Am J Cancer Res 2023;13(6):2254-2268
www.ajcr.us /ISSN:2156-6976/ajcr0150139

Original Article

A novel nomogram for predicting post-recurrence survival in recurrent neuroblastoma patients

Wei-Ming Chen[1*], Yuan-Yuan Fang[1*], Ping Lin[2*], Jian-Xi Bai[1], Yi-Fan Fang[1], Bing Zhang[1]

[1]Department of Oncology Surgery, Fujian Children's Hospital (Fujian Branch of Shanghai Children's Medical Center), College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, Fujian, China; [2]Department of Hematological Oncology, Fujian Children's Hospital (Fujian Branch of Shanghai Children's Medical Center), College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, Fujian, China. [*]Equal contributors.

Received March 14, 2023; Accepted May 31, 2023; Epub June 15, 2023; Published June 30, 2023

Abstract: Patients with recurrent neuroblastoma (NB) have a broad range of prognoses. This research aimed to develop a nomogram to assess post-recurrence survival (PRS) in patients with recurrent neuroblastoma. The TARGET database was utilized to enroll 825 individuals diagnosed with neuroblastoma between 1986 and 2012, 250 of whom were diagnosed with recurrent NB. These patients were randomly divided into a training group (n = 175) and a validation group (n = 75) at a ratio of 7:3. The Kaplan-Meier method was used for survival analysis. A prognosis nomogram was constructed based on post-recurrence survival indicators identified through Cox regression and LASSO analysis. The nomogram's capability for classification and calibration was assessed using the calibration curve, the area under the time-dependent receiver operating characteristic curve (AUC), and the consistency index (C-index). The nomogram was verified in the validation cohort, and its clinical applicabilities were assessed using the decision curve analysis (DCA). Four PRS predictors, COG risk group, INSS stage, MYCN status, and age, were identified to construct the nomogram, which showed good discrimination and calibration in the training and validation sets. The C-index of the training and validation sets was 0.681 [95% confidence interval (CI), 0.632-0.730] and 0.666 [95% CI, 0.593-0.739], respectively. The nomogram's AUC values for the training and validation sets at 1, 3, and 5 years were 0.747, 0.775, and 0.782 vs. 0.721, 0.757, and 0.776. The nomogram's AUC values were consistently higher than those of the COG risk groups and INSS stage, indicating that the nomogram had superior differentiation compared to the INSS stage and COG risk group. The DCA curve also demonstrated that the nomogram we developed outperformed conventional COG risk groups and INSS stage regarding clinical advantage. In the present study, we developed and validated a novel nomogram that should facilitate more accurate and personalized assessment of the survival probability of children with relapsed neuroblastoma. This model should assist physicians in their clinical decision-making process.

Keywords: Neuroblastoma, post-recurrence survival, nomogram, prognostic factors

Introduction

Neuroblastoma (NB) is the most frequently found extracranial solid tumor in children, highly malignant and often progressing rapidly. The primary cause of mortality in children with NB is tumor metastasis, which occurs in approximately 50% of patients at diagnosis [1-3]. The combination of surgical resection, radiotherapy, and biological therapy for pediatric neuroblastoma patients has moderate effects and can improve the survival rate [4, 5]. Unfortunately, nearly 30% of NB patients will relapse following full remission, with only ~20% 5-year survival rate in these recurrent NB patients [6, 7]. Consequently, it is imperative to identify the variables that contribute to post-relapse survival (PRS) of recurring NB patients.

The prognostic factors of PRS in patients with recurrent NB are rarely discussed in the literature. Factors such as age, MYCN status, bone marrow metastases at diagnosis, histology, latency to first relapse, INSS stage, and serum LDH levels have been identified to be associated with PRS in patients with recurrent NB [6-11]. However, previous studies on PRS were based on univariate/multivariate analysis,

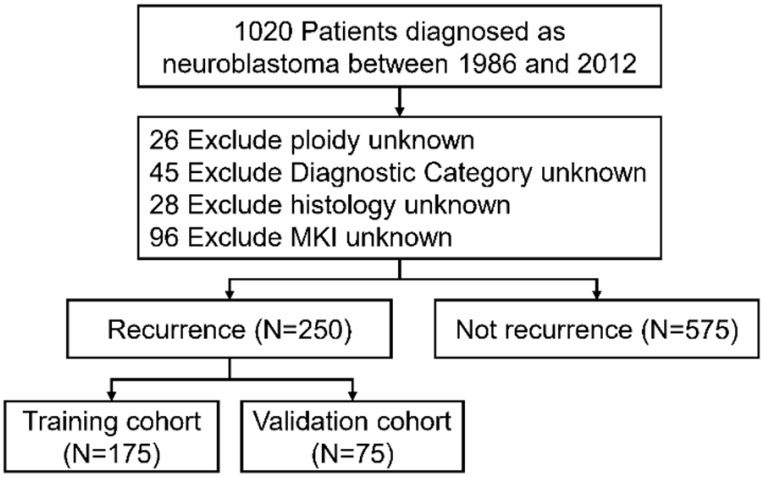

Figure 1. Flowchart of sample selection.

which cannot determine the proportion of these variables that contribute to patient survival. Nomograms are generally regarded as effective models for predicting individual prognosis. They simplify statistical models to anticipated probabilities of clinical results through more intuitive and user-friendly charts [12]. They have proven more advantageous than traditional staging systems in prognostic prediction in various cancers [13-15]. However, there is still not a well-established model that can forecast patients' PRS, even though numerous nomograms have been established to determine event-free survival (EFS) and overall survival (OS) of NB patients. It is therefore necessary to develop a nomogram for identifying PRS in individuals with neuroblastoma in order to treat these patients more effectively.

In this study, a nomogram was developed to assess recurrent neuroblastoma patients' 1-, 3-, and 5-year survival rates based on clinical data from 250 individuals diagnosed from 1986 to 2012 in the TARGET database. We thus developed for the first time a nomogram to predict PRS in 175 patients with recurrent neuroblastoma. We then validated the predictive model in an independent cohort of 75 NB patients. These findings should assist physicians in their clinical decision-making process when treating patients with recurrent NB.

Material and methods

Patient selection and study design

The NCI's Office of Cancer Genomics and Cancer Therapy Evaluation Programs' database, Therapeutically Applicable Research to Generate Effective Treatments (TARGET; https://ocg.cancer.gov/), provided all the information used in this study. Molecular changes control the initiation and progression of childhood cancer, and the TARGET pediatric cancer database employs a multi-omics approach to determine these variations. Clinical information, including MYCN status, INSS stage, COG risk group, age, gender, primary tumor site, DNA ploidy, pathological type, MKI, histology, site of relapse, recurrence-free survival time, survival status, and post-recurrence survival time, was obtained for neuroblastoma patients diagnosed between 1986 and 2012. The best cutoff values found using the X-tile tool (Yale University, CT, USA) were used to group patients based on age (≤10 months and >10 months) and recurrence-free survival time (>12 months, 6-12 months, and ≤6 months) (**Figure 1**).

Inclusion criteria: (1) pathologically confirmed neuroblastoma between 1986 and 2012; (2) complete follow-up information. Exclusion criteria: incomplete clinical information (e.g., MYCN status, primary tumor site, DNA ploidy, pathological type, MKI, histological classification, and survival information) (**Figure 2**). A total of 825 neuroblastoma patients, 250 of whom had recurrent neuroblastoma, were recruited for this investigation according to the aforementioned criteria. A training set (n = 175) and a validation set (n = 75) were randomly selected from the dataset. The endpoint of interest in the present study was post-recurrence survival (PRS). PRS was calculated by comparing the date of recurrence to the date of death or last follow-up appointment. Patient information identification has been removed from the TARGET database. Before receiving treatment, patients had signed informed consent forms, and the information is made publicly available following institutional review board and ethics committee guidelines.

