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A nomogram predicting subclinical extension of cutaneous squamous cell carcinoma in Chinese individuals

A retrospective study

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Abstract

Cutaneous squamous cell carcinoma usually extends beyond the visible margin. Little is known about the predictors for cutaneous squamous cell carcinoma with subclinical extension in Chinese individuals. This study aimed to construct a nomogram for predicting the probability of subclinical extension of cutaneous squamous cell carcinoma in Chinese patients.

A retrospective analysis was conducted using data from Mohs micrographic surgery-treated cutaneous squamous cell carcinoma patients at a single institution between December 1, 2009 and October 31, 2019. Subclinical extension was defined as a lesion requiring ≥ 2 Mohs stages or with final safe margins of ≥ 5 mm. A nomogram predicting the probability of subclinical extension was constructed using the predictors identified in multivariable analysis.

Of 274 patients included, 119 (43.4%) had subclinical extension. In multivariable analysis, male sex (odds ratio [OR], 2.45; 95% confidence interval [CI], 1.40–4.29; $P = .002$), lesions on mucocutaneous areas (OR, 3.71; 95% CI, 1.34–10.32; $P = .012$) and extremities (OR, 2.40; 95% CI, 1.20–4.78; $P = .013$), maximum diameter of 10 to 19 mm (OR, 14.15; 95% CI, 4.24–47.28; $P < .001$), and 20 to 29 mm (OR, 9.21; 95% CI, 2.80–30.29; $P < .001$) were associated with subclinical extension. A nomogram incorporating these 3 variables demonstrated promising predictive ability (C statistics = 0.78; 95% CI, 0.67–0.89).

The nomogram incorporating sex, tumor location, and maximum diameter can provide individualized prediction for subclinical extension in Chinese patients with cutaneous squamous cell carcinoma. This information may help surgeons determine appropriate margins at the first Mohs stage.

Abbreviations: CI = confidence interval, cSCC = cutaneous squamous cell carcinoma, HPV = human papilloma virus, MMS = Mohs micrographic surgery, NCCN = National Comprehensive Cancer Network, NMSC = nonmelanoma skin cancer, SCE = subclinical extension, SD = standard deviation, UV = ultraviolet.

Keywords: cutaneous squamous cell carcinoma, Mohs, nomogram, safe margins, subclinical extension

1. Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy involving skin. The lifetime incidence of cSCC in Caucasians was 7% to 11%, while the incidence of cSCC was 2.6 to 2.9 per 100,000 among Chinese Asians.[1,2] Though most cSCC has a favorable prognosis, the estimated annual number of deaths from cSCC in the United States ranges from 2500 to 8000, likely approaching mortality from melanoma.[3] cSCC usually extends beyond the visible margin. Without sufficient margins, residual tumor from microscopic infiltration may result in recurrence. Mohs micrographic surgery (MMS) is the most accurate technique in identifying subclinical extension (SCE), thanks to its ability to examine the entire surgical margins.[4] Therefore, it is a preferred option for cSCC, especially those with high-risk features.[5] Preoperative recognition of risk factors for SCE is paramount to determine appropriate margins at the first Mohs stage.

Several studies from fair-skinned populations have identified certain clinical characteristics of cSCC with SCE. A retrospective study of 1131 nonmelanoma skin cancer (NMSC) cases indicated that tumor size greater than 25 mm and location on the eyelid, temple, and ear helix were significantly associated with SCE (defined as requiring ≥ 3 Mohs stages).[4] In addition, Goldenberg

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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et al[6] conducted a retrospective study of 954 cSCC cases treated with MMS, 31% showed SCE (defined as a lesion requiring ≥ 3 Mohs stages with surgical safe margins of ≥ 1 cm). Sex, history of NMSC, Fitzpatrick skin type II and III, immunosuppression related to solid organ transplantation, and cigarette use were significant predictors for SCE.[6] Compared with those in fair-skinned populations, cSCC in Asians not only has lower incidence, but also differs in risk factors and invasiveness.[7] However, studies reporting risk factors of cSCC with SCE in Asian populations were scarce.

