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Original Article

Risk factors analysis and nomogram for predicting recurrence in periocular basal cell carcinoma

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Objectives: Aim to develop a nomogram to effectively predict the potential for recurrence after surgical resection in patients with periocular basal cell carcinoma (BCC).

Methods: We conducted a retrospective study involving 329 patients with eyelid BCC. Univariate and multivariate Cox proportional risk regression was used to screen for independent factors affecting BCC recurrence. Kaplan-Meier survival curve analysis was performed to evaluate their impact on prognosis. On the basis of the results obtained from Cox regression analysis, a nomogram was established for the 1-, 2-, and 3-year recurrence-free survival (RFS) rates of BCC.

Results: In this study, a total of 15 patients out of 329 patients (4.6%) developed local recurrence. Multivariate analysis revealed that age, pathological type, previous history of BCC, and the number of surgeries were independent risk factors for BCC recurrence ($p < 0.05$, respectively). These risk factors were utilized to construct a nomogram to predict postoperative recurrence for these patients. The C-index of the nomogram was 0.867 (95% CI: 0.817−0.916), and the receiver operating characteristic curves were used to assess the discriminatory degree of the nomogram, with area under the curve values of 0.978, 0.870, and 0.916 at 1, 2, and 3 years, respectively. The calibration curves were basically fitted to the ideal curves.

Conclusions: Age, pathological type, previous history of BCC, and the number of surgeries are significant risk factors for periocular BCC recurrence. Establishing a nomogram related to recurrence risk factors can more accurately predict the recurrence-free survival of individual patients.

Objectifs: Créer un nomogramme permettant de prédire efficacement le risque de récurrence du carcinome basocellulaire (CBC) périoculaire après la résection chirurgicale.

Méthodes: Nous avons réalisé une étude rétrospective qui regroupait 329 patients atteints d'un CBC palpébral. Les modèles de régression à risques proportionnels de Cox univarié et multivarié ont fait ressortir les facteurs indépendants de récurrence du CBC. La courbe de survie de Kaplan-Meier a permis d'évaluer leurs répercussions sur le pronostic. Les résultats des analyses de régression de Cox ont donné lieu à un nomogramme des taux de survie sans récurrence à 1, à 2 et à 3 ans dans le CBC.

Résultats: On a enregistré une récurrence locale chez un total de 15 patients sur 329 (4,6 %) pendant notre étude. L'analyse multivariée a révélé que l'âge, le type anatomopathologique, les antécédents de CBC et le nombre de chirurgies constituaient des facteurs de risque indépendants d'une récurrence du CBC ($p < 0,05$, respectivement). On a construit un nomogramme permettant de prédire le risque de récurrence postopératoire de nos patients à partir de ces facteurs de risque. L'indice C du nomogramme se chiffrait à 0,867 (intervalle de confiance à 95 % [IC] : 0,817–0,916), et les courbes caractéristiques de la performance (ROC, pour *receiver operating characteristics*) ont permis d'évaluer le degré de discrimination du nomogramme, les valeurs de l'aire sous la courbe s'élevant à 0,978, à 0,870 et à 0,916 à 1, à 2 et à 3 ans, respectivement. Les courbes d'étalonnage ont essentiellement été ajustées aux courbes idéales.

Conclusions: L'âge, le type anatomopathologique, les antécédents de CBC et le nombre de chirurgies constituaient des facteurs de risque significatifs d'une récurrence du CBC périoculaire. La création d'un nomogramme des facteurs de risque de récurrence peut aider à prédire plus précisément la survie sans récurrence de patients donnés.

Basal cell carcinoma (BCC) is a slow-growing, locally aggressive malignant tumour that originates in the epidermis. It accounts for 75% of all nonmelanoma skin cancers and is the most common form of skin cancer worldwide.[1,2] It is also the most common periocular malignancy, accounting for 90% of periocular malignancies.[3,4] While periocular BCC is rarely life-threatening, it can significantly impact a patient's quality of life by causing extensive local tissue damage and, in severe cases, invading the orbit and leading to vision impairment. Within the maxillofacial region, the periorbital region has been shown to be at high risk for recurrence,[5] and recurrences are more aggressive, infiltrative, and destructive, with most having a worse prognosis than the primary tumour.[6] In recent years, the substantial and increasing incidence of BCC, along with its associated morbidity,[7] has exerted a significant burden on health care systems worldwide, particularly concerning the post-treatment monitoring of BCC patients.[8] Consequently, evaluating the risk of recurrence after BCC treatment and implementing preventive measures against recurrence have become pivotal facets of BCC management.

