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Research article

Development and validation of a prognostic nomogram for patients with ganglioneuroblastoma: A SEER-based study

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ABSTRACT

Background: The objective of this study was to construct a prognostic nomogram for ganglioneuroblastoma (GNB), as the prognosis of GNB is difficult to accurately predict before therapy.
Methods: The data were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The patients included in this study were randomly divided into a development group and a validation group at a ratio of 7:3. Univariate and multivariate Cox regression analyses were used to filter the variables. Receiver operating characteristic (ROC) curves and calibration curves were used to assess the nomogram. All patients were redivided into two groups based on their nomogram total points, and overall survival was compared.
Results: A total of 1194 GNB patients were retrospectively included, with 835 and 359 patients in the development and validation groups, respectively. Five independent prognostic factors, including age, primary tumor site, SEER stage, surgery and chemotherapy, were screened out and included in the nomogram. The consistency index (C-index) of the Cox regression model was 0.862 and 0.827 in the development group and the validation group, respectively. The areas under the receiver operating characteristic (ROC) curve (AUC) showed that the nomogram had good accuracy in predicting 3-, 5- and 10-year overall survival for GNB patients. The calibration curves of the nomogram showed good agreement between the predicted outcomes and the actual observations. The Kaplan-Meier (KM) survival curves revealed that patients with nomogram scores below the median had a better prognosis.
Conclusions: Age, primary tumor site, SEER stage, surgery and chemotherapy may be independent prognostic factors for GNB. We constructed a nomogram based on the SEER database to predict the prognosis of GNB, but further optimization by adding more risk factors is needed for clinical application.

1. Introduction

Ganglioneuroblastoma (GNB) is, a rare malignant tumor of the nervous system that is derived from the neuronal cells of the

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sympathetic nervous system [1]. According to the international neuroblastoma classification system, GNB is considered less malignant than neuroblastoma and more malignant than ganglioblastoma [2,3]. The histopathology of GNB includes nodular and intermixed types [2,3]. Intermixed GNB is classified as having favourable histology, whereas nodular GNB encompasses both favourable and unfavourable histology [4]. The categorization of nodular GNB into specific histological types is determined by individual factors, including age-related assessment of neuroblastic differentiation grade and the mitosis-karyorrhexis index [4]. GNB primarily affects children – its incidence rate in this population is no more than 5 cases per million children – but it can also occur in adolescents and adults [5]. Age is an independent prognostic factor for GNB [6,7]. A retrospective study suggested that the 5-year survival rate of GNB patients was approximately 88 % [8]. In contrast, other studies suggested that GNB had a poor prognosis in adolescents and adults [9,10]. In addition, the histological and genetic characteristics of GNB are also prognostic factors [11,12]. A retrospective study showed that intermixed GNB was more likely to have a favourable prognosis than nodular GNB [11]. *MYCN* oncogene amplification was reported to be associated with poor clinical outcomes and was observed in approximately 20 % of all peripheral neuroblastic tumors [13]. However, *MYCN* amplification was almost exclusively found in GNB with unfavourable histology, indicating a low incidence of *MYCN* amplification in GNB [14–16]. Okamatsu C. et al. reported that *MYCN*-amplified tumors accounted for 1.9 % (4/210) and 3 % (6/237) of GNB tumor with favourable histology [4]. In addition, researchers observed that *MYCN* amplification did not seem to have an adverse effect on prognosis; however, they explained that their analysis could not yield a strong conclusion regarding the prognostic impact of *MYCN* status.

Accurately predicting the prognosis of GNB at the patient on an individual level is crucial. However, no efficient prognostic tool specific to GNB has been developed to date. Therefore, it is imperative to create a precise and efficient predictive model that could assist clinicians in providing individualized and effective therapeutic schedules for GNB patients.

The Surveillance, Epidemiology, and End Results (SEER) database is a comprehensive tumor registry in North America that contains clinical data from multiple cancer patient registries in the United States. This database has a sample size that represents approximately 28 % of the entire US population, making it the most representative large-scale tumor registry in North America. The SEER database is characterized by its vast sample size and complete collection of clinical data.

As a tool for visually displaying proportional hazards models, nomograms have been widely used in clinical research [17]. Nomogram can score the impact coefficient of each prognostic factor and obtain the total score to predict the risk of the outcome event.