As most patients required 1 Mohs stage to clear cSCC lesions in our center and second surgery would cause extra expense, a lesion requiring ≥ 2 Mohs stages was regarded as SCE. According to the data in our center, generally, 2- to 3-mm margin was employed at the first Mohs stage. Another 2-mm margin was required at subsequent stages. Therefore, a lesion with final safe margins of ≥ 5 mm was also regarded as SCE. Therefore, we defined SCE to be a lesion requiring ≥ 2 Mohs stages or with final safe margins of ≥ 5 mm.

Nomogram was first used in oncology to quantify risks associated with prognoses by incorporating important factors.[8] It can also be applied to probability calculation of any events based on multivariable analysis to quantify risk factors. Here, we conducted a 10-year retrospective study in a single academic institution to investigate the predictors and to construct a nomogram for cSCC with SCE in Chinese population.

2. Methods

2.1. Study patients

This retrospective study was performed at the Department of Dermatology and Venereology in Peking University First Hospital, China. The study was approved via expedited review by Peking University First Hospital Ethics Committee.

Electronic medical record was comprehensively reviewed between December 1, 2009 and October 31, 2019. We included all biopsy-confirmed cSCC patients (n = 383). Exclusion criteria were as follows: patients who did not receive MMS; patients who had positive margins following local excision and referred for MMS; patients who had missing clinicopathological variables of interest; and nail SCC, due to difficulty in determining size and surgical margins. The study flowchart was shown in Figure 1. A total of 109 patients were excluded.

SCE was defined as a lesion requiring ≥ 2 Mohs stages or with final safe margins of ≥ 5 mm. From each patient's electronic medical record, we extracted all available prognostic factors outlined in the 2013 National Comprehensive Cancer Network (NCCN) clinical practice guideline and the eighth edition of the American Joint Committee on Cancer (AJCC) staging system into our univariable analysis, including age, sex, immune status, cigarette use, history of prior NMSC, anatomic site, tumor diameter, recurrent stage, previous inflammation or trauma, Clark grade and histological differentiation.[9,10]

In patients with multiple cSCC lesions, each lesion that underwent MMS was counted as a separate primary tumor. Immunocompromised status was defined as prior solid organ transplantation, hematological malignancy, or receipt of chemotherapy or immunosuppressants. Cigarette index was calculated by multiplying the average number of cigarettes smoked per day by the number of years the person has smoked. Cigarette index ≥ 400 was classified as a heavy smoker and <400 was a light smoker.[11] Previous inflammation or trauma was documented when there was a history of eczema, psoriasis, or other chronic inflammatory skin diseases, or trauma such as bruise or cuts prior to cSCC onset. Lesion location was divided into 3 zones, according to the 2013 NCCN guideline.[10] Mucocutaneous areas included the lips and the genitalia. Preoperative size was represented by the maximum diameter measured by a millimeter ruler. Recurrence was defined as lesions that recurred after local excision. Final safe margins were the sums of the margins required at all Mohs stages, that is, the distance between clinically visible tumor margins and the final surgical margins. The histological differentiation was assessed by 2 experienced dermatological pathologists according to the widely accepted definition.[12]

2.2. Development and validation of the prediction model

The aim of the statistical analysis was to construct a prediction model calculating the probability of SCE in cSCC. Continuous features were summarized using mean ± standard deviation (SD) for normally distributed data, and median and range for non-normally distributed data; categorical features were summarized with frequency count and percentage. Data was analyzed via independent t test for normally distributed variables, nonparametric test for non-normally distributed variables, and χ^2 or Fisher exact test for categorical variables. Then binomial logistic regression model was applied, using backward likelihood ratio technique with removal set at $P = .1$ in SPSS (version 25.0; IBM Corp). All tests were 2 sided, and P values of $< .05$ were considered statistically significant.

Based on the multivariable analysis, a nomogram was established to predict the probability of SCE in cSCC. The mathematical formula of the model was generated using the nomogramEx package in R software (version 3.6.2; Free Software Foundation, Inc). The model was then validated for discrimination and calibration abilities, using the rms package in R software. Discrimination is defined as a model's ability to correctly distinguish non-events and events, which can be quantified by calculating the C statistics. The calibration curve, with the Hosmer–Lemeshow χ^2 test, was used to assess the agreement between the predicted probability and the actual results.

