT n = 758 (87.8%)	Patient without MT n = 107 (12.2%)	*P* value
Gender				
Male	374 (42.7%)	339 (90.6%)	35 (9.4%)	0.025*
Female	501 (57.3%)	429 (85.6%)	72 (14.4%)	
Age				
<50	300 (34.3%)	277 (92.3%)	23 (7.7%)	0.003**
≥50	575 (65.7%)	491 (85.4%)	84 (14.6%)	
Site				
Tongue	340 (38.9%)	283 (83.2%)	57 (16.8%)	0.002**
Buccal mucosa	314 (35.9%)	289 (92.0%)	25 (8.0%)	
Gum	111 (12.7%)	100 (90.1%)	11 (9.1%)	
Palate	32 (3.7%)	30 (93.8%)	2 (6.3%)	
Lip	18 (2.1%)	13 (72.2%)	5 (27.8%)	
Floor of the mouth	6 (0.7%)	4 (66.7%)	2 (33.3%)	
Multiple sites	54 (6.2%)	49 (90.7%)	5 (9.3%)	
Size				
<2 cm^2	598 (68.3%)	534 (89.3%)	64 (10.7%)	0.022*
≥2 cm^2, <5 cm^2	236 (27%)	203 (86.0%)	33 (14.0%)	
≥5 cm^2	41 (4.7%)	31 (75.6%)	10 (24.4%)	
Diameter				
<2 cm	665 (76%)	593 (89.2%)	72 (10.8%)	0.024*
≥2 cm	210 (24%)	175 (83.3%)	35 (16.7%)	
Dysplasia type				
No dysplasia	490 (56%)	472 (96.3%)	18 (3.7%)	<0.001**
Mild and moderate	276 (31.5%)	223 (80.8%)	53 (19.2%)	
Severe	69 (7.9%)	38 (55.1%)	31 (44.9%)	
PVL	40 (4.6%)	35 (87.5%)	5 (12.5%)	
Smoking history				
Current	165 (18.9%)	160 (97%)	5 (3%)	<0.001**
Never and former	710 (81.1%)	608 (85.6%)	102 (14.4%)	
Drinking history				
Current	113 (12.9%)	103 (91.2%)	10 (8.8%)	0.24
Never and former	762 (87.1%)	665 (87.3%)	97 (12.7%)	
Treatment				
Drugs only	640 (73.1%)	575 (89.8%)	65 (10.2%)	0.001**
Photodynamic	40 (4.6%)	38 (95.0%)	2 (5.0%)	
Surgery	156 (17.8%)	124 (79.5%)	32 (20.5%)	
No treatment	39 (4.5%)	31 (79.5%)	8 (20.5%)	

Abbreviation: PVL, proliferative verrucous leukoplakia.
*P value < 0.05.
**P value < 0.01.

effectively reduce the incidence of OSCC.[3] Although several studies have investigated the risk factors for malignant transformation of OL, currently, there are no available practical prognostic risk models for clinicians in China. The purpose of this study was to develop a new risk prediction model and to validate its accuracy. There were 875 patients enrolled in the current study, which makes the current study the largest cohort study on OL predictive risk factors to present date. Besides, this cohort had long-term follow-up, which furthermore promoted the accuracy of the prediction model.

Cancer nomogram is currently the most widely used disease-specific prediction tool in oncology. Furthermore, the nomogram predictions are tailored to the risk posed by the characteristics of

TABLE 2 Univariate and multivariate COX regression analysis for the primary cohort