Nomogram construction and validation

By developing a penalty function to compress select coefficients while reducing others to

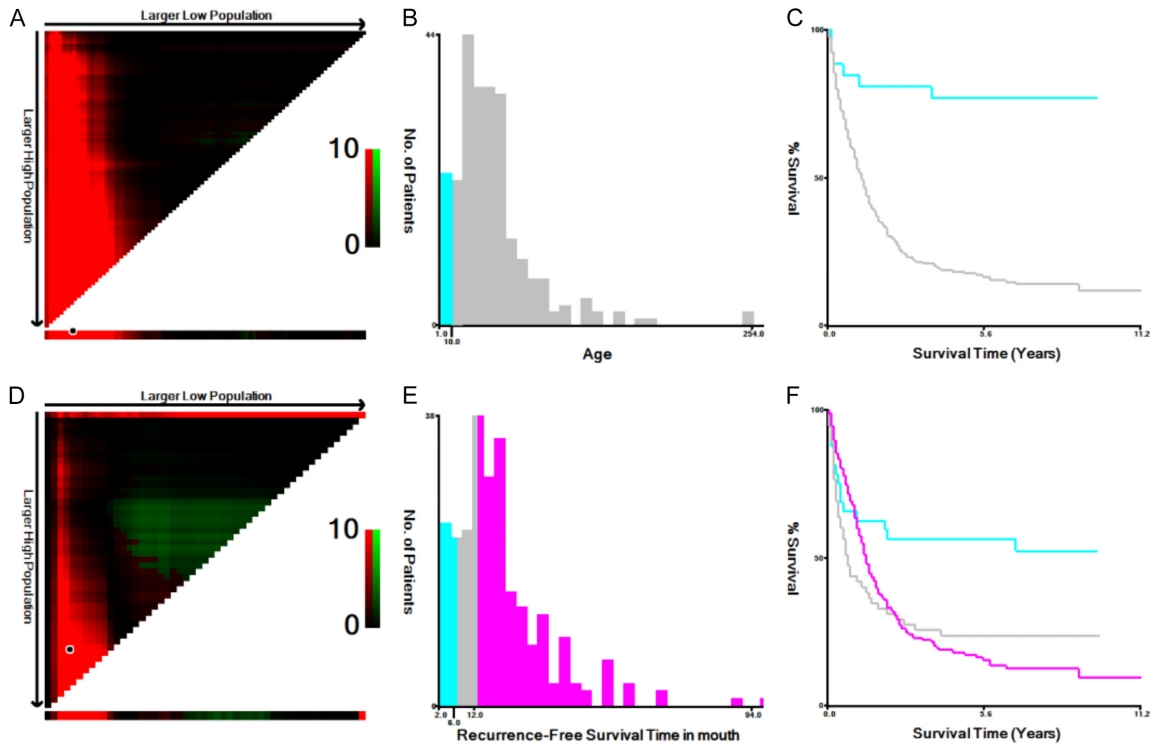

Figure 2. The optimal cutoff values of age and recurrence-free survival time identified by X-tile. A, B. The optimal cutoff value of age. C. The Kaplan-Meier curves for the subgroups of age (≤10 m, >10 m) for PRS. D, E. The cutoff value of recurrence-free survival time. F. The Kaplan-Meier curves for the subgroups of recurrence-free survival time (≤6 m, 6-12 m, >12 m) for PRS.

zero, the least absolute shrinkage and selection operator (LASSO) addresses the drawbacks of the incremental selection procedure of Cox regression. LASSO regression effectively selects variables into the model, which results in better performance parameters and reduces complexity, thereby avoiding overfitting. Using the "glmnet" R package, a LASSO analysis was conducted to evaluate clinicopathological and recurrence features. Variables were then subjected to univariate and multivariate Cox regression analyses to determine the more accurate indicators. Next, a nomogram was developed to anticipate PRS in patients with recurrent NB by integrating these prognostic factors. This study used sub-sample validation, and 1000 bootstrap resamples for internal validation to verify prediction accuracy. C-index, calibration curve, and ROC curve analyses were used to evaluate the calibration and discrimination capacity of the nomogram. The C-index statistic's range of values was 0.5 (no prejudice) to 1 (perfect discrimination) [16]. The total clinical benefit of the nomogram was evaluated using the decision curve analysis (DCA).

Statistical analysis

The R and SPSS (v.26.0; IBM Corporation, NY, USA) software were used for all statistical analyses (v.4.2.0). A statistical significance variation was defined as $P<0.05$. Between the training and validation sets, categorical factors were assessed using the chi-square or Fisher's exact test. Mann-Whitney or T-tests Continuous factors were analyzed utilizing U-tests. Univariable and multivariable logistic regression models were then employed to identify independent predictors of recurrence. Differences in survival between categories were examined using the Kaplan-Meier analysis and log-rank tests.

Results

Baseline features

A total of 825 children with neuroblastoma were included in this study. The median duration of follow-up was 81 months, and overall survival (OS) rates at 1-, 3-, and 5 years were 92.2%, 75.6%, and 68.3%, respectively. Patients with MYCN amplification accounted for

Table 1. Baseline characteristics of patients with or without recurrence and multivariate analysis for associations between risk factors and recurrence

Variables	Whole cohort (N = 825), n (%)	No recurrence (N = 575), n (%)	Recurrence (N = 250), n (%)	p	Multivariate analysis		
					OR	95% CI	p
Gender				0.541			0.298
Male	470 (57.0)	332 (57.7)	138 (55.2)			Reference	
Female	355 (43.0)	243 (42.3)	112 (44.8)		1.185	0.860-1.633	
Age				<0.001			0.336
<18 m	275 (33.3)	231 (40.2)	44 (17.6)			Reference	
≥18 m	550 (66.7)	344 (59.8)	206 (82.4)		0.734	0.391-1.379	
INSS stage				<0.001			<0.001
Stage 1	79 (9.6)	74 (12.9)	5 (2.0)			Reference	
Stage 2	58 (7.0)	41 (7.1)	17 (6.8)		8.129	2.630-25.122	<0.001
Stage 3	86 (10.4)	76 (13.2)	10 (4.0)		4.851	0.813-28.930	0.083
Stage 4	554 (67.2)	341 (59.3)	213 (85.2)		16.135	3.030-85.910	0.001
Stage 4S	48 (5.8)	43 (7.5)	5 (2.0)		2.375	0.629-8.963	0.202
MYCN status				0.009			0.610
Amplified	234 (28.4)	147 (25.6)	87 (34.8)			Reference	
Not Amplified	591 (71.6)	428 (74.4)	163 (65.2)		1.116	0.731-1.704	
Ploidy				<0.001			0.125
Diploid (DI = 1)	296 (35.9)	179 (31.1)	117 (46.8)			Reference	
Hyperdiploid (DI>1)	529 (64.1)	396 (68.9)	133 (53.2)		0.768	0.548-1.076	
Histology				<0.001			0.039
Favorable	252 (30.5)	222 (38.6)	30 (12.0)			Reference	
Unfavorable	573 (69.5)	353 (61.4)	220 (88.0)		2.533	1.047-6.125	
MKI				0.001			0.647
Low	335 (40.6)	257 (44.7)	78 (31.2)			Reference	
Intermediate	250 (30.3)	166 (28.9)	84 (33.6)		1.113	0.739-1.674	0.609
High	240 (29.1)	152 (26.4)	88 (35.2)		0.912	0.565-1.473	0.707
Diagnostic Category				0.465			0.195
Neuroblastoma	736 (89.2)	516 (89.7)	220 (88.0)			Reference	
Ganglioneurobl-astoma	89 (10.8)	59 (10.3)	30 (12.0)		0.713	0.428-1.188	
Primary Site				0.107			0.602
Adrenal gland	347 (42.1)	231 (40.2)	116 (46.4)			Reference	
Other	478 (57.9)	344 (59.8)	134 (53.6)		0.917	0.661-1.271	
COG Risk Group				<0.001			0.014
Low	151 (18.3)	127 (22.1)	24 (9.6)			Reference	
Intermediate	104 (12.6)	96 (16.7)	8 (3.2)		0.128	0.030-0.555	0.006
High	570 (69.1)	352 (61.2)	218 (87.2)		0.359	0.080-1.620	0.183

INSS, International Neuroblastoma Staging System; MYCN, v-myc myelocytomatosis viral related oncogene, neuroblastoma derived; MKI, Mitosis-karyorrhexis index; COG, Children's Oncology Group.