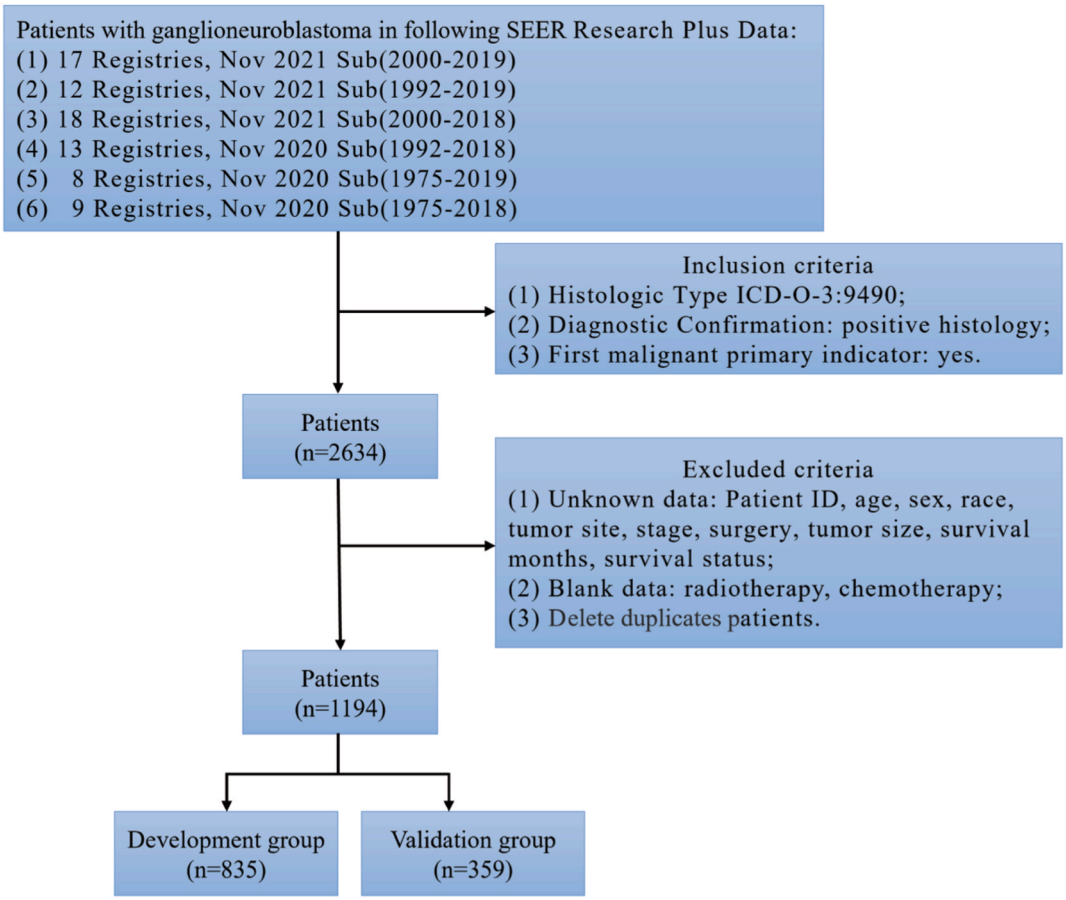

Fig. 1. Flowchart of inclusion and exclusion.

At present, many prognostic nomograms for cancer have been developed and show good application prospects [18–20].

To assess the prognostic factors of patients with GNB more accurately and provide personalized treatment, we developed and validated a prognostic nomogram for GNB patients based on data from the SEER database.

2. Methods

2.1. Study data from SEER

The data used in this retrospective study are publicly available. Therefore, the need for informed consent from the patients was waived. No separate ethical approval was required for this study.

We used SEER*Stat (https://seer.cancer.gov/seerstat/) software (version 8.4.0) to obtain the clinical data of GNB patients.

The research data were extracted from the following six Incidence-SEER Research Plus Data: 17 Registries, Nov 2021 Sub (2000–2019); 12 Registries, Nov 2021 Sub (1992–2019); 18 Registries, Nov 2021 Sub (2000–2018); 13 Registries, Nov 2020 Sub (1992–2018); 8 Registries, Nov 2020 Sub (1975–2019); and 9 Registries, Nov 2020 Sub (1975–2018).

The third edition of the International Classification of Oncological Diseases (ICD-*O*-3) code for GNB is 9490. The inclusion criteria were as follows: (1) GNB patients ("Histologic Type ICD-*O*-3", 9490); (2) positive pathology ("Diagnostic Confirmation", positive histology); and (3) GNB was the first primary malignant tumor ("First malignant primary indicator", Yes).

The exclusion criteria were as follows: (1) any cases with missing data including: patient ID, age at diagnosis, sex, race, primary tumor site, SEER stage, surgery, tumor size, survival months, and survival status; (2) blank radiotherapy or chemotherapy; (3) deletion of duplicate patients.

Fig. 1 shows the screening process for GNB patients.

2.2. Study variables

The following clinical data were obtained from the database: patient ID, age at diagnosis, sex, race, primary tumor site, SEER stage, radiotherapy, chemotherapy, surgery, tumor size, survival months, and survival status. The race was recorded as white, black, and others. In the SEER database, others under race included American Indians/Alaska Natives and Asian/Pacific Islanders. Based on the

Table 1
Baseline characteristics of patients with Ganglioneuroblastoma.

	Overall (N = 1194)	Development group(N = 835)	Validation group(N = 359)	P value
Sex				
Female	56.3 %	57.0 %	54.6 %	0.446
Male	43.7 %	43.0 %	45.4 %	
Age (years)				
Mean (SD)	6.15 (9.65)	6.34 (10.2)	5.72 (8.13)	0.267
Race				
Black	12.6 %	13.1 %	11.7 %	0.416
Others	8.5 %	7.9 %	10.0 %	
White	78.8 %	79.0 %	78.3 %	
Site				
AdrenalGland	29.9 %	28.6 %	32.9 %	0.601
HeartMediastinum	14.5 %	15.2 %	12.8 %	
Others	6.0 %	6.2 %	5.6 %	
Retroperitoneum	12.1 %	12.1 %	12.3 %	
SoftTissue	37.4 %	37.8 %	36.5 %	
SEER stage				
Distant	20.2 %	19.0 %	22.8 %	0.109
Localized	48.1 %	47.5 %	49.3 %	
Regional	31.7 %	33.4 %	27.9 %	
Surgery				
No	4.4 %	4.0 %	5.3 %	0.353
Yes	95.6 %	96.0 %	94.7 %	
Radiotherapy				
None/Unknown	88.8 %	88.7 %	88.9 %	1.000
Yes	11.2 %	11.3 %	11.1 %	
Chemotherapy				
No/Unknown	67.1 %	67.1 %	67.1 %	1.000
Yes	32.9 %	32.9 %	32.9 %	
Tumorsize (mm)				
Mean (SD)	68.6 (38.0)	68.3 (37.7)	69.4 (38.7)	0.635
Overall survival				
3-year	73.9 %	73.3 %	75.2 %	0.518
5-year	61.2 %	61.6 %	60.4 %	0.746
10-year	40.8 %	40.7 %	40.9 %	0.949

