

Development and validation of a nomogram to predict the overall survival of patients with neuroblastoma

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Abstract

Neuroblastoma is the most prevalent malignancy in infants characterized by heterogeneous prognosis. It is critical to stratify the risks for patients with neuroblastoma. To stratify the risks for neuroblastoma, clinical characteristics of neuroblastoma patients were retrieved from the Therapeutically Applicable Research to Generate Effective Treatment program. All patients were randomly sampled into the development and validation sets. Cox regression was used to construct a prediction nomogram. The discrimination and calibration capacity of the nomogram was assessed. Prognostic index (PI) was calculated and tested to evaluate the performance of the nomogram. This nomogram demonstrated reasonable discrimination and calibration capacity. The nomogram derived PI exhibited acceptable accuracy in predicting the prognosis for neuroblastoma patients. The overall survival rate was significantly different between the PI discriminated high and low-risk patient subgroups. In conclusion, besides traditional staging systems, some newly defined risk factors could be involved in risk stratification for patients with neuroblastoma. Our nomogram may aid the risk stratification for neuroblastoma patients.

Abbreviations: AUC = area under the curve, COG = Children's Oncology Group, DCA = decision curve analysis, INRGSS = the International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, MKI = mitosis-karyorrhexis index, OS = overall survival, PI = prognostic index, ROC = receiver operating curve, TARGET = the Therapeutically Applicable Research to Generate Effective Treatment.

Keywords: neuroblastoma, nomogram, overall survival, prognosis, risk stratification

1. Introduction

Neuroblastoma is an embryonic cancer arising from the neural crest stem cells. It is the most prevalent malignancy in infants and extracranial solid tumor in children, which accounts for 6% to 10% of all childhood tumors and 12% to 15% of all childhood cancer-related deaths.^[1] Half cases with neuroblastoma were diagnosed within 17 to 18 months after birth, and only 5% were older than 10 years.^[2,3] Neuroblastoma is characterized by widely clinical heterogeneity ranging from spontaneous regression to treatment-refractory progression despite intensive therapy.

Several staging systems have been developed for risk stratification for neuroblastoma. The International Neuroblastoma Staging

System (INSS) was released in 1988,^[4] which was intended for postsurgical staging. In 2009, a new staging system, the International Neuroblastoma Risk Group Staging System (INRGSS) was developed to stratify the risks of neuroblastoma before surgical intervention.^[5] These systems are now used in parallel. Shortcomings have been proposed for these staging systems. For example, in INSS, the same tumor could either be staged as grade 1 or 3 depending on the extent of surgical excision, making a direct comparison of clinical trials based on INSS difficult.^[5,6] For INRGSS, the risks of the disease were based on the image defined risk factors at diagnosis.^[5] However, other risk factors, such as age, pathological gene expression configurations, which could greatly influence the treatment response, could not be analyzed.^[7] Furthermore, a total of four stages were proposed in INRGSS, and the result was obscure for a specified individual with distinct imaging and pathological characteristics.

The Therapeutically Applicable Research to Generate Effective Treatment (TARGET) program applies a comprehensive genomic approach to determine molecular changes that drive childhood cancers. Now, the TARGET database (<https://ocg.cancer.gov/>) is open to researchers. In this manuscript, we used the clinical data for neuroblastoma to develop a nomogram for predicting the 3 or 5 years of overall survival (OS) probabilities for patients with neuroblastoma. The performance of the nomogram was validated in a separate set.

2. Materials and methods

2.1. Data acquisition and preparation

The clinical data was downloaded from the website of the TARGET database (<https://ocg.cancer.gov/>). Two excel format files containing the clinical characteristics of the patients with neuroblastoma were downloaded and merged into one single file.

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Records with absent variables were excluded for further analysis. The data was derived from an open-access database, and no consent form was needed. This study was approved by the ethics committee of Qilu hospital (QLYY-2019-0228).

2.2. Development of the nomogram

These records were randomly separated into the development and validation set (7:3). The development set was applied to construct the nomogram. Survival package in R software (version 3.3.5, Vienna, Austria; www.r-project.org) was used to develop the survival regression model, and rms package was used to construct the nomogram with the results from survival analysis. Variates with points of less than 10 were omitted to simplify the nomogram, and the final nomogram was developed based on a repeated Cox regression with the rest variates.