28.4% of the cohort, whose 5-year OS was 54.0%, compared to the 5-year OS of the non-MYCN amplification group at 73.5%. The percentage of patients with recurrent NB was 30.3%, with 1-, 3-, and 5-year OS at 90.4%, 51.5%, and 33.0%. The 1-, 3- and 5-year PRS was 57.7%, 26.6%, and 23.8%, respectively.

Disparities for each parameter between the recurring and non-recurrence groups are shown in **Table 1**. A multivariate logistic regression analysis revealed that COG risk group, pathological type, and INSS stage were independent recurrence-influencing variables. The basic clinicopathological and sociodemographic features of patients with recurrent NB in the training and validation groups are summarized in **Table 2**. The baseline data were not substantially different between the training and validation groups. The KM curve indicated that pediatric NB patients who were ≥18 m of age and showed features such as MYCN amplification, INSS stage 4, COG high-risk group, MKI high expression, diploid, and unfavourable histological types had shorter recurrence-free survival time (**Figure 3**).

Table 2. Demographic characteristics and clinicopathological features of 250 recurrent NB patients

Variables	Whole cohort (N = 250), n (%)	Training cohort (N = 175), n (%)	Validation cohort (N = 75), n (%)	p
Gender				1
Male	138 (55.2)	97 (55.4)	41 (54.7)	
Female	112 (44.8)	78 (44.6)	34 (45.3)	
Age				0.824
≤10 m	26 (10.4)	19 (10.9)	7 (9.3)	
>10 m	224 (89.6)	156 (89.1)	68 (90.7)	
INSS stage				1
Stage 1-2, 4S	27 (10.8)	19 (10.9)	8 (10.7)	
Stage 3-4	223 (89.2)	156 (89.1)	67 (89.3)	
MYCN status				1
Amplified	87 (34.8)	61 (34.9)	26 (34.7)	
Not Amplified	163 (65.2)	114 (65.1)	49 (65.3)	
Ploidy				0.678
Diploid (DI = 1)	117 (46.8)	82 (46.9)	35 (46.7)	
Hyperdiploid (DI>1)	133 (53.2)	93 (53.1)	40 (53.3)	
Histology				0.675
Favorable	30 (12.0)	20 (11.4)	10 (13.3)	
Unfavorable	220 (88.0)	155 (88.6)	65 (86.7)	
MKI				0.925
Low	78 (31.2)	56 (32.0)	22 (29.3)	
Intermediate	84 (33.6)	58 (33.1)	26 (34.7)	
High	88 (35.2)	61 (34.9)	27 (36.0)	
Diagnostic Category				1
Neuroblastoma	220 (88.0)	154 (88.0)	66 (88.0)	
Ganglioneuroblastoma	30 (12.0)	21 (12.0)	9 (12.0)	
Primary Site				0.490
Adrenal gland	116 (46.4)	84 (48.0)	32 (42.7)	
Other	134 (53.6)	91 (52.0)	43 (57.3)	
COG Risk Group				0.68
Low-Intermediate	32 (12.8)	24 (13.7)	8 (10.7)	
High	218 (87.2)	151 (86.3)	67 (89.3)	
RFS Time				0.822
≤6 m	30 (12.0)	20 (11.4)	10 (13.3)	
6-12 m	63 (25.2)	43 (24.6)	20 (26.7)	
>12 m	157 (62.8)	112 (64.0)	45 (60.0)	
Site of Relapse				0.881
Primary Site	76 (30.4)	54 (30.9)	22 (29.3)	
Other	174 (69.6)	121 (69.1)	53 (70.7)	
Status				0.869
Alive	55 (22.0)	38 (21.7)	17 (22.7)	
Dead	195 (78.0)	137 (78.3)	58 (77.3)	
PRS (media (IQR))	15 (40)	16 (40)	12 (28)	0.07

INSS, International Neuroblastoma Staging System; MYCN, v-myc myelocytomatosis viral related oncogene, neuroblastoma derived; MKI, Mitosis-karyorrhexis index; COG, Children's Oncology Group; RFS, recurrence-free survival; PRS, post-recurrence survival; IQR, interquartile range.

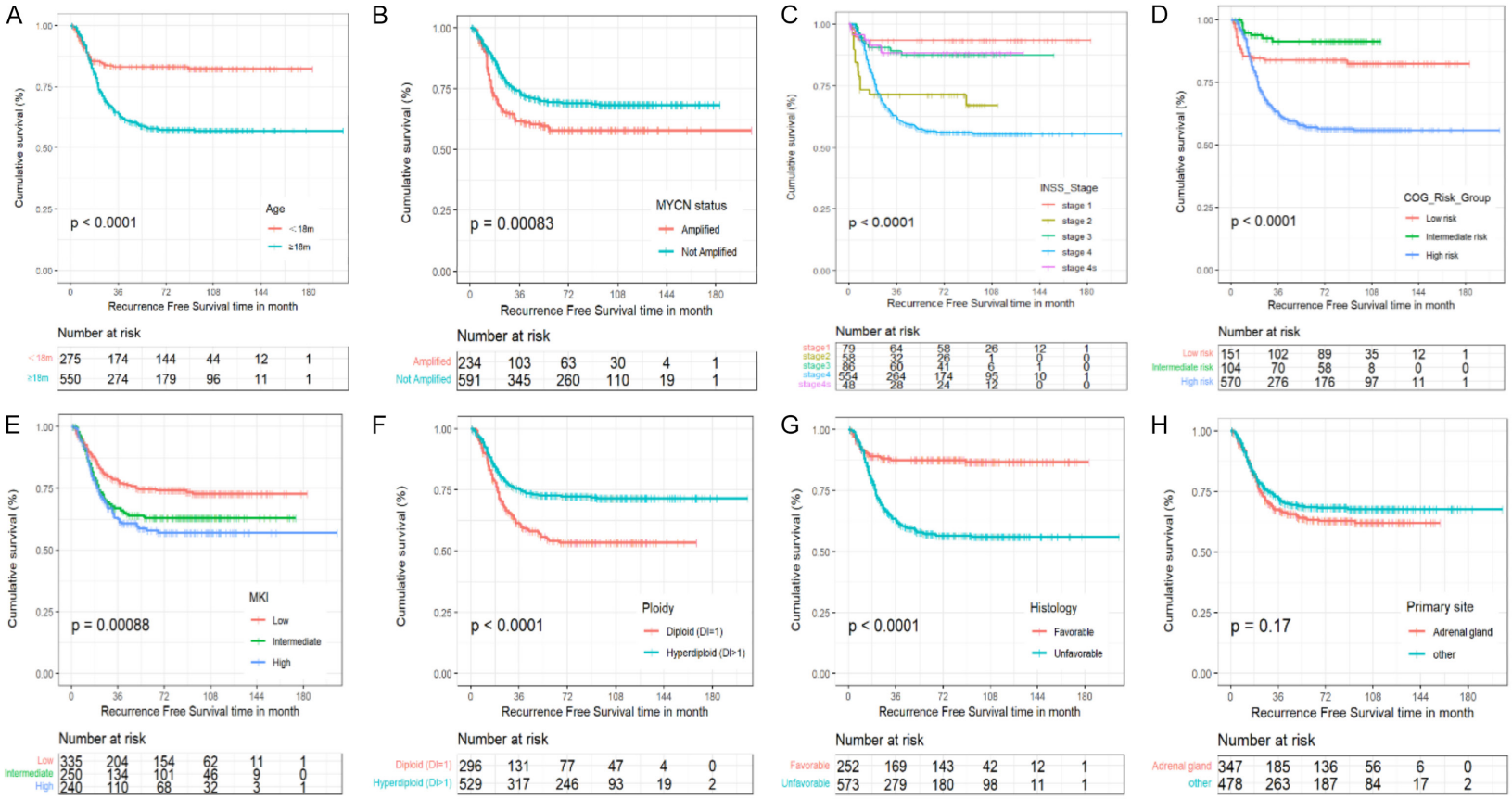

Figure 3. The Kaplan-Meier curves for recurrence-free survival. A. Age. B. MYCN status. C. INSS stage. D. COG risk group. E. MKI. F. Ploidy. G. Histology. H. Primary tumor site.