3. Results

3.1. Patient characteristics

In total, 274 cases of cSCC were included in the analysis. Among them, 119 (43.4%) showed SCE (Table 1). Median final safe margins (range) were 3 mm (2–4 mm) and 5 mm (3–15 mm) in groups of cSCC without and with SCE, respectively ($P < .001$). The mean age of cSCC without and with SCE were 70.3 and 68.7 years, respectively ($P = .303$). Males were more likely to have SCE than females ($P = .001$). Other patient parameters, including immune status, cigarette use, and history of prior NMSC, were not associated with SCE. When the location was analyzed by risk stratification of the 2013 NCCN guideline, high-risk zones revealed lower possibility of SCE than low risk zones ($P = .046$). Hence, we decided to look into the association between anatomic sites and SCE. Compared with the head and neck regions, lesions on the mucocutaneous areas and extremities were more likely to develop SCE (P values of .003 and .001, respectively). Median

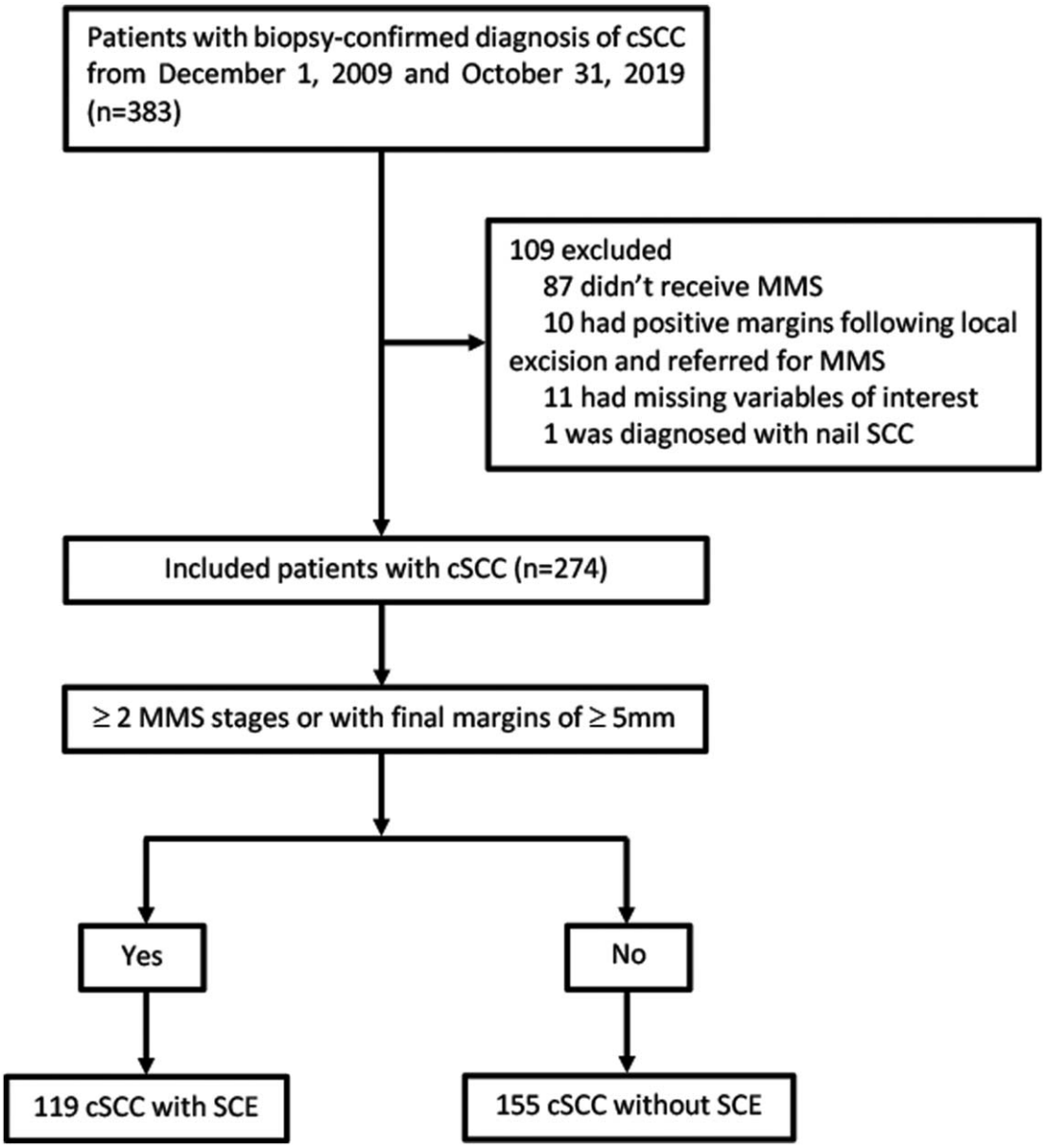

Figure 1. The flowchart of selection process for the model. cSCC = cutaneous squamous cell carcinoma, MMS = Mohs micrographic surgery.

maximum diameter (range) of cSCC without and with SCE were 15 mm (2–60 mm) and 25 mm (6–136 mm), respectively ($P < .001$). Moderately- or poorly differentiated cSCC was more likely to have SCE than well-differentiated cSCC ($P = .047$). Lesions with Clark grade greater than III were significantly associated with SCE ($P = .025$).

3.2. Final safe margins required for tumor clearance

Median surgical margins of 3 mm and 2 mm were reported at the first and subsequent Mohs stages in our study. In cSCC without SCE, tumor clearance was achieved in 98.1% of lesions with final safe margins of 3 mm. However, in cSCC with SCE, a much wider margin (10 mm) was required to achieve tumor clearance in 97.5% of lesions. In the group of cSCC with SCE, final safe margins of 5 mm, 6 mm, 7 mm, and 8 mm could achieve tumor clearance of 67.2%, 78.2%, 80.7%, and 85.7%, respectively.

3.3. Construction and validation of the prediction model