2.3. Validation of the nomogram

The nomogram was validated with the validation set. C-index was calculated to demonstrate the discrimination capacity of the nomogram. The calibration plot was used to demonstrate the consistency of the nomogram. Decision curve analysis (DCA) was used to evaluate the net benefit of the nomogram. Prognostic index (PI) was calculated for each patient with the nomogram. The receiver operating characteristic curve (ROC) was built and area under the curve (AUC) was calculated to evaluate the application of the nomogram calculated PI in predicting the 3 and 5-year survival probabilities. The optimal cut off values of PI in these ROCs were calculated according to the Youden index to stratify the patients into high or low-risk subgroups. The 3 and 5-year survival curves were built and compared between the PI discriminated low and high-risk subgroups in both the development and validation sets.

2.4. Statistical analysis

Figures plotting and statistical analysis were conducted with the R software (version 3.3.5, Vienna, Austria; www.r-project.org). Survival curves comparison between the nomogram predicted low and high-risk groups were conducted with log-rank test with a *P* value less than .05 as significant different. The main packages used in this manuscript include rms, foreign, caret, Survival, and survivalROC.

3. Results

3.1. Data characteristics

A total of 1119 records were downloaded from the TARGET database. After deleting the records with absent variables, 737 records were reserved. The candidate variates for constructing the initial nomogram include Survival time, Vital status, Gender, Race, Ethnicity, Age, INSS stage, MYCN status, Ploidy value, Histology, Grade, Mitosis-karyorrhexis index (MKI), Diagnostic Category, and Children’s Oncology Group (COG) Risk Group. There are 312 girls and 425 boys in this cohort. The median survival time of this cohort is 53.53 months (interquartile range: 31.87–77.77 months). 330 patients were diagnosed when they were less than 2 years old, and the rest 407 were older than 2. As to MYCN status, 220 cases were amplified and the rest 517 were not amplified.

3.2. Constitution of the nomogram

Initially, Gender, Race, Ethnicity, Age, INSS stage, MYCN status, Ploidy value, Histology, Grade, MKI, Diagnostic Category, and COG Risk Group were enrolled in Cox regression and to establish the full variable nomogram. Then variables with a point of less than 10 were excluded to simplify the nomogram and to yield the final nomogram. The excluded variates were Ethnicity, Age, MYCN status MKI and Diagnostic category. The final