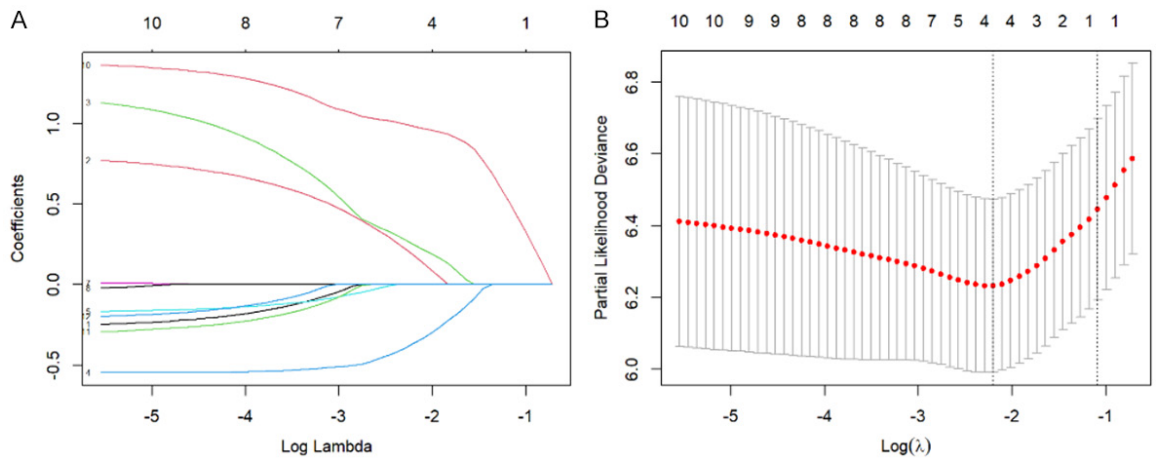

Figure 4. Feature selection using the least absolute shrinkage and selection operator (LASSO) Cox regression model. LASSO coefficient profiles of variables against the log lambda sequence for PRS (A) and tuning parameter (λ) selection in the LASSO model for PRS (B).

Prognostic factors of PRS

By 10-fold cross-validation, the LASSO regression model determined the tuning parameter (lambda, λ) correlating to the threshold level of Partial Likelihood Deviance. In **Figure 4A**, a colored line represents change in the value of the regression coefficient β of a variable. The number below the X-axis is Log (λ), and the number of variables remaining at that value is above the X-axis. **Figure 4B** illustrates the curve of the partial likelihood bias as a function of Log (λ), where a smaller value indicates better model fit. Based on the λ value corresponding to the least partial likelihood deviation of the LASSO Cox regression analysis, four variables with nonzero coefficients were finally selected: COG risk group, INSS stage, MYCN status, and age. In the training group, 175 patients underwent univariate cox regression analysis. The *P* values for these four factors were all <0.001, showing a strong correlation with PRS (**Table 3**). The results of KM analysis showed that prognostic factors associated with PRS in neuroblastoma patients included the following: age, MYCN status, DNA ploidy, MKI, histology, COG risk group, INSS stage, site of relapse, and recurrence-free survival time (**Figure 5**).

Nomogram construction

In order to develop a nomogram for determining 1-, 3-, and 5-year PRS in neuroblastoma cases, the four predictive variables were combined (**Figure 6**). The probability of patient survival after relapse can be easily calculated by totaling the scores conforming to each variable. For example, for a one-year-old patient (69 points), MYCN amplification (58 points), COG high-risk group (0 points), and INSS stage 4 (73 points) resulted in a total score of 43%, 36%, and 26% for the probabilities of 1-, 3-, and 5-year PRS.

Assessment and validation of the nomogram

The C-index was 0.666 [95% CI, 0.593-0.739] for the validation set, and 0.681 [95% CI, 0.632-0.730] for the training set. The nomogram's AUC values at 1, 3, and 5 years were 0.747, 0.775, and 0.782 for the training set, and 0.721, 0.757, and 0.776 for the validation set (**Figure 7A**, **7E**). Additionally, the nomogram's AUC values were all higher than those of the COG risk group and INSS stage, indicating a stronger predicative capacity of the prediction model (**Figure 7B-D**, **7F-H**). The calibration curve can graphically display the nomogram's empirical and real probability values. The X-axis represents the 1-, 3- and 5-year post-recurrence survival probabilities predicted by the nomogram, while the Y-axis represents the actual 1-, 3- and 5-year post-recurrence survival probabilities. This study's calibration curve demonstrated that perfect compatibility of the validation and training sets' actual effects and the nomogram's anticipated results (**Figure 8**). According to the DCA curve, the prediction probability threshold of the nomogram showed higher net benefits in a wide range (**Figure 9A**, **9E**), and the prediction model in this study had higher net benefits than COG grouping and INSS staging (**Figure 9B-D**, **9F-H**).

Table 3. Univariate and multivariate Cox regression analysis for post-recurrence survival in patients with neuroblastoma

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Gender						
Male		Reference				
Female	0.825	0.588-1.158	0.267			
Age						
≤10 m		Reference			Reference	
>10 m	5.813	2.369-14.270	<0.001	1.964	0.714-5.403	0.191
INSS stage						
Stage 1-2, 4S		Reference				
Stage 3-4	12.190	3.852-38.590	<0.001	2.035	0.302-13.688	0.465
MYCN status						
Amplified		Reference			Reference	
Not Amplified	0.418	0.295-0.592	<0.001	0.508	0.325-0.796	0.003
Ploidy						
Diploid (DI = 1)		Reference			Reference	
Hyperdiploid (DI>1)	0.597	0.426-0.836	0.003	0.773	0.545-1.095	0.147
Histology						
Favorable		Reference			Reference	
Unfavorable	9.371	3.447-25.470	<0.001	0.974	0.118-8.050	0.980
MKI						
Low		Reference			Reference	
Intermediate	2.074	1.338-3.216	0.001	1.563	0.979-2.495	0.061
High	2.247	1.461-3.458	<0.001	1.092	0.632-1.888	0.753
Diagnostic Category						
Neuroblastoma		Reference				
Ganglioneuroblastoma	0.958	0.576-1.594	0.869			
Primary Site						
Adrenal gland		Reference				
Other	0.912	0.653-1.276	0.591			
COG Risk Group						
Low-Intermediate		Reference			Reference	
High	9.907	4.025-24.380	<0.001	3.311	0.915-11.987	0.206
RFS Time						
≤6 m		Reference			Reference	
6-12 m	4.692	2.078-10.590	<0.001	1.875	0.781-4.502	0.160
>12 m	3.528	1.629-7.640	0.001	1.017	0.444-2.327	0.969
Site of Relapse						
Primary Site		Reference			Reference	
Other	1.658	1.124-2.444	0.011	0.844	0.553-1.289	0.433

INSS, International Neuroblastoma Staging System; MYCN, v-myc myelocytomatosis viral related oncogene, neuroblastoma derived; MKI, Mitosis-karyorrhexis index; COG, Children's Oncology Group; RFS, recurrence-free survival; PRS, post-recurrence survival.

The PRS prediction tool

To illustrate the nomogram, a simple online program (https://nbnomogram.shinyapps.io/DynNomapp/) was created. A patient's PRS curve and probability can be observed by choosing the appropriate clinical characteristics and follow-up interval (**Figure 10**).

