# Predictive Nomogram for the Prediction of Recurrence of Cutaneous Squamous Cell Cancer

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**Research Article**

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# Abstract

Aim: The prognosis of cutaneous squamous cell cancer (cSCC) individuals after curative resection is not satisfactory due to the recurrence with poor prognosis. We tried to identify the affecting clinical features of recurrence in cSCC patients.

Methods: A total of 393 patients were retrospectively incorporated into our study. The χ test and logistic regression analysis were utilized to screen for the significant clinical indexes associated with the presence of cSCC recurrence. Recurrent nomogram was created based on the above informative clinical features to predict the probability of recurrence. The concordance index, area under curve (AUC), and calibration plots were used to assess the performance of the nomogram model and the NCCN Guidelines®. Moreover, the recurrent nomogram exhibited not only encouraging calibration ability, but also great clinical utility comparing with NCCN Guidelines®.

Results: Of the 393 patients included in this study, 36 patients sufferred from recurrence. The multivariate analysis showed that exposure, tumor size, ulcer, precancerous lesions, and neural invasion at diagnosis were independent clinical factors affecting the prognosis of patients with cSCC. For the verification of results, the C-index was 0.818 respectively. The calibration curve also showed that the actual observation of recurrence was in good agreement with the prediction of the nomograms. Additionally, both DCA and CIC showed that the recurrent nomogram had good clinical application value. According to the score of each patient, the risk stratification system of cSCC patients was further established by perfectly dividing these patients into three groups, namely, low risk, medium risk, and high risk, in all queues.

Conclusion: Exposure, tumor size, ulcer, precancerous lesions, and neural invasion were closely correlated with the presence of recurrence of cSCC patients. The recurrent nomogram held well predictive ability for the identification of cSCC patients with recurrence.


# 1 Introduction

Cutaneous squamous cell carcinoma (cSCC) is classified as non-melanoma skin cancer (NMSC) together with basal cell carcinoma and is one of the most common skin cancers affecting Caucasian [1]. cSCC is the second most common skin cancer and accounts for 20% of keratinocyte carcinomas[2, 3]. Most primary cSCC are indolent cSCC which rarely cause metastasis and of almost 90% cure rate[4]. Most cases of cSCC portend an excellent prognosis following surgical removal[5]. But there were still 3.7–5.2% of patients with lymph node metastasis and of 1.5–2.1% death rate[4, 6–9]. 30–50% of patients with cSCC diagnosed for the first time may reoccur cSCC within 5 years [10]. After 10 years of follow-up, the local recurrence rate of cSCC was 3–36.8%, and the lymph node metastasis rate was 2.3–26.3%[11].

Thompson et al illustrated that there existed several risk factors were related to higher recurrence of cSCC including tumor thickness of more than 2 mm, tumor invasion beyond subcutaneous fat, tumor diameter of more than 20 mm, poor differentiation of the tumor, presence of perineural invasion and tumor location in the temple area[12]. Marrazzo et al. revealed that although Mohs micrographic surgery (MMS)

had a higher cure rate than conventional wide excision in cSCC removal, patients still tended to recur with invasion beyond subcutaneous fat or poor histological differentiation in the histopathologic response after surgery[13, 14].

National Comprehensive Cancer Network (NCCN) guidelines® outline management pathways for low-risk and high-risk cSCC patients. Within this framework, the NCCN guidelines® are both suitable for patients who have a low likelihood of recurrence and/or metastasis, and those who consider high risk for developing recurrence and/or metastasis[15]. As mentioned, borders of tumor, primary/recurrent lesions, immunosuppression, rapid growing tumor, prior RT or chronic inflammatory process and neurologic symptoms were the risk factors of cSCC recurrence in the clinical features before surgery in Caucasian populations[16]. However, the frequency and risk factors of cSCC recurrence in Chinese populations has not been demonstrated. Currently, the diagnosis of cSCC is determined upon clinical physical examination and postoperative histologic examination. Meanwhile, surgical margins should be carefully checked through intraoperative frozen sections to ensure the clearance of the tumor. Although MMS was of lower recurrence rate and metastasis rate apparently, there was still about 10–20% recurrence rate in those cases with negative margins in frozen sections[17]. Accurate estimation for the recurrence risk before surgery can help surgeons to choose appropriate surgical approach and define safe resection margins during MMS.

It is necessary to construct a nomogram model based on preoperative clinical data incorporating risk factors related to cSCC recurrence in Chinese population, which can provide evidence-based and personalized risk assessment to facilitate risk relapses and prognosis assessment. Thus, based on this model, our intent was to investigate the clinical features potentially associated with recurrence in patients with cSCC. We also verified the predictive efficiency of the recurrent nomogram and its calibration ability.

## 2 Materials And Methods

# 2.1 Case selection and clinical variables

We retrospectively collected information of patients with cSCC at our institute from January 2013 to June 2020, and finally selected 393 postoperative individuals. A case-control study was applied to figure out the internal relationship between tumor recurrence and clinical features.