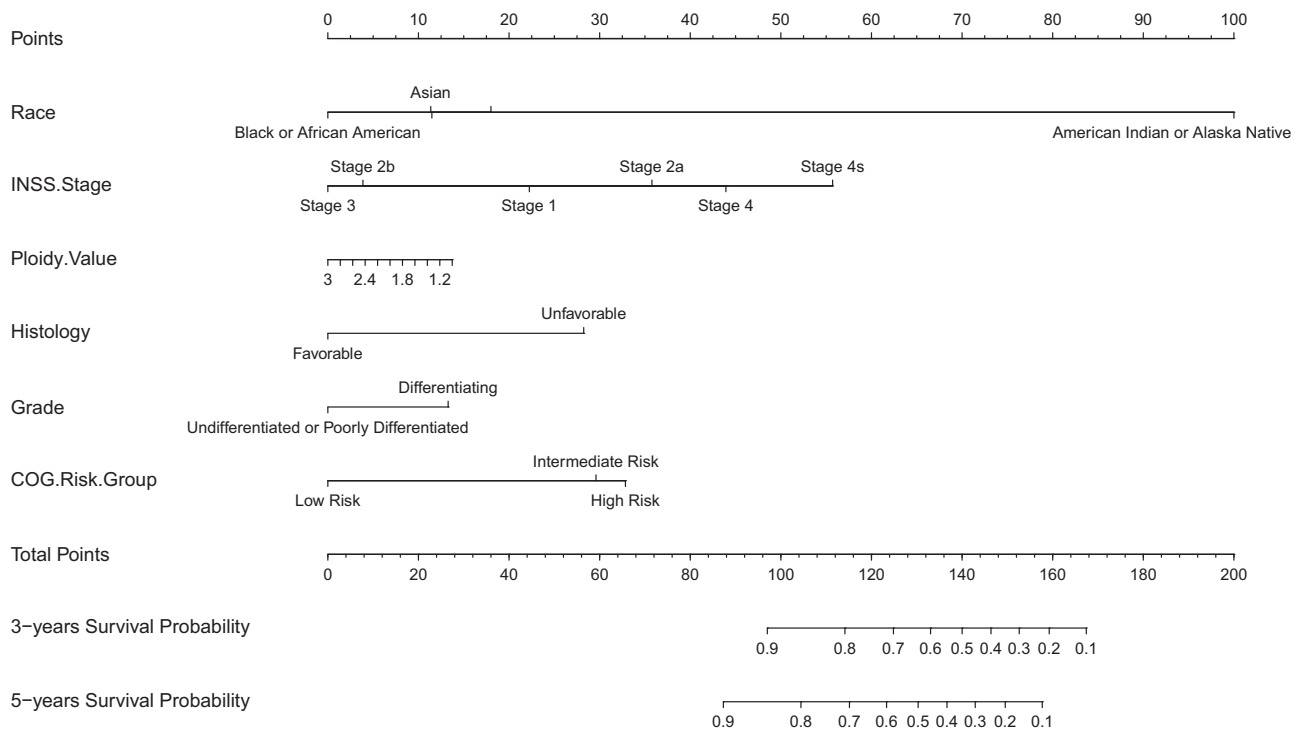


Figure 1. Constitution of the nomogram.

nomogram for predicting the 3 and 5-year OS was shown in Figure 1. The enrolled variables included: Race, INSS Stage, Ploidy Value, Histology, Grade, and COG Risk Group.

3.3. Validation of the nomogram

The nomogram was both validated internally and externally. Internal validation with the development set yielded a C-index of 0.706. The external validation was performed with the validation set, resulting a C-index of 0.718. Calibration plots of the nomogram in the validation set showed favorable consistency between the nomogram predicted 3 and 5-year OS and actual observed results (Fig. 2A-B). Similar results were observed in the validation set (Fig. 2C-D). DCA revealed the net benefit of the nomogram for predicting 3 and 5-year OS in both the development (Fig. 3A-B) and validation (Fig. 3C-D) sets.

3.4. Performance of the nomogram in predicting 3 and 5-year OS

With the nomogram, the 3 and 5-year prognostic index (PI) for each patient was calculated. ROCs were built with PI to predict the 3 and 5-year OS and the optimal cutoff value of PI was calculated to discriminate the low from the high risk-subgroups for the patients. As Figure 4 showed, AUCs of the PI predicted 3 and 5-year OS for predicting the actual OS was 0.698 (Fig. 4A) and 0.728 (Fig. 4B) in the development set, and 0.691 (Fig. 4C) and 0.714 (Fig. 4D) in the validation set. The cutoff value of PI in the development and validation set was 1.556 and 1.020, respectively. The patients in the development and validation set were classified into low and high-risk subgroups with their optimal PI cutoff value, respectively. Survival curves of the low and high-risk subgroups in the development and validation sets

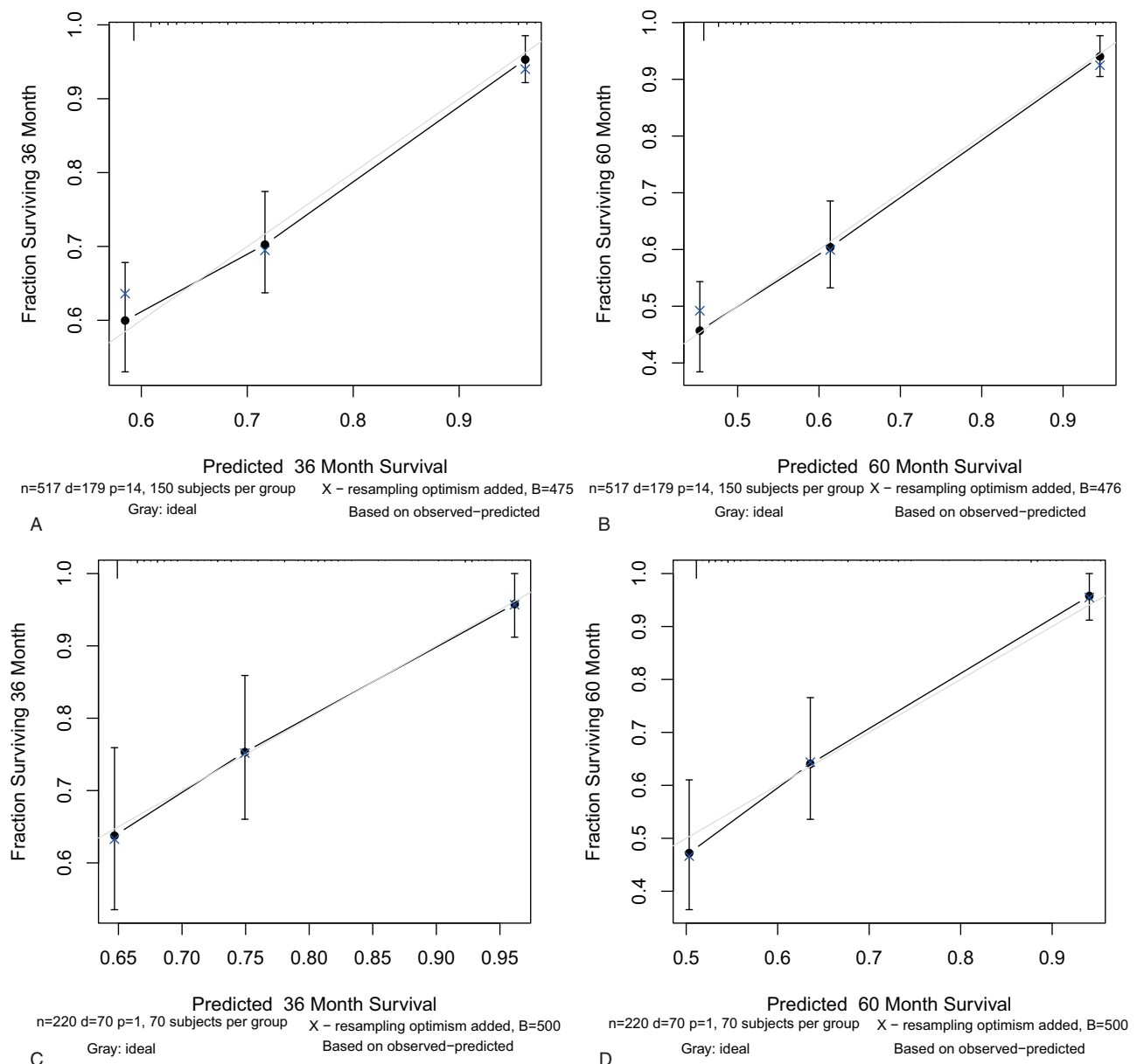


Figure 2. Calibration plots of the nomogram in the development and validation sets. Calibration plots of the nomogram for predicting the 3-year (A) and 5-year (B) OS in the development set. Calibration plots of the nomogram for predicting the 3-year (C) and 5-year (D) OS in the validation set.

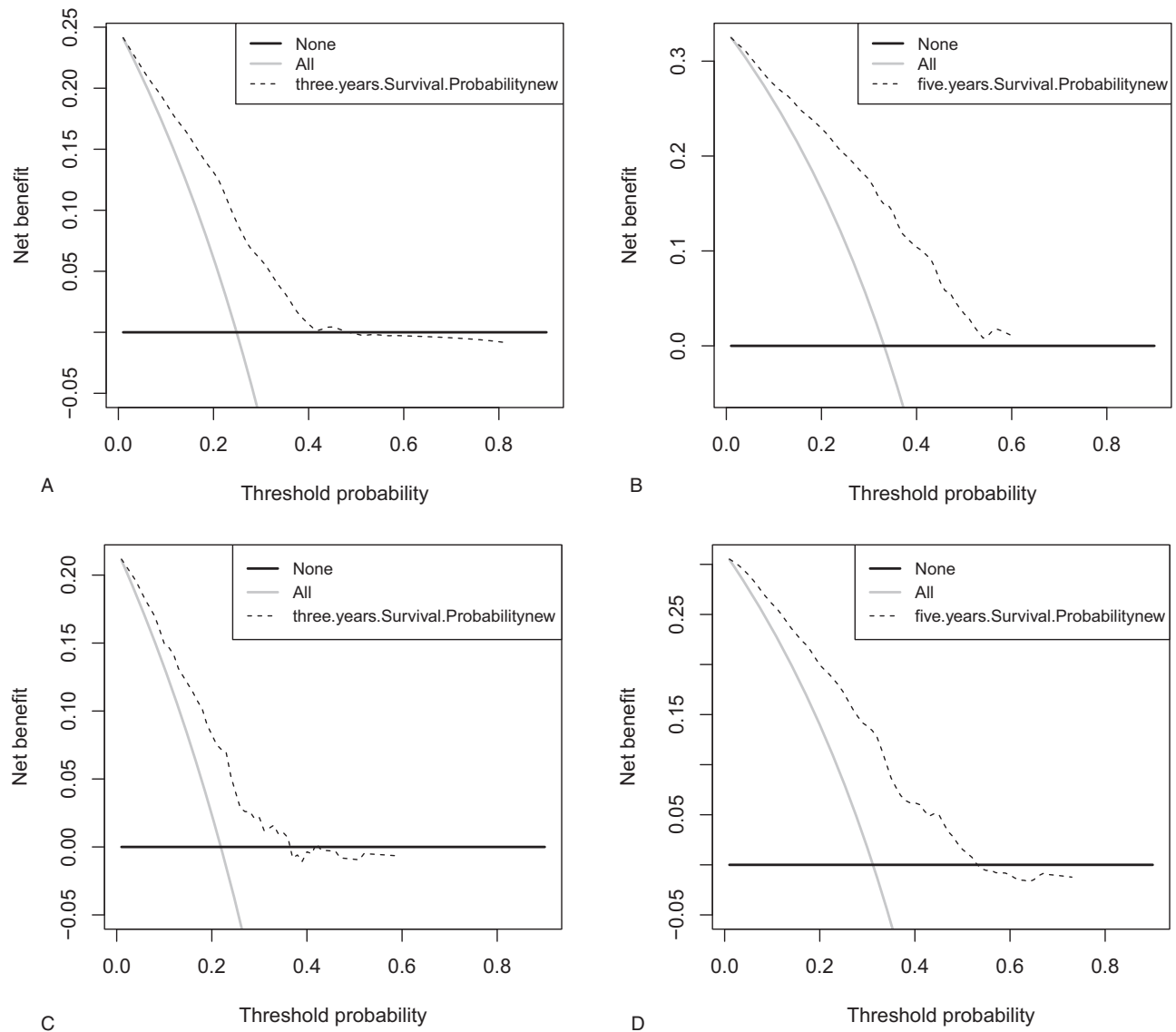


Figure 3. DCA analysis of the nomogram. Net benefit analysis of the nomogram in predicting the 3-year (A) and 5-year (B) OS in the development set. Net benefit analysis of the nomogram in predicting the 3-year (C) and 5-year (D) OS in the validation set.

were built and compared with the log-rank test. As shown by Figure 5, the patients of high-risk subgroup demonstrated a significant poor survival probability than the low-risk subgroup in both the development (Fig. 5A, $P < .001$) and validation sets (Fig. 5B, $P < .001$).

4. Discussion

This study established a nomogram for predicting the 3 and 5-year OS for neuroblastoma with reasonable discrimination, calibration, and prediction capability.

Clinical heterogeneity is the most distinct characteristic of neuroblastoma, thus raising the critical issue of risk stratification. INSS was proposed in 1988, and it was based on clinical, radiographic, and surgical evaluation of children with neuroblastoma.^[8] As the surgeon's definition of resectability was enrolled in this system, and this definition varied widely between

surgeons in different countries, the INSS could not be used for comparison of clinical trial results and limited its utility in international collaborations.^[9] The INSS was only used for assessing the patients after operation. To overcome these shortcomings, the INRGSS was proposed, which was based on the presence of objective image-defined risk factors and not influenced by the extent of resection.^[9] The INRGSS brings the probability of assessing the risks before the operation. Staging with the INRGSS greatly relied on the imaging findings at diagnosis, and for subtle disease, multiple complex imaging examinations should be performed to gain a precise risk assessment. The INRGSS was developed not to institute for the INSS, but it was anticipated that most cooperative groups would continue to use INSS in parallel with INRGSS.^[5] The important similarity of the two systems is that INRGSS retains the prognostic value of staging that has been well documented for INSS staging, with statistically significantly higher EFS for L1