SD: Standard deviation.

prevalence probability of GNB being the primary site of GNB, we classified the primary tumor site as the adrenal gland (C74.9, C74.0, C74.1), heart mediastinum (C38.1, C38.2, C38.3), retroperitoneum (C48.0), soft tissue (C47.0-C47.9, C49.0-C49.9), and others. The surgery variable was classified into "Yes" (code 10–90) or "No" (code 00–09).

2.3. Analysis

The data were analysed by R (version 4.2.0) software.

The included patients were randomly divided into a development group and a validation group. The development group accounted for 70 % of all included patients, and the validation group accounted for 30 % of all included patients. Univariate and multivariate Cox regression analyses were used to filter the variables. The Schoenfeld residual test and Kaplan–Meier (KM) curve were used to test whether the selected variables satisfied the proportional hazards assumption. A prognostic nomogram was developed based on the selected variables to predict 3-, 5- and 10-year survival probabilities for GNB patients.

The discrimination between the predicted outcome and the actual result was evaluated by the consistency index (C-index). The "rms" package was used to plot the calibration curve. The 3-, 5- and 10-year survival probabilities of GNB patients were calculated. Using the survival probability as a continuous variable, the receiver operating characteristic (ROC) curve of survival probability was plotted by the "survival ROC" package. The area under the ROC curve (AUC) was calculated. All patients were scored by the nomogram and redivided into two groups based on the median of the nomogram total score. The difference in survival rate between the two groups was analysed. Survival analysis between the two groups was performed by KM survival curves. P values less than 0.05 were considered to indicate statistical significance.

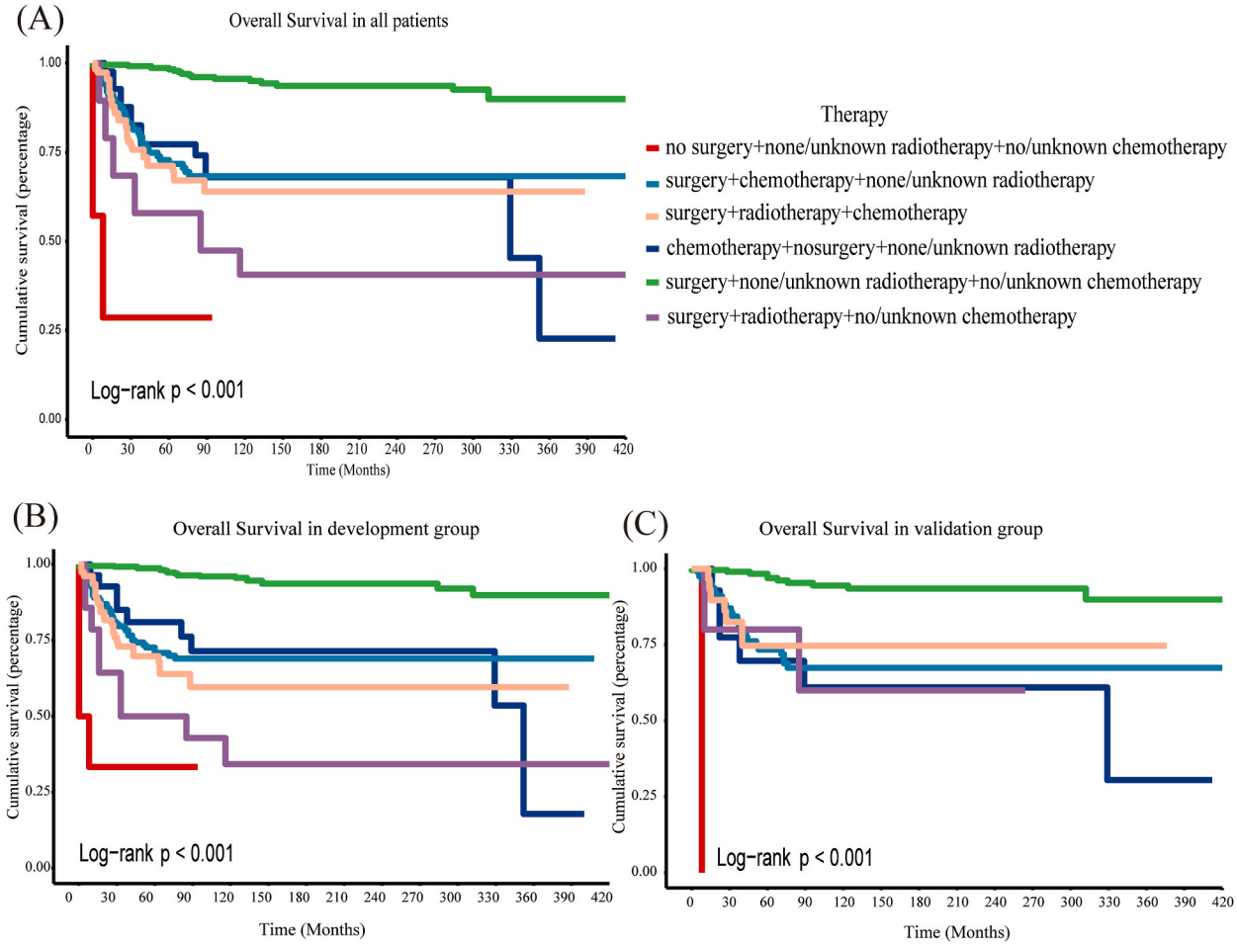

Fig. 2. The KM curve shows the OS of GNB patients with different therapy in the overall, development, and validation groups. (A): Overall; (B): Development groups; (C): Validation groups. OS, overall survival; GNB, Ganglioneuroblastoma.