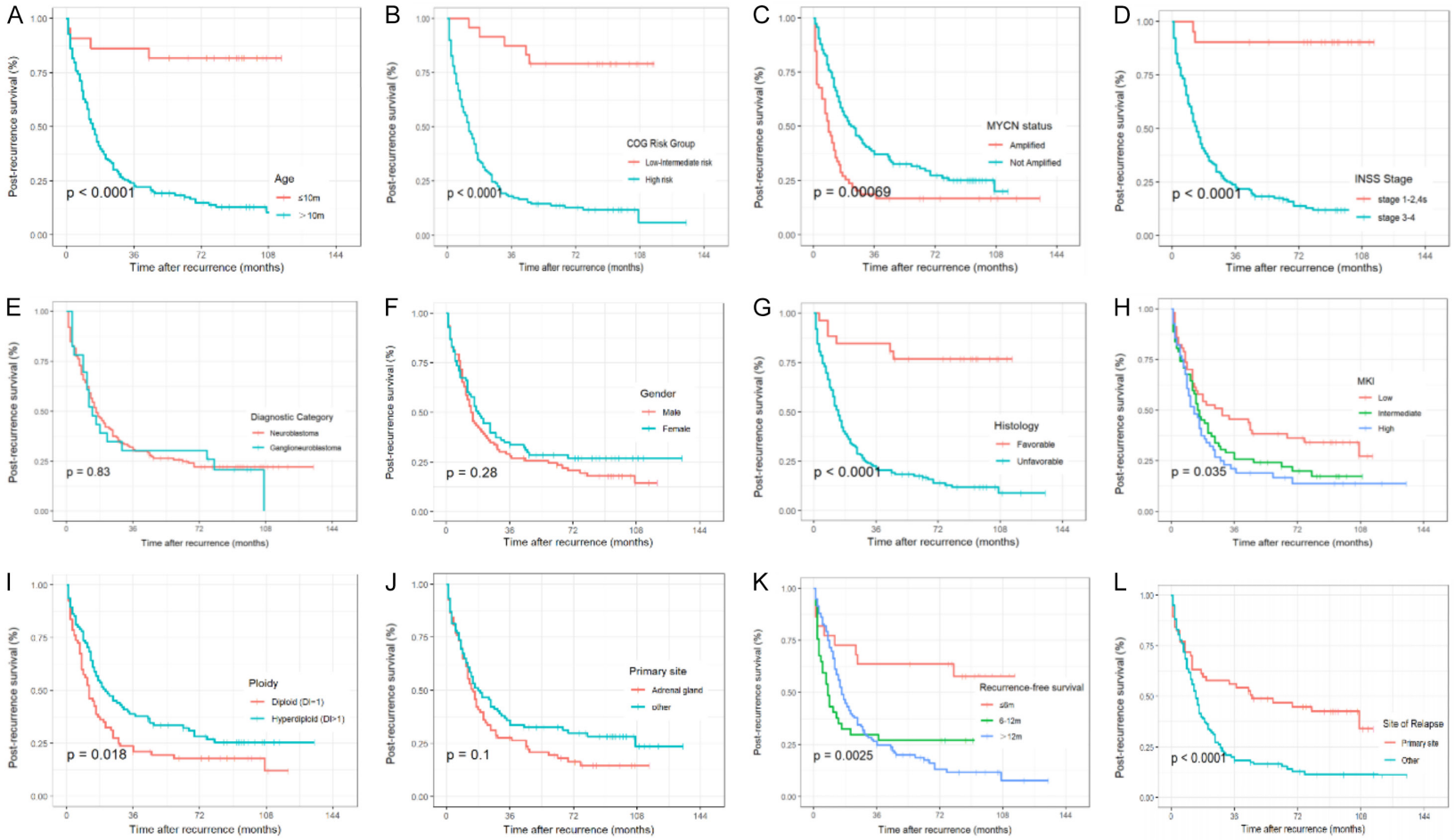

Figure 5. The Kaplan-Meier curves for post-recurrence survival. A. Age. B. COG risk group. C. MYCN status. D. INSS stage. E. Diagnostic category. F. Gender. G. Histology. H. MKI. I. Ploidy. J. Primary tumor site. K. Recurrence free survival time. L. Site of relapse.

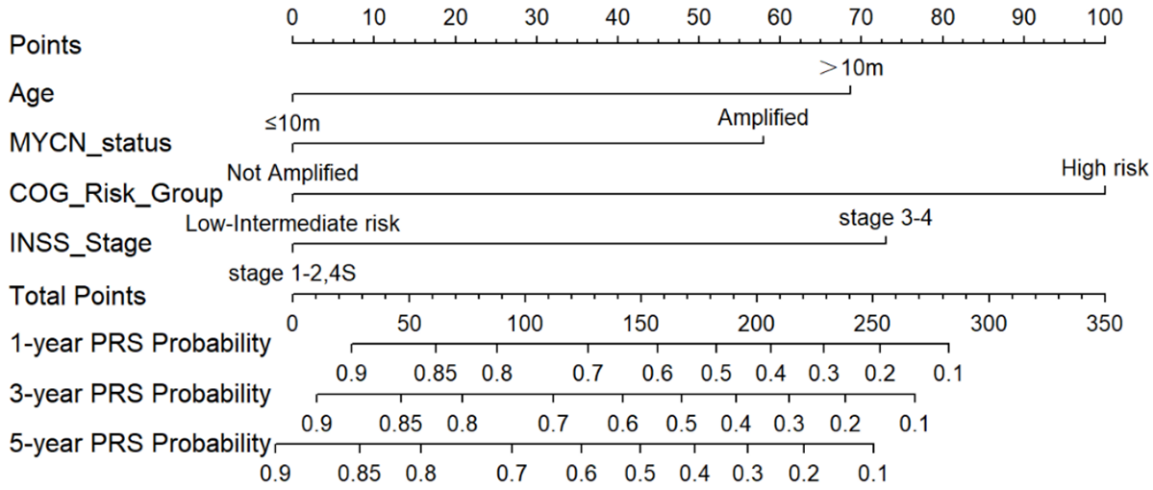

Figure 6. Nomogram for predicting 1-, 3-, and 5-year post-recurrence survival in recurrent NB patients.

Discussion

Patients with neuroblastoma often experience relapse, which can seriously impact cancer prognosis and patient survival [17, 18]. An estimated 30% of NB patients will suffer tumor recurrence, and the 5-year survival rate after relapse is only 20%, according to earlier research [6, 7]. In the present study, we found similar trends where the recurrence rate was 30.3% and the 5-year post-recurrence survival of NB children was only 23.8%. It is therefore imperative to design an efficient predictive model for anticipating PRS in NB patients. Based on our retrospective analysis of the TARGET database, factors such as age at diagnosis (>10 months), MYCN amplification, COG high-risk group, and INSS stage 4 were significant prognostic indicators for poor PRS. We developed a nomogram using these potential risk factors to enable easier and more effective determination of NB patient survival rates following their first recurrence. The possibility of survival will undoubtedly influence the decision to seek further treatment after NB recurrence. Therefore, clinicians can use the nomogram to more accurately calculate the PRS of children with recurrent NB and work with their parents to make the best possible clinical decisions.

Several prognostic factors, including age at diagnosis, MYCN status, INSS stage, and tumor histology, were used for risk stratification of neuroblastoma [19-21]. These factors are also important in determining the response to treatment at relapse [6-11]. Our study also supports the significance of several well-known prognostic factors for PRS, including MYCN status and age at diagnosis. Previous studies have found that NB children identified before 18 months are more likely to experience spontaneous regression or have a good prognosis with simple surgical resection. In contrast, older children are more likely to have early recurrence [22, 23]. However, there are still differences in the relationship between age at diagnosis and PRS in NB patients. In a large INRG study of neuroblastoma patients with first relapse (n = 2,266), London *et al.* demonstrated that NB children younger than 547 days had longer overall survival after recurrence [6]. In contrast, Garaventa *et al.* found 17 months or younger as prognostic indicators of worse OS after the first relapse [18]. In the present study, we used the X-tile program to divide children into ≤10 m and >10 m groups. We found that children ≤10 m had higher PRS, which agrees with the reported outcomes from London *et al*.