Variables with $P < .1$ from univariable analysis were further adjusted in the multivariable logistic regression model. Only sex, tumor location, and maximum diameter remained significant predictors for SCE (Table 2); therefore, they were incorporated into the nomogram (Fig. 2). Specifically, males had more than twice the odds of SCE than females ($P = .002$). Lesions on mucocutaneous areas ($P = .012$) and extremities ($P = .013$) were significant predictors for SCE. Maximum diameter was divided into 4 categories to better fit into the nomogram, and it showed significant association with SCE.

Table 1

Demographics and univariable analysis of selected variables.

Variable	Value	cSCC without SCE (%)	cSCC with SCE (%)	OR (95% CI)	*P* value
Total no. of patients		155 (56.6)	119 (43.4)	—	—
Age, mean ± SD		70.3 ± 11.3	68.7 ± 13.2	—	.303
Sex	Male	62 (40.0)	72 (60.5)	0.44 (0.27, 0.71)	.001
	Female	93 (60.0)	47 (39.5)		
Final safe margins, median (range)		3 (2, 4)	5 (3,15)	—	< .001
Immunosuppression	Absent	138 (89.0)	108 (90.8)	0.83 (0.37, 1.84)	.641
	Present	17 (11.0)	11 (9.2)		
Cigarette index	< 400	148 (95.5)	108 (90.8)	2.15 (0.81, 5.74)	.117
	≥ 400	7 (4.5)	11 (9.2)		
History of prior NMSC	Absent	141 (91.0)	111 (93.3)	0.73 (0.29, 1.79)	.486
	Present	14 (9.0)	8 (6.7)		
Previous inflammation or trauma	Absent	138 (89.0)	96 (80.7)	1.95 (0.99, 3.83)	.052
	Present	17 (11.0)	23 (19.3)		
Location 1*	Low risk (ref.)	13 (8.4)	19 (16.0)	—	—
	Moderate risk	64 (41.3)	49 (41.2)	0.52 (0.24, 1.16)	.112
	High risk	78 (50.3)	51 (42.8)	0.45 (0.20, 0.99)	.046
Location 2†	Head and neck regions (ref.)	111 (71.6)	55 (46.2)	—	—
	Mucocutaneous areas	8 (5.2)	16 (13.4)	4.04 (1.63, 10.01)	.003
	Extremities	24 (15.5)	35 (29.4)	2.94 (1.60, 5.43)	.001
	Trunk	12 (7.7)	13 (10.9)	2.19 (0.94, 5.11)	.071
Maximum diameter, median (range)		15 (2, 60)	25 (6, 136))	—	<.001
Recurrence	Absent	147 (94.8)	110 (92.4)	1.50 (0.56, 4.02)	.414
	Present	8 (5.2)	9 (7.6)		
Histological differentiation	Well	133 (85.8)	91 (76.5)	1.86 (1.00, 3.45)	.047
	Moderately or poorly	22 (14.2)	28 (23.5)		
Clark grade	I, II, or III	77 (49.7)	43 (36.1)	1.75 (1.07, 2.85)	.025
	IV or V	78 (50.3)	76 (63.9)		