3. Result

3.1. Patient characteristics

A total of 1194 GNB patients were included between 1975 and 2018. After grouping at a ratio of 7:3, there were 835 patients in the development group and 359 patients in the validation group (Table 1). There were 476 females (57.0 %) and 359 males (43.0 %) in the development group and 196 females (54.6 %) and 163 males (45.4 %) in the validation group.

KM curves showed that GNB patients who underwent surgery alone had the longest overall survival (OS) in the overall sample as well as in the development group (Fig. 2B) and validation groups (Fig. 2C). In the case of combination therapy, OS of the surgery plus chemotherapy group was longer than that of the surgery plus radiotherapy group (Fig. 2A–C).

3.2. Construction of the prognostic nomogram

Six variables were initially selected by univariate analysis (Table 2). Further multivariate analysis identified five prognostic variables, including age, site, SEER stage, surgery, and chemotherapy (Table 3), all of which satisfied the proportional hazards assumption (Fig. S1–Fig. S5). The C-index of the Cox regression model was 0.862 and 0.827 in the development group and the validation group, respectively. A prognostic nomogram was established (Fig. 3) that effectively predicted the 3-, 5-, and 10-year survival of GNB patients.

To evaluate its accuracy, we plotted ROC curves for the 3-, 5-, and 10-year survival probabilities in both the development and validation groups. Fig. 4A shows the accuracy of the nomogram in predicting the survival probability of GNB patients, with AUC values of 0.875, 0.875, and 0.872 for the 3-, 5-, and 10-year survival rates, respectively, in the development group. Correspondingly, the AUC values of the validation group (Fig. 4B) were 0.817, 0.836, and 0.835, respectively.

The calibration curves of the development group (Fig. 5A, C, 5E) and the validation group (Fig. 5B, D, 5F) showed a good agreement between the predicted outcomes and the actual observations.

3.3. Overall survival based on the nomogram score

The median nomogram score for all patients was 42.017. A total of 741 patients were categorized into group I (nomogram score $\leq$42), and 453 patients were placed into group II (nomogram score >42). The KM survival curves showed that group I had a longer survival time than did group II (Fig. 6).

Table 2
Univariate analysis.

	HR (95%CI)	P value
Age	1.04 (1.03,1.04)	<0.001
Sex		
Male	1.00	–
Female	1.02 (0.71,1.48)	0.91
Race		
Black	1.00	–
White	0.99 (0.56,1.74)	0.97
Other	1.64 (0.77,3.50)	0.20
Site		
AdrenalGland	1.00	–
HeartMediastinum	0.26 (0.12,0.55)	<0.001
Retroperitoneum	0.70 (0.41,1.18)	0.18
SoftTissue	0.14 (0.07,0.27)	<0.001
other	1.93 (1.15,3.24)	0.01
SEER stage		
Distant	1.00	–
Localized	0.12 (0.07,0.19)	<0.001
Regional	0.16 (0.10,0.25)	<0.001
Surgery		
No	1.00	–
Yes	0.30 (0.17,0.53)	<0.001
Radiotherapy		
None/Unknown	1.00	
Yes	4.16 (2.80,6.18)	<0.001
Chemotherapy		
No/Unknown	1.00	
Yes	5.36 (3.60,7.98)	<0.001
Tumorsize	1.00 (1.00,1.01)	0.08

HR: Hazard ratio. SEER: Surveillance, Epidemiology, and End Results database.

Table 3
Multivariate analysis.

	HR (95%CI)	P value
Age	1.05 (1.04,1.06)	<0.001
Site		
AdrenalGland	1.00	–
HeartMediastinum	0.49 (0.22,1.08)	0.08
Retroperitoneum	0.62 (0.35,1.11)	0.11
SoftTissue	0.33 (0.17,0.65)	0.001
other	2.01 (1.15,3.50)	0.01
SEER stage		
Distant	1.00	–
Localized	0.19 (0.10,0.36)	<0.001
Regional	0.28 (0.16,0.49)	<0.001
Surgery		
No	1.00	–
Yes	0.51 (0.28,0.95)	0.03
Radiotherapy		
None/Unknown	1.00	
Yes	1.13 (0.71,1.79)	0.61
Chemotherapy		
No/Unknown	1.00	
Yes	2.14 (1.19,3.86)	0.01

HR: Hazard ratio. SEER: Surveillance, Epidemiology, and End Results database.

