Nomogram predicting long-term overall and cancer-specific survival of patients with buccal mucosa cancer

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Abstract

Background: Few models about the personalized prognosis evaluation of buccal mucosa cancer (BMC) patients were reported. We aimed to establish predictive models to forecast the prognosis of BMC patients.

Methods: The complete clinicopathological information of BMC patients from the surveillance, epidemiology and end results program was collected and reviewed retrospectively. Two nomograms were established and validated to predict long-term overall survival (OS) and cancer-specific survival (CSS) of BMC patients based on multivariate Cox regression survival analysis.

Results: 1155 patients were included. 693 and 462 patients were distributed into modeling and validation groups with 6:4 split-ratio via a random split-sample method. Based on the survival analysis, independent prognostic risk factors (variables that can be used to estimate disease recovery and relapse chance) influencing OS and CSS were obtained to establish nomograms. Then, we divided the modeling group into high- and low-risk cohorts. The low-risk cohort had improved OS and CSS compared to the high-risk cohort, which was statistically significant after the Log-rank test ($p < 0.05$). Furthermore, we used the concordance index (C-index), calibration curve to validate the nomograms, showing high accuracy. The decision curve analyses (DCA) revealed that the nomograms had evident clinical value.

Conclusions: We constructed two credible nomogram models, which would give the surgeons reference to provide an individualized assessment of BMC patients.

Keywords: Buccal mucosa cancer (BMC), Nomogram, Overall survival, Cancer-specific survival, Decision curve

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Background

Oral squamous cell carcinoma (OSCC) ranks sixth among all the cancer categories [1]. OSCC mainly includes tongue, buccal, floor of mouth, hard and soft palate cancers [2, 3]. Frequently, BMC accounts for the second or third proportion of OSCC, especially among the population of Southeast Asia due to the habit of chewing betel quid [1]. The buccal mucosa is adjacent to bone, skin and mastication muscles, leading to early involvement of these sites in BMC. This pattern contributes to a large percentage of BMC being categorized

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as T4 stage [4, 5]. In almost all studies the prognosis of buccal cancer is poor because of its aggressive tumor behavior and high local recurrence rate. However, compared with other oral cancers, few studies comprehensively evaluate the prognosis of patients with BMC [6]. Generally, most researches assess how different BMC characteristics and treatment influence the prognosis of patients with BMC [7]. Numerous researches have reported the prognosis of the general OSCC [8]. However, few studies regarding BMC patients' prognosis were documented. Thus, more emphasis should be laid on the prognosis research of patients with BMC.

National Comprehensive Cancer Network (NCCN) clinical guideline suggests assessing the prognosis of OSCC patients via the 7th American Joint Committee on Cancer (AJCC) Staging Manual merely based on TNM staging [9]. However, other relevant clinicopathological parameters also influence the prognosis of the BMC patients such as age, tumor size, tumor thickness, neck nodal metastasis, surgical margin, and grade [10, 11]. Hence, taking the relevant factors into account would provide an accurate prediction of the prognosis of BMC patients. The OS and CSS nomogram is a novel tool to predict the personalized prognosis evaluation.

Nomogram can transform the independent risk factors from Cox regression survival analysis into visual graphics [12], which was widely applied to conduct personalized prognosis evaluation including prostate cancer [13], pulmonary adenocarcinoma [14], oral squamous cell carcinoma [15], oropharyngeal squamous cell carcinoma [16]. Most importantly, the 8th version of the AJCC staging manual recommended that the future version would embrace the nomogram to realize the pursuit of personalized medicine [17]. We sought to establish two nomograms forecasting long-term OS and CSS of the BMC patients by integrating diverse prognostic variables obtained from the Kaplan–Meier and Cox regression model.

Methods
Patients' characteristics and survival analysis
The study was approved by the Ethic Committee of Stomatological Hospital of the Fourth Military Medical University (Approval number: IRB-REV-2020059). We collected the detailed clinicopathological information of 1155 patients with buccal cancer, from the years 2004–2013, from the SEER database: http://seer.cancer.gov. The inclusion criteria were as follows: clear tumor location; detailed clinicopathological information and active OS and CSS follow-up data. Data collected from death certificate or autopsy was excluded. 1155 BMC patients' detailed information was collected from the SEER database including age, sex, race, origin, grade,

surgery, radiation, T stage, N stage, M stage, OS, CSS and survival time (Table 1). The original variable included non-spanish-hispanic-latino and spanish-hispanic-latino. The meanings of grade I, II, III, IV were well differentiated, moderately differentiated, poorly differentiated and undifferentiated respectively. Based on SAS variables "sur_time_mon", "STAT_REC", "VSRTSADX" in the SEER database, we obtained patients' OS, CSS and survival time information. The OS duration time was determined as the period from the diagnosis to death or the last follow-up time. However, CSS focused on the death caused by BMC only.

According to the random split-sample method, we divided the patients into modeling group (n=693) and validation group (n=462). Based on the modeling group, we conduct the univariate OS and CSS analysis and log-rank test firstly. The variables with statistical significance were incorporated into the multivariate Cox regression model to determine the final independent prognostic risk indicators secondly via SPSS 21.0 software for windows [18]. Two-side p value was applied and $p < 0.05$ was considered statistically significant.

Nomogram construction and risk classification
We integrated all the independent prognostic risk factors to construct the nomogram through the "rms" package of the R. 3.2.4 software, which can transform the clinicopathological information into linear graphs. In the graph, every indicator axis was assigned a corresponding score according to every single patient's information. Thus, each patient's total scores were calculated and the modeling group's patients were divided into high- and low-risk cohorts according to cut-off value via R survminer and maxstat packages. We compared the OS and CSS of the above two cohorts via Kaplan–Meier and Log-rank tests.

