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# Development and validation of a nomogram prediction model for malignant transformation of oral potentially malignant disorders

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ABSTRACT

*Objective:* Oral potentially malignant disorders have increased the risk of oral squamous cell carcinoma. This study developed a nomogram model to assess the risks of malignant transformation of oral potentially malignant disorders.

*Materials and methods:* A retrospective analysis of patients diagnosed with oral potentially malignant disorders confirmed by pre-treatment biopsy was performed between 2010 and 2017 at the Peking University Hospital of Stomatology. The candidate risk factors for malignant transformation were screened from clinicopathological variables using Cox and stepwise regression analyses. The nomogram model was constructed based on the regression results and was validated through receiver operating characteristic curves and calibration curves. Decision curve analysis was used to estimate clinical usefulness.

*Results:* A total of 6964 cases of oral potentially malignant disorders were assessed. The malignant transformation rate of oral potentially malignant disorders was 2.00%. Risk factors (age, site, kind of oral potentially malignant disorder, existence of dysplasia and its grade, and other cancers) derived from the regression analyses were entered into the nomogram model. Time-dependent receiver operating characteristic curve, calibration curve, and decision curve analyses showed high levels of predictive value and clinical relevance, although not for all oral potentially malignant disorders.

*Conclusion:* A specific dynamic nomogram could be adopted to predict the malignant transformation of oral potentially malignant disorders and implement interventions.

## Introduction

Oral squamous cell carcinoma (OSCC) is the most common oral and maxillofacial cancer, and seriously affects human health [1]. From 1990 to 2017, the incidence and mortality of oral cancer increased steadily worldwide. China had the highest estimated annual percentage change in the age-standardized rate of incidence [2]. The number of oral cancer cases has increased by 289.2%, and the number of deaths has increased by 196.8% in the last 28 years [3]. OSCC originates from oral epithelial keratinocytes [1]. Potentially malignant disorders of the oral mucosa are associated with increased risk of OSCC [1].

Oral potentially malignant disorders (OPMDs) are defined as "any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer." [4] The World Health Organization

*Abbreviations:* OSCC, Oral squamous cell carcinoma; OPMDs, Oral potentially malignant disorders; OLK, Oral leukoplakia; OE, Oral erythroplakia; OLP, Oral lichen planus; OSF, Oral submucous fibrosis; AC, Actinic cheilitis; OLE, Oral lupus erythematosus; OLL, Oral lichenoid lesion; OGVHD, Oral graft versus host disease; CHC, Chronic hyperplastic candidosis; ROC, Receiver operating characteristic; DCA, Decision curve analysis; VLT/FOM, Ventral/ lateral surface of tongue/ floor of mouth; AIC, Akaike information criterion; AUC, Area under the curve.

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(WHO) Oral Cancer Collaboration Centre reviewed the latest knowledge about OPMDs and identified several kinds of potentially malignant oral lesions: oral leukoplakia (OLK), oral erythroplakia (OE), oral lichen planus (OLP), oral submucous fibrosis (OSF), actinic cheilitis (AC), oral lupus erythematosus (OLE), oral lichenoid lesion (OLL), oral graft versus host disease (OGVHD), and chronic hyperplastic candidosis (CHC) [4]. The prevalence of OPMD is 4.47% [5], and the malignancy rates of OPMDs range from 2.6% to 7.9% [6–10]. Numerous studies have reported a variety of risk factors for malignant transformation of OPMDs, such as age, sex, site, epithelial dysplasia, tobacco smoking, alcohol drinking, and areca nut chewing [7–9]. Additionally, some biomarkers such as interleukin 1-beta (IL-1β), IL-6, and IL-8 can predict the malignant transformation of OPMDs; however, the clinical use of these biomarkers is not yet possible [11]. Moreover, the rates of malignant transformation differ according to the kind of OPMD [7–9]. There are currently few clinical predictive models for malignant transformation of OPMDs [12].

Nomograms are widely used for prognostic models because of their ability to reduce statistical predictive models into a single numerical estimate of the probability of an event, which is useful in clinical decision-making during clinical encounters [13]. At present, research into large-scale cohorts of patients with OPMDs in mainland China is relatively rare. The aim of this study was to develop and validate a novel clinical predictive nomogram model of malignant transformation among OPMD patients, based on a large cohort. Such a model could be used by clinicians to evaluate high-risk individuals and implement interventions to decrease the incidence of OSCC.

## Materials and methods

### *Study population*

The study population was drawn from the Peking University Hospital of Stomatology (Beijing, China) from January 2010 to December 2017. Inclusion criteria were as follows: all OPMDs were diagnosed and reviewed based on biopsies by three experienced pathologists; the disorders were histologically classified according to the standard drafted by WHO [4]; all malignant transformations were diagnosed as OSCC by biopsies; and all patients were followed up until December 2020 with an average follow up of 74 months. Exclusion criteria were as follows: patients newly diagnosed with an OPMD concomitant with OSCC, and patients who had OSCC before the occurrence of OPMD. This study in compliance with the Declaration of Helsinki, and the data were collected after approval of the institutional review board of the hospital (No. PKUSSIRB-202164075).

### *Data collection*

For each case, the following data were collected: personal characteristics (age, sex); habits of tobacco smoking, alcohol drinking, and areca nut chewing; clinicopathological parameters (site, epithelial dysplasia, kind of OPMD); systemic diseases (diabetes mellitus, hypertension, hyperlipoidemia, and coronary heart disease); history of other cancers except oral cancer; and type of treatment method.

### *Statistical analyses*

Univariate Cox regression analyses were used to identify the risk factors for malignant transformation of OPMDs, and multivariate Cox regression analyses were used to eliminate the interference of confounding factors. The backward selection stepwise regression method was used to verify the variables that were entered into the multivariate Cox regression model one by one to ensure that each independent variable in the regression model was significant. The nomogram prediction model was constructed based on the results of the regression analyses. The receiver operating characteristic (ROC) curve analysis, calibration curve analysis, and decision curve analysis (DCA) were used to estimate the predictive discrimination, calibration, and clinical usefulness of the model, respectively. Univariate and multivariate Cox regression analyses were performed using IBM SPSS Statistics 24.0. The stepwise regression analysis, nomogram prediction model, ROC curve analysis, calibration curve analysis, and DCA were performed using R version 4.0.5 (http://www.R-project.org). $P < 0.05$ was considered statistically significant.