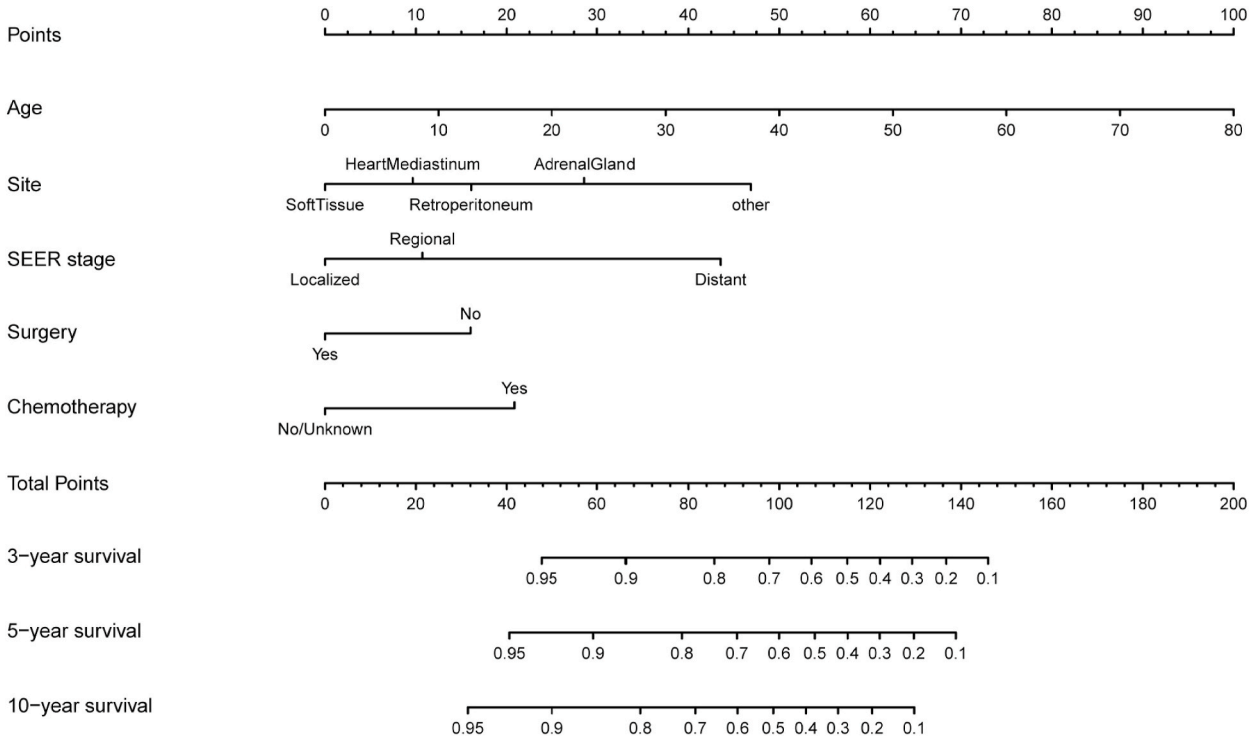

Fig. 3. Prognostic nomogram of patients with GNB based on five prognostic factors. GNB, Ganglioneuroblastoma.

4. Discussion

To the best of our knowledge, this is the first study to develop and validate a clinical prognostic nomogram for GNB patients. Moreover, this study had the largest sample size of GNB patients among all comparable studies. We initially identified variables with potential predictive risk values and further narrowed them down to five independent prognostic factors. We then developed a prognostic nomogram capable of predicting the 3-, 5-, and 10-year survival probability of GNB patients. Finally, the nomogram was verified to have good accuracy and performance through internal validation.

Our results demonstrated that age was an independent prognostic factor for GNB. We found that younger GNB patients had a higher