Nomogram validation
We used 1000 resamples bootstrapping and ten-fold cross-validation method to conduct internal and external validation [12]. C-index and calibration curves were applied to evaluate the accuracy of the nomogram model. The calibration curves included two main lines: the 45-degree reference line and the actual line. The distance between the above two lines reflected the precision of the model. Moreover, decision curves were plotted to mirror the clinical value of the predicted nomogram model. In the decision curve, the abscissa and ordinate represented the threshold probability and net benefit respectively. The horizontal line and oblique line indicated that all samples were negative and positive accordingly, corresponding to a different net benefit.

The C-index, calibration curve and decision curve were realized using "Hmisc", "rms" and "stdca.R" packages.

Table 1 Patients' detailed data

Variables	Modeling group (n = 693)		Validation group (n = 462)	
	n	%	n	%
Age				
< 35	21	3.0	14	3.0
36–45	51	7.4	37	8.0
46–55	124	17.9	80	17.3
56–65	156	22.5	96	20.8
66–75	162	23.4	107	23.2
76–85	120	17.3	93	20.1
85 +	59	8.5	35	7.6
Sex				
Male	379	54.7	251	54.3
Female	314	45.3	211	45.7
Race				
White	530	76.5	354	76.6
Black	67	9.7	38	8.2
Others	96	13.9	70	15.2
Origin				
NSHL	632	91.2	424	91.8
SHL	61	8.8	38	8.2
Grade				
I	211	30.4	140	30.3
II	367	53.0	240	51.9
III	112	16.2	77	16.7
IV	3	0.4	5	1.1
Surgery				
Performed	585	84.4	394	85.3
None	108	15.6	68	14.7
Radiation				
Yes	335	48.3	225	48.7
No	358	51.7	237	51.3
T stage				
T1	272	39.2	170	36.8
T2	231	33.3	160	34.6
T3	87	12.6	48	10.4
T4	103	14.9	84	18.2
N stage				
N0	459	66.2	313	67.7
N1	101	14.6	61	13.2
N2	129	18.6	86	18.6
N3	4	0.6	2	0.4
M stage				
M0	680	98.1	454	98.3
M1	13	1.9	8	1.7

NSHL: Non-Spanish-Hispanic-Latino. SHL: Spanish-Hispanic-Latino. Grade I: Well differentiated. II: Moderately differentiated. III: Poorly differentiated. IV: Undifferentiated

Results

Patients' characteristics and survival analysis

693 and 462 patients were assigned into the modeling and validation groups, applying the random split-sample method with 6:4 split-ratio. In the modeling group, 379 were male and 530 patients were white. 61 patients' origin was Spanish-Hispanic-Latino. In addition, 367 and 211 patients had moderate and well differentiated buccal carcinomas respectively. Of these modeling group, 585 and 335 patients received surgery and radiotherapy respectively. What's more, patients with T1–T2 stage accounted for 72.5%. The proportion of patients with N1-3 stage and M1 stage was 33.8% and 1.9% respectively. Also, the statistic for the validation group were given in Table 1.

The modeling and validation groups' median follow-up times were 24 months (0–119 months) and 23 months (0–119 months) respectively. In the modeling group, 277 patients died in the latest follow-up. 202 patients died of BMC. In addition, 75 patients died of other reasons rather than BMC.

Among the modeling group, the Kaplan–Meier univariate survival analysis showed that age, race, grade, surgery, radiation, T stage, N stage and M stage were related elements affecting OS ($p < 0.05$). Cox multivariate regression analysis revealed that age, grade, surgery, T stage and N stage were independent prognostic risk factors ($p < 0.05$). Moreover, about CSS analysis, age, grade, surgery, T stage, N stage and M stage were independent prognostic risk factors after Kaplan–Meier and Cox multivariate regression analysis. The detailed statistical data was shown in Tables 2 and 3.

Nomogram construction and risk classification

We incorporated the above OS- and CSS-relevant prognostic risk factors to construct the nomograms, which was shown in Fig. 1. Based on the scores calculated according to nomograms, we obtained the cut-off values to divide the patients into high- and low-risk parts. The cut-off values regarding OS and CSS were 73 and 58 respectively. The survival curves were shown in Fig. 2.

Nomogram validation

The C-indexes of OS and CSS in internal validation were 0.782 (95% CI: 0.756–0.808) and 0.793 (95% CI: 0.763–0.823) respectively. External validation showed that the C-indexes of OS and CSS were 0.784 (95% CI: 0.754–0.814) and 0.785 (95% CI: 0.751–0.817), respectively. All the C-indexes were higher than 0.7, indicating excellent consistency. What's more, OS and

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Table 2 OS analysis in modeling group

Variables	Univariate analysis	Multivariate analysis	
	p Value	HR(95% CI)	*p* Value
Age	< 0.001		< 0.001
< 35		0.110(0.034–0.363)	< 0.001
36–45		0.189(0.099–0.360)	< 0.001
46–55		0.263(0.165–0.418)	< 0.001
56–65		0.307(0.199–0.474)	< 0.001
66–75		0.418(0.280–0.623)	< 0.001
76–85		0.525(0.349–0.791)	0.002
85 +		Reference	
Race	< 0.001		0.791
White			
Black			
Others			
Grade	< 0.001		< 0.001
I		0.048(0.011–0.212)	< 0.001
II		0.054(0.012–0.236)	< 0.001
III		0.072(0.016–0.317)	0.001
IV		Reference	
Surgery	< 0.001		< 0.001
Performed		Reference	
None		2.549(1.842–3.528)	< 0.001
Radiation	< 0.001		0.276
Yes			
No			
T stage	< 0.001		< 0.001
T1		0.513(0.340–0.773)	0.001
T2		0.651(0.454–0.933)	0.019
T3		0.909(0.595–1.388)	0.658
T4		Reference	
N stage	< 0.001		< 0.001
N0		0.135(0.047–0.383)	< 0.001
N1		0.287(0.100–0.821)	0.020
N2		0.392(0.139–1.107)	0.077
N3		Reference	
M stage	< 0.001		0.067
M0			
M1			