## Results

### *Baseline characteristics of the study population*

A total of 6964 patients with OPMD were enrolled in the study, including 5238 cases of OLP (75.21%), 983 cases of OLK (14.12%), 390 cases of OLE (5.60%), 153 cases of OLL (2.20%), 109 cases of OSF (1.57%), 69 cases of CHC (0.99%), 16 cases of OE (0.23%), four cases of OGVHD (0.06%), and two cases of AC (0.03%). The malignant transformation rate of the total OPMD population was 2.00% (139 patients). OPMDs were most common in females (4327 cases, 62.13%) and in the buccal mucosa (3776 cases, 54.22%). Most OPMD patients presented without dysplasia (6420 cases, 92.19%), while 339 (4.87%) patients had concomitant mild dysplasia and 205 (2.94%) patients had concomitant moderate/severe dysplasia. The habits of OPMD patients included tobacco smoking (1360 cases, 19.53%), alcohol drinking (1068 cases,15.34%), and areca nut chewing (157 cases, 2.25%). Some patients developed OPMD concomitant with systemic diseases (1525 cases, 21.90%), and with a history of other cancers (except oral cancer) (94 cases, 1.35%). A total of 6824 OPMD patients (97.99%) were treated with drugs. The baseline characteristics of the study population are shown in Table 1.

### *Univariate and multivariate Cox regression analyses of risk factors for malignant transformation of OPMDs*

Table 2 shows the univariate and multivariate Cox regression analyses of risk factors for malignant transformation of OPMDs. Univariate Cox regression showed that the risk of malignant transformation of OPMDs increased with age (hazard ratio [HR] = 1.07, 95% confidence interval [CI]: 1.06–1.09; $P = 0.000$). The risk of malignant transformation of OPMDs was higher on the ventral/lateral surface of tongue/floor of the mouth (VLT/FOM) (HR = 10.67, 95% CI: 6.97–16.32; $P = 0.000$), gingiva (HR = 4.80, 95% CI: 2.70–8.53; $P = 0.000$) and palate (HR = 13.20, 95% CI: 5.12–34.02; $P = 0.000$) than on the buccal mucosa. The risk of malignant transformation of OLP (HR = 0.03, 95% CI: 0.02–0.05; $P = 0.000$) and OLE (HR = 0.11, 95% CI: 0.05–0.27; $P = 0.000$) was lower than that of OLK, while the risk of malignant transformation of OE (HR = 2.73, 95% CI: 1.00–7.40; $P = 0.049$) was higher than that of OLK. Compared with OPMD without dysplasia, OPMD with mild dysplasia (HR = 16.75, 95% CI: 10.79–25.99; $P = 0.000$) and moderate/severe dysplasia (HR = 52.63, 95% CI: 35.63–78.03; $P = 0.000$) had an increased risk of malignant transformation. Patients with OPMDs concomitant with systemic diseases (HR = 3.01, 95% CI: 2.15–4.20; $P = 0.000$) and a history of other cancers (HR = 4.18, 95% CI: 1.96–8.94; $P = 0.000$) had an increased risk of malignant transformation. Patients with OPMDs treated by photodynamic therapy (HR = 19.09, 95% CI: 9.95–36.65; $P = 0.000$) or surgery (HR = 14.93, 95% CI: 9.26–24.06; $P = 0.000$) had a greater risk of malignant transformation than those treated with drugs.

Multivariate Cox regression showed that the risk of malignant transformation of OPMDs increased with age (HR = 1.03, 95% CI: 1.01–1.04; $P = 0.001$). The risk of malignant transformation of OPMDs in VLT/FOM (HR = 2.45, 95% CI: 1.53–3.91; $P = 0.000$) and gingiva (HR = 1.92, 95% CI: 1.06–3.49; $P = 0.031$) was higher than that in the buccal mucosa. The risk of malignant transformation of OLP (HR = 0.14, 95% CI: 0.07–0.27; $P = 0.000$) was lower than that of OLK. Compared

**Table 1**
Baseline characteristics of the study population.

| Variable | No malignant transformation | | Malignant transformation | |
|---|---|---|---|---|
| | Number | % | Number | % |
| Age (years) | 48.29 ± 13.40 | | 59.35 ± 12.07 | |
| Sex | | | | |
| Female | 4238 | 62.10 | 89 | 64.03 |
| Male | 2587 | 37.90 | 50 | 35.97 |
| Sites | | | | |
| Buccal | 3746 | 54.89 | 30 | 21.58 |
| Dorsum of tongue | 1209 | 17.71 | 5 | 3.60 |
| VLT/FOM | 812 | 11.90 | 73 | 52.52 |
| Lip | 539 | 7.90 | 7 | 5.04 |
| Gingiva | 475 | 6.96 | 19 | 13.67 |
| Palate | 44 | 0.64 | 5 | 3.60 |
| Kinds of OPMD | | | | |
| OLK | 875 | 12.82 | 108 | 77.70 |
| OLP | 5221 | 76.50 | 17 | 12.23 |
| OLL | 153 | 2.24 | 0 | 0.00 |
| OLE | 385 | 5.64 | 5 | 3.60 |
| OSF | 109 | 1.60 | 0 | 0.00 |
| CHC | 64 | 0.94 | 5 | 3.60 |
| OE | 12 | 0.18 | 4 | 2.88 |
| OGVHD | 4 | 0.06 | 0 | 0.00 |
| AC | 2 | 0.03 | 0 | 0.00 |
| Epithelial dysplasia | | | | |
| Without dysplasia | 6377 | 93.44 | 43 | 30.94 |
| Mild dysplasia | 302 | 4.42 | 37 | 26.62 |
| Moderate/ severe dysplasia | 146 | 2.14 | 59 | 42.45 |
| Tobacco smoking | | | | |
| No | 5490 | 80.44 | 114 | 82.01 |
| Yes | 1335 | 19.56 | 25 | 17.99 |
| Alcohol drinking | | | | |
| No | 5775 | 84.62 | 121 | 87.05 |
| Yes | 1050 | 15.38 | 18 | 12.95 |
| Areca nut chewing | | | | |
| No | 6670 | 97.73 | 137 | 98.56 |
| Yes | 155 | 2.27 | 2 | 1.44 |
| Systemic diseases | | | | |
| No | 5363 | 78.58 | 76 | 54.68 |
| Yes | 1462 | 21.42 | 63 | 45.32 |
| Other cancers | | | | |
| No | 6738 | 98.73 | 132 | 94.96 |
| Yes | 87 | 1.27 | 7 | 5.04 |
| Treatment | | | | |
| Drug | 6715 | 98.39 | 109 | 78.42 |
| Photodynamic therapy | 36 | 0.53 | 10 | 7.19 |
| Surgery | 74 | 1.08 | 20 | 14.39 |

Notes: VLT/FOM: Ventral/ lateral surface of tongue/ floor of mouth, OLK: oral leukoplakia, OLP: oral lichen planus, OLL: oral lichenoid lesion, OLE: oral lupus erythematosus, OSF: oral submucous fibrosis, CHC: chronic hyperplastic candidosis, OE: oral erythroplakia, OGVHD: oral graft versus host disease, AC: actinic cheilitis.

with OPMDs without dysplasia, OPMDs with mild dysplasia (HR = 2.38, 95% CI: 1.37–4.12; $P = 0.002$) and moderate/severe dysplasia (HR = 5.63, 95% CI: 3.26–9.73; $P = 0.000$) had an increased risk of malignant transformation. Patients with OPMDs concomitant with a history of other cancers (HR = 3.30, 95% CI: 1.50–7.26; $P = 0.003$) had an increased risk of malignant transformation. The backward selection stepwise regression method was used to verify the variables that were selected for the multivariate Cox regression model. Starting with the model including all independent variables, one independent variable was deleted at each iteration until the quality of the model declined. Table 3 shows that the Akaike information criterion (AIC) of the all-variable model was higher than that of the no-variable model, so the no-variable model was eliminated. Five variables (age, site, kind of OPMD, epithelial dysplasia, and other cancers) were included in the predictive model.