CI = confidence interval, cSCC = cutaneous squamous cell carcinoma, NMSC = nonmelanoma skin cancer, OR = odds ratio, SD = standard deviation.

* Location 1 was classified by 2013 NCCN guideline as follows: Zone of high risk: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Zone of moderate risk: cheeks, forehead, scalp, neck, and pretibial.

Zone of low risk: trunk and extremities excluding pretibial, hands, feet, nail units, and ankles. Zone of low risk was taken as reference.

† Lips were excluded from the head and neck regions; mucocutaneous areas included the lips and the genitalia. Head and neck regions were taken as reference.

As outlined in the legend of Figure 2, the probability of SCE could be estimated before surgery with the proposed nomogram, using the mathematical formula of $-2.59 \times 10^{-7} \times A^3 + 7.87 \times 10^{-5} \times A^2 - 0.0013 \times A + 0.096$. A was the value of total points, that is, the sum of points from each variable (location, sex, and maximum diameter). Based on this model, a man (points = 33.69) who has a cSCC lesion on the lip (points = 47.21) with a maximum diameter of 15 mm (points = 39.41) has total points of 120.31, and therefore, 62.77% probability of having SCE.

The C statistics for the nomogram was 0.78 (95% confidence interval, 0.67–0.89), indicating promising predictive ability. The calibration curve showed good agreement between the predictive

Table 2

Adjusted results from the logistic regression model.

Variable	Value	B	*P* value	OR	95% CI
Sex*	Male	.90	.002	2.45	(1.40, 4.29)
Location†	Mucocutaneous areas	1.31	.012	3.71	(1.34, 10.32)
	Extremities	.87	.013	2.40	(1.20, 4.78)
	Trunk	.32	.519	1.37	(0.53, 3.56)
Maximum diameter‡	10–19 mm	2.65	.000	14.15	(4.24, 47.28)
	20–29 mm	2.22	.000	9.21	(2.80, 30.29)
	≥ 30 mm	1.05	.077	2.87	(0.89, 9.20)
Clark grade§	IV or V	.52	.075	1.68	(0.95, 2.98)

Variables included in the logistic regression model: sex, previous inflammation or trauma, location, maximum diameter, histological differentiation, and Clark grade. Only variables included in the final step were displayed in the table. One binary outcome of cSCC with SCE (yes/no). Constant was −3.05.

CI = confidence interval, OR = odds ratio.

* Female was taken as reference.

† Head and neck regions were taken as reference.

‡ Maximum diameter was categorized into 4 groups: < 10 mm, 10 to 19 mm, 20 to 29 mm, and ≥ 30 mm. Group of < 10 mm was taken as reference.

§ Clark grades of I, II, and III were taken as reference.