Others: American Indian/AK Native, Asian/Pacific Islander. Grade I: Well differentiated. II: Moderately differentiated. III: Poorly differentiated. IV: Undifferentiated

Table 3 CSS analysis in modeling group

Variables	Univariate analysis	Multivariate analysis	
	p Value	HR(95% CI)	*p* Value
Age	< 0.001		< 0.001
< 35		0.239(0.070–0.825)	0.023
36–45		0.378(0.187–0.762)	0.007
46–55		0.467(0.266–0.821)	0.008
56–65		0.470(0.269–0.821)	0.008
66–75		0.718(0.430–1.200)	0.206
76–85		0.704(0.411–1.205)	0.201
85 +		Reference	
Grade	< 0.001		< 0.001
I		0.040(0.009–0.185)	< 0.001
II		0.044(0.010–0.200)	< 0.001
III		0.058(0.013–0.265)	< 0.001
IV		Reference	
Surgery	< 0.001		< 0.001
Performed		Reference	
None		2.560(1.780–3.681)	< 0.001
Radiation	< 0.001		0.296
Yes			
No			
T stage	< 0.001		0.001
T1		0.421(0.260–0.680)	< 0.001
T2		0.596(0.398–0.894)	0.012
T3		0.929(0.583–1.479)	0.755
T4		Reference	
N stage	< 0.001		< 0.001
N0		0.163(0.049–0.541)	< 0.001
N1		0.415(0.125–1.379)	0.151
N2		0.563(0.172–1.845)	0.343
N3		Reference	
M stage	< 0.001		0.040
M0		0.490(0.249–0.968)	
M1		Reference	

Grade I: Well differentiated. II: Moderately differentiated. III: Poorly differentiated. IV: Undifferentiated

CSS nomograms' calibration curves revealed that the observed 5- and 8-year survival probabilities were approach to the 45-degree reference line (Figs. 3, 4). Notably, the 5- and 8-year DCA curves showed that both nomogram models exerted net benefit in the validation group, demonstrating positive clinical value (Fig. 5).

Discussion

Smoking, alcohol consumption, chewing betel quid increase the incidence of BMC around the world [10, 19]. Smoking has a deleterious impact on the development of oral cancer [20]. Cytomorphometry research shows that smoking has adverse effects on the buccal mucosa [21]. In a 10-year follow-up study of 12,212 people, smoking cessation reduced the incidence of oral mucosal lesions [22]. Epidemiological data shows that about 600 million people chew betel quid worldwide. The betel leaf, areca nut, and lime inside are important causes of the high incidence of BMC in the Pacific Islands, South Asia,

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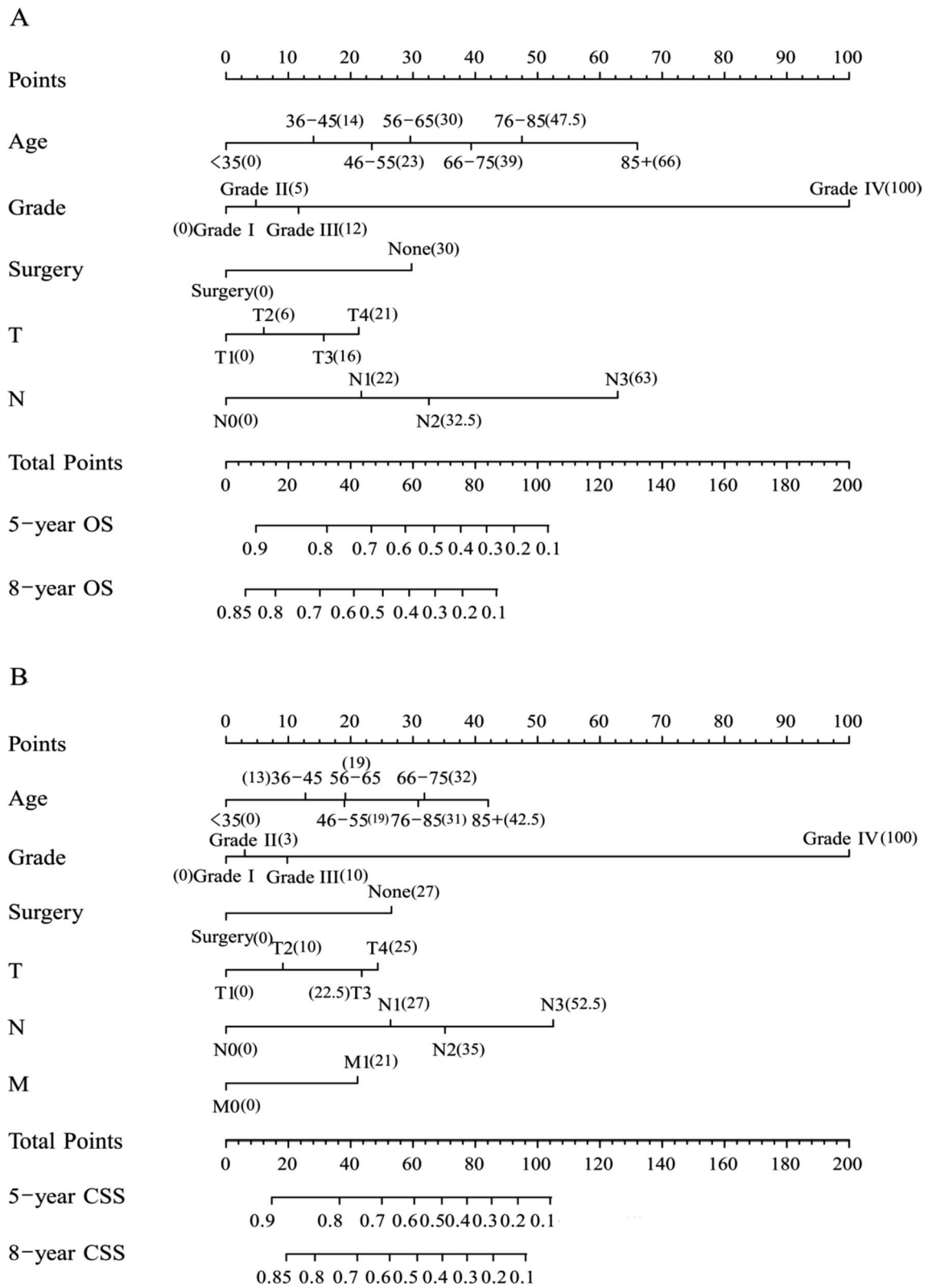
Fig. 1 Nomogram forecasting long-term OS (**A**) and CSS (**B**) of patients with BMC. The nomogram scores for each subcategory of the clinical parameters are shown in brackets