**Table 2**
Univariate and multivariate cox regression analyses of risk factors of malignant transformation of OPMD.

| Variable | Univariate Cox regression analyses | | Multivariate Cox regression analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Age (years) | 1.07 (1.06, 1.09) | 0.000* | 1.03 (1.01, 1.04) | 0.001* |
| Sex | | | | |
| Female | Reference | | | |
| Male | 0.93 (0.66, 1.32) | 0.679 | | |
| Sites | | | | |
| Buccal | Reference | | Reference | |
| Dorsum of tongue | 0.52 (0.20, 1.33) | 0.169 | 0.61 (0.23, 1.60) | 0.312 |
| VLT/FOM | 10.67 (6.97, 16.32) | 0.000* | 2.45 (1.53, 3.91) | 0.000* |
| Lip | 1.58 (0.69, 3.59) | 0.279 | 0.98 (0.27, 3.59) | 0.976 |
| Gingiva | 4.80 (2.70, 8.53) | 0.000* | 1.92 (1.06, 3.49) | 0.031* |
| Palate | 13.20 (5.12, 34.02) | 0.000* | 2.03 (0.75, 5.54) | 0.165 |
| Kinds of OPMD | | | | |
| OLK | Reference | | Reference | |
| OLP | 0.03 (0.02, 0.05) | 0.000* | 0.14 (0.07, 0.27) | 0.000* |
| OLL | NA | | NA | |
| OLE | 0.11 (0.05, 0.27) | 0.000* | 0.48 (0.10, 2.19) | 0.342 |
| OSF | NA | | NA | |
| CHC | 0.66 (0.27, 1.61) | 0.357 | 1.56 (0.62, 3.93) | 0.346 |
| OE | 2.73 (1.00, 7.40) | 0.049* | 0.75 (0.26, 2.16) | 0.597 |
| OGVHD | NA | | NA | |
| AC | NA | | NA | |
| Epithelial dysplasia | | | | |
| Without dysplasia | Reference | | Reference | |
| Mild dysplasia | 16.75 (10.79, 25.99) | 0.000* | 2.38 (1.37, 4.12) | 0.002* |
| Moderate/ severe dysplasia | 52.63 (35.49, 78.03) | 0.000* | 5.63 (3.26, 9.73) | 0.000* |
| Tobacco smoking | | | | |
| No | Reference | | | |
| Yes | 0.91 (0.59, 1.40) | 0.668 | | |
| Alcohol drinking | | | | |
| No | Reference | | | |
| Yes | 0.85 (0.52, 1.40) | 0.524 | | |
| Areca nut chewing | | | | |
| No | Reference | | | |
| Yes | 0.65 (0.16, 2.62) | 0.543 | | |
| Systemic diseases | | | | |
| No | Reference | | Reference | |
| Yes | 3.01 (2.15, 4.20) | 0.000* | 1.32 (0.92, 1.89) | 0.134 |
| Other cancers | | | | |
| No | Reference | | Reference | |
| Yes | 4.18 (1.96, 8.94) | 0.000* | 3.30 (1.50, 7.26) | 0.003* |
| Treatment | | | | |
| Drug | Reference | | Reference | |
| Photodynamic therapy | 19.09 (9.95, 36.65) | 0.000* | 1.78 (0.90, 3.50) | 0.096 |
| Surgery | 14.93 (9.26, 24.06) | 0.000* | 1.36 (0.81, 2.28) | 0.253 |

Notes: HR: Hazard ratio, CI: confidence interval, VLT/FOM: Ventral/ lateral surface of tongue/ floor of mouth, OLK: oral leukoplakia, OLP: oral lichen planus, OLL: oral lichenoid lesion, OLE: oral lupus erythematosus, OSF: oral submucous fibrosis, CHC: chronic hyperplastic candidosis, OE: oral erythroplakia, OGVHD: oral graft versus host disease, AC: actinic cheilitis.

**Table 3**
Backward selection stepwise regression of risk factors of malignant transformation of OPMD.

| Variable | AIC | HR (95% CI) | *P* value |
|---|---|---|---|
| None | 1966.6 | | |
| Other cancers | 1970.7 | | |
| No | | Reference | |
| Yes | | 3.17 (1.44, 6.99) | 0.004* |
| Age (years) | 1979.9 | 1.03 (1.01, 1.04) | 0.000* |
| Sites | 1980.5 | | |
| Buccal | | Reference | |
| Dorsum of tongue | | 0.62 (0.24, 1.64) | 0.226 |
| VLT/FOM | | 2.56 (1.61, 4.08) | 0.000* |
| Lip | | 0.98 (0.27, 3.57) | 0.978 |
| Gingiva | | 2.01 (1.11, 3.64) | 0.021* |
| Palate | | 2.30 (0.86, 6.16) | 0.098 |
| Kinds of OPMD | 1990.5 | | |
| OLK | | Reference | |
| OLP | | 0.13 (0.07, 0.26) | 0.000* |
| OLL | | NA | |
| OLE | | 0.48 (0.10, 2.17) | 0.337 |
| OSF | | NA | |
| CHC | | 1.48 (0.59, 3.73) | 0.404 |
| OE | | 0.78 (0.27, 2.24) | 0.643 |
| OGVHD | | NA | |
| AC | | NA | |
| Epithelial dysplasia | 2014.1 | | |
| Without dysplasia | | Reference | |
| Mild dysplasia | | 2.45 (1.42, 4.24) | 0.001* |
| Moderate/ severe dysplasia | | 6.22 (3.66, 10.57) | 0.000* |

Notes: AIC: Akaike information criterion, HR: Hazard ratio, CI: confidence interval, VLT/FOM: Ventral/ lateral surface of tongue/ floor of mouth, OLK: oral leukoplakia, OLP: oral lichen planus, OLL: oral lichenoid lesion, OLE: oral lupus erythematosus, OSF: oral submucous fibrosis, CHC: chronic hyperplastic candidosis, OE: oral erythroplakia, OGVHD: oral graft versus host disease, AC: actinic cheilitis.