Increasing evidence shows that certain genomic variations can be potent prognostic indicators that highly correlate with clinical outcomes [24]. Among these factors, MYCN amplification was proposed earlier as one of the most important factors in the malignant progression and poor prognosis of neuroblastoma [25, 26]. Approximately 20-30% of all NB children harbor MYCN amplification, and only 50% of these children will survive overall [27, 28]. According to a current Children's Oncology Group study, patients with wild-type MYCN had significantly improved EFS and OS values than individuals

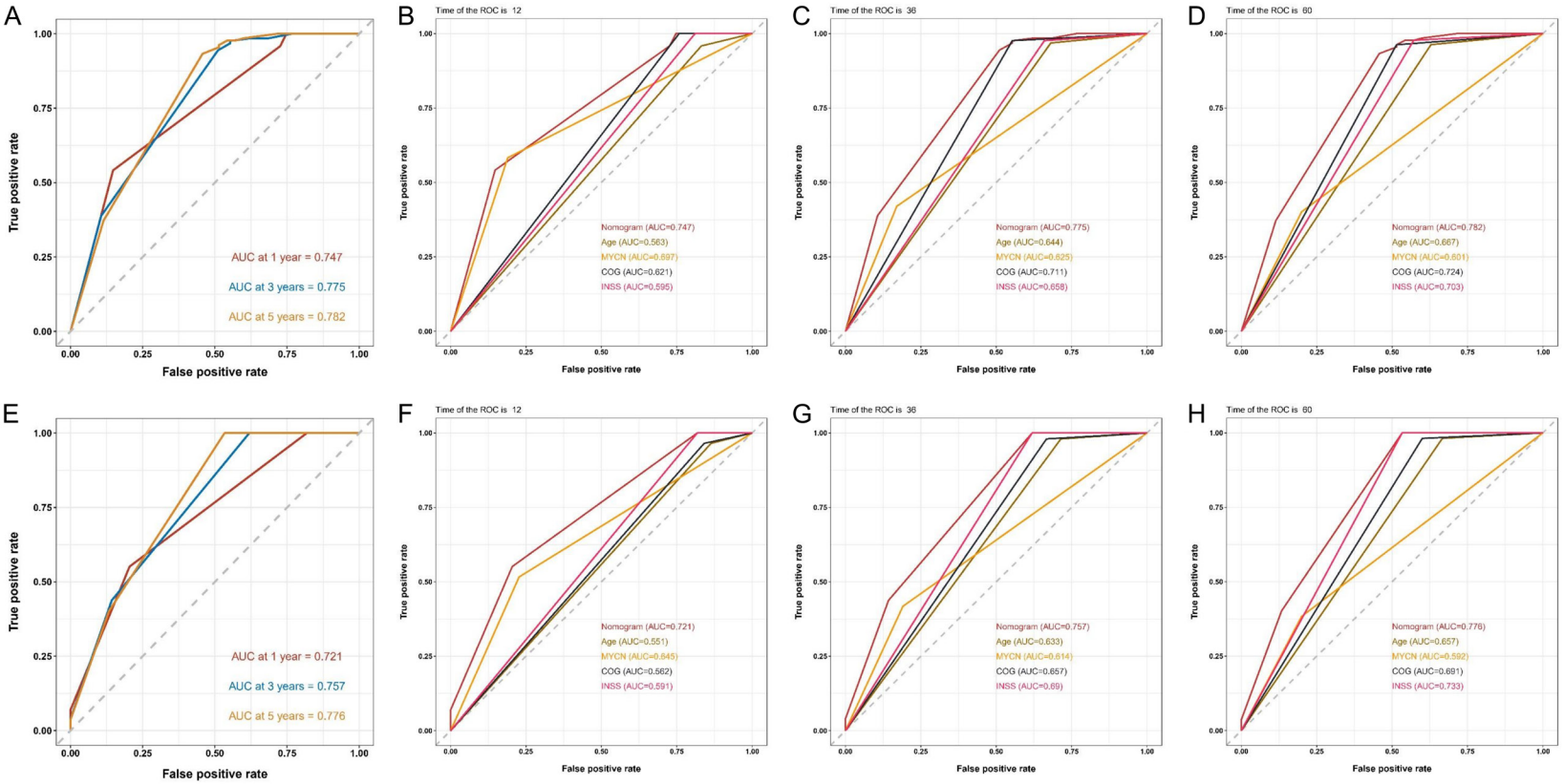

Figure 7. ROC curves of the nomogram for predicting 1- (B, F), 3- (C, G), and 5-year (D, H) post-recurrence survival in the training cohort (A-D) and the validation cohort (E-H).

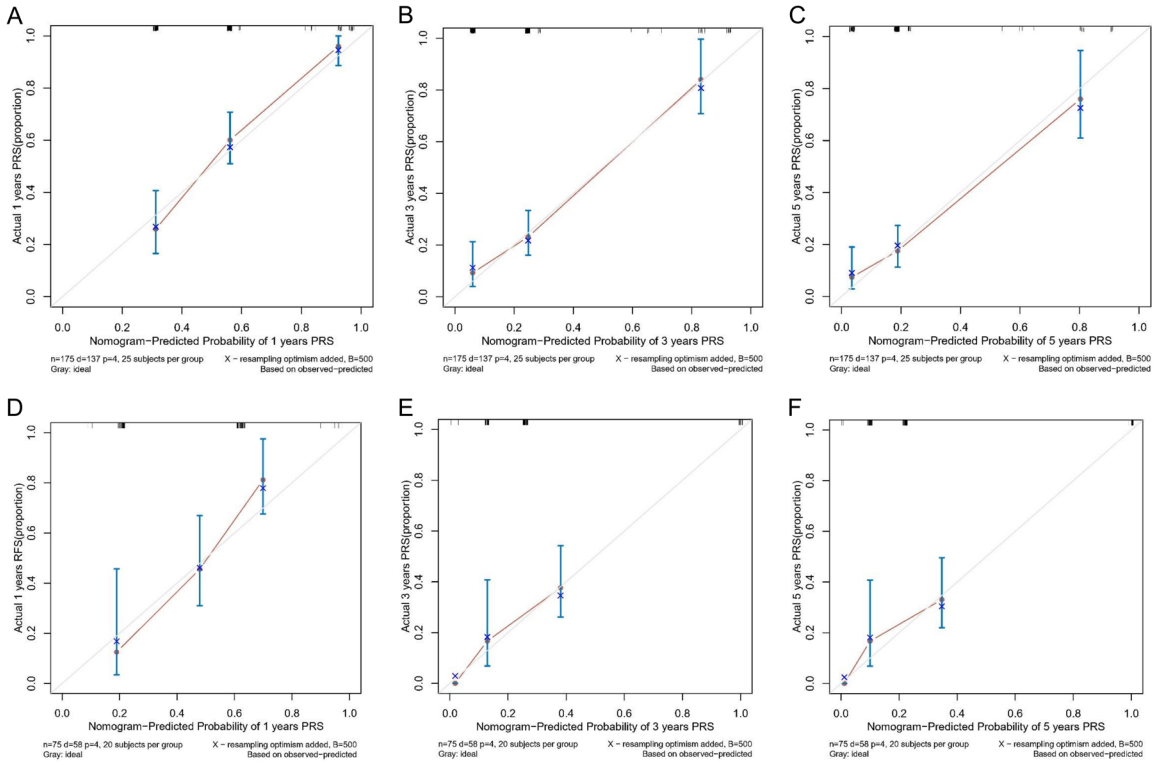

Figure 8. The calibration curves of the prognostic nomogram for predicting 1- (A, D), 3- (B, E), and 5-year (C, F) PRS in the training cohort (A-C) and the validation cohort (D-F).

with MNA [11]. Sun *et al*. discovered that NB children with MYCN amplification recovered at a younger age and that MYCN status was a unique influencing factor for relapse survival [29]. The current analysis found that approximately 28% of children with MYCN amplification had a 5-year overall survival rate of 54%, which is consistent with earlier studies. Furthermore, our findings show that NB children with MYCN amplification had poorer recurrence-free or post-recurrence survival than children without MYCN amplification.