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Fig. 2 Survival curves for high- and low-risk group patients according to nomogram scores. **A** For OS. **B** For CSS
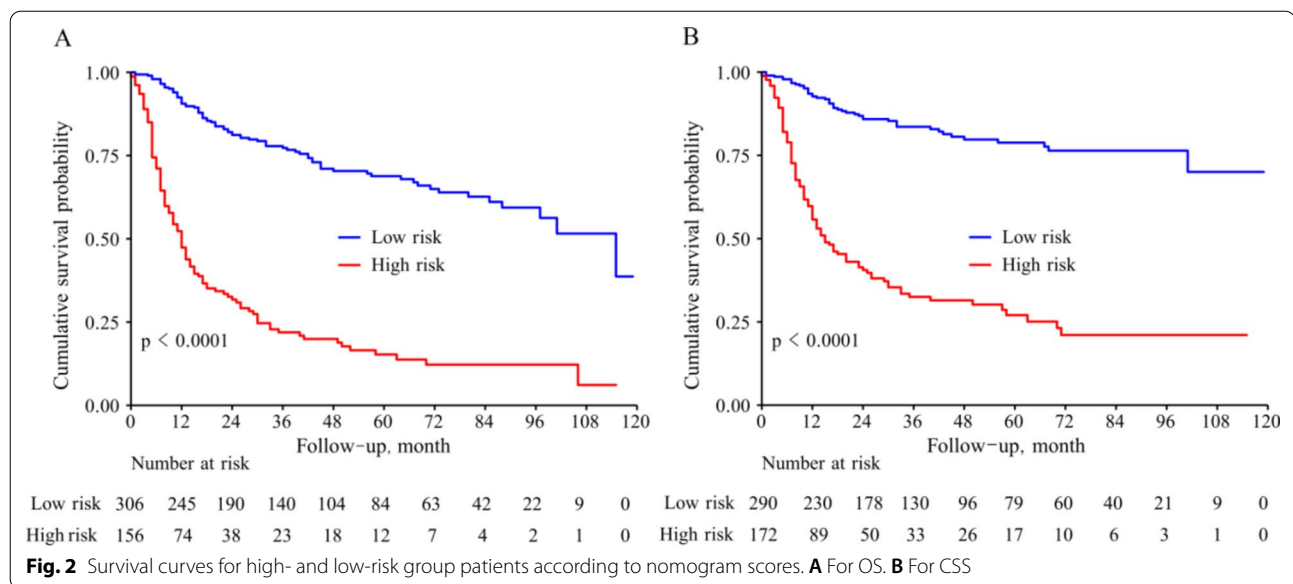
and Southeast Asia [23, 24]. In India, risk habits such as chewing tobacco and putting the tobacco-containing quid into the gingivobuccal sulcus existed and BMC incidence accounted for 41% of oral cancers [25].

Usually, surgery, radiation and chemotherapy are the main modalities to treat BMC [26, 27]. Relevant literature shows that BMC is aggressive and the patients' prognosis is poor [6]. Bachar et al. [28] has found that the overall recurrence rate was 41%, with 57.5% local control ratio. Hence, exploring risk factors related to the prognosis of patients with BMC has become increasingly important. Although many researchers have tried to reveal the prognostic factors, the main obstacle is the small sample size. In addition, BMC is always studied together with other oral cancers rather than conducted separately, leading to biased results [10]. Notably, the AJCC TNM staging manual is considered to be the most commonly used for prognostic assessment. However, many relevant parameters could affect the prognosis to a great extent. Therefore, personalized evaluation of BMC patients' prognosis has emerged as an important trend. Numerous studies have proved that nomogram is fully qualified for patient-specific prognosis prediction [12]. To construct and validate the nomogram model, we applied the random split-sample method, which was used commonly and popularly [29, 30].

After the survival analysis, we found that age was of great importance to influence the OS and CSS, which is in agreement with the current research [31–33]. In our research, the age group "< 35 years" has the best OS and CSS, locating the far left of the age axis (Fig. 1). Tumor differentiation has a significant impact on the OS and CSS, which is in accordance with the research [34, 35].

TNM stages also play an important role in the prognosis of BMC patients [36, 37].