The inclusion criteria were: (1) cSCC as the primary cancer diagnosis; (2) cSCC diagnosed with pathological examination. Additional exclusion criteria included: (1) incomplete treatment or incomplete medical records; (2) cSCC patients who underwent chemotherapy and radiotherapy before initial diagnosis of cSCC at our institute; (3) cSCC patients lacking follow-up information. The clinical study was executed in line with the Helsinki Declaration. Patients with cSCC all gave their informed consent to our clinical research, and our research was approved by the clinical research ethics committee of Xinhua Hospital affiliated with Shanghai Jiao Tong University School of Medicine. Patients did not receive financial compensation.

The specific baseline clinical variables were reported in Table 1. The table included gender, age, sun-exposure site, tumor size, ulcer, other skin disease history, precancerous lesions (such as actinic keratosis), neural invasion, lymph nodes metastasis and multiple tumor lesions. All clinical specimens underwent routine clinical examinations performed independently by two dermatologists. Whether tumor recrudesce occurred was determined based on postoperative pathological results. All patients were reassessed retrospectively according to the new NCCN Guidelines® (Version 1.2020 — October 2, 2019), based on clinical and dermos copic features. Recurrence information according to risk factors for local recurrence were displayed in Table 2.

2.2 Statistical Analysis

Collected data were analyzed using SPSS (version 21.0) in combination with R software (https://www.r-project.org). We reported the frequency (percentage) for categorical variables, mean (standard deviation) for normal-distributed continuous variables, and median (quartile) for variables without normal distribution. The χ test was used to analyze the potentially informative differential indexes which were closely correlated to recurrence of cSCC (categoric variables). Student *t*-tests were applied for continuous variables(age) if variables were normally distributed while Kruskal-Willus tests were used for highly-skewed variables. Furtherly, multivariate Logistic proportional hazard regression was used to analyze the prognostic clinical factors that were considered as potential correlation in univariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) for these variables were calculated. And then, according to the variables that remained statistically significant ($p < 0.05$) in multivariate analysis, a nomogram was formulated using R's rms package version 3.0. Harrell's concordance index (C-index) was measured to quantify the discrimination ability of the nomogram, while the receiver operating characteristic (ROC) curve was used to determine the sensitivity, specificity and area under curve (AUC) was calculated to evaluate the diagnostic efficiency of the nomogram model and clinical risk factors model of NCCN Guidelines®. To evaluate the clinical utility of the combined model, decision curve analysis (DCA) and clinical impact curve (CIC) were performed, which explored the clinical benefit of nomogram models by calculating the net benefit of decision strategy at each threshold probability. Sankey diagram was also constructed to descript the relationship of selected recurrence risk factors of our patients.

In addition, the optimal cutoff value of cSCC recurrence was set by using Xtile version 3.6.1 (http://tissuearray.org/). Patients with different points were segregated into low, medium and high-risk group.

# 3 Results

# 3.1 Patient Characteristics

A total of 393 patients were identified who met the inclusion criteria. The characteristics of all enrolled patients are summarized in Table 1. Among the 393 patients enrolled in this study, 195 were male (49.6%) and 198 were female (50.4%). The average age of patients was 72.1, and the median age was 73 years (range: 8–97 years). cSCC had a higher probability of affecting the sun-exposed sites [260 patients (66.2%)] including face, scalp, neck, forearm and shin. The tumor size of cSCC was classified into three

levels: tumor diameter smaller than 2 cm defined as small size [135 patients (34.3%)]; smaller than 4 cm while greater than or equal to 2 cm defined as medium size [195 patients (49.6%)]; smaller than 6 cm while greater than or equal to 4 cm defined as large size [63 patients (16.0%)]. Ulcer is a classical clinical feature of cSCC and we assumed that tumor with ulcer tended to recurrence. Therefore, patients were divided into lesions with ulcer [116 patients (29.5%)] and without ulcer [277 patients (70.5%)] under the examination of dermoscopy. As exhibited in Table 1, the proportions of patients with precancerous lesion on the tumor was statistically different between the patients with recurrence [21 patients (58.3%)] and with no recurrence groups [99 patients (27.7%)]. Furthermore, among all the patients, patients with neural invasion [11 patients (30.6%)] seemed to recure more easily than those without neural invasion [25 patients (69.4%)]. Also, the proportions of patients with recurrence were greater in lymph nodes metastasis [5 patients (13.9%)]. But the difference was not statistically significant in between patients with or without recurrence in suffering from other skin diseases and with multiple cSCC lesions.

The primary objective of our study was to establish comprehensive prognostic nomograms and compare them with the NCCN guidelines®. Recurrence information according to NCCN guidelines® was displayed in Supplemental Table. During follow-up, borders of tumor, primary/recurrent lesions, and neurologic symptoms were significantly higher in recurrence group compared with that in no-recurrence group ($P < 0.05$). However, immunosuppression, rapid growing tumor, prior RT or chronic inflammatory process were not significant independent risk factors of recurrence in our study.