Patients with neuroblastoma frequently use the International Neuroblastoma Staging System, which is also frequently utilized as a predictive marker [30]. This research divides NB patients into stages 1, 2, 4S, and 3-4. In a previous study, no statistically significant difference in survival was found among children with stages 1, 2, and 4S NB [23]. Consistent with previous studies, the prognosis of children with INSS stages 3-4 is significantly worse than that of children with INSS stages 1, 2, and 4S [31]. In addition, the INSS stage was also the most important independent prognostic factor for OS after relapse. The risk of post-relapse death in INSS stages 4 and 3 was 6.9 and 4.3 times higher respectively than in INSS stages 1-2 [6]. In 1998, the Children's Oncology Group developed the New Brunswick risk stratification system. Clinical and biological data obtained from the tumor served as the basis for this stratification. The survival rate of individuals with neuroblastoma has significantly increased due to the introduction of risk stratification systems [32]. We designed a nomogram to determine PRS in NB individuals using the four factors, COG risk group, INSS stage, MYCN status, and age. The nomogram exhibited good consistency with the actual PRS. In addition, the AUC of the nomogram was higher than that predicted by the COG risk group and INSS stage. DCA analysis also indicated higher clinical benefits of the nomogram, suggesting that our nomogram can more accurately and specifically predict PRS in NB patients based on the INSS stage and COG risk group.

However, several limitations of this study need to be noted. First, the sample size is still relatively small. We hope to enroll more patients

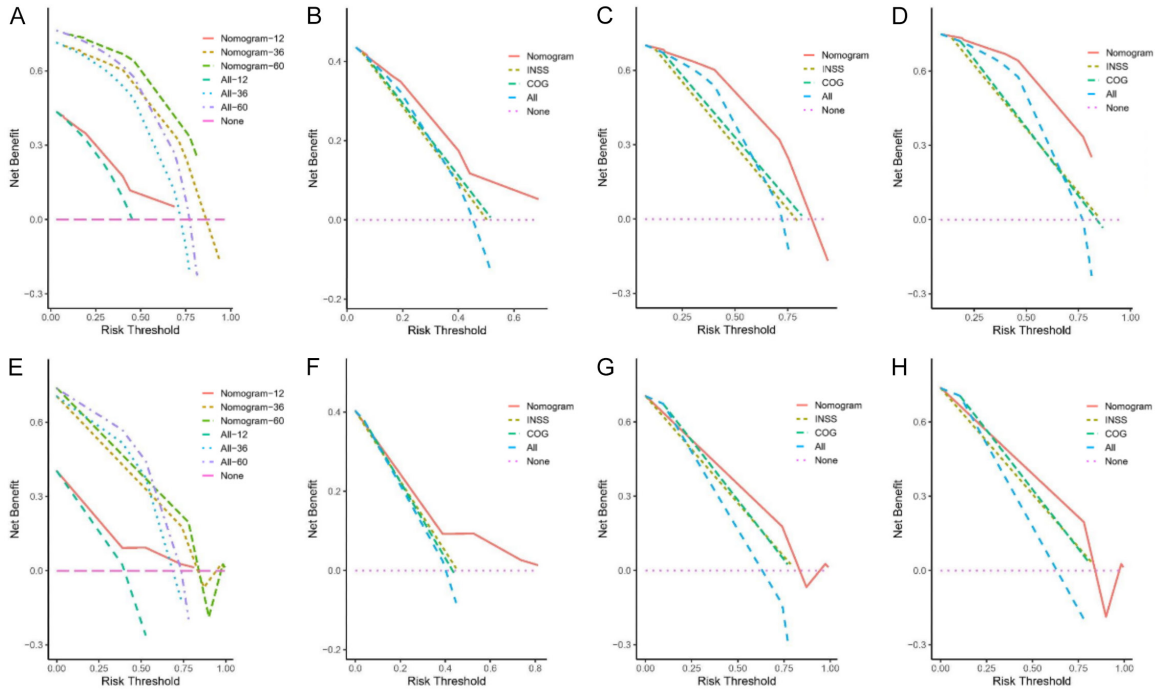

Figure 9. The decision curve analysis of the nomogram for predicting 1- (B, F), 3- (C, G), and 5-year (D, H) post-recurrence survival in the training cohort (A-D) and the validation cohort (E-H).

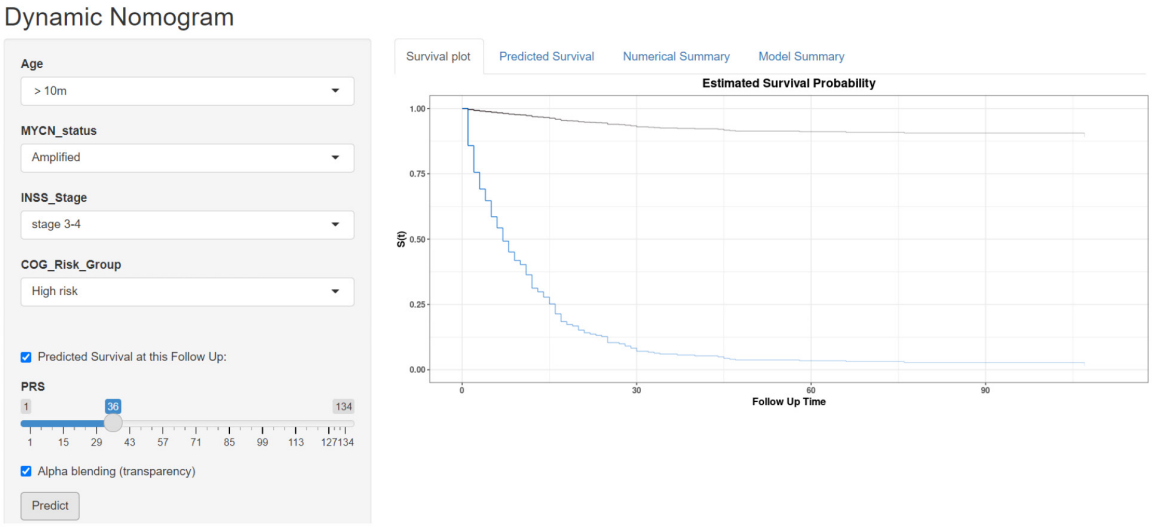

Figure 10. The interface of the web-based nomogram, and survival plot of the PRS probability.

and validate our model in future studies. In addition, both the validation and training cohorts were derived from the TARGET database and therefore include cases from years ago. Although our predictive model validation showed good fitness, a more independent and up-to-date cohort would be ideal for further validation of our nomogram.

In conclusion, we designed and verified a customized model for predicting the post-recurrence survival of pediatric neuroblastoma patients. Clinicians can utilize the nomogram developed in the present study to help determine the post-recurrence survival of children with recurrent NB. This simple and effective nomogram promises to become an essential

instrument that will assist clinicians in their decision-making process.

Acknowledgements

This study was supported by the Health Science and Technology Project of Fujian Province (2020CXA018), the Startup Fund for scientific research, Fujian Medical University (2021QH-1168), and the Natural Science Foundation of Fujian Province, China (2022J01437).

Disclosure of conflict of interest

None.

Address correspondence to: Bing Zhang and Yi-Fan Fang, Department of Oncology Surgery, Fujian Children's Hospital (Fujian Branch of Shanghai Children's Medical Center), College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, 966 Hengyu Road, Fuzhou 350011, Fujian, China. Tel: +86-13375069970; E-mail: fjsetyyxewk@163.com (BZ); Fyf0599@163.com (YFF)

References

[1] Maris JM, Hogarty MD, Bagatell R and Cohn SL. Neuroblastoma. Lancet 2007; 369: 2106-2120.

[2] Maris JM. Recent advances in neuroblastoma. N Engl J Med 2010; 362: 2202-2211.

[3] Ponzoni M, Bachetti T, Corrias MV, Brignole C, Pastorino F, Calarco E, Bensa V, Giusto E, Ceccherini I and Perri P. Recent advances in the developmental origin of neuroblastoma: an overview. J Exp Clin Cancer Res 2022; 41: 92.