C-index is applied to measure the discrimination of the nomograms, with a scale from 0.5 to 1. In the process of validating the nomogram models, all the C-indexes are greater than 0.7, demonstrating high accuracy. Calibration curves are used to evaluate the fitting degree between the predicted probability of 5- and 8-year survival and observed risk [12]. In our research, the calibration curves fitted excellently with the diagonal reference line (Figs. 3, 4). Moreover, two nomogram's decision curves possess good 5- and 8- year net benefit in the validation group, showing promising clinical value [38] (Fig. 5).
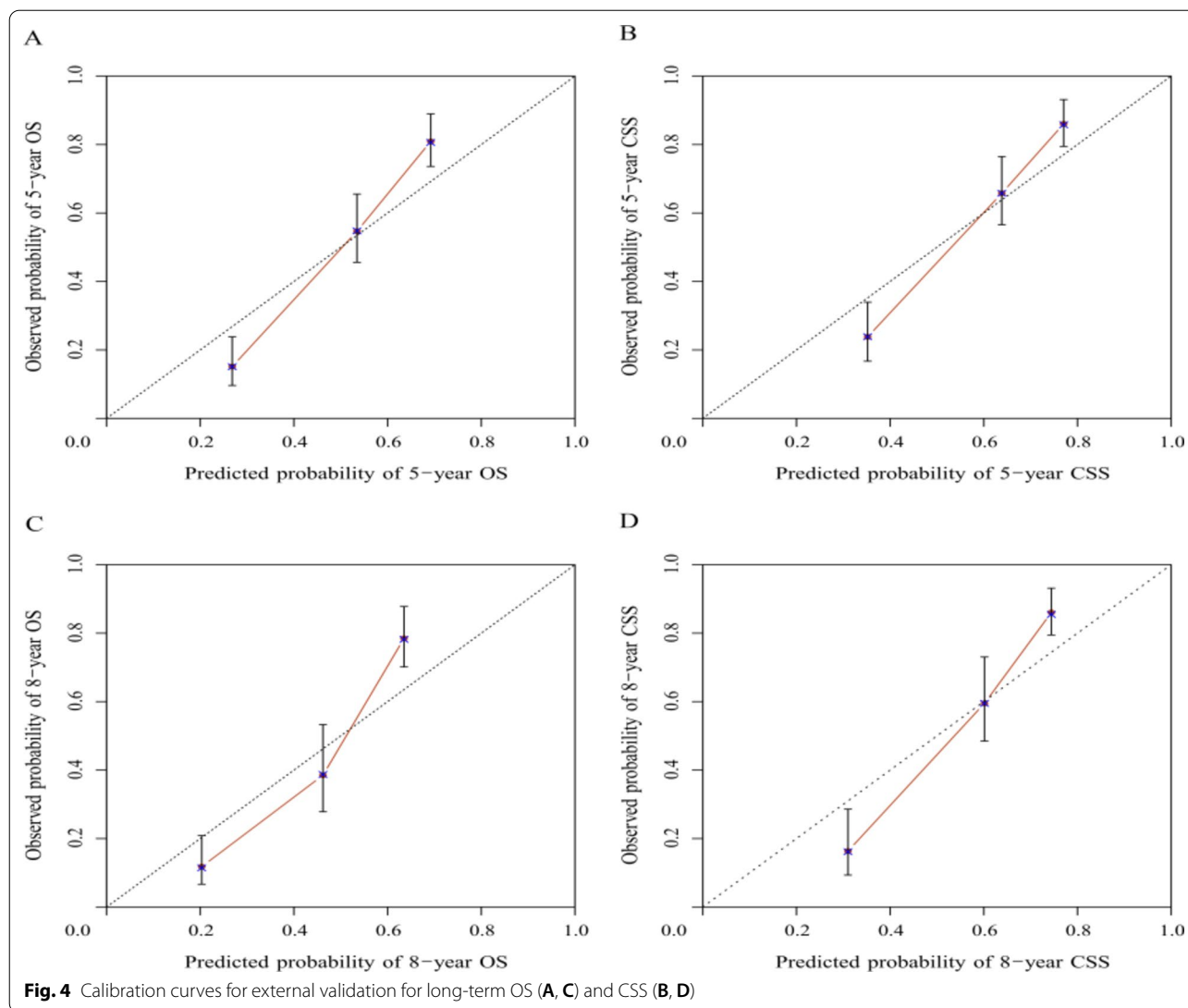
It is simple and practical to evaluate the individualized prognosis through nomogram. For example, nomogram graph includes various sub-categories axes. Each axis is marked with a different number. We draw a vertical line to the top point axis based on the personalized situation. In the same way, we add the points represented by each indicator to get the total points. Furthermore, we draw a vertical line from the total points axis to the 5- and 8-year OS and CSS axis to obtain the estimated survival rate. Notably, combined personalized total nomogram points with OS and CSS information, we acquire the optimal cut-off to divide patients into high- and low-risk cohorts (Fig. 2). Stateworthy, the nomogram was relatively more accurate than TNM staging. For instance, we set two T3N1M0 patients as an example (Additional files 1 and 2: Figs. 1 and 2). Patient 1: 60 years old, white, Grade II, Surgery, T3N1M0; Patient 2: 55 years old, black, Grade III, non-surgery, radiation, T3N1M0. If we evaluated the above patient's prognosis using TNM staging,