Many studies have explored the risk factors that influence recurrence in patients with BCC.[6,9,10] However, there is a notable absence of established predictive models designed

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to guide clinical diagnosis and treatment. A nomogram is a statistical prediction tool that can provide an evidence-based, personalized risk estimate to facilitate management decision-making and prognostic assessment.[11–14] On the basis of multiple regression analysis, the nomogram integrates multiple predictive indicators to predict the risk of outcome occurrence, transforming complex equations into visual graphics. It can reasonably accurately predict the future incidence and recurrence rates of certain diseases.[15] Therefore, our primary objective is to establish a nomogram model through a retrospective study, identify independent factors influencing the recurrence of BCC patients after surgical resection, create nomograms for predicting 1-, 2-, and 3-year recurrence-free survival (RFS) rates for BCC after surgery, and validate its diagnostic efficiency. This nomogram aims to guide patient follow-up and serves as a reference for clinical prevention of BCC recurrence and the development of effective personalized treatment plans.

Materials and Methods

Study population

This retrospective study was conducted at the Department of Ophthalmology at the University of Cologne. It was conducted following the Helsinki Declaration and received approval from the Ethics Committee of the University of Cologne. (19-1025). The study conducted a comprehensive retrospective analysis of patients with BCC occurring in the periorbital region between January 2017 and December 2022. The periocular region consists of the upper and lower eyelids, medial canthus, and lateral canthus. Patients with duplicate records or tumours lacking essential information were excluded. Patients included in this study were aged ≥18 years and all were without Gorlin syndrome or immune suppression. The study was conducted following the Helsinki Declaration and received approval from the Institutional Review Board. Each patient underwent tumour excision as the treatment approach. The surgical procedure aimed to fully excise the entire tumour tissue using a non-Mohs' rapid paraffin technique, with the margins sent for pathological biopsy. If postoperative biopsy revealed tumour tissue at the margins, re-excision was performed until histologically confirmed tumour-free margins were achieved. Recurrence was defined as the appearance of a new lesion in the same area as the histologically proven lesion. Recurrence-free survival (RFS) was defined as the time from the date of surgery to tumour recurrence or to the last follow-up without recurrence.

Clinical variables and tumour characteristics

Clinical variables and tumour characteristics encompassed data extracted from the medical records of patients, including patient demographics, history of BCC without periocular BCC, lesion location, tumour size, surgical resection details, histologic subtype, orbital invasion, recurrence rate, and follow-up time. On the basis of histologic differentiation, BCC can be classified as nodular, infiltrative, superficial, basosquamous, or unknown. If mixed-type tumours were identified on biopsy, they were classified according to the most aggressive subtype.

Statistical analysis

Descriptive statistics were employed to present categorical variables in terms of frequency (n) and percentage (%), normally distributed continuous variables as the mean ± standard deviation (SD), and non-normally distributed variables as the median (interquartile range). The analysis was performed using SPSS 26.0 (IBM Corporation, 2019, USA). Chi-square tests and Fisher's exact tests were used to analyze count data. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. For continuous variables, *t*-tests were employed when the measured data followed a normal distribution, while nonparametric Mann–Whitney *U*-tests were used for non-normally distributed data. A univariate Cox proportional hazard analysis was performed to identify potential independent risk factors for BCC recurrence, followed by a multivariate Cox regression analysis of selected variables. $P < 0.05$ was considered statistically significant. On the basis of the results selected from the multivariate Cox regression analysis, a nomogram was constructed using the RMS package in R software (R4.2.2). Kaplan–Meier survival curve analysis was conducted to assess the impact of risk factors on recurrence. Validation and evaluation of the nomogram were carried out using the concordance index (C-index), receiver operating characteristic (ROC) curve, area under the curve (AUC), and calibration curve.