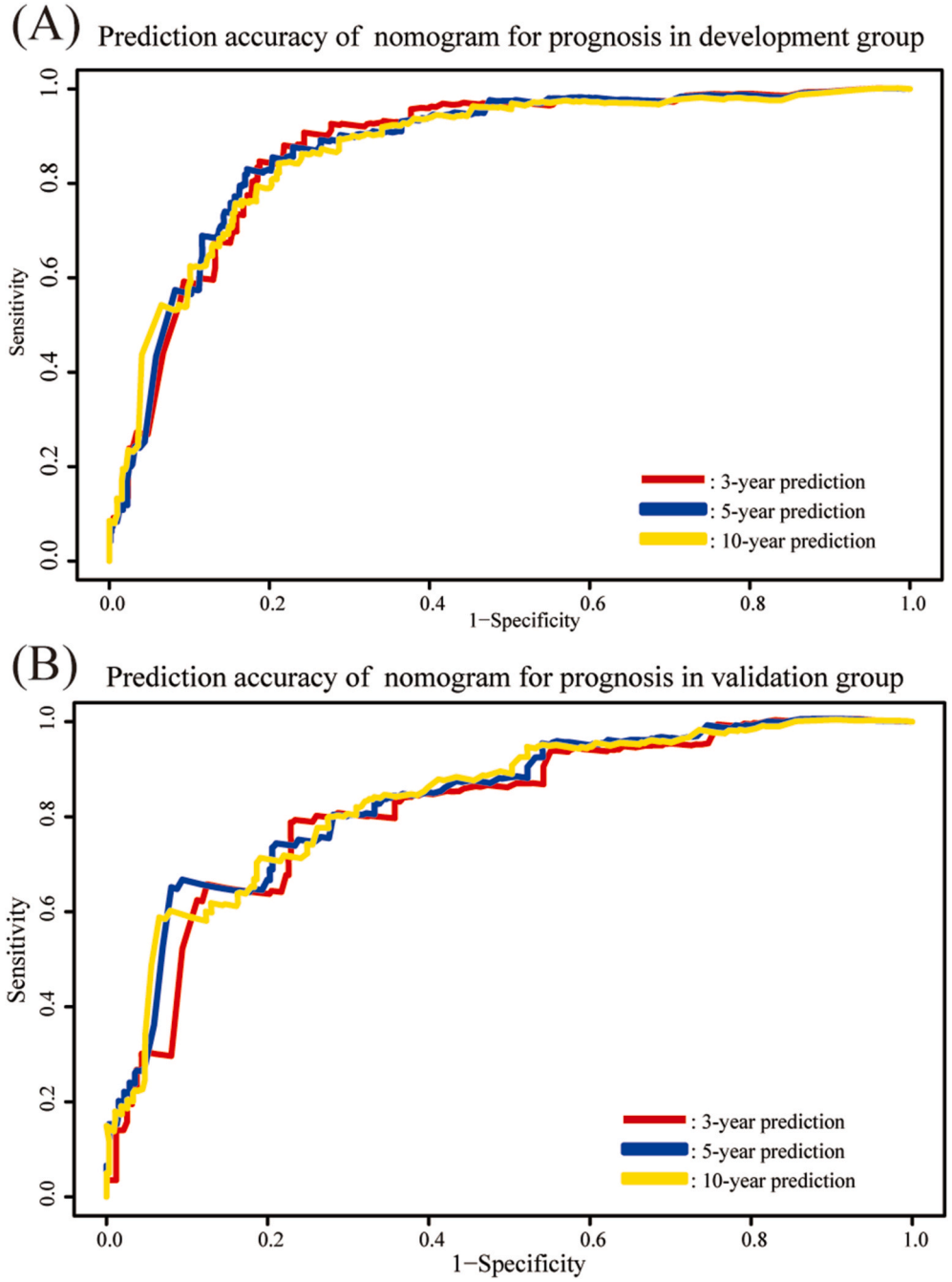

Fig. 4. ROC curves to assess the accuracy of the prognostic nomogram. (A) The AUC values for 3-, 5-, and 10-year survival probabilities in the development group were 0.875, 0.875, and 0.872, respectively; (B) The AUC values for 3-, 5-, and 10-year survival probabilities in the development group were 0.817, 0.836, and 0.835, respectively. AUC, Area Under the Curve.

probability of having a favourable prognosis. Andrew et al. reported that the 5-year survival probability of patients with GNB was approximately 88 % and that the prognosis of children with GNB was better than that of adolescents and adults with GNB [8]. In a survival analysis of 232 GNB patients, Paola Angelini et al. reported that age was an independent prognostic risk factor for GNB [7]. Many studies have revealed that ageing increases the risk of cancer, which is possibly related to the accumulation of gene mutations throughout the life cycle [21,22]. In this study, we found that age is highly important for assessing the prognosis of GNB.

In addition, the primary tumor site was a potential predictor for GNB. In this study, the most common sites of GNB were the adrenal gland (30.5 %), heart mediastinum (13.9 %), retroperitoneum (11.7 %), and soft tissue (38.2 %). According to the analysis of the fields in the SEER database, soft tissues in the primary tumor site included peripheral nerves, autonomic connective tissue, and subcutaneous