*Development and validation of nomogram prediction*

The nomogram was used to calculate a total score for each patient by adding the score obtained from individual characteristics. The calculated scores could identify the probabilities of 3-, 5- and 7-year periods for the nonmalignant rate (Fig. 1). A dynamic nomogram was also constructed and published in shinyapps.io (https://qingfeng.shinyapps.io/DynNomapp/). In the dynamic nomogram, age, site, kind of OPMD (OPMD_kinds), existence of dysplasia and its grade, other cancers (history of other cancers except oral cancer, OtherCA), and follow-up time can be selected to predict the risk of malignant transformation of OPMD patients. For example, as shown in Figure 2, the nonmalignant risk of a 69-year-old patient with OLK in VLT/FOM with moderate/severe dysplasia with a follow-up time of 84 months (7 years) was 15.1%, and the malignancy rate was 84.9%. The sensitivity and specificity of the nomogram were measured using time-dependent ROC curve analyses, and the area under the curve (AUC) for the model was 0.913 (95% CI: 0.861–0.965, 1-year follow-up), 0.934 (95% CI: 0.909–0.959, 3-year follow-up), 0.928 (95% CI: 0.904–0.952, 5-year follow-up), and 0.920 (95% CI: 0.891–0.949, 7-year follow-up), which showed that the model had a high level of predictive value (Fig. 3). Additionally, the calibration curve with bootstrap (1500 resample) validation showed that the predicted line overlapped well with the reference line for 1-, 3-, 5-, and 7-year follow-up, demonstrating the good performance of the nomogram (Fig. 4). Furthermore, DCA was performed to evaluate the net benefit of the nomogram to verify whether the model was clinically useful. The results showed that the nomogram offered clinical relevance in a mean time of 74 months and over a 7 year span (Fig. 5).

## Discussion

OPMDs comprise a group of diseases diagnosed by clinical and pathological features. In March 2020, the WHO organized a seminar to discuss the latest research into OPMDs [4]. It is necessary to determine the potential risk of malignant transformation of patients with an OPMD based on clinicopathological parameters. This study developed and validated a novel nomogram prediction model for the malignant transformation of OPMDs.

In this study, we found that the rate of malignant transformation of OPMDs was 2.00%. Studies have shown different malignant transformation rates ranging from 2.6% to 7.9% [6–10]. Different kinds of OPMD were included in each study, with differing prevalence recorded in various regions. Populations in different regions with various risk factors and genetic susceptibilities may lead to diversity in the malignant transformation rate. A variety of oral mucosal diseases have been defined as OPMDs; however, the differences in the risk of malignant transformation are not clearly stated in the classification and definition. It has been proposed that OPMDs should be graded according to the risk of malignant transformation [14]. OPMDs can be divided into three groups: low-risk group (rate of malignant transformation: 0– 3%, including OLP, OLL, OLE), moderate-risk group (rate of malignant transformation: 4– 15%, including OLK, OSF, CHC), and high-risk group

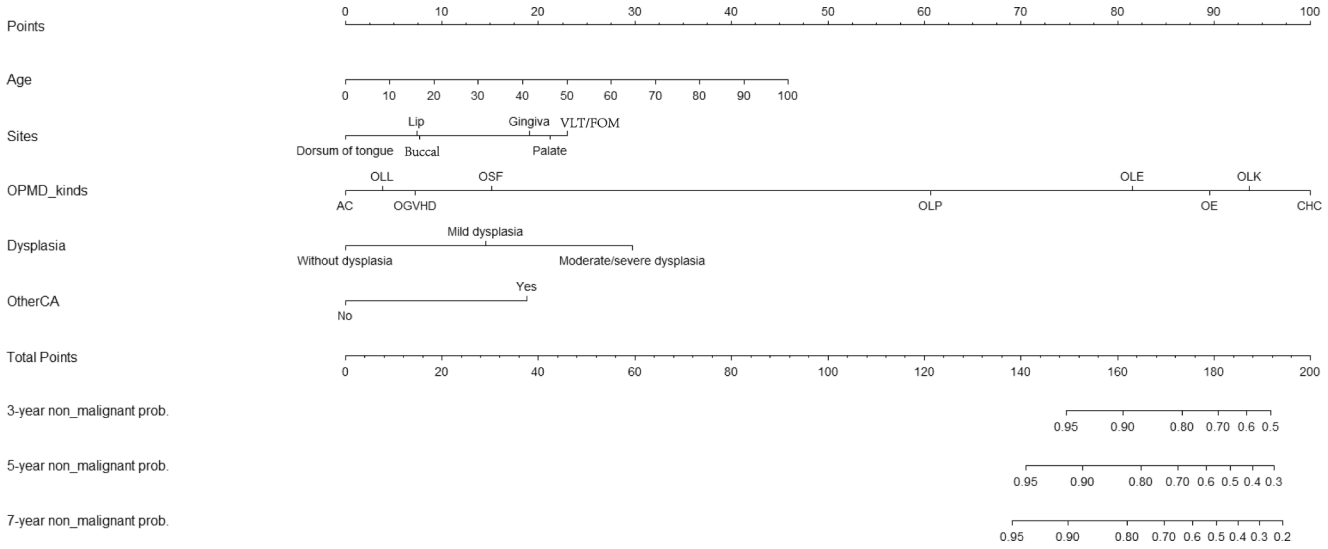


**Fig. 1.** Nomogram prediction model. The nomogram was used to calculate a total score for each patient by adding the scores obtained from individual characteristics. The calculated scores identify the probabilities for 3-, 5- and 7-year follow-up periods for the nonmalignant transformation rate.

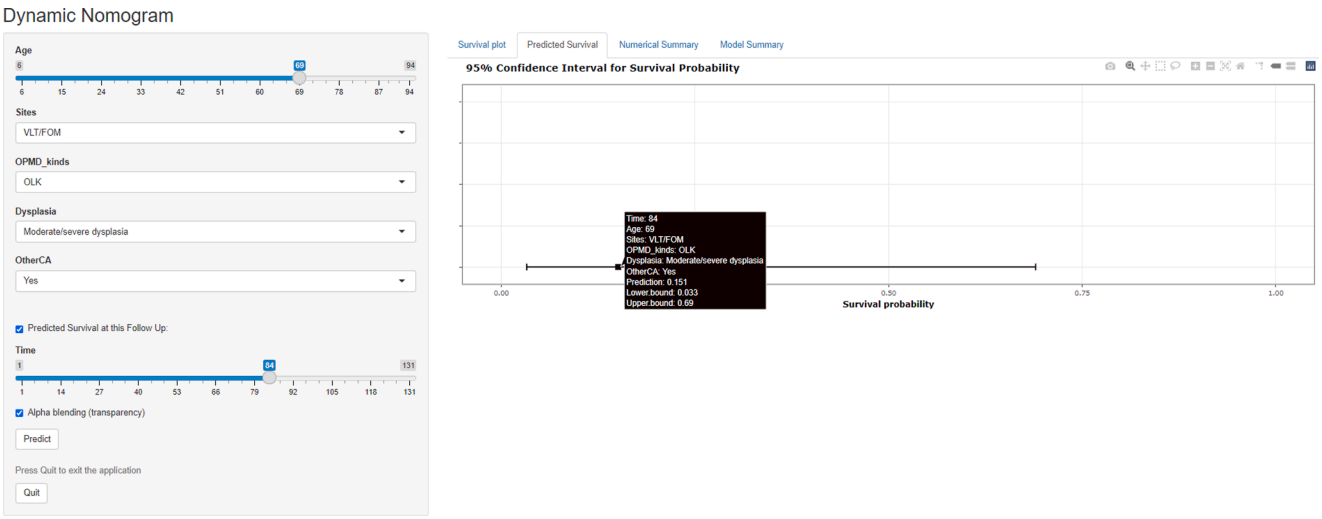


**Fig. 2.** Dynamic nomogram (https://qingfeng.shinyapps.io/DynNomapp/). The nonmalignant risk for a 69-year-old patient with oral leukoplakia (OLK) in the ventral/lateral surface of tongue / floor of mouth (VLT/FOM) with moderate/severe dysplasia with a follow-up time of 84 months (7 years) was 15.1%, and the malignant rate was 84.9%.