# 3.2 Construction and Validation of Recurrent Nomogram

All variables involved in this analysis were derived from preoperative data. All the tumor-related clinical features were assessed before surgery. After analyzing the clinical features by chi-square tests (categorical variables) and independent sample t tests (continuous variables), clinical features with a $P < 0.05$ were included as predictors in the multivariate predictive model. The multivariate logistic analysis showed that exposure, tumor size, ulcer, precancerous lesions and lymph nodes metastasis were significantly correlated with recurrence of cSCC. Therefore, the final multivariable model included sun exposure(OR, 6.505, 95% CI, 2.033–20.821, P = 0.002), tumor size (small as reference; medium: OR, 2.998, 95% CI, 0.960–9.363, P = 0.050; large: OR,6.286, 95% CI, 1.753–22.545, P = 0.005), ulcer (OR, 2.754, 95% CI, 1.267–5.982, P = 0.011), precancerous lesions (OR, 2.180, 95% CI, 0.999–4.758, P = 0.050), and neural invasion (OR, 9.260, 95% CI, 13.249–26.391, P < 0.001) as the five clinical features significantly associated with recurrence of cSCC **(**Table 2**).**

According to the regression coefficients estimated in multivariate analysis (Fig. 1A), a prognostic nomogram model based on clinical variables including exposure site, tumor size, ulcer, precancerous lesions and neural invasion was established to determine the recurrence of cSCC (Fig. 1B). As displayed, all the five informative indexes assigned a corresponding point value following by nomogram model on the recurrence of cSCC. The total risk points were calculated by adding up all the points of each informative indexes, corresponding to the axis of “Probability of recurrence”. Sankey plot analysis for relationships between clinical factors, and a map for visualizing the distribution of clinical factors related to the recurrence of cSCC (Fig. 1C).

The calibration plot graphically showed the consistency of recurrence of cSCC with the actual risk of cSCC recurrence, which showed that the risk predicted by the nomogram was more accurate than that predicted by the recurrence model analyzed by NCCN guidelines® (Fig. 2). In addition, the AUC of the nomogram for predicting cSCC recurrence (0.818, 95% CI: 0.725–0.833) was superior compared with the recurrence model analyzed by NCCN guidelines® (0.726, 95% CI: 0.556–0.779) (Fig. 3). Then we exploited decision curve analysis (DCA) to determine the clinical utilities of the recurrent nomogram (Fig. 4). The DCA indicated that, compared with the NCCN guidelines®, the nomogram had a better clinical net benefit and a larger threshold probability range in predicting recurrence of cSCC. Also, according to the consequence of DCA, clinical impact curves (CIC) were generated to evaluate the clinical performance of the nomogram further (Fig. 5). At each threshold probability, the number of patients classified as high risk in a nomogram and the outcome of recurrence was both displayed in the CIC. The results showed the number of predicted high-risk cases was larger than that of true positive cases when the risk threshold was in the range of 0–0.66 for patients in our study. Furthermore, it was also satisfactory for the cost-benefit ratios at each risk threshold mentioned above. The CIC of the nomogram depicted the predicted number of cSCC patients and true positive patients at different threshold probabilities (Fig. 6B). The nomogram shows good clinical usefulness the same as NCCN guidelines® in our samples. In a word, the recurrent nomogram exhibited not only excellent predictive performance, but also great clinical utility.

# 4 Discussion

Cutaneous squamous cell carcinoma(cSCC) is one of the most common non‐melanoma skin cancers (NMSC). In recent years, the research on pathogenesis and treatment of cSCC has made great progress [18]. However, currently there is still no authoritative and reliable cSCC diagnosis and treatment guidelines or consensus in China, which is not conducive to the development of epidemiological investigations, clinical research, standardized diagnosis and treatment of the disease. According to the ranking conducted by the Lancet in 2018, China received the lowest ratings over all in medical quality and accessibility of NMSC, and the level of diagnosis and treatment of cSCC in China needed to be improved urgently[19]. For this reason, we formulated the Chinese cSCC diagnosis and treatment nomogram as the basis and guarantee for standardized and precise diagnosis and treatment. At present, the NCCN (The National Comprehensive Cancer Network) guidelines® remain the predominate basis for staging and analyzing cSCC in clinical practice[16]. However, risk factors of recurrence according to the NCCN guidelines® are not appropriate for Chinese as different race, skin color, risk genes, living quality and skincare consciousness comparing with Caucasians. Concerning with skin color and risk genes, Chinese supposed to be less vulnerable to skin cancers. However, with low sun care consciousness and ignorance of skin diseases, the incidence of skin cancer is still worryingly high with poor prognosis especially in the aged. Additionally, the classification attributes and definition in NCCN guidelines® are not quite suitable for Chinese such as tumor location/size, borders, immunosuppression, prior radiotherapy since few Chinese cSCC patients would take positive intervention and treatment measure before the first visit in hospital. Basing on the specialty of low understanding and visiting hospital of Chinese cSCC population, we found it important to collect demographic and clinical characteristics of patients before surgery to

figure out a better clinical net and a larger threshold probability range in predicting the recurrence of cSCC.