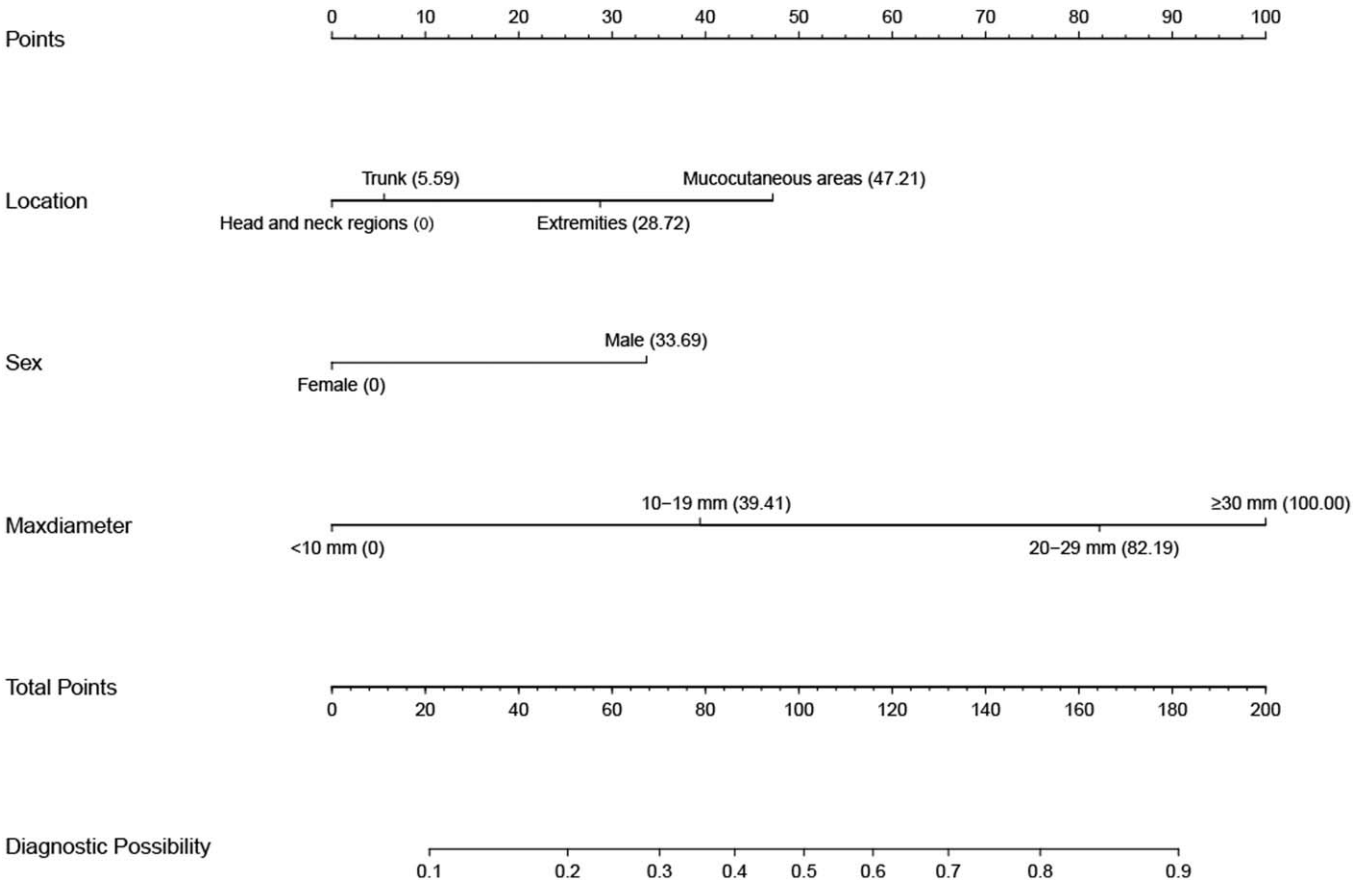

Figure 2. The nomogram was established from 3 parameters (sex, location, and maximum diameter). To calculate a patient's possibility of SCE, points for each parameter can be identified from corresponding values on the "points" axis, and sum of the points was plotted on "total points" axis. The patient's possibility of SCE is the value at a vertical line from the corresponding total points. SCE = subclinical extension.

risk and the actual probability (Fig. 3). The Hosmer–Lemeshow χ^2 statistics was 3.18 ($P=.922$), suggesting there was no significant deviation.

4. Discussion

In this single-center retrospective study of Chinese cSCC patients, we constructed a nomogram to predict the possibility of SCE by incorporating demographic features identified in the logistic regression model. Male sex, lesions on mucocutaneous areas, and extremities as well as maximum diameter were significantly associated with SCE in our prediction model. These easily-attainable clinical variables could offer valuable insights into the probability of SCE in cSCC, and help physicians determine margins required at the first Mohs stage.