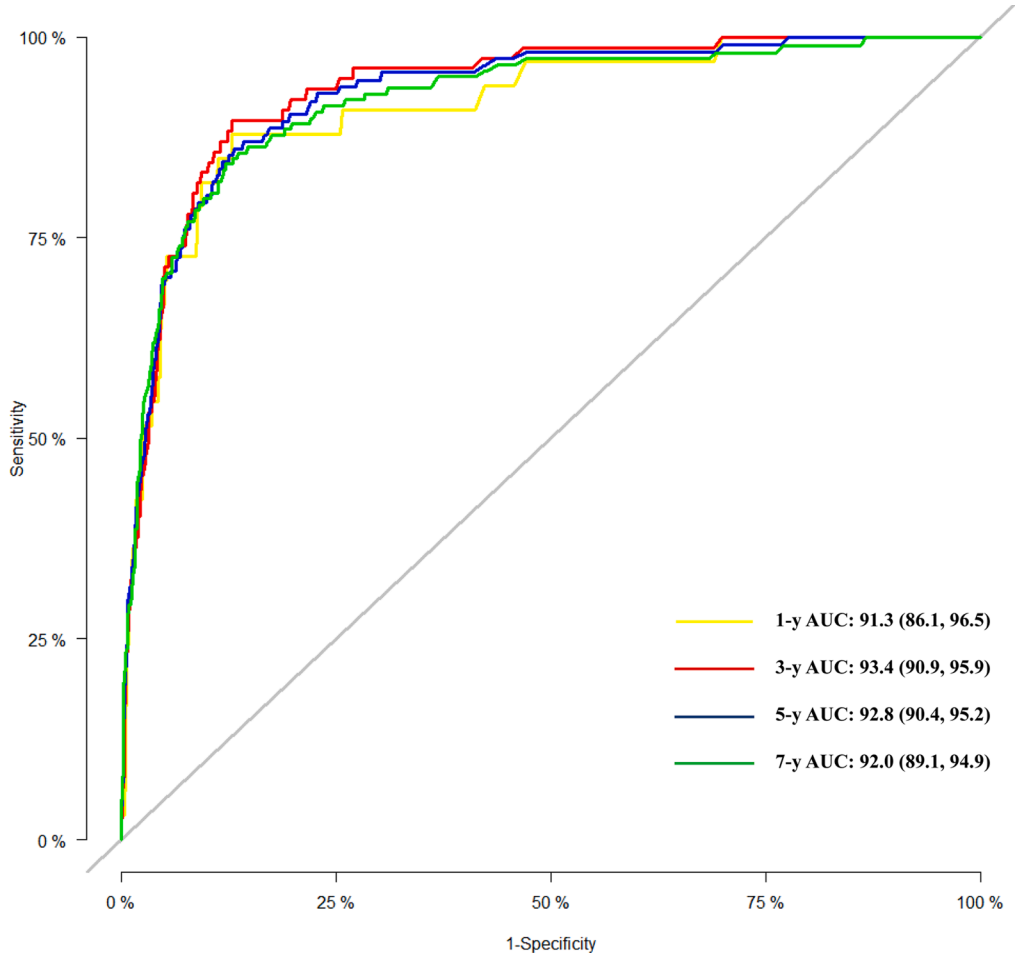


**Fig. 3.** Time-dependent receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) for the model was 0.913 (95% CI: 0.861–0.965, 1-year follow-up), 0.934 (95% CI: 0.909–0.959, 3-year follow-up), 0.928 (95% CI: 0.904–0.952, 5-year follow-up), and 0.920 (95% CI: 0.891–0.949, 7-year follow-up).

(rate of malignant transformation: 15%, including OE) [14]. Although this stratification is based on studies with a high level of evidence and a large sample size, it may change over time and region. For example, Chuang *et al.* [8] reported that the risk of malignant transformation was OE (8.18%) > OSF (7.69%) > OLK (4.72%) in Taiwan in 2018, while Chiu *et al.* [6] found that the risk of malignant transformation was OSF (5.03%) > OE (3.91%) > OLP (1.77%) > OLK (1.68%) in Taiwan in 2021. By reviewing studies from different regions, Iocca *et al.* [7]