According to the NCCN guidelines®, high-risk factors in clinical inquiry and physical examination might be classified as: (i) tumor-related high-risk factors including tumor diameter (> 2 cm), localisation on “mask areas” of face, genitalia, hands, and feet, recurrent lesion, poorly defined borders, rapid growing, site of prior RT or chronic inflammatory process, neurologic symptoms, (ii) patient-related high-risk factors including immunosuppression[20]. However, since a considerable number of patients were from rural areas and the economic level was low, there was a lack of health awareness, and delays in treatment were very common; patients often ignored the skin lesions until they developed severe symptoms, such as recurrent large ulcers, or lymph nodes involved. Based on different race and low recognition of skin cancers, we found that NCCN guidelines® was not quite appropriate to evaluate the risk factors of recurrence in our patients, so we summarized several indicators that could measure the risk scores of Chinese cSCC patients better. As we all knew that cSCC could be cured by proper surgical resection (such as MMS) and reduced the chance of relapse if it was diagnosed and preoperative assessment was improved early [21, 22].

In this study, we improved the classification of tumor size into three levels: small(< 2cm), medium(2cm ≤ diameter 4cm) and large((4cm ≤ diameter 6cm) with a $P = 0.002$. Ulcer was one of the typical clinical characteristics of cSCC which was also crucial to measure the depth of tumor invasion and infiltration[12]. We also found that tumor with ulcer lesion was an important affected factor in evaluating the recurrence of Chinese cSCC patients with a $P < 0.001$ in the multivariate predictive model. Besides, precancerous lesion of cSCC (such as preceding AK, burn, verruca with atypical hyperplasia) was also a common risk factor in patients with cSCC and its large value indicated a high risk of recurrence. As ultraviolet radiation was the most important risk factor for cSCC, it was not difficult to understand that SCC mostly occurred in populations over 60 years old, and we also found that cSCC in sun-exposed location was easier to recur than that in non-exposed location with p = 0.008[23]. From our observation, higher recurrence was consistent with lymph nodes metastasis and perineural invasion.

Nowadays, nomograms have become an important modern predictive tool to analyze and predict the risk of recurrence or survival outcomes [24, 25]. The model integrates a variety of risk factors which is notably associated with disease and quantify and score each variable’s influence and to visualize the ending of each patient [26, 27]. Through univariate and multivariate logistic analysis, we found that sun-exposure, tumor size, ulcer, precancerous lesions and neural invasion were strong prognostic variables of recurrence in postoperative patients with cSCC.

In most studies, nomograms are established for predicting overall survival in cancers, and few nomograms are applied in the prediction of recurrence in patients with skin non-melanoma cancers[28, 29]. This report constituted the first retrospective series of Chinese patients with cSCC and was the first nomogram in existence that was simultaneously based on abundant clinical data and had excellent predictive ability through the evaluation of C-indexes and calibration plots. Compared with NCCN

guidelines®, the nomogram showed better accuracy in predicting recurrence according to ROC analyses' outcomes. Nevertheless, great discrimination performance and strong calibration power did not necessarily mean the established model could be useful in daily clinical application[26]. Thus, DCA was performed to evaluate the nomograms' clinical usefulness, and also this nomogram was of better clinical utility in the proper range than NCCN guidelines® in Chinese patients in our samples. Additionally, CICs based on DCA in the nomogram further demonstrated the good discriminatory ability. Moreover, prediction points of recurrence's probability were defined as a new prognostic factor in Chinese patients with cSCC [30, 31]. About 14% ~ 15% of primary and 23% ~ 50% of recurrent cSCC have subclinical infiltration (not clinically visible, only histopathologically can be confirmed), so we should pay attention to the margin inspection of cSCC with high-risk scores and appropriate clinical interventions (such as resection margin extension or sentinel lymph node biopsy and dissection) should be carried out[32, 33].

Patients were divided into three prognostic groups according to the optimal cutoff value: low-risk group, medium-risk group and high-risk group (Figure S1). Patients with fewer than 116 points were considered to have low risk of recurrence. Patients with points between 117 and 167 points belonged to medium-risk group and were recommended to expand incisal edge properly to decrease the possibility of recurrence. If recurrence was confirmed, ultrasonography of the adjacent lymph nodes, chest CT and abdominal ultrasonography as well as PET-CT if necessary were recommended to exclude the possibility of lymph node metastases, neural invasion and distant organ or blood metastases. Patients scoring higher than 168 points were at high risk in cSCC recurrence. Thus, perienchyma CT and MRI, ultrasonography of lymph nodes, chest CT, abdominal ultrasonography and PET-CT were recommended to guide the choice of surgical approach. Close follow-up is essential for patients of high-risk group.

In the present study, we focused on the prognostic value of clinical observation and physical examination at initial diagnosis and didn't incorporate the pathology indicators into our nomogram. Compared with routine diagnostic examinations combined with clinical observation and pathologic examination, the novel predictive model was more suited to low rate of understanding skin cancers and visiting doctor, and also mitigated the economic burden for patients. Through comparing our model with NCCN guidelines®, our nomogram was more comprehensive with a high degree of concordance index, which could facilitate better prognosis and decrease the recurrence rate. However, as this was a single center and retrospective study, there is inevitable selection bias, as well as referral bias. Thus, external validation of the prognostic models is extremely important to test their prognostic significance and identify potential weaknesses, which could be improved in subsequent studies. A lack of external validation is a limitation of this study.