Male sex is a common risk factor for SCE.[6,13] Several explanations may be underlying men's susceptibility of having more subclinically aggressive cSCC. First, cumulative ultraviolet (UV) dose has long been regarded as a risk factor for cSCC. Men tend to get higher UV exposure due to more outdoor activities and lower rates of sunscreen application.[14] Furthermore, men do not seek medical help as often as women,[15] which often leads to delayed treatment and more advanced lesions. Finally, whether sex hormones play a role in this difference is controversial. A recent review suggested an increased risk of SCC with menopausal hormone therapy,[16] which was contradictory to higher incidence of cSCC in men. Further studies are required to evaluate sex distribution and the role of sex hormones in cSCC.

Lesions on mucocutaneous areas (lips and genitalia) and extremities were significant predictors for SCE in our study. Lips and genitalia are both high-risk zones defined by the 2013 NCCN guideline.[10] Human papillomavirus (HPV) might lead to subclinical invasiveness on mucocutaneous areas as these areas were prone to trauma, which allowed for viruses to enter basal cells and establish infection.[17] While associations between HPV and cSCC are less clearly delineated, Nadhan et al[18] found that up to 67% of SCC lesions in the anogenital area of non-White transplant patients carried high-risk HPV subtypes. Primary SCC on the lips exhibited higher rates of nodal spread, mortality, and poor clinical outcome.[19] Our study confirmed that SCC on the lips and genitalia warranted wider margins for tumor clearance. cSCC predominantly presents on the head and neck regions in fair-skinned populations. In contrast, it shows a predilection in sun-protected areas, including the lower limbs and anogenital regions, in patients with skin of color.[20] In fair-skinned individuals, SCE is more likely to be present in cSCC on the head and neck regions than on the extremities.[13,21] These observations point to the possibility that high-risk anatomic locations in fair-skinned populations may not apply to the Asian population. In our study, lesions on the extremities were associated with higher risks of previous inflammation or trauma than on head and neck regions (32.2% vs 9.9%, $P<.001$).

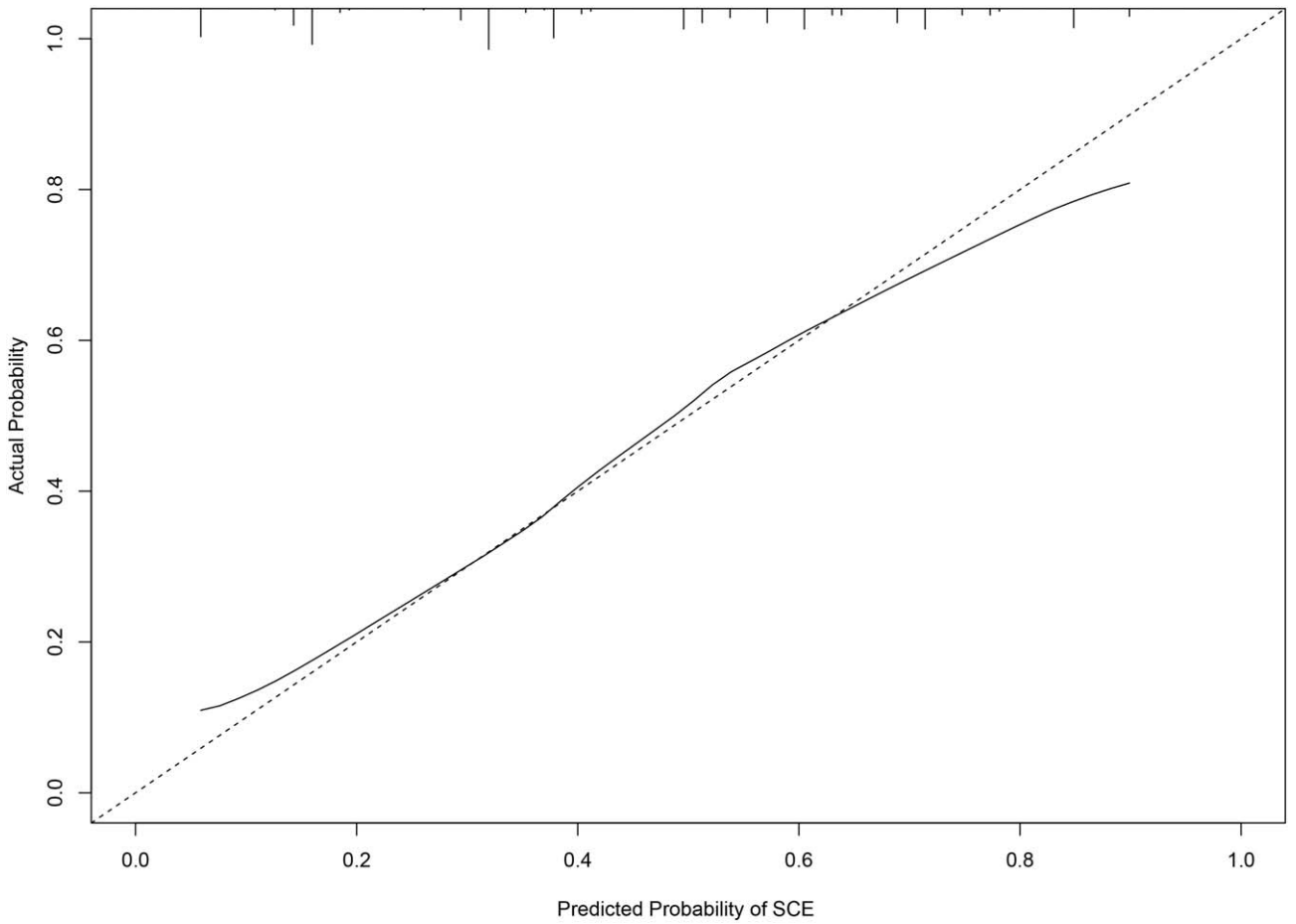

Figure 3. The calibration curve for the predicted probability of SCE. A plot along the 45-degree line represents a perfect calibration model. The predicted probability is identical to the actual outcome. SCE = subclinical extension.

Chronic scarring and inflammation were reported to be major risks of cSCC in Black and Asian individuals,[22] which might contribute to SCE in these populations.

Larger maximum diameter was also a significant indicator for SCE. Tumor size is an important parameter in cSCC staging in clinical guidelines.[23] Tumors greater than 2 cm in diameter are twice more likely to recur locally and 3 times more likely to metastasize, in comparison with tumors smaller than 2 cm.[24] Wider margins are therefore recommended for cSCC greater than 2 cm in diameter.[21] Similarly, greater subclinical infiltration in larger lesions would be anticipated.

Tumor clearance of greater than 95% was achieved with final safe margins of 3 mm in the group of cSCC without SCE and 10 mm in the group of cSCC with SCE. Of note, safe margins of 10 mm in the latter group were much wider than the recommended margins of 6 mm in fair-skinned populations with high-risk cSCC.[21] A possible explanation is that Asian individuals tend to have high-risk cSCC lesions on the extremities, which were larger than lesions on head and neck regions. Meanwhile, in our study, median margins of 3 and 2 mm were reported in the first and subsequent Mohs stages, which were also wider than margins adopted in other studies with initial and subsequent margins of 2 mm and 1 to 2 mm, respectively.[21] Further studies with narrower surgical margins in each Mohs stage are required to accurately define the appropriate margins for tumor clearance.

This study has several limitations. First, its retrospective design is prone to biases. Since all cases were from a single tertiary hospital with a strong academic focus, patients would have more advanced diseases than those treated in the community, and selection biases would be expected. Second, multiple Mohs surgeons were involved in this study, and there may be variations in the assessing process. As there were no set rules for surgical margins during each Mohs stage in treating cSCC, different surgeons may have their own preferences in determining margins. Furthermore, certain risk factors could not be collected, such as sun exposure or performance status. With regards to the nomogram, the validation step was conducted by simple application of the model on the whole dataset, which may carry a risk of overfitting. Finally, the cohort was limited in sample size and race, confining its application to Chinese population, whether it is applicable to other Asians warrants further investigation.

In conclusion, we developed and validated a nomogram, to predict the probability of SCE in Chinese patients with cSCC. This nomogram incorporated easily accessible clinical parameters, namely sex, lesion location, and maximum diameter, and may facilitate margin determination at the first Mohs stage, according to the risk of SCE. External validation studies, and further studies with larger sample size are warranted to refine the predictors for SCE and appropriate margins in Asian individuals.

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