Results

Descriptive statistics

Three hundred and thirty eight eyes of 329 patients were involved in the study: 198 males and 140 females. After a median follow-up period of 29 months (IQR = 16–48 months), 15 patients (4.4%) had local recurrence. The median recurrence time was 16 months (IQR = 14–28 months). In the recurrent group, different surgical reconstruction methods were employed. Specifically, three patients underwent direct closure, six patients were treated with local flaps, two patients had skin grafts, and four patients received a combination of flap and graft for eyelid reconstruction. The median age of the patients was 76 years, ranging from 20 to 100 years. The most common regions of tumour growth were the lower lid (231, 68.3%), followed by the medial canthus (58, 17.2%), upper eyelid (40, 11.8%), and lateral canthus (9, 2.7%), respectively. Pathologically, 209 eyes (61.8%) had the nodular type, the predominant form, while 106 eyes (31.4%) had the infiltrative (sclerosing/morphoeic/micronodular),[16] 15 eyes (4.4%) had the superficial type, and basosquamous and unknown types

Table 1—Patient and tumor characteristics in BCC

Variables number (%)	Total	BCCs with recurrence	BCCs with no recurrence	*P* value
Total cases	338	15 (4.4)	323 (95.6)	
Recurrence-free survival (months) median (IQR)	29 (16–48)	16 (14–28)	28 (17–48)	-
Age (years) median (IQR)	76 (65–82)	68 (56–79)	76 (66–82)	0.008
Gender				
Male	198 (58.6)	7 (2.1)	191(56.5)	0.338*
Female	140 (41.4)	8 (2.4)	132 (39.1)	
Side				
Right	167 (49.4)	5 (1.5)	162 (47.9)	0.203*
Left	171 (50.6)	10 (3.0)	161 (47.6)	
Tumor sizes (mm)				
0-5	123 (36.4)	3 (0.9)	120 (35.5)	0.190†
6-10	129 (38.2)	8 (2.4)	121 (35.8)	
11–15	54 (16.0)	1 (0.3)	53 (15.7)	
16–20	20 (5.9)	2 (0.6)	18 (5.3)	
>20	12 (3.5)	1 (0.3)	11 (3.2)	
Localization				
Lower eyelid	231 (68.3)	8 (2.4)	223 (65.9)	0.325†
Medial canthus	58 (17.2)	5 (1.5)	53 (15.7)	
Upper eyelid	40 (11.8)	2 (0.6)	38 (11.2)	
Lateral canthus	9 (2.7)	0	9 (2.7)	
Histological type				
Nodular	209 (61.8)	4 (1.2)	205 (60.6)	0.008†
Infiltrative	106 (31.4)	10 (3.0)	96 (28.4)	
Superficial	15 (4.4)	0	15 (4.4)	
Basosquamous	5 (1.5)	0	5(1.5)	
Unknown	3 (0.9)	1 (0.3)	2 (0.6)	
Orbital involved				
Yes	3 (0.9)	1 (0.3)	2 (0.6)	0.128†
No	335 (99.1)	14 (4.1)	321 (9.5)	
History of BCC				
Yes	78 (23.1)	9 (2.7)	69 (20.4)	0.002†
No	260 (76.9)	6 (1.8)	254 (75.1)	
Number of excisions				
1	190 (56.2)	5 (1.5)	185 (54.7)	0.024†
2	128 (37.9)	8 (2.4)	120 (35.5)	
3	13 (3.8)	0	13 (3.8)	
4 or more	7 (2.1)	2 (0.6)	5 (1.5)	

BCC = basal cell carcinoma; IQR = interquartile range.
*Chi-squared test.
†Fisher's exact test.

accounted for 5 (1.5%) and 3 (0.9%) eyes, respectively. Table 1 summarizes specific demographic and baseline clinical characteristics.