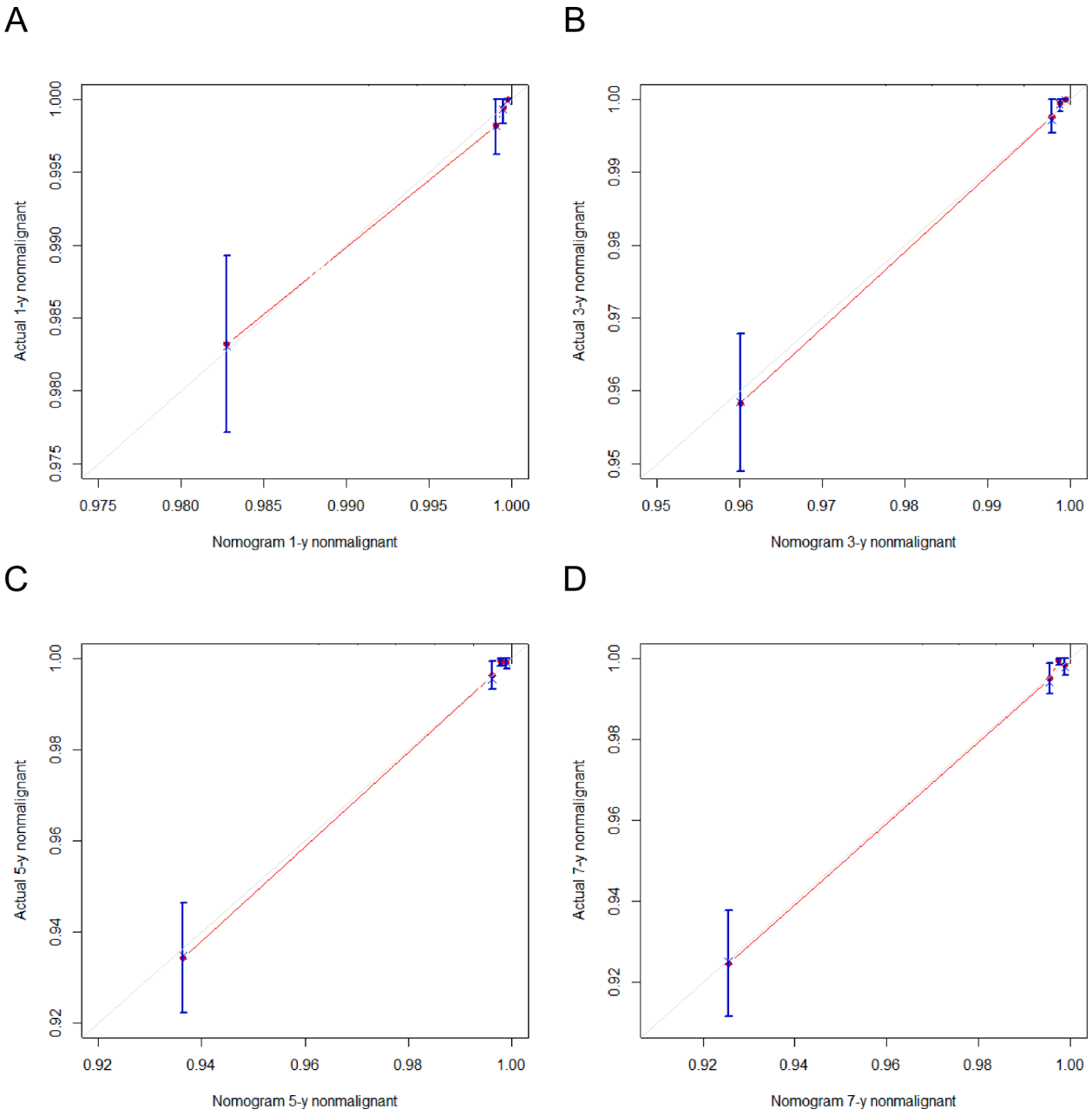


**Fig. 4.** Calibration curve with bootstrap (1500 resample) validation showing that the predicted line overlapped well with the reference line both in 1-year (A), 3-year (B), 5-year (C) and 7-year (D) follow-up periods.

identified higher rates of malignant transformation for OE (33.1%), OLK (9.5%), OSF (5.2%), OLL (3.8%), and OLP (1.4%).

In this study, the rates of malignant transformation for OLK, OLP, OLE, CHC, and OE were 10.99%, 0.32%, 1.30%, 7.25%, and 25.00%, respectively. Additionally, 153 cases of OLL, 112 cases of OSF, four cases of OGVHD, and two cases of AC had no malignant transformation. OGVHD and AC are relatively rare in China, so few cases were included in this study. OE is probably the OPMD with highest risk of malignant transformation [15]. Oreste *et al.* [7] found that the rate of malignant transformation was 33.1% based on a review of 92 studies. Our findings also demonstrated that the rate of transformation of OE was the highest of all of the OPMDs, and that there was a high rate of malignant transformation in OLK patients, consistent with the findings of other studies (1.3– 22.9%) [16–19]. The risk of malignant transformation was significantly lower for OLP than for OLK. It has been reported that the malignant transformation rate for OLP is 0.07%–0.9% [20–23], although when concomitant with dysplasia, the rate increases to 2.8%–2.84% [23,24]. In our study, OLP was diagnosed without dysplasia according to the WHO diagnostic criteria [25]. In literature reviews conducted in 2014 and 2017 respectively, Sarah *et al.* [26] found that 3.2% cases of OLL patients evolved into malignancy, while Sana *et al.* [27] found that the rate was 3.1% cases. Our study showed no malignant transformation of OLL. Both studies identified a low risk of malignant transformation of OLL. CHC presents as white patches caused by candida albicans [4]. Shukla *et al.* [28] reviewed the malignant transformation of candida infection and found only three studies, which reported malignant transformation rates of 4.4%, 6.5%, and 28.7%. Our study identified a malignant transformation rate of 7.25% for CHC. Although there was no malignant transformation of OSF in the patients in this study, no evidence was found that OSF is not an OPMD. Jian *et al.* [29] reported that the rate of malignant transformation of OSF was 5.6% in Hunan, China, with an average time to malignancy of 8.6 years. Most patients