Factors	Univariate analysis Hazard ratio (95% CI)	*P* value	Multivariate analysis Hazard ratio (95% CI)	*P* value
Factors selected				
Age				
<50	1		1	
≥50	1.848 (1.164-2.934)	0.009**	1.542 (0.957-2.484)	0.075
Site				
Tongue	3.801 (1.512-9.555)	0.005*	2.528 (0.997-6.410)	0.050
Buccal mucosa	1.382 (0.528-3.618)	0.509	1.380 (0.526-3.624)	0.513
Gum	2.220 (0.769-6.412)	0.14	2.406 (0.828-6.986)	0.107
Palate	1.557 (0.301-8.040)	0.597	1.205 (0.232-6.259)	0.824
Lip	5.943 (1.711-20.648)	0.005**	3.747 (1.031-13.625)	0.045*
Floor of the mouth	3.988 (0.772-20.600)	0.005**	2.570 (0.488-13.536)	0.266
Multiple sites	1		1	
Dysplasia type				
No Dysplasia	1		1	
Mild and moderate	5.338 (3.124-9.121)	0**	4.320 (2.466-7.568)	0**
Severe	11.666 (6.492-20.961)	0**	9.282 (5.059-17.030)	0**
PVL	3.212 (1.183-8.719)	0.022*	2.765 (0.946-8.083)	0.063
Smoking history				
Current	1		1	
Never and former	3.392 (1.381-8.336)	0.008**	2.221 (0.883-5.587)	0.09
Factors not selected				
Gender				
Male	1			
Female	1,305 (0.871-1.956)	0.197		
Size				
<2 cm^2	1			
≥2 cm^2, <5 cm^2	1.060 (0.696-1.615)	0.786		
≥5 cm^2	1.711 (0.877-3.339)	0.115		
Diameter				
<2 cm	1			
≥2 cm	1.272 (0.848-1.907)	0.252		
Drinking history				
Current	1			
Never and Former	1.147	0.681		
Treatment				
Drugs	1			
Photodynamic	0.498 (0.122-2.035)	0.001**		
Surgery	1.988 (1.301-3.037)	0.332		
No treatment	5.086 (2.421-10.684)	0**		

Abbreviations: PVL, proliferative verrucous leukoplakia; CI, confidence interval; HR, hazard Ratio.
**P* value < 0.05.
***P* value < 0.01.

an individual's cancer, which is more relevant to the patient than group-level probabilities. In this study, we found that the MT rate was 12.2%. In addition, the lesions were more common in females (57.3%); however, no significant difference in malignant progression was found between females and males. Moreover, OL was more common among older people, and its prevalence increased with age; patients over 50 years were considered a high-risk group. Among previous studies, tobacco use and alcohol consumption have been