# 5 Conclusion

In this study, nomogram was established for predicting recurrence in patients with cSCC. Our nomogram had better calibration and discriminatory ability than NCCN guidelines® in evaluating the recurrence rate and could be used for clinically meaningful prognostic assessment of Chinese patients with cSCC, although more cases and external validation were required. Inevitably, several limitations still existed in our study. First, the clinical information was from a retrospective cohort rather than a prospective cohort,

so the inherent bias of selection might limit our study. Second, the clinical data were from a single cohort (Xinhua Hospital), so the number of cases was not enough for internal validation and also no data from other hospitals were available for the external validation. As the first nomogram based on Chinese cSCC series, we believed that the well-established nomogram and the important findings from our study could guide follow-up management strategies for elderly patients with cSCC and help clinicians improve personal treatment.

# Declarations


### Acknowledgements

None.


### Authors' contributions

WQZ: conceptualization, study design, quality control of data and algorithms, manuscript editing, manuscript review; CLW: study design, manuscript preparation, manuscript editing; KLZ: data acquisition, manuscript preparation; YC: quality control of data and algorithms, data analysis and interpretation; WGZ: data acquisition, data analysis and interpretation; XZ: manuscript review; DD: conceptualization, manuscript review. All authors read and approved the final manuscript.


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### Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

### Declarations

### Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University (Shanghai, China). All patients provided written informed consent prior to participation.

### Consent for publication

All authors have read and approved the content and agree to submit for consideration for publication in the journal.

### 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 conflict of interest.


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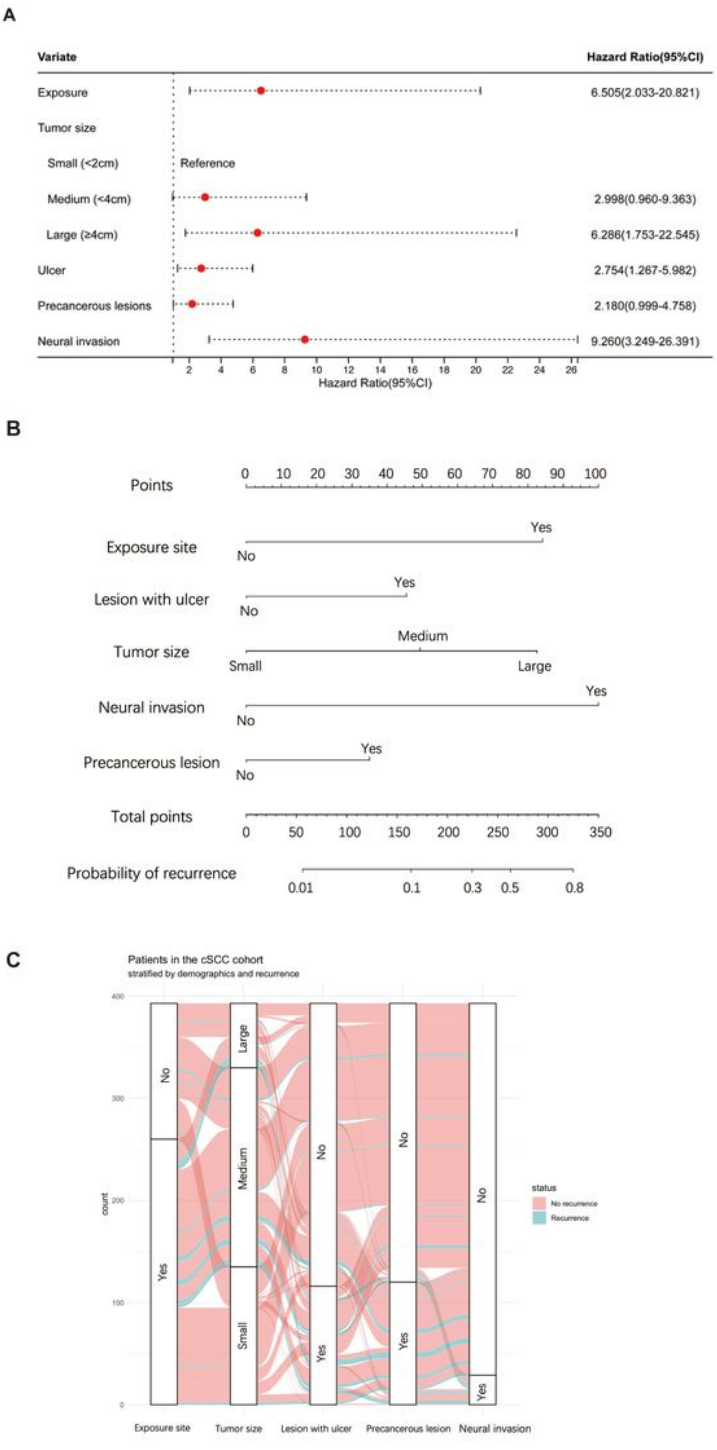
# Tables

Tables 1 and 2 are available in the Supplementary Files section.