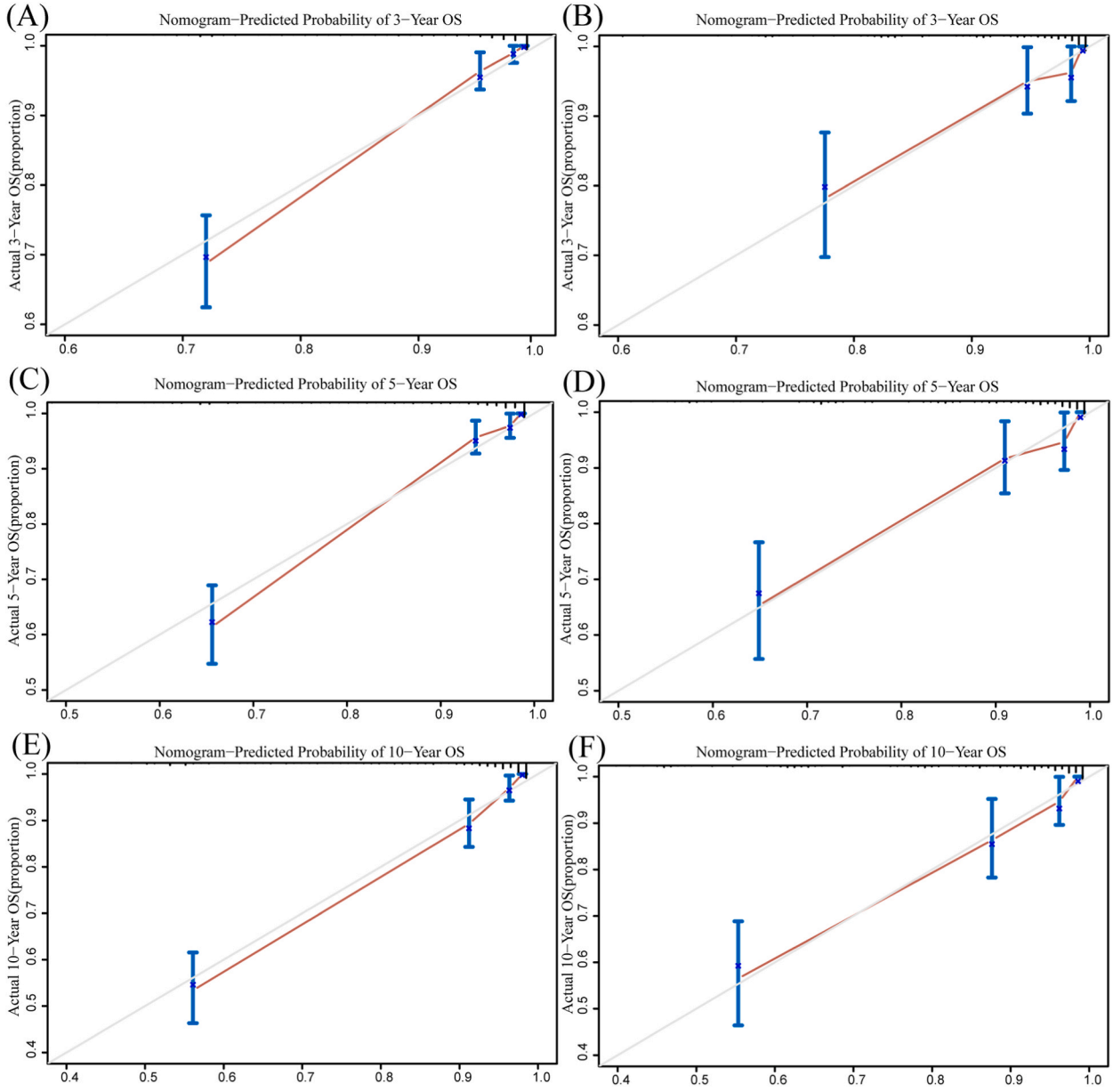

Fig. 5. Calibration curve of the prognostic nomogram for development group and validation group. (A) 3-year calibration curve of the development group; (B) 3-year calibration curve of the validation group; (C) 5-year calibration curve of the development group; (D) 5-year calibration curve of the validation group; (E) 10-year calibration curve of the development group; (F) 10-year calibration curve of the validation group.

nervous system tissues. Therefore, tumors located in soft tissues had multiple sites in this study. A previous study revealed that the adrenal gland (35 %), posterior peritoneum (30 %), and posterior mediastinum (20 %) are the predominant sites for GNB [9]. Thus, the adrenal gland, posterior peritoneum, and mediastinum are possibly common sites of GNB. In addition, our results showed that compared with GNB with the primary site in the soft tissue, the nomogram predicted a higher survival rate for GNB with the primary site in the adrenal gland, heart mediastinum and retroperitoneum. The possible reason for this finding was that the range of surgical resection of the primary GNB in those sites was clear, thus making it easier to achieve complete resection of the tumor.

Our results showed that the SEER stage was an independent risk factor for predicting the prognosis of GNB. The nomogram exhibited a substantially higher score for distant metastasis than for regional infiltration and localized lesions, indicating that GNB patients with distant metastasis suffer from a considerably worse prognosis. Furthermore, the prognostic nomogram revealed that GNB patients with local infiltration had a higher local infiltration score than GNB patients without metastasis, suggesting that GNB patients with local infiltration had a worse prognosis. Previous research conducted by Coldman AJ et al. demonstrated that survival rates were superior in higher for patients with stage I and II neuroblastoma than for patients with stage III and IV [6]. Similarly, Ping Yan et al.