Risk factors of BCC recurrence

In this study, we selected several candidate factors based on previous literature, including age, gender, tumour size, location, pathological type, history of BCC, and the number of surgical resections.[9,17–19] We employed univariate Cox proportional hazard regression and the AIC method (stepwise regression) to screen potential risk factors. The consistent results from both methods indicated that age, pathological type, history of BCC, and the number of surgeries significantly influenced the recurrence of patients ($p < 0.05$). Therefore, these four risk factors were further included in a multivariate Cox proportional hazards regression analysis, revealing that all four factors were significant risk factors for BCC recurrence ($p < 0.05$) (Table 2). Further impact analysis on patient prognosis was conducted using Kaplan–Meier survival curves. The optimal cutoff value for age was determined to be 59 years using the R software's survminer package (Fig. 1). On the basis of this cutoff value, patients were divided into 2 groups (<60 years and ≥60 years). The results showed that patients under 60 years old, with infiltrative and unknown types, a history of BCC, and four or more surgeries had a higher probability of recurrence ($p < 0.05$) (Fig. 2).

Construction of a nomogram

According to the four independent factors affecting BCC recurrence identified by filtering, a nomogram for 1-year, 2-year, and 3-year RFS was constructed. The endpoint of each variable extends vertically upward to the point axis at the top of the nomogram to obtain the corresponding score. The sum of the scores for the four variables yields a total score, and the patient's RFS probability is determined at the bottom of the nomogram based on the total score. As shown in Figure 3, the higher the summed score, the lower the corresponding RFS, which means a greater chance of recurrence, for patients with infiltrative pathologic staging, a history of BCC, younger age, and the greater the number of surgical procedures.

Table 2—Univariate and multivariate analyses of periocular BCC

	Univariable HR 95% CI *p*	Multivariable HR 95% CI *p*
Gender		
Male	Reference	
Female	1.675 0.607–4.620 0.319	
Age(year)	0.998 0.997–0.999 0.001†	0.998 0.997–0.999 0.005†
Side involved		
Left	Reference	
Right	0.476 0.162–1.394 0.175	
Tumor sizes(mm)		
0–5 mm	Reference	
6–10 mm	2.227 0.590–8.408 0.238	
11–15 mm	0.743 0.077–7.148 0.797	
16–20 mm	3.039 0.506–18.268 0.224	
≥21 mm	3.389 0.352–32.590 0.291	
Localization		
Lower lid	Reference	
Upper lid	1.418 0.301–6.680 0.659	
Medial canthus	2.511 0.821–7.677 0.106	
Lateral canthus	0.000 0.000 0.958	
Histological type		
Nodular	Reference	
Infiltrative	5.652 1.764–18.110 0.004†	4.735 1.404–15.970 0.012*
Superficial	0.000 0.000 0.987	0.000 0.000 0.983
Basosquamous	0.000 0.000 0.992	0.000 0.000 0.994
Others	16.271 1.801–146.992 0.013*	26.361 2.626–264.622 0.005†
History of BCC		
No	Reference	4.375 1.433–13.361 0.01†
Yes	5.208 1.854–14.635 0.002†	
Number of excisions		8.026 1.745–36.912 0.007†
<4 times	Reference	
≥4 times	9.167 2.063–40.724 0.004*	

HR, hazards ratio; CI, confidential interval.
*$p<0.05$.
†$p<0.01$.