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Fig. 3 Calibration curves for internal validation for long-term OS (**A**, **C**) and CSS (**B**, **D**)
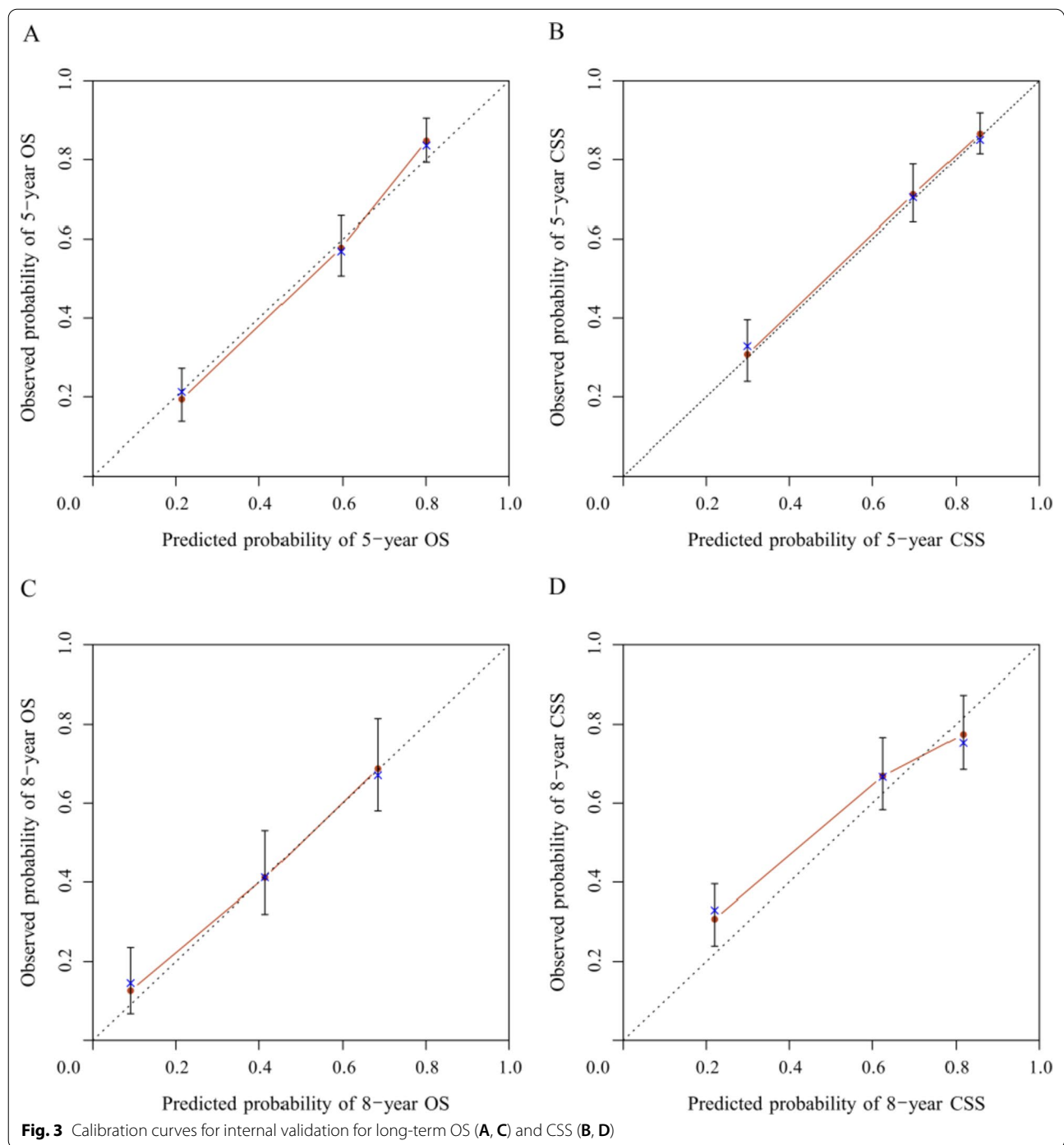
their prognosis is the same as each other. But the OS and CSS were different via our nomogram model. The 5-year OS of the two patients were 43% and 10%. 8-year OS of the two patients were 24% and lower than 10% respectively. Moreover, the 5-year CSS of the two patients was 48% and 10%. The 8-year CSS was 38% and lower than 10% respectively. Hence, personal prognosis evaluation

is of great importance than merely the TNM staging manual.

Our research owes apparent advantages and limited drawbacks. We collected the detailed information of BMC patients from the credible SEER database. Based on the data, we conducted a survival analysis to obtain the independent prognostic risk factors and establish

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Fig. 4 Calibration curves for external validation for long-term OS (**A**, **C**) and CSS (**B**, **D**)

two nomograms. However, other relevant indicators such as comorbidity [39], alcohol [40], extracapsular spread [32], chemotherapy [41] are also important factors affecting the prognosis, which are not included in the SEER database. In addition, the SEER program hasn't incorporated disease-free survival, cumulative survival and progression-free survival. Moreover, we haven't applied the 8th AJCC Staging manual (published October 2017) as our cases spanned the period 2004–2013. Some patients' T and N stages will be upstaged accordingly based on new protocols. As the lack of depth of invasion (DOI) and perineural invasion (PNI) information in SEER, it is impossible to restage each patient. Nevertheless, research shows that the c-indexes of the nomograms constructed using the 7th and 8th AJCC staging manuals are about the same [42]. More research is required to compare and validate

the predictive power of nomogram models established applying 8th AJCC staging manual versions.

Traditionally, the prognostic estimate is based on the patients' population. That makes individualized management a challenge for clinicians. The TNM staging system is widely accepted for prognostic estimation, although it only accounts for tumor factors, many other factors such as grade, age, sex, ethnicity are not considered though these are also very important. Clinicians need to incorporate all this information to estimate specific individual outcome empirically. Nomogram is a useful tool to incorporate all these factors in a quantitative manner. By summing up the scores of each risk factor, the 5- and 8-year OS and CSS of specific BMC patient can be predicted, which would enhance the screening and early intervention of controllable risk factors. In addition, the nomogram score is used to stratify patients by risk, so clinicians