# Figures



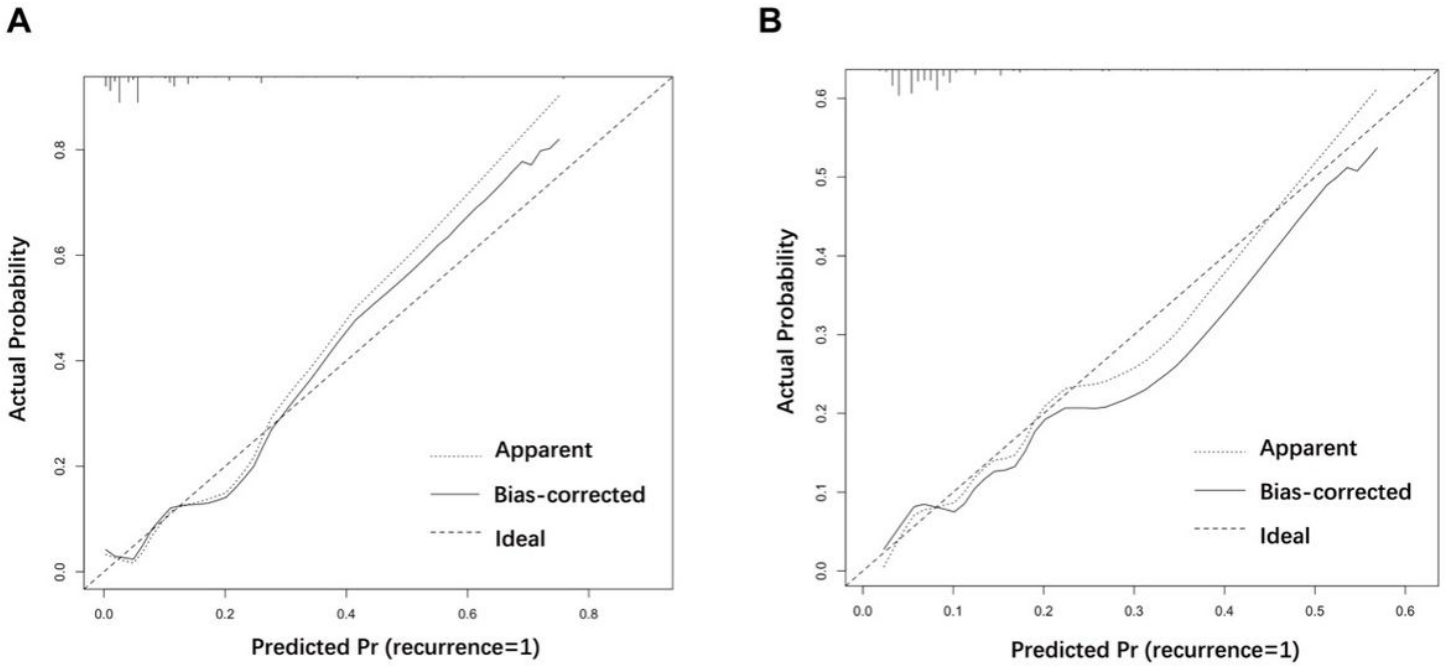

## Figure 1

Nomogram to predict the risk of recurrence in patients of cSCC.

(A) The multivariate logistic regression stratified analysis of recurrence of cSCC.

(B) The recurrent nomogram was established on the basis of exposure, tumor size, ulcer, precancerous lesions and neural invasion

(C) Flows of patients provides users with a convenient and intuitive interface for the correlation of different clinical factors with recurrence of cSCC.




## Figure 2

Calibration ability of the recurrent nomogram. The recurrent nomogram exhibited a higher correlation between the actual probability and predicted probability of recurrence than NCCN guidelines®. (A) calibration curve for nomogram; (B) calibration curve for NCCN guidelines®.