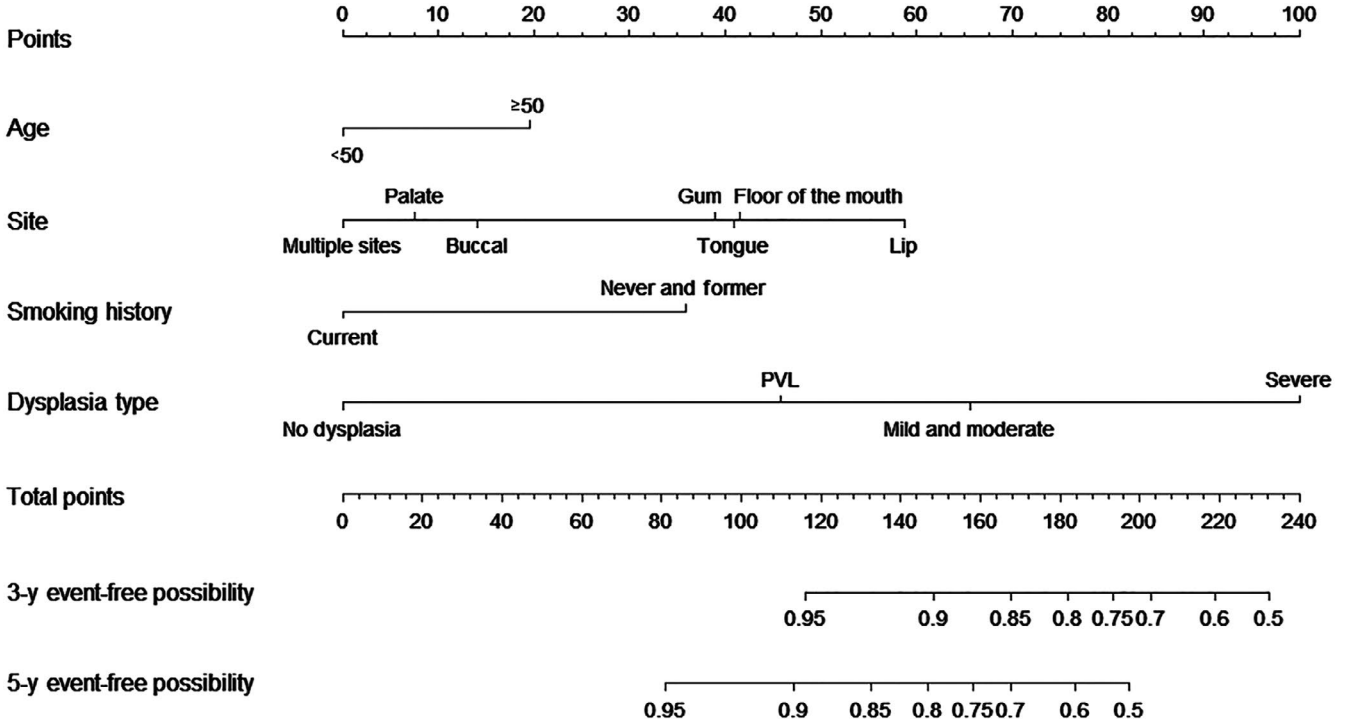


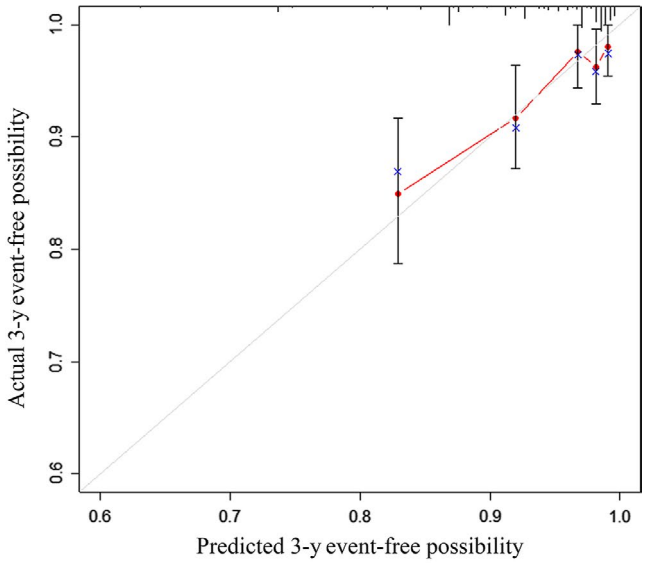
FIGURE 1 Nomogram to predict the 3-y and 5-y event-free possibility. For example, a 70-y-old (19 points) non-smoker (36 points), with tongue OL (41 points) and pathologically confirmed mild dysplasia (65 points), had 161 total points with an estimated 3-y and 5-y event-free possibility of 87% and 73%, and the 3-y and 5-y MT probabilities of 13% and 27%, respectively

established as etiologic factors for the development of OL, but there was also evidence that progression risk is related to the practice of these habits.[18] Some studies have reported that smoking might have a major role in the occurrence of leukoplakia, while it may not be a main cause of malignant transformation.[6,20,21] Contrary, other studies have suggested that lesions found in non-smokers have higher probabilities of progressing to cancer.[18,20] In our study, 3% among 165 currently smoking patients (5/165) developed carcinoma, and 14.4% among 710 non-smokers (102/710) developed carcinoma, which indicated that smoking was not a risk factor for MT. Researches have suggested that even though tobacco is an important etiologic factor for the formation of OL, other factors must be more important for progression of these lesions to malignancy.[18,21] The cigarette ingredients may cause local inflammation and immune-active environment. Nevertheless, not all studies have been able to demonstrate a relationship between tobacco use and progression.[18] A systematic review is necessary to investigate this issue.

Lesion site was also a critical determinant for the MT of OL. Although the most common sites of OL were not on the lip and floor of mouth, they had higher MT rate. Moreover, the lesion location may be related to geographic location and local habits. Accordingly, most of the buccal mucosa were associated with tobacco.[18] In other populations, other sites may be more important and may be associated with specific tobacco habits.[6] Amagasaki et al[20] have reported that leukoplakia of tongue has a high risk of MT compared to other oral sites. Furthermore, Holmstrup and his team have reported that size is the only factor that is statistically correlated with malignant transformation; if the size of lesion exceeds 200 mm^2, the odds for cancer to occur are 5.4 as opposed to smaller lesions.[12] In the present study, lesions exceed 2 cm has a higher rate of MT, but the size of lesion was not substantially evidenced to predict malignant progression.

Among all the risk factors, the histologic assessment of epithelial dysplasia was the most reliable standard for detecting high-risk malignant transformation. Oral dysplasia carries a significant transformation rate to oral cancer, which occurs over a period of years, even when treated by surgical excision.[12] This suggests that patients with biopsy-confirmed OL should be kept under long-term surveillance and observation.[22]

Different treatment may also influence the rate of MT. Unfortunately, despite extensive investigations a standard systemic therapy for patients with OL is yet to be developed.[12] Drug intervention appears as a favorable option for the non-surgical treatment while several studies have shown the questionable treatment outcomes. Bleomycin, retinoic acid (vitamin A), and carotenoids have shown to be unsuccessful in the treatment of OL.[23] Randomized controlled trials for non-surgical treatment of OL have revealed no evidence of effectiveness in preventing MT and recurrence.[24] Furthermore, surgical excision appears to decrease the risk of MT, but does not eliminate it.[20,22] Photodynamic therapy (PDT) with aminolaevulinic acid (ALA) is a non-surgical method for OL which has shown promising effects in regression of OL.[24,25] The advantages of PDT are non-invasiveness, good tolerance, and excellent cosmetic effect.[24] Our study also indicated that PDT therapy has the ability to prevent the malignant progression.