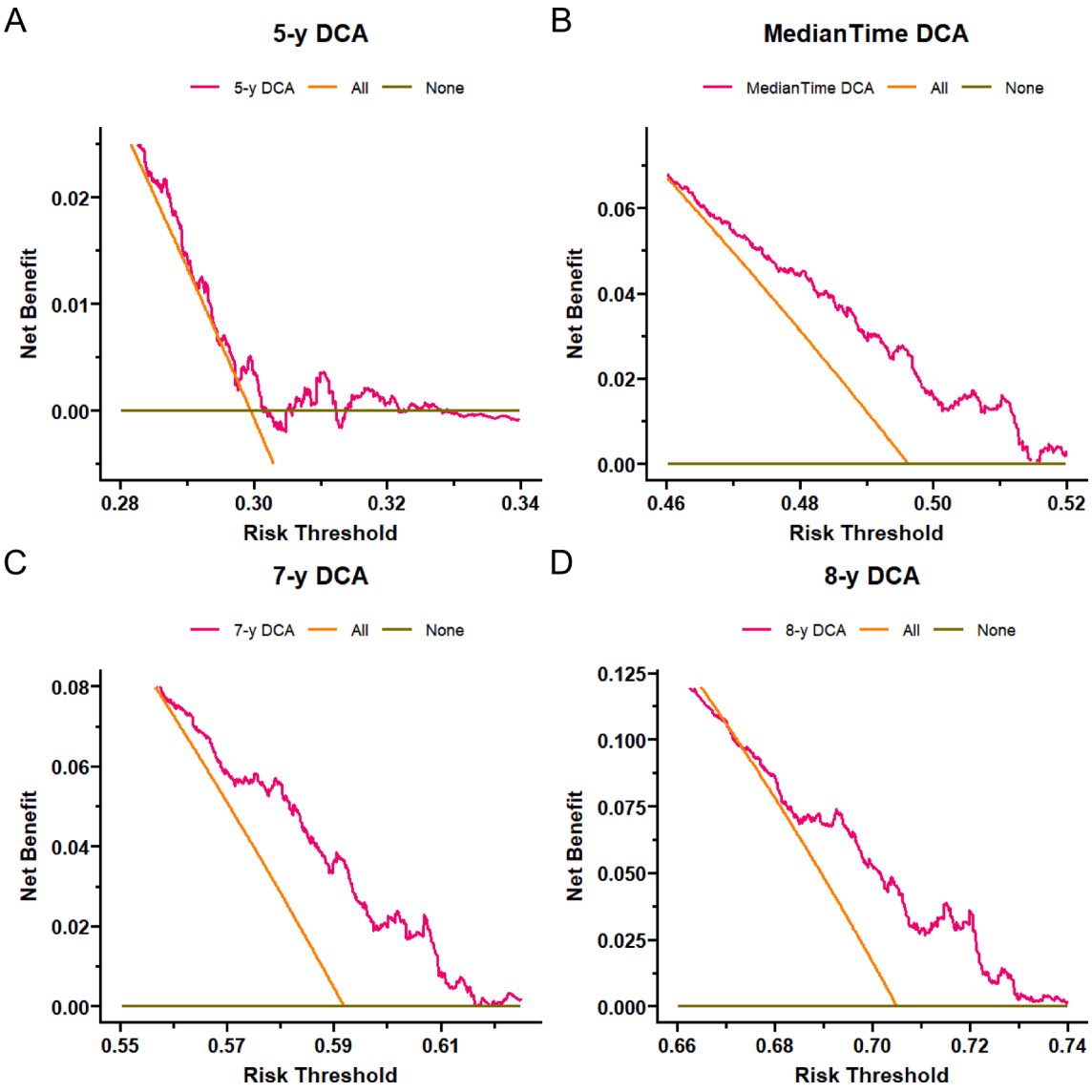


**Fig. 5.** Decision curve analysis [DCA, 5-year follow-up (A), mean time (B), 7-year follow-up (C), 8-year follow-up (D)] showing that the nomogram offered clinical relevance in a mean time of 74-month and over a 7 year span.

did not develop cancer until 10–19 years later [29]. Areca nut chewing accelerates the progression to malignant transformation [29]. The follow-up period for the malignant transformation of OSF may not have been long enough in this study; therefore further follow-up is needed. Additionally, few people chew areca nut in northern China, and the frequency and duration of areca nut chewing is much lower than that in Hunan, Hainan, and Taiwan where areca nut chewing people gather, so it is predictable that no malignant transformation of OSF was observed in this study.

OPMD refers to a statistically increased risk of malignant transformation, which does not mean that all lesions progress to malignancy. Other factors such as age, sites, and dysplasia must be taken into account to predict the malignant transformation of OPMDs [30]. In this study, increased age, lesions in the VLT/FOM and gingiva, mild dysplasia, and moderate/severe dysplasia concomitant with other cancers (e.g., breast cancer, endometrial carcinoma, and thyroid cancer) increased the risk of malignant transformation of OPMD. It is now believed that epithelial dysplasia has a significant risk of malignant transformation, which must be taken into account in the clinical management of OPMD [30]. The risk of malignant transformation increases with the grade of dysplasia [7,10] and with increasing age [10,30]. When stratified by age, it was found that patients older than 45 years at diagnosis showed higher malignant potential than younger patients [9]. *In vivo* studies have shown that the incidence of severe dysplasia and OSCC in old mice is higher than that in young mice. This may be due to immune aging and the increased sensitivity of older animals to carcinogens. Hypofunction and the damage to immune function and tissue regeneration caused by aging may affect the progression and malignant transformation of OPMDs [31]. OPMD lesions located in the tongue have a higher risk of malignant transformation [9]. In this study, although OPMDs were most commonly located in the buccal mucosa, the site with the highest risk of malignant transformation was the VLT/FOM. The VLT/FOM may become an oral risk zone for malignant transformation because of excessive exposure to carcinogens via accumulation of alcohol and tobacco in the saliva [30]. Wang *et al.* [9] found that male patients with OPMDs were significantly associated with malignant transformation; however, another study reported that female patients had a higher risk of malignant transformation [30]. Our study showed that the sex of the patient was not significantly related to malignant transformation of OPMDs. Therefore, the role of sex on the malignant transformation of OPMDs still needs further investigation. Tobacco smoking, alcohol drinking, and areca nut chewing may also increase the risk of malignant

transformation of some kinds of OPMDs [8]. However, there is also evidence that these factors are not significantly associated with malignant transformation of OPMDs [30]. Tobacco smoking, alcohol drinking, and areca nut chewing may be independent risk factors for OPMDs and OSCC, but they play a limited role in the malignant transformation of OPMDs. Diabetes mellitus not only increased the prevalence of OPMDs and OSCC, but also increased the risk of malignant transformation of OPMDs [32,33]. Our study also demonstrated that systemic diseases may increase the risk of malignant transformation of OPMDs, although multivariate analysis did not show any statistical significance; however, it is necessary to assess the general condition of OPMD patients clinically. Additionally, although univariate analysis showed that treatment might be associated with malignant transformation, this association was ruled out by multivariate analysis. The type of treatment was determined by the severity of the OPMD. Patients without dysplasia were usually treated with drugs only, while patients with severe dysplasia sometimes required surgery to completely remove the lesions, especially OE and OLK. Therefore, treatment differences affected the univariate analyses, while in multivariate analyses, the influence of confounding factors and multicollinearity was excluded, indicating that treatment is not a risk factor for malignant transformation.

The advantage of this study lies in the innovation and verification of a dynamic nomogram prediction model containing five risk factors, based on a large-scale cohort study. Although it has been proven to have high discrimination, accuracy, and clinical relevance, the nomogram still has some limitations. First, there were few cases of OGVHD and AC, so this model might not be well adapted to these kinds of OPMD. Additionally, the clinicopathological parameters of OSF patients were not universal, so there are doubts about the prediction of this disease. Second, the nomogram prediction model includes only clinicopathological parameters, but does not include potential predictive variables, such as molecular markers and genetic mutations. Third, this study is based on a single-center cohort study; therefore, a larger cohort study in multiple centers and rigorous prospective trials need to be conducted to verify the model. In general, further research is needed to improve the applicability and universality of the model.

## Conclusion

This study produces evidence that age, sites, kinds of OPMD, existence of dysplasia and its grade, and other cancers could be involved in the malignant transformation of OPMDs. A dynamic nomogram has been developed and validated to predict malignant transformation in Chinese patients with OPMDs.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

[1] Chen SH, Hsiao SY, Chang KY, Chang JY. New Insights Into Oral Squamous Cell Carcinoma: From Clinical Aspects to Molecular Tumorigenesis. *Int J Mol Sci*. Feb 24 2021;22(5) 10.3390/ijms22052252.

[2] Ren Z-H, Hu C-Y, He H-R, Li Y-J, Lyu J. Global and regional burdens of oral cancer from 1990 to 2017: Results from the global burden of disease study. Cancer Commun (Lond). 2020;40(2-3):81–92. https://doi.org/10.1002/cac2.v40.2-310.1002/cac2.12009.

[3] Yang Y, Zhou M, Zeng X, Wang C. The burden of oral cancer in China, 1990-2017: an analysis for the Global Burden of Disease, Injuries, and Risk Factors Study 2017. *BMC Oral Health*. Jan 28 2021;21(1):44. 10.1186/s12903-020-01386-y.

[4] Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, et al. Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. *Oral Dis*. Oct 31 2020; 10.1111/odi.13704.

[5] Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, et al. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J Oral Pathol Med. 2018;47(7):633–40. https://doi.org/10.1111/jop.2018.47.issue-710.1111/jop.12726.

[6] Chiu SF, Ho CH, Chen YC, et al. Malignant transformation of oral potentially malignant disorders in Taiwan: An observational nationwide population database study. *Medicine (Baltimore)*. Mar 5 2021;100(9):e24934. 10.1097/MD.0000000000024934.