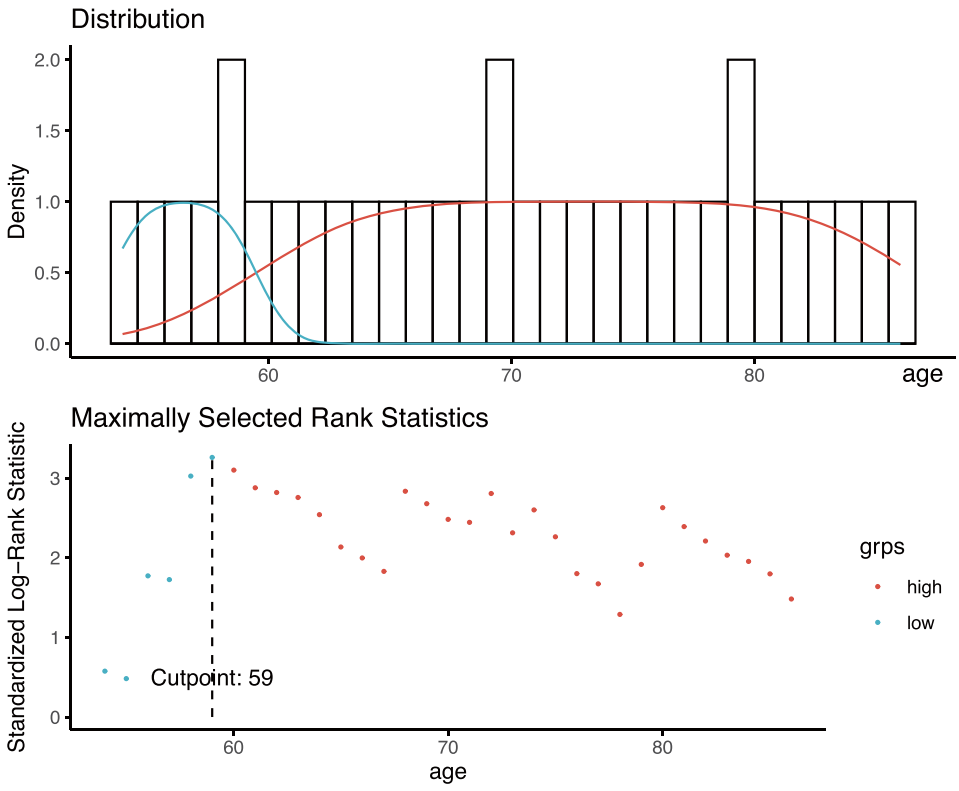

Fig. 1—Determination of the optimal age cutoff by R software analysis.