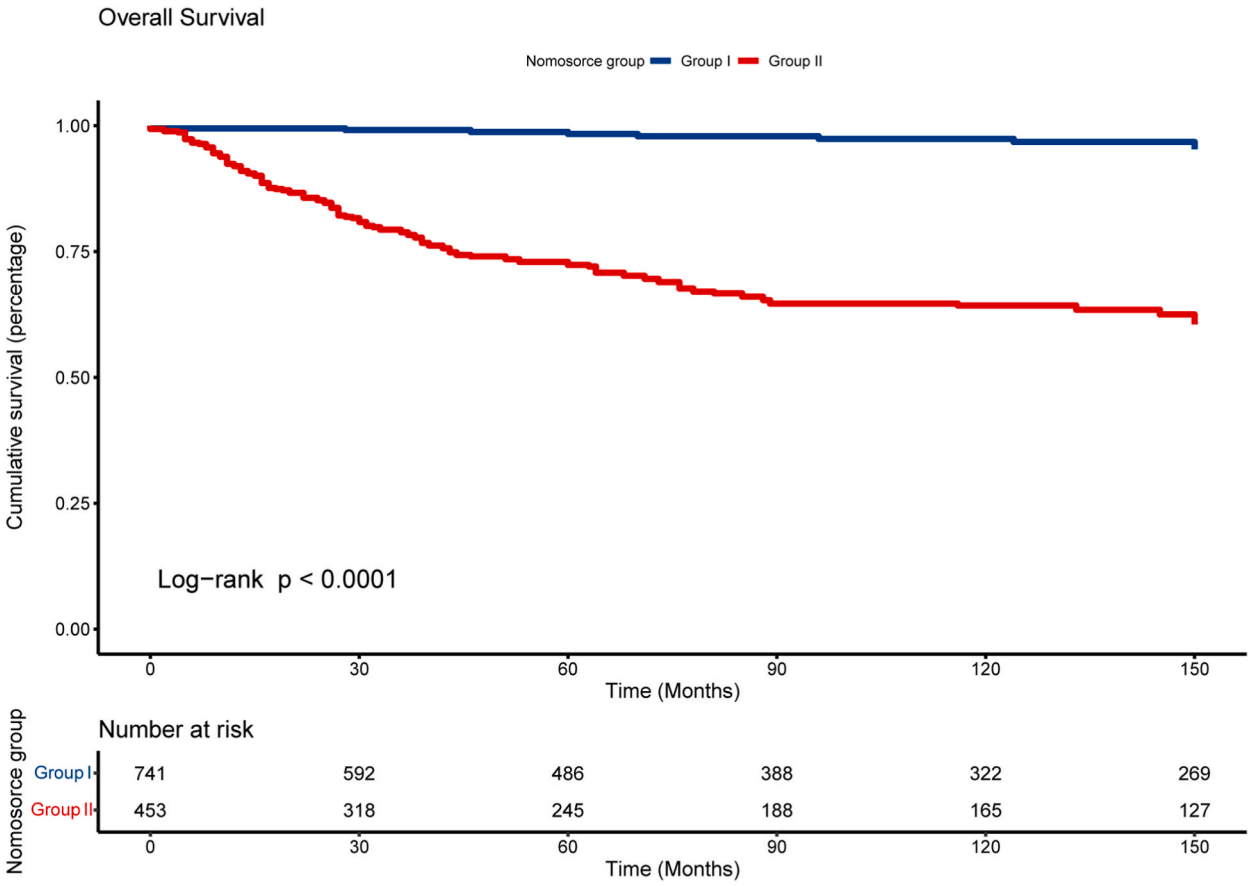

Fig. 6. Survival analysis between two groups based on the nomogram score showed significant statistical difference (P values < 0.001).

showed that among patients with neuroblastoma, the survival rates were highest for patients in the localized lesion group, followed by patients in the local infiltration group and patients in the distant metastasis group [23]. However, their analysis did not differentiate between GNB and neuroblastoma, and thus did not specifically assess GNB.

According to the nomogram of this study, surgery and chemotherapy are independent risk factors for predicting the prognosis of GNB, and surgical treatment alone is conducive to a better prognosis in GNB patients. Surgical treatment is the standard treatment for GNB [24]. Decarolis B et al. suggested that surgical resection was a sufficient treatment for GNB patients. Alexander F suggested that chemotherapy may lead to tumor regression and may be conducive to surgical resection. For tumors that are difficult to completely resect, radical resection after chemotherapy is recommended [25]. In contrast, some studies have shown that GNB survival may not be affected by chemotherapy [26]. Decarolis B et al. reported that 10 % of patients with intermixed GNB received chemotherapy without substantial effects [10]. A similar study reported that chemotherapy was not effective for GNB patients [27]. We found that patients who received chemotherapy had an adverse prognosis compared with those who did not receive or had an unknown chemotherapy status. Similarly, a SEER-based study of adrenal tumors in children reported a worse prognosis for patients in the chemotherapy group [28]. Notably, in the SEER database, patients who did not receive chemotherapy and those with unknown chemotherapy were grouped together, which might lead to bias in the results regarding value of chemotherapy. However, the effect of chemotherapy on the prognosis of GNB remains unclear. Chemotherapy possibly contributes to tumor shrinkage, but it has significant side effects, which may be the cause of poor prognosis. In addition, the worse prognosis in the chemotherapy group is likely the result of unfavourable histology and/or *MYCN* amplification.

We constructed the first effective prognostic nomogram for GNB based on the SEER database. The prognostic nomogram had high accuracy in the development group and the validation group. In addition, ROC curve analysis revealed that the prognostic nomogram model had high accuracy. We regrouped all GNB patients into two groups based on the nomogram score and found that the group with a high nomogram score (above the mean) had a significantly better prognosis than the group with a low nomogram score. Based on the SEER database, the nomogram performed well in the accurately predicting the prognosis of GNB. We hypothesized that age, primary tumor site, SEER stage, surgery and chemotherapy might be risk factors associated with prognosis.

This study has several limitations. First, some risk factors associated with prognosis were not registered in the SEER database, such as histological characteristics (intermixed/nodular), catecholamine levels, genetic characteristics (*MYCN* amplification), and imaging data [29]. Further studies with the above complete data should be conducted to improve the accuracy of the prognostic model.

Furthermore, considering the unique characteristics of these subtypes, further studies are expected to develop specific prognostic models for nodular GNB or intermixed GNB. Second, selection bias was inevitable in this retrospective study, and we lacked randomized controlled trials to confirm our results. In addition, this study lacked samples from patients who received radiotherapy alone, limiting our ability to analyse the independent prognostic effects of radiotherapy on the prognosis of GNB. Future high-quality randomized controlled trials should be conducted to compare the difference in prognosis between patients receiving radiotherapy alone and those receiving chemotherapy alone. Third, we lack external validation data to verify the accuracy of the prognostic nomogram, which may limit its generalizability to other populations. Future studies should aim to validate the prognostic nomogram in external datasets to evaluate its performance in diverse patient populations.

5. Conclusions

Age, primary tumor site, SEER stage, surgery and chemotherapy may be independent prognostic factors for GNB. A prognostic nomogram for GNB was constructed based on the SEER database, which may be a possible tool for providing individualized treatment. However, more risk factors still need to be taken into account in clinical application.

Ethics statement

The data of our study were publicly available. Informed consent of patients was waived. No separate ethical approval was required for this study.

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Data availability statement

The dataset supporting the conclusions of this article is available in the Surveillance, Epidemiology, and End Results (SEER) repository, and hyperlink to dataset in https://seer.cancer.gov/seerstat/, version number 8.4.0. The data included in this study will be made available on request.

CRediT authorship contribution statement

Weiyu Li: Data curation. **Zhaoxing Ou:** Writing – review & editing, Writing – original draft, Formal analysis. **Zhanghai Wu:** Data curation. **Liujun Li:** Writing – original draft. **Feile Ye:** Writing – original draft. **Xin Wen:** Supervision. **Dalin Ye:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30891.

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