[4] Qiu B and Matthay KK. Advancing therapy for neuroblastoma. Nat Rev Clin Oncol 2022; 19: 515-533.

[5] DuBois SG and Bagatell R. Improving outcomes in children with high-risk neuroblastoma: the role of randomized trials. J Clin Oncol 2021; 39: 2525-2527.

[6] London WB, Castel V, Monclair T, Ambros PF, Pearson AD, Cohn SL, Berthold F, Nakagawara A, Ladenstein RL, Iehara T and Matthay KK. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group project. J Clin Oncol 2011; 29: 3286-3292.

[7] Youlden DR, Jones BC, Cundy TP, Karpelowsky J, Aitken JF and McBride CA. Incidence and outcomes of neuroblastoma in Australian children: a population-based study (1983-2015). J Paediatr Child Health 2020; 56: 1046-1052.

[8] Basta NO, Halliday GC, Makin G, Birch J, Feltbower R, Bown N, Elliott M, Moreno L, Barone G, Pearson AD, James PW, Tweddle DA and McNally RJ. Factors associated with recurrence and survival length following relapse in patients with neuroblastoma. Br J Cancer 2016; 115: 1048-1057.

[9] Li F, Zhang W, Hu H, Zhang Y, Li J and Huang D. Factors of recurrence after complete response in children with neuroblastoma: a 16-year retrospective study of 179 cases. Cancer Manag Res 2022; 14: 107-122.

[10] Berlanga P, Pasqualini C, Potschger U, Sanguesa C, Castellani MR, Canete A, Luksch R, Elliot M, Schreier G, Kropf M, Morgenstern D, Papadakis V, Ash S, Ruud E, Brock P, Wieczorek A, Kogner P, Trahair T, Ambros P, Boterberg T, Castel V, Valteau-Couanet D and Ladenstein R. Central nervous system relapse in high-risk stage 4 neuroblastoma: the HR-NBL1/SIOPEN trial experience. Eur J Cancer 2021; 144: 1-8.

[11] Campbell K, Kao P, Naranjo A, Kamijo T, Ramanujachar R, London W and DuBois S. Clinical and biological features prognostic of survival after relapse of INRGSS-stage MS pattern neuroblastoma: a report from the International Neuroblastoma Risk Group (INRG) project. J Clin Oncol 2022; 40: 10044.

[12] Iasonos A, Schrag D, Raj GV and Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008; 26: 1364-1370.

[13] Wang R, Dai W, Gong J, Huang M, Hu T, Li H, Lin K, Tan C, Hu H, Tong T and Cai G. Development of a novel combined nomogram model integrating deep learning-pathomics, radiomics and immunoscore to predict postoperative outcome of colorectal cancer lung metastasis patients. J Hematol Oncol 2022; 15: 11.

[14] Huang X, Luo Z, Liang W, Xie G, Lang X, Gou J, Liu C, Xu X and Fu D. Survival nomogram for young breast cancer patients based on the SEER database and an external validation cohort. Ann Surg Oncol 2022; 29: 5772-5781.

[15] Tao Q, Zeng Q, Liu W, Liu J, Jiang L, Tu X, Li K, Zhao P, Tang X, Liu Z, Wang L, Xu Q and Zheng Y. A novel prognostic nomogram for hepatocellular carcinoma after thermal ablation. Am J Cancer Res 2021; 11: 5126-5140.

[16] Bianco FJ Jr. Nomograms and medicine. Eur Urol 2006; 50: 884-886.

[17] Lau L, Tai D, Weitzman S, Grant R, Baruchel S and Malkin D. Factors influencing survival in children with recurrent neuroblastoma. J Pediatr Hematol Oncol 2004; 26: 227-232.

[18] Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, Casale F, Viscardi E, Bianchi M, D'Angelo P, Zanazzo GA, Luksch R,

Favre C, Tamburini A and Haupt R. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer 2009; 45: 2835-2842.

[19] London WB, Boni L, Simon T, Berthold F, Twist C, Schmidt ML, Castleberry RP, Matthay KK, Cohn SL and De Bernardi B. The role of age in neuroblastoma risk stratification: the German, Italian, and Children's Oncology Group perspectives. Cancer Lett 2005; 228: 257-266.

[20] Campbell K, Shyr D, Bagatell R, Fischer M, Nakagawara A, Nieto AC, Brodeur GM, Matthay KK, London WB and DuBois SG. Comprehensive evaluation of context dependence of the prognostic impact of MYCN amplification in neuroblastoma: a report from the International Neuroblastoma Risk Group (INRG) project. Pediatr Blood Cancer 2019; 66: e27819.

[21] Campbell K, Naranjo A, Hibbitts E, Gastier-Foster JM, Bagatell R, Irwin MS, Shimada H, Hogarty M, Park JR and DuBois SG. Association of heterogeneous MYCN amplification with clinical features, biological characteristics and outcomes in neuroblastoma: a report from the Children's Oncology Group. Eur J Cancer 2020; 133: 112-119.

[22] Irwin M, Naranjo A, Cohn S, London W, Gastier-Foster J, Maris J, Bagatell R, Park J and Hogarty M. A revised Children's Oncology Group (COG) neuroblastoma risk classification system: report from the COG biology study ANBL00B1. J Clin Oncol 2019; 37: 10012.

[23] Sokol E, Desai AV, Applebaum MA, Valteau-Couanet D, Park JR, Pearson ADJ, Schleiermacher G, Irwin MS, Hogarty M, Naranjo A, Volchenboum S, Cohn SL and London WB. Age, diagnostic category, tumor grade, and mitosis-karyorrhexis index are independently prognostic in neuroblastoma: an INRG project. J Clin Oncol 2020; 38: 1906-1918.

[24] Fetahu IS and Taschner-Mandl S. Neuroblastoma and the epigenome. Cancer Metastasis Rev 2021; 40: 173-189.

[25] Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY and Hammond D. Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Engl J Med 1985; 313: 1111-1116.

[26] Bartolucci D, Montemurro L, Raieli S, Lampis S, Pession A, Hrelia P and Tonelli R. MYCN impact on high-risk neuroblastoma: from diagnosis and prognosis to targeted treatment. Cancers (Basel) 2022; 14: 4421.

[27] Huang M and Weiss WA. Neuroblastoma and MYCN. Cold Spring Harb Perspect Med 2013; 3: a014415.

[28] Schneiderman J, London WB, Brodeur GM, Castleberry RP, Look AT and Cohn SL. Clinical significance of MYCN amplification and ploidy in favorable-stage neuroblastoma: a report from the Children's Oncology Group. J Clin Oncol 2008; 26: 913-918.

[29] Sun Q, Chen Y, Jin Q and Yuan X. A nomogram for predicting recurrence-free survival of intermediate and high-risk neuroblastoma. Eur J Pediatr 2022; 181: 4135-4147.

[30] Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, Stram DO, Gerbing RB, Lukens JN, Matthay KK and Castleberry RP. The international neuroblastoma pathology classification (the Shimada system). Cancer 1999; 86: 364-372.

[31] Cangelosi D, Brignole C, Bensa V, Tamma R, Malaguti F, Carlini B, Giusto E, Calarco E, Perri P, Ribatti D, Fonseca NA, Moreira JN, Eva A, Amoroso L, Conte M, Garaventa A, Sementa AR, Corrias MV, Ponzoni M and Pastorino F. Nucleolin expression has prognostic value in neuroblastoma patients. EBioMedicine 2022; 85: 104300.

[32] Irwin MS, Naranjo A, Zhang FF, Cohn SL, London WB, Gastier-Foster JM, Ramirez NC, Pfau R, Reshmi S, Wagner E, Nuchtern J, Asgharzadeh S, Shimada H, Maris JM, Bagatell R, Park JR and Hogarty MD. Revised neuroblastoma risk classification system: a report from the Children's Oncology Group. J Clin Oncol 2021; 39: 3229-3241.