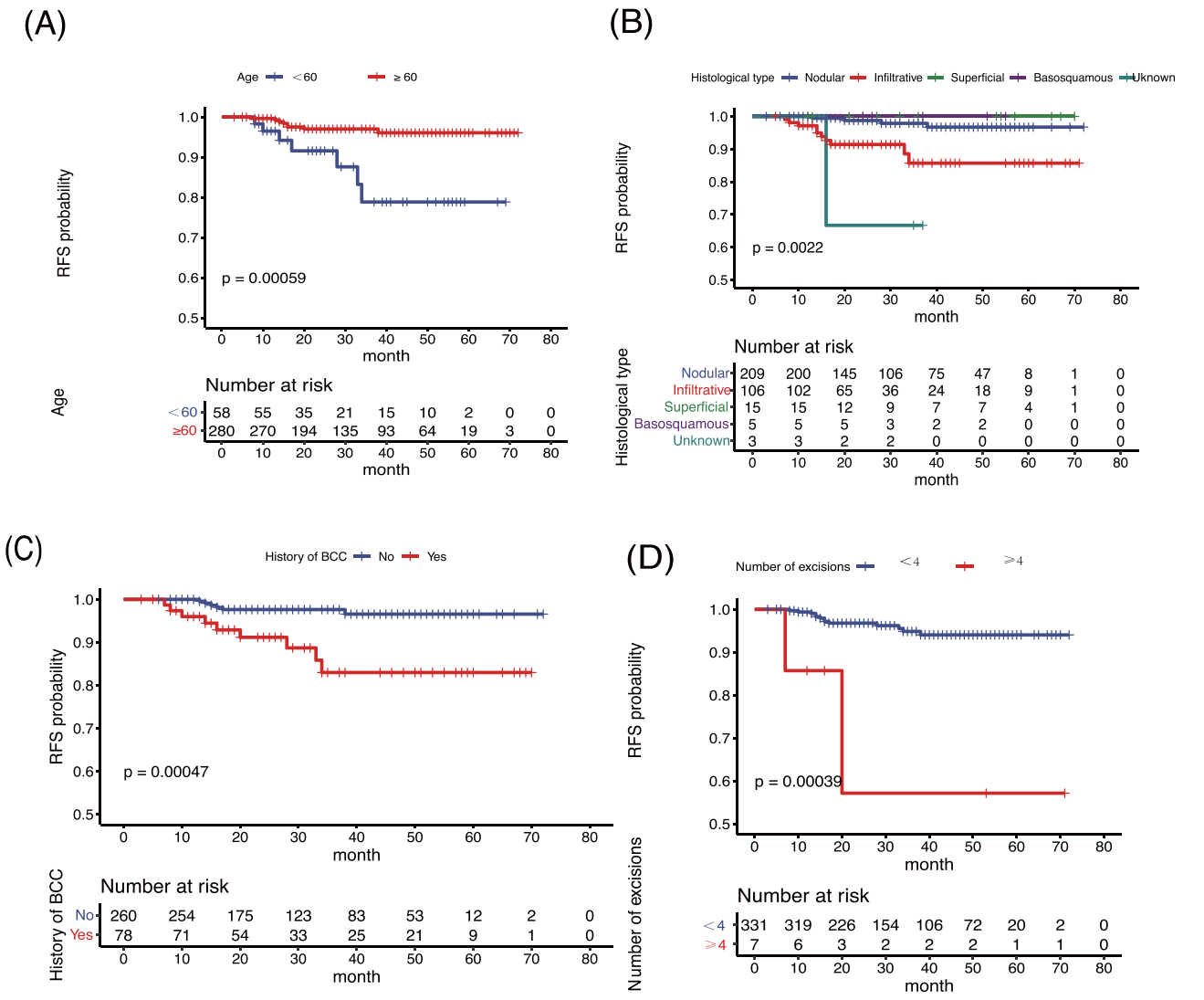

Fig. 2—(A) Kaplan–Meier curves of RFS based on the age. (B) Kaplan–Meier curves of RFS based on the pathologic staging. (C) Kaplan–Meier curves of RFS based on the history of BCC. (D) Kaplan–Meier curves of RFS based on the number of surgical excisions. RFS, recurrence–free survival.

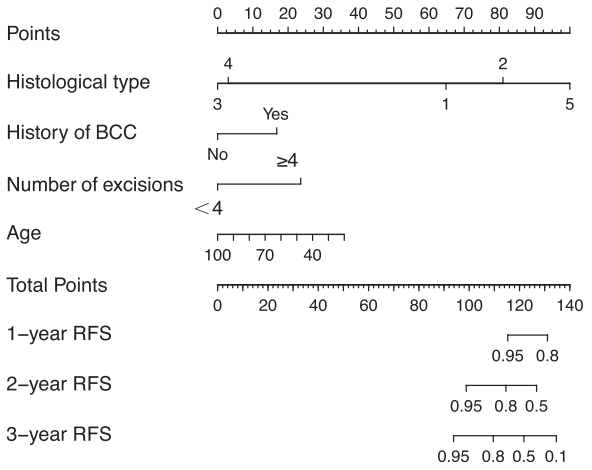

Fig. 3—Nomogram to predict the probability of RFS at 1, 2, and 3 years.

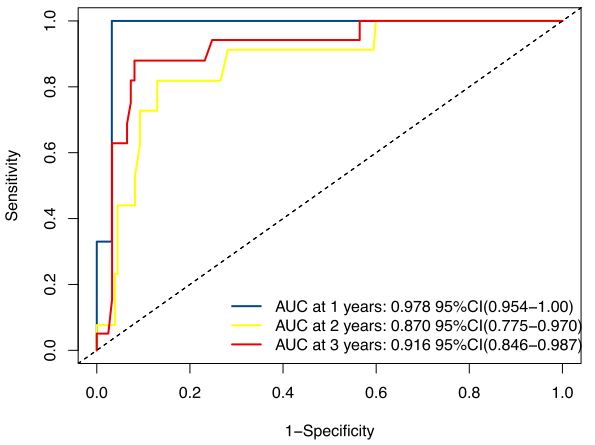

Fig. 4—ROC curve for 1-, 2-, and 3-year RFS based on the nomogram. AUC, area under the curve; ROC, receiver operating characteristic.