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Fig. 5 Decision curves of OS and CSS in validation group
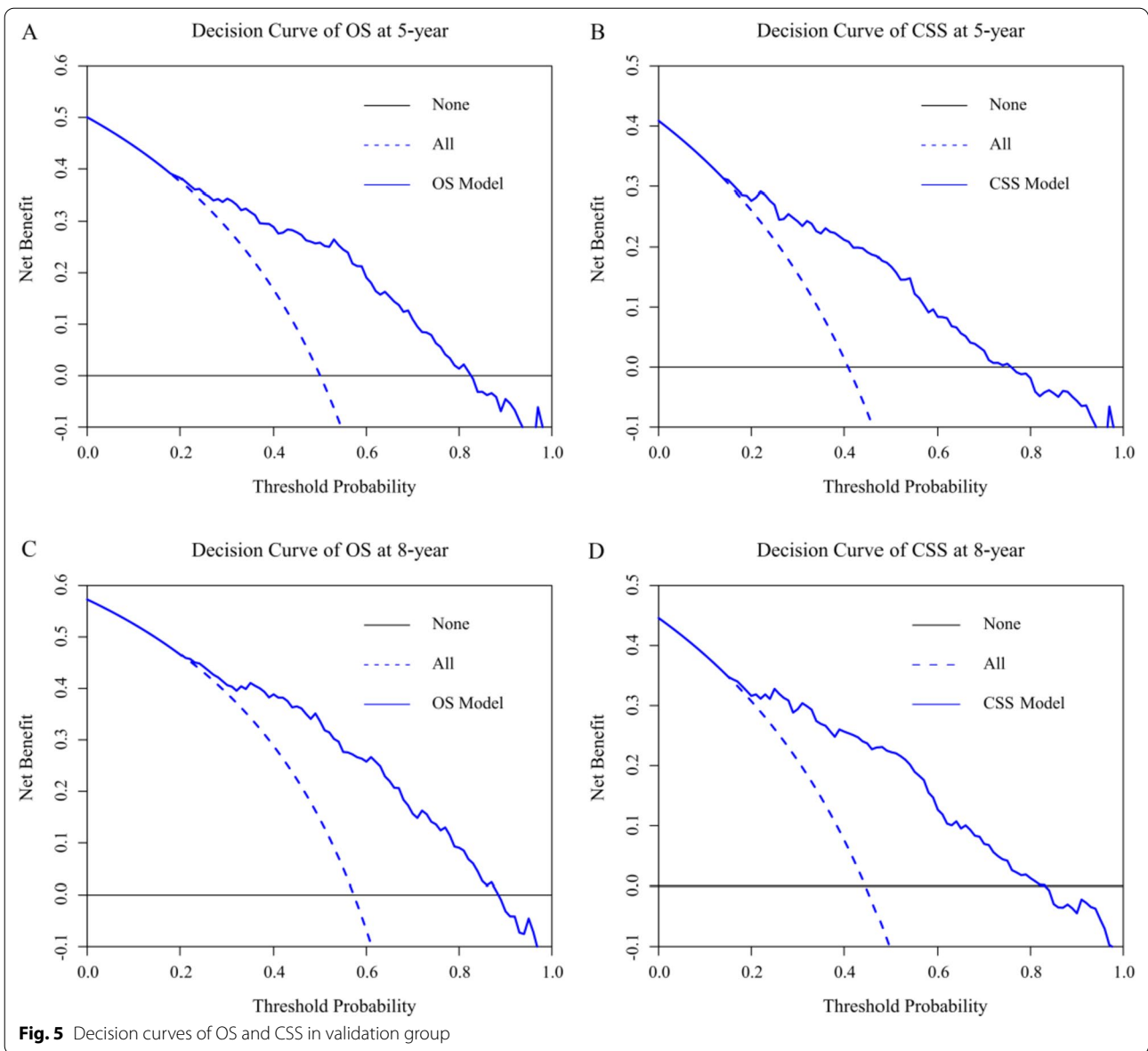
should lay more emphasis on high-risk patients with high malignancy and multiple risk factors, then plan individualized treatment modality and follow-up strategy.

This is a retrospective study and is limited by the fact that many risk factors are not included in the SEER database. In the future, multi-center prospective studies are to be conducted to validate and improve the nomogram of BMC for better individual treatment planning and prognosis assessment.

Conclusions

In our study, we established two nomogram models successfully and the models demonstrated excellent discrimination, performance after verification.

Abbreviations
BMC: Buccal mucosa cancer; SEER: Surveillance, epidemiology and end results; OS: Overall survival; CSS: Cancer-specific survival; C-index: Concordance index; DCA: The decision curve analyses; OSCC: Oral squamous cell carcinoma; NCCN: National comprehensive cancer network; DOI: Depth of invasion; PNI: Perineural invasion.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12903-022-02147-9.

Additional file 1. OS and CSS predictions for the first patient mentioned in the discussion.

Additional file 2. OS and CSS predictions for the second patient mentioned in the discussion.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethic Committee of Stomatological Hospital of the Fourth Military Medical University (Approval number: IRB-REV-2020059). Because the data collected from SEER database, patient consent could not be obtained. The data used in this study was anonymised before its use. No administrative permissions were required to access the raw data used in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

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References
1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45:309–16.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
3. Thompson L. World Health Organization classification of tumours: pathology and genetics of head and neck tumours. Ear Nose Throat J. 2006;85:74.
4. Liao CT, Wen YW, Lee SR, Liu TW, Tsai ST, Tsai MH, et al. Clinical outcomes of Taiwanese patients with cT4 oral cavity squamous cell carcinoma: toward the identification of the optimal initial treatment approach for cT4b patients. Ann Surg Oncol. 2017;24:785–93.
5. Trivedi NP. Oral cancer involving masticator space (T4b): review of literature and future directions. Head Neck. 2018;40:2288–94.
6. Camilon PR, Stokes WA, Fuller CW, Nguyen SA, Lentsch EJ. Does buccal cancer have worse prognosis than other oral cavity cancers? Laryngoscope. 2014;124:1386–91.
7. Lubek JE, Dyalram D, Perera EH, Liu X, Ord RA. A retrospective analysis of squamous carcinoma of the buccal mucosa: an aggressive subsite within the oral cavity. J Oral Maxillofac Surg. 2013;71:1126–31.
8. Zanoni DK, Montero PH, Migliacci JC, Shah JP, Wong RJ, Ganly I, et al. Survival outcomes after treatment of cancer of the oral cavity (1985–2015). Oral Oncol. 2019;90:115–21.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471–4.
10. Jan JC, Hsu WH, Liu SA, Wong YK, Poon CK, Jiang RS, et al. Prognostic factors in patients with buccal squamous cell carcinoma: 10-year experience. J Oral Maxillofac Surg. 2011;69:396–404.
11. Lo WL, Kao SY, Chi LY, Wong YK, Chang RC. Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. J Oral Maxillofac Surg. 2003;61:751–8.
12. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16:e173–80.
13. Rocco B, Sighinolfi MC, Sandri M, Puliatti S, Bianchi G. A novel nomogram for predicting ECE of prostate cancer. BJU Int. 2018;122:916–8.
14. Jin C, Cao J, Cai Y, Wang L, Liu K, Shen W, et al. A nomogram for predicting the risk of invasive pulmonary adenocarcinoma for patients with solitary peripheral subsolid nodules. J Thorac Cardiovasc Surg. 2017;153:462-469.e1.
15. Wang F, Zhang H, Wen J, Zhou J, Liu Y, Cheng B, et al. Nomograms forecasting long-term overall and cancer-specific survival of patients with oral squamous cell carcinoma. Cancer Med. 2018;7:943–52.
16. Wang F, Wen J, Yang X, Jia T, Du F, Wei J. Applying nomograms based on the surveillance, epidemiology and end results database to predict long-term overall survival and cancer-specific survival in patients with oropharyngeal squamous cell carcinomas: a case-control research. Medicine (Baltimore). 2020;99:e20703.
17. Lydiatt WM, Patel SG, Osullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:122–37.
18. Zumsteg ZS, Cook-Wiens G, Yoshida E, Shiao SL, Lee NY, Mita A, et al. Incidence of oropharyngeal cancer among elderly patients in the United States. JAMA Oncol. 2016;2:1617–23.
19. Chhetri DK, Rawnsley JD, Calcaterra TC. Carcinoma of the buccal mucosa. Otolaryngol Head Neck Surg. 2000;123:566–71.
20. Warnakulasuriya S, Dietrich T, Bornstein MM, Casals PE, Preshaw PM, Walter C, et al. Oral health risks of tobacco use and effects of cessation. Int Dent J. 2010;60:7–30.
21. Singh M, Sircar K, Tandon A, Chowdhry A, Popli DB. The role of tobacco as an etiological agent for oral cancer: cytomorphometrical analysis of the buccal mucosa in tobacco users. Dent Res J (Isfahan). 2014;11:649–55.
22. Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ. Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. Oral Dis. 1995;1:54–8.
23. Fang FM, Leung SW, Huang CC, Liu YT, Wang CJ, Chen HC, et al. Combined-modality therapy for squamous carcinoma of the buccal mucosa: treatment results and prognostic factors. Head Neck. 1997;19:506–12.
24. Auluck A, Hislop G, Poh C, Zhang L, Rosin MP. Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening. Rural Remote Health. 2009;9:1118.