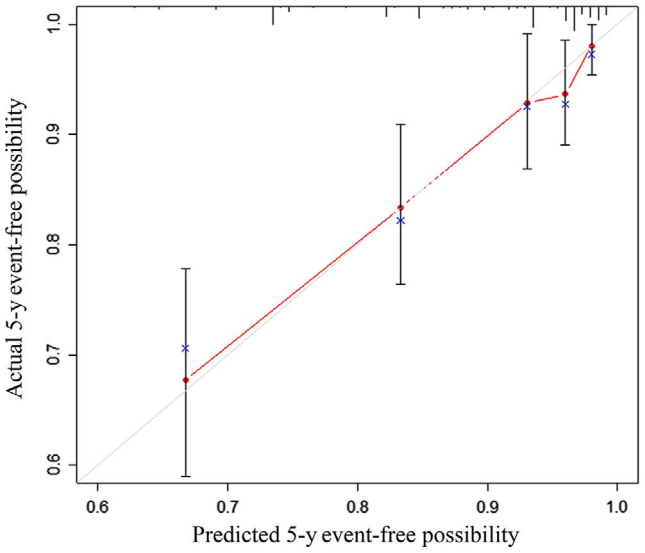


FIGURE 2 The 3-y and 5-y calibration plots of nomograms in the primary cohorts. The horizontal axes display the nomogram-predicted probabilities of non-progression, whereas the vertical axes display the actual non-progression rates estimated. The diagonal line from the lower left to the upper right corner of the plot area is a reference line indicating the ideal prediction

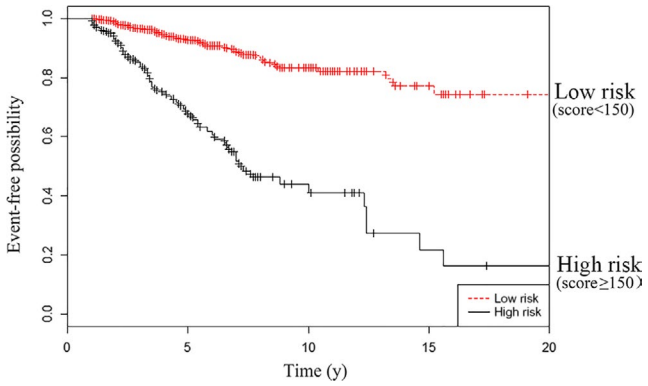


FIGURE 3 Kaplan-Meier survival curves based on cutoff value using the total points assigned by the nomogram. The *P* value from the comparison of the curves using the log-rank test was 2e-16 ($P < 0.05$)

The predictive risk model was conductive to screening high-risk patients and guiding the treatment procedure. We constructed our risk model and validated it based on the large-scale cohort study, which proved to be of high accuracy. Despite its popularity and validated accuracy, the nomogram still has several limitations. First, this nomogram only included the clinical and histological data while some potential predictive variables such as molecular markers were not included. Second, this study was established based on a single-center cohort study; thus, future studies with larger cohorts in multi-centers are needed to externally validate our results. Third, the study was conducted using the data from 1998 to 2017, and since more advanced PDT therapies have been in use since 2016, this might have improved the outcomes predicted by our nomogram. In addition, treatment strategies for patients might have influenced the outcome.

Our research is based on the largest series of MT in patient with OL, which describes an initial diagnosis of OL in oral cancer development and is constructed based on a large-scale population. Moreover, our nomogram was a well-validated statistical tool for prediction of clinical MT factors in patients with OL. Although there were only four increased risk factors, this nomogram is still valuable and can be used by physicians and patients for treatment planning and risk prediction. Further studies are required to predict the relation between the risk of integrates histopathology and multiple predictive molecular markers with well-established clinical parameters including comprehensive baseline data and long-term follow-up in multi-center.

5 | CONCLUSION

Our study confirmed that risk models could reasonably predict that patients with OL who are over 50 years old, non-smokers with dysplasia, and the lesion involving the lip, the floor of mouth, and tongue carry an increased risk of MT, which is conductive to screening high-risk patients and guiding the treatment procedure.