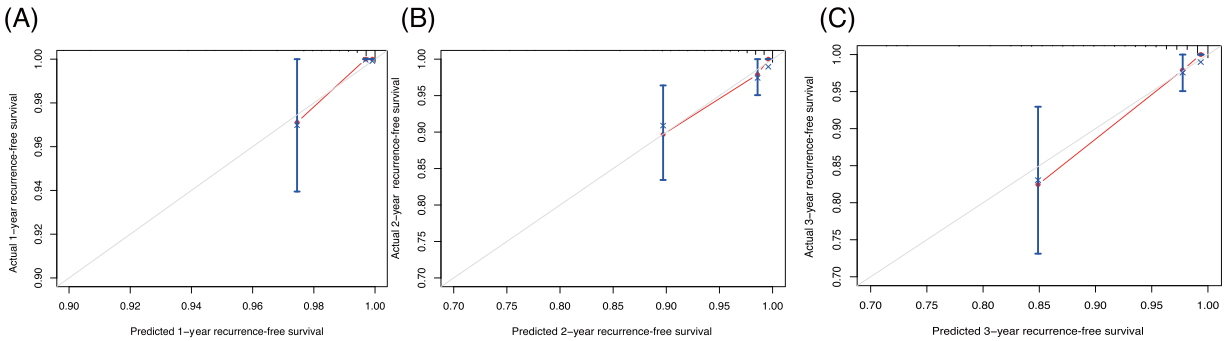

Fig. 5—Calibration plots for RFS probability at 1 (A), 2 (B), and 3 years (C). The vertical lines represent the 95% confidence intervals of the estimates. The gray lines represent the ideal lines. Red dot denotes predicted probabilities based on the nomogram, and blue cross denotes bootstrap−corrected estimates.

Evaluation and validation of the nomogram

The nomogram is validated in terms of discrimination, calibration, and clinical utility. The model's C-index is 0.867 (95% CI: 0.817−0.916), and the areas under the ROC curves for 1 year, 2 years, and 3 years are 0.978, 0.870, and 0.916, respectively, indicating good predictive performance of the model (Fig. 4).

Calibration curves are used to assess the consistency between predicted and actual outcomes. Employing Bootstrap resampling for 1,000 iterations for internal validation, the calibration curves for 1-, 2-, and 3-year RFS probability are close to the ideal 45° reference line, demonstrating good consistency between predicted values and actual survival rates (Fig. 5).

Discussion

Our study is the first comprehensive retrospective study to build a nomogram to predict the risk of recurrence in BCC patients. While earlier studies have explored risk factors for BCC recurrence, they have not predicted the potential for BCC recurrence. We found that independent risk factors age, pathological type, history of BCC, and the number of surgeries influencing the recurrence after BCC excision, as reported by previous studies. On the basis of our results, we constructed a nomogram to quantify the postoperative recurrence risk. Furthermore, ROC curves and calibration plots indicate that the nomogram has excellent predictive ability. This tool will enable a more targeted follow-up in clinical practice for BCC patients, alleviate the burden on health care systems, and provide guidance for clinical prevention of BCC recurrence, as well as the development of effective personalized treatment plans.

Risk factors for BCC recurrence

In this study, we ultimately identified four independent risk factors, including age, pathologic type, history of previous BCC, and the number of surgeries. In our investigation, we found that age ($p = 0.005$) is an independent risk factor for BCC recurrence, with a higher chance of recurrence in younger individuals. This is consistent with previous research, showing that BCC occurring in young individuals (under 35 years old) may have a more aggressive clinical course.[20,21] Therefore, close attention should be paid to young individuals during clinical follow-up.

The pathological classification of BCC can be categorized into indolent growth or aggressive growth subgroups. The aggressive type includes the infiltrative subtype, while the indolent type comprises the nodular and superficial subtypes. Aggressive growth exhibits the highest variability, while indolent growth has the lowest variability.[22] Numerous studies have indicated that BCC with invasive growth has a higher recurrence rate compared to other types.[18,23−26] Our study also demonstrated that the infiltrative subtype of BCC is a high-risk factor for tumour recurrence ($p = 0.012$). It is worth mentioning that, in our research, the unknown subtype is also a risk factor for recurrence. However, because of the limited sample size and unknown characteristics of this subtype, we do not recommend classifying it as an independent risk factor for BCC recurrence.