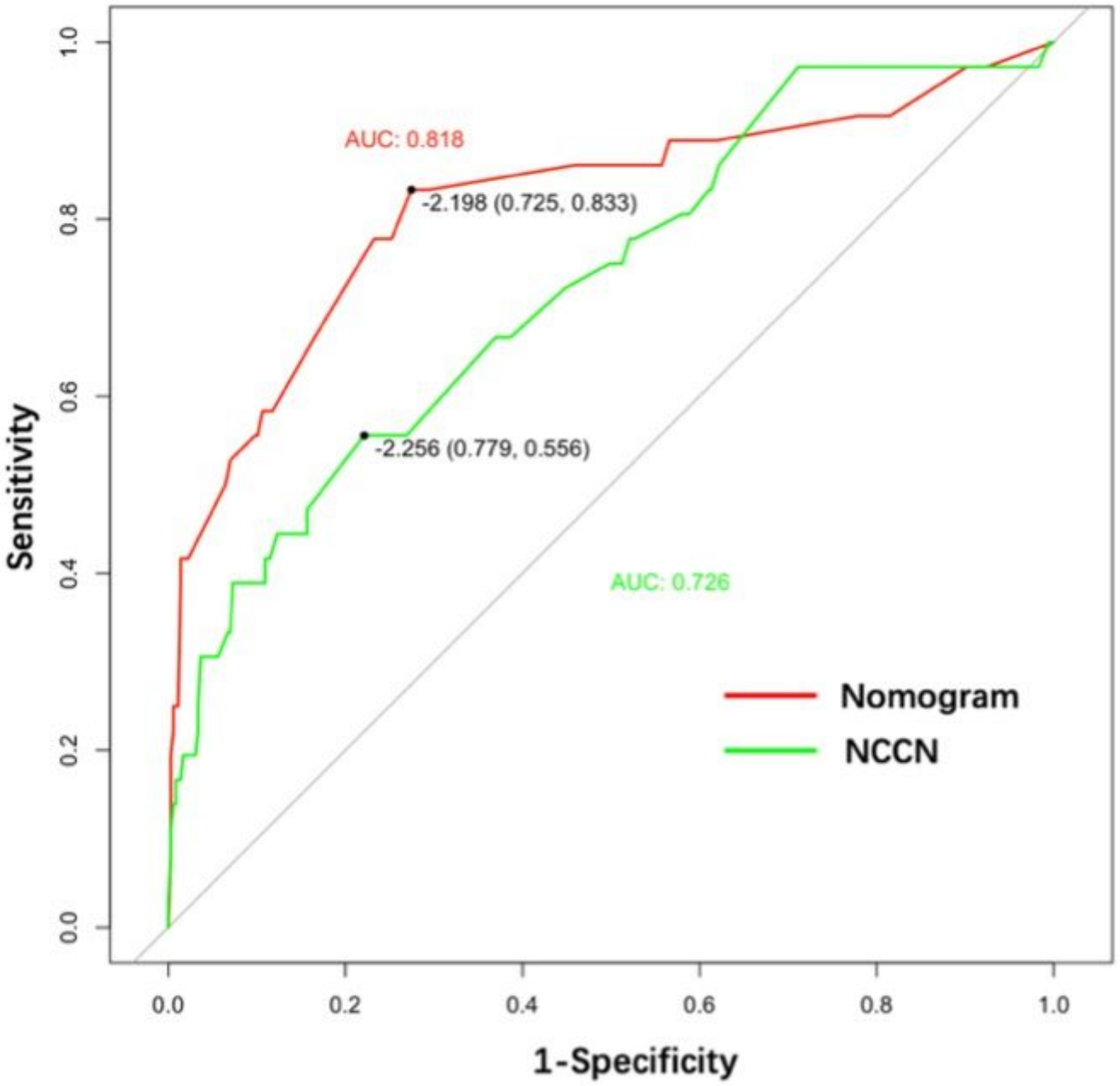
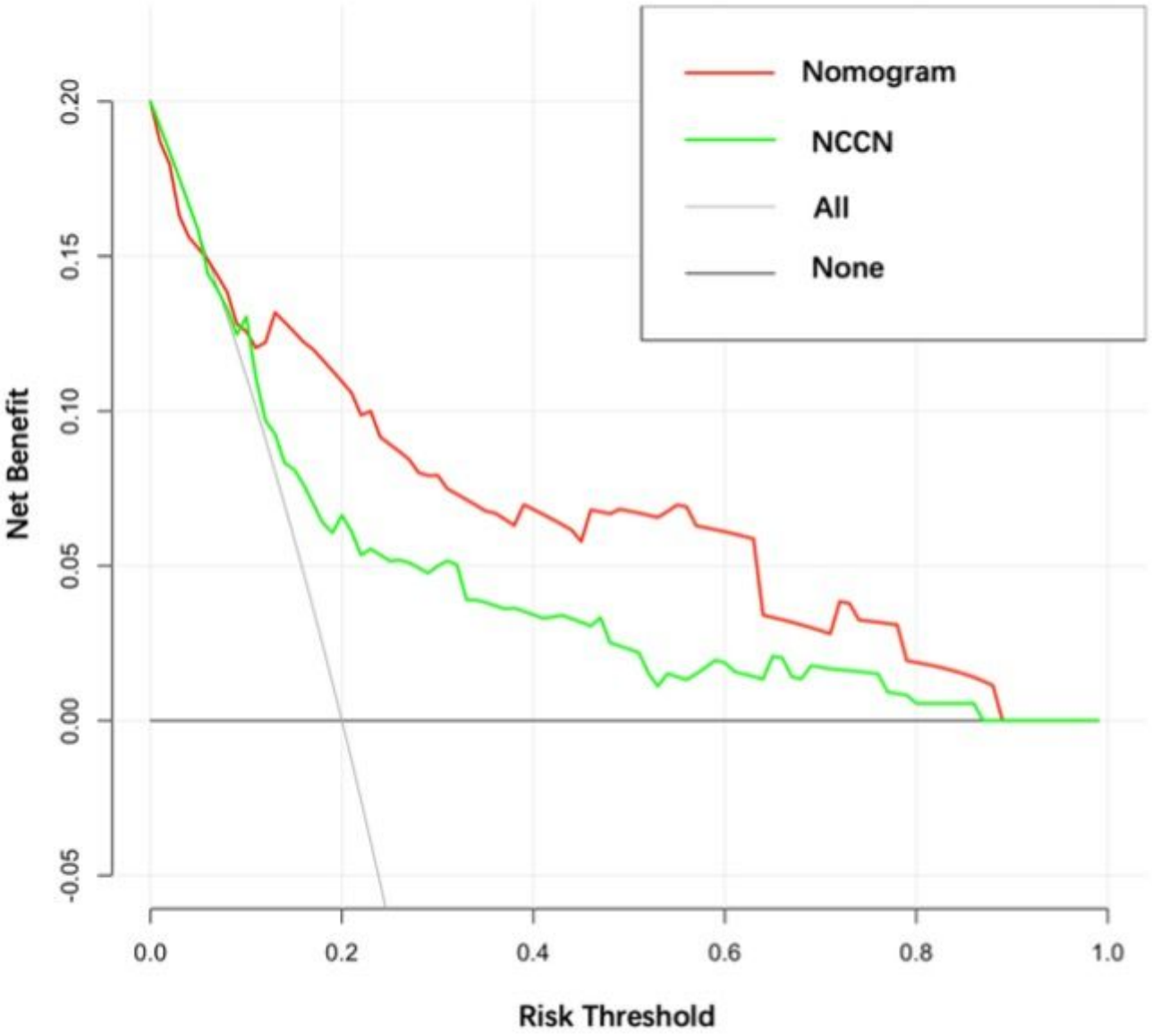