ACKNOWLEDGEMENTS

The National Natural Science Foundation of China (grant numbers 81470707 & 81672664) supported this work.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

ORCID

Tianjiao Wang https://orcid.org/0000-0001-6518-9682

REFERENCES

1. Frame S, Crombie R, Liddell J, et al. Epithelial carcinogenesis in the mouse: correlating the genetics and the biology. *Philos Trans R Soc Lond B Biol Sci*. 1998;353:839-845.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359–386.
3. Weatherspoon DJ, Chattopadhyay A, Boroumand S, Garcia I. Oral cavity and oropharyngeal cancer incidence trends and disparities in the United States: 2000–2010. *Cancer Epidemiol*. 2015;39:497-504.
4. Zavras A, Andreopoulos N, Katsikeris N, Zavras D, Cartsos V, Vamvakidis A. Oral cancer treatment costs in Greece and the effect of advanced disease. *BMC Public Health*. 2002;2:12.
5. Van der Waal I. Oral potentially malignant disorders: is malignant transformation predictable and preventable? *Med Oral Patol Oral Cir Bucal*. 2014;19:e386-e390.
6. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncol*. 2010;46:423-425.
7. Scheifele C, Reichart PA. Oral leukoplakia in manifest squamous epithelial carcinoma. A clinical prospective study of 101 patients. *Mund Kiefer Gesichtschir*. 1998;2:326.
8. Haya-Fernández MC, Bagán JV, Murillo-Cortés J, Poveda-Roda R, Calabuig C. The prevalence of oral leukoplakia in 138 patients with oral squamous cell carcinoma. *Oral Dis*. 2010;10:346-348.
9. Reibel J. Prognosis of oral pre-malignant lesions: significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med*. 2003;14:47.
10. Ho PS, Chen PL, Warnakulasuriya S, Shieh TY, Chen YK, Huang IY. Malignant transformation of oral potentially malignant disorders in males: a retrospective cohort study. *BMC Cancer*. 2009;9:1-7.
11. Lee J-J, Hung H-C, Cheng S-J, et al. Carcinoma and dysplasia in oral leukoplakias in Taiwan: prevalence and risk factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101:472-480.
12. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. *Oral Oncol*. 2006;42:461-474.
13. Lingen MW, Pinto A, Mendes RA, et al. Genetics/epigenetics of oral premalignancy: current status and future research. *Oral Dis*. 2015;17:7-22.
14. Warnakulasuriya S, Johnson NW, Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med*. 2007;36:575–580.
15. Tang JG, Jian XF, Gao ML, Ling TY, Zhang KH. Epidemiological survey of oral submucous fibrosis in Xiangtan City, Hunan Province, China. *Community Dent Oral Epidemiol*. 1997;25:177–180.
16. Dikshit RP, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. *Int J Epidemiol*. 2000;29:609–614.
17. Waal I, Axéll T. Oral leukoplakia: a proposal for uniform reporting. *Oral Oncol*. 2002;38:521–526.
18. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;125:612–627.
19. Kuonen D, Kuonen D, Kuonen D. Book review: regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. *Stat Methods Med Res*. 2004;13:415–416.
20. Amagasa T, Yamashiro M, Uzawa N. Oral premalignant lesions: from a clinical perspective. *Int J Clin Oncol*. 2011;16:5.
21. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med*. 2016;45:155–166.
22. Mehanna HM, Rattay T, Smith J, Mcconkey CC. Treatment and follow-up of oral dysplasia-a systematic review and meta-analysis. *Head Neck*. 2010;31:1600–1609.
23. Kuribayashi Y, Tsushima F, Morita K-I, et al. Long-term outcome of non-surgical treatment in patients with oral leukoplakia. *Oral Oncol*. 2015;51:1020–1025.
24. Ribeiro AS, Salles PR, Da TS, Mesquita RA. A review of the nonsurgical treatment of oral leukoplakia. *Int J Dent*. 2010;2010:186018.
25. Wong SJ, Campbell B, Massey B, et al. A phase I trial of aminolevulinic acid-photodynamic therapy for treatment of oral leukoplakia. *Oral Oncol*. 2013;49:970–976.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Wang T, Wang L, Yang H, et al. Development and validation of nomogram for prediction of malignant transformation in oral leukoplakia: A large-scale cohort study. *J Oral Pathol Med*. 2019;48:491–498. https://doi.org/10.1111/jop.12862