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25. Pradhan SA. Surgery for cancer of the buccal mucosa. Semin Surg Oncol. 1989;5:318–21.

26. Lin CS, Jen YM, Cheng MF, Lin YS, Su WF, Hwang JM, et al. Squamous cell carcinoma of the buccal mucosa: an aggressive cancer requiring multi-modality treatment. Head Neck. 2006;28:150–7.

27. Coppen C, de Wilde PC, Pop LA, van den Hoogen FJ, Merkx MA. Treatment results of patients with a squamous cell carcinoma of the buccal mucosa. Oral Oncol. 2006;42:795–9.

28. Bachar G, Goldstein DP, Barker E, Lea J, O'Sullivan B, Brown DH, et al. Squamous cell carcinoma of the buccal mucosa: outcomes of treatment in the modern era. Laryngoscope. 2012;122:1552–7.

29. Fujita M, Nagashima K, Takahashi S, Suzuki K, Fujisawa T, Hata A. Hand-held flow meter improves COPD detectability regardless of using a conventional questionnaire: a split-sample validation study. Respirology. 2020;25:191–7.

30. Gallina A, Chun FK, Briganti A, Shariat SF, Montorsi F, Salonia A, et al. Development and split-sample validation of a nomogram predicting the probability of seminal vesicle invasion at radical prostatectomy. Eur Urol. 2007;52:98–105.

31. Huang CH, Chu ST, Ger LP, Hou YY, Sun CP. Clinicopathologic evaluation of prognostic factors for squamous cell carcinoma of the buccal mucosa. J Chin Med Assoc. 2007;70:164–70.

32. Bobdey S, Sathwara J, Jain A, Saoba S, Balasubramaniam G. Squamous cell carcinoma of buccal mucosa: an analysis of prognostic factors. South Asian J Cancer. 2018;7:49–54.

33. Markopoulos AK. Current aspects on oral squamous cell carcinoma. Open Dent J. 2012;6:126–30.

34. Lin CY, Lee LY, Huang SF, Kang CJ, Fan KH, Wang HM, et al. Treatment outcome of combined modalities for buccal cancers: unilateral or bilateral neck radiation? Int J Radiat Oncol Biol Phys. 2008;70:1373–81.

35. Fang QG, Shi S, Li ZN, Zhang X, Liua FY, Xu ZF, et al. Squamous cell carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors. Mol Clin Oncol. 2013;1:531–4.

36. Pillai V, Yadav V, Kekatpure V, Trivedi N, Chandrashekar NH, Shetty V, et al. Prognostic determinants of locally advanced buccal mucosa cancer: do we need to relook the current staging criteria? Oral Oncol. 2019;95:43–51.

37. Bobdey S, Mair M, Nair S, Nair D, Balasubramaniam G, Chaturvedi P. A nomogram based prognostic score that is superior to conventional TNM staging in predicting outcome of surgically treated T4 buccal mucosa cancer: time to think beyond TNM. Oral Oncol. 2018;81:10–5.

38. Van Calster B, Wynants L, Verbeek J, Verbakel JY, Christodoulou E, Vickers AJ, et al. Reporting and interpreting decision curve analysis: a guide for investigators. Eur Urol. 2018;74:796–804.

39. Ribeiro KC, Kowalski LP, Latorre MR. Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. Arch Otolaryngol Head Neck Surg. 2000;126:1079–85.

40. Ghoshal S, Mallick I, Panda N, Sharma SC. Carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors. Oral Oncol. 2006;42:533–9.

41. Sakamoto Y, Matsushita Y, Yamada S, Yanamoto S, Shiraishi T, Asahina I, et al. Risk factors of distant metastasis in patients with squamous cell carcinoma of the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121:474–80.

42. Tham T, Machado R, Herman SW, Kraus D, Costantino P, Roche A. Personalized prognostication in head and neck cancer: a systematic review of nomograms according to the AJCC precision medicine core (PMC) criteria. Head Neck. 2019;41:2811–22.

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