**Figure 3**

Comparison of nomogram (A) and NCCN guidelines® (B) on AUC curve.




## Figure 4

Decision curves of the nomogram and NCCN guidelines® predicting recurrence of cSCC. The x-axis represents the threshold probabilities, and the y-axis measures the net benefit, which is calculated by adding the true positives and subtracting the false positives. (A) DCA for nomogram; (B) DCA for NCCN guidelines®.

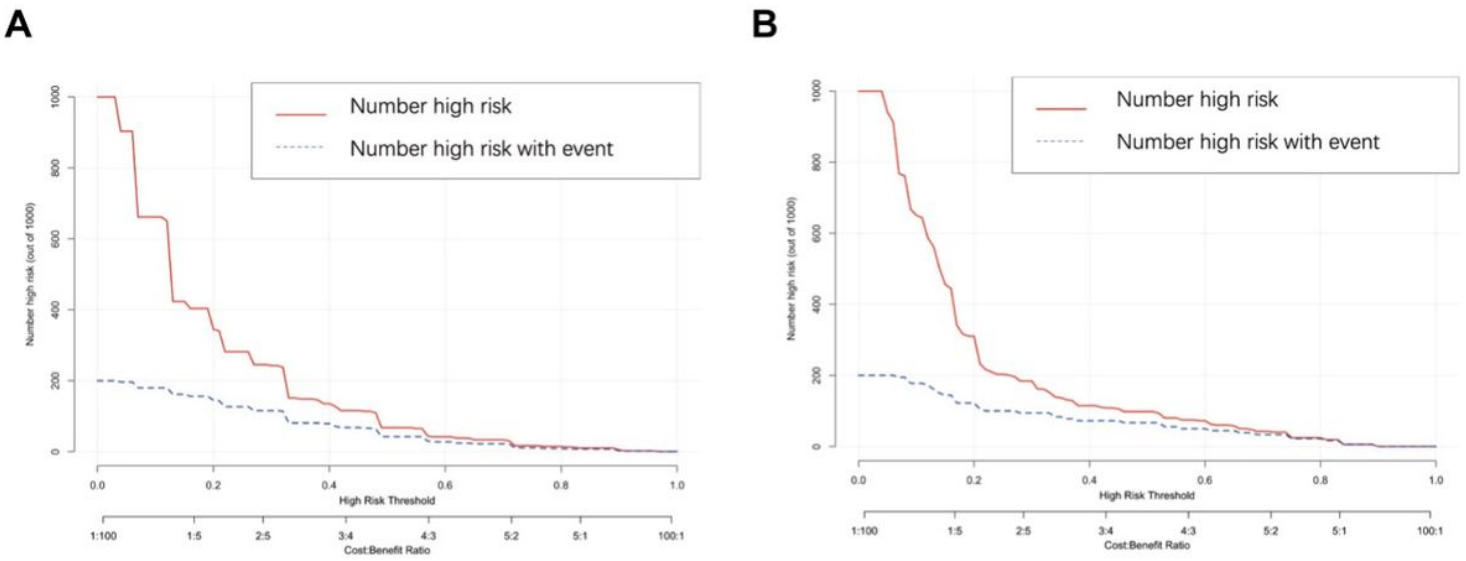



**Figure 5**

Clinical impact curves showed that both curves of nomogram and NCCN guidelines® displayed a superior overall net benefit over the entire range of threshold probabilities. (A) CIC for nomogram; (B) CIC for NCCN guidelines®.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLE1and2.docx
- SupplementalInformation.docx