Some studies have proven that patients with a prior history of BCC need to be followed up for at least 5 years after surgery because they have a higher potential for recurrence and extensive progression.[26,27] M. R. Karagas et al.[19] investigated patients with BCC and found that people with a history of nonmelanoma skin cancer had a high risk of developing another tumour of the same histologic type within 5 years and was associated with the number of previous tumours. Our study also indicates that the history of previous BCC is an independent risk factor for tumour recurrence ($p = 0.01$). Therefore, for patients with a history of BCC and multiple tumours, intensive follow-up within 5 years is crucial.

Regarding the number of surgeries, some studies have shown that the more surgeries a patient undergoes, the greater the chance of recurrence. Pieh et al.'s study proved that BCC patients had a recurrence rate of 5.36% after the first surgery. The recurrence rate increased to 14.7% after the second surgery and reached 50% after the third and fourth surgeries.[28] Additionally, a retrospective analysis by Batra and Kelley that involved 1 095 cases of nonmelanoma

skin cancer identified a high risk factor for extensive tumour spread as having undergone 3 or more surgeries.[29] Our study also suggests that undergoing surgery 4 or more times is an independent risk factor for BCC recurrence. This emphasizes the importance of achieving as complete tumour removal as possible during the initial excisional surgery.

Furthermore, we found that the most affected areas for BCC were the lower eyelid and medial canthus. It was not proven that the location is a risk factor for tumour recurrence ($p > 0.05$). Nevertheless, many studies suggest that the tumour's location is associated with tumour recurrence and is an independent risk factor.[18,30] Particularly, patients in the medial canthal region have a high risk of recurrence after conventional treatment.[25,28,31,32] The reason for this difference may be that previously published results indicated that the medial canthus region was prone to the residual tumour after surgical resection, whereas all patients included in our study underwent complete resection. Therefore, our study does not identify the location as a risk factor for BCC recurrence.

Establishment and verification of prediction models

This study constructed a nomogram based on the factors influencing BCC recurrence mentioned above. The results indicated that pathological type had the greatest impact on patient prognosis, followed by age, and the number of surgeries. One study has constructed a nomogram for evaluating the risk of SCC orbital invasion, achieving a model c-index of 0.77.[33] Additionally, other studies have developed predictive models for assessing the prognosis and recurrence of sebaceous gland carcinoma, with c-index values of 0.887 and 0.817, respectively.[34,35] As for our study, validation through C-index (0.867), ROC curves, and calibration plots all demonstrated the accuracy of the model in predicting the RFS rate for BCC. Therefore, in clinical practice, this nomogram can serve as an effective tool to guide surgeon decision-making. For instance, it can be used to recommend more frequent follow-ups for patients with a higher risk of recurrence, while for those with a lower risk, follow-up visits can be appropriately reduced, thereby, conserving health care resources.

Limitations

Our study has some limitations. First, because of the limited number of recurrent cases, we did not perform internal validation of the model and lacked a large external validation set. Second, as this is a single-center retrospective study, the sample size is limited and may not be universally representative. Therefore, we hope to include more relevant factors in the future to further refine the nomogram model. We also aim to conduct large-sample, multicenter prospective studies to guide future diagnosis and treatment.

Conclusions

This study confirmed that patient age, BCC pathologic staging, previous history of BCC, and the number of surgical excisions are independent prognostic factors for postoperative recurrence of BCC. Furthermore, on the basis of the risk assessment of these factors, we constructed a prediction model and validated its high accuracy, thereby setting the stage for future clinical implementation. This nomogram can be used not only for the prediction of individual patients' recurrence risk but also for identifying high-risk populations for close follow-up and treatment. It can effectively assist clinicians in providing personalized treatment and save medical resources.

CRediT Author Statement

Xincen Hou: Writing — review & editing, Writing — original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Alexander C. Rokohl:** Supervision, Project administration. **Katharina Berndt:** Investigation, Formal analysis, Data curation. **Senmao Li:** Conceptualization. **Xiaojun Ju:** Writing — review & editing. **Philomena A. Wawer Matos:** Writing — review & editing. **Wanlin Fan:** Writing — review & editing, Supervision. **Ludwig M. Heindl:** Writing — review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

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