[7] Iocca O, Sollecito TP, Alawi F, Weinstein GS, Newman JG, De Virgilio A, 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(3):539–55. https://doi.org/10.1002/hed.v42.310.1002/hed.26006.

[8] Chuang S-L, Wang C-P, Chen M-K, Su W-Y, Su C-W, Chen S-S, et al. Malignant transformation to oral cancer by subtype of oral potentially malignant disorder: A prospective cohort study of Taiwanese nationwide oral cancer screening program. Oral Oncol. 2018;87:58–63. https://doi.org/10.1016/j.oraloncology.2018.10.021.

[9] Wang YY, Tail YH, Wang WC, et al. Malignant transformation in 5071 southern Taiwanese patients with potentially malignant oral mucosal disorders. *BMC Oral Health*. Aug 5 2014;14:99. 10.1186/1472-6831-14-99.

[10] Warnakulasuriya S, Kovacevic T, Madden P, et al. Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. *J Oral Pathol Med*. Oct 2011;40(9):677-83. 10.1111/j.1600-0714.2011.01054.x.

[11] Piyarathne NS, Rasnayake R, Angammana R, et al. Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors - A systematic review. *Expert Rev Mol Diagn*. Jun 21 2021; 10.1080/14737159.2021.1944106.

[12] Goodson ML, Smith DR, Thomson PJ. The"Newcastle Nomogram"-Statistical modelling predicts malignant transformation in potentially malignant disorders. J Oral Pathol Med. 2019;48(8):662–8. https://doi.org/10.1111/jop.v48.810.1111/jop.12881.

[13] Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26(8):1364–70. https://doi.org/10.1200/JCO.2007.12.9791.

[14] Sarode GS, Sarode SC, Maniyar N, Sam Regi R, Aruna A, Patil S. Malignant transformation rate based stratification model for oral potentially malignant disorders: A potential idea. *J Oral Biol Craniofac Res*. Oct-Dec 2020;10(4):490–1. https://doi.org/10.1016/j.jobcr.2020.07.017.

[15] Brignardello-Petersen R. Proliferative verrucous leukoplakia and erythroplakia are probably the disorders with the highest rate of malignant transformation. J Am Dent Assoc. 2020;151(8):e62. https://doi.org/10.1016/j.adaj.2020.01.035.

[16] Evren I, Brouns ER, Wils LJ, Poell JB, Peeters CFW, Brakenhoff RH, et al. Annual malignant transformation rate of oral leukoplakia remains consistent: A long-term follow-up study. Oral Oncol. 2020;110:105014. https://doi.org/10.1016/j.oraloncology.2020.105014.

[17] Wang T, Wang L, Yang H, Lu H, Zhang J, Li N, 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(6):491–8. https://doi.org/10.1111/jop.2019.48.issue-610.1111/jop.12862.

[18] Shearston K, Fateh B, Tai S, Hove D, Farah CS. Malignant transformation rate of oral leukoplakia in an Australian population. J Oral Pathol Med. 2019;48(7):530–7. https://doi.org/10.1111/jop.v48.710.1111/jop.12899.

[19] Zhang X, Kim KY, Zheng Z, Bazarsad S, Kim J. Nomogram for risk prediction of malignant transformation in oral leukoplakia patients using combined biomarkers. Oral Oncol. Sep 2017;72:132–9. https://doi.org/10.1016/j.oraloncology.2017.07.015.

[20] Budimir V, Richter I, Andabak-Rogulj A, Vucicevic-Boras V, Budimir J, Brailo V. Oral lichen planus - retrospective study of 563 Croatian patients. Med Oral Patol Oral Cir Bucal. 2014;19(3):e255–60. https://doi.org/10.4317/medoral.18940.

[21] Bombeccari GP, Guzzi G, Tettamanti M, Giannì AB, Baj A, Pallotti F, et al. Oral lichen planus and malignant transformation: a longitudinal cohort study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(3):328–34. https://doi.org/10.1016/j.tripleo.2011.04.009.

[22] Pakfetrat A, Javadzadeh-Bolouri A, Basir-Shabestari S, Falaki F. Oral Lichen Planus: a retrospective study of 420 Iranian patients. Med Oral Patol Oral Cir Bucal. 2009;14(7):E315–8.

[23] Bornstein MM, Kalas L, Lemp S, Altermatt HJ, Rees TD, Buser D. Oral lichen planus and malignant transformation: a retrospective follow-up study of clinical and histopathologic data. Quintessence Int. Apr 2006;37(4):261–71.

[24] Guan G, Mei L, Polonowita A, Hussaini H, Seo B, Rich AM. Malignant transformation in oral lichen planus and lichenoid lesions: a 14-year longitudinal retrospective cohort study of 829 patients in New Zealand. Oral Surg Oral Med Oral Pathol Oral Radiol. Oct 2020;130(4):411–8. https://doi.org/10.1016/j.oooo.2020.07.002.

[25] van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria

and suggestions for modifications. J Oral Pathol Med. Oct 2003;32(9):507–12. https://doi.org/10.1034/j.1600-0714.2003.00125.x.

[26] Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc*. Jan 2014; 145(1):45-56. 10.14219/jada.2013.10.

[27] Aghbari SMH, Abushouk AI, Attia A, Elmaraezy A, Menshawy A, Ahmed MS, et al. Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. Oral Oncol. 2017;68:92–102. https://doi.org/10.1016/j.oraloncology.2017.03.012.

[28] Shukla K, Vun I, Lov I, Laparidis G, McCamley C, Ariyawardana A. Role of Candida infection in the malignant transformation of oral leukoplakia: A systematic review of observational studies. 2019;4:2057178X19828229. 10.1177/2057178x19828229.

[29] Jian X, Jian Y, Wu X, et al. Oral submucous fibrosis transforming into squamous cell carcinoma: a prospective study over 31 years in mainland China. *Clin Oral Investig*. Aug 25 2020; 10.1007/s00784-020-03541-9.

[30] Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. Jun 2018; 125(6):612–27. https://doi.org/10.1016/j.oooo.2017.12.011.

[31] Vincent-Chong VK, DeJong H, Rich LJ, Patti A, Merzianu M, Hershberger PA, et al. Impact of Age on Disease Progression and Microenvironment in Oral Cancer. J Dent Res. 2018;97(11):1268–76. https://doi.org/10.1177/0022034518775736.

[32] Bastos AS, Leite AR, Spin-Neto R, Nassar PO, Massucato EM, Orrico SR. Diabetes mellitus and oral mucosa alterations: prevalence and risk factors. Diabetes Res Clin Pract. Apr 2011;92(1):100–5. https://doi.org/10.1016/j.diabres.2011.01.011.

[33] Ramos-Garcia P, Roca-Rodriguez MDM, Aguilar-Diosdado M, Gonzalez-Moles MA. Diabetes mellitus and oral cancer/oral potentially malignant disorders: A systematic review and meta-analysis. Oral Dis. 2021;27(3):404–21. https://doi.org/10.1111/odi.v27.310.1111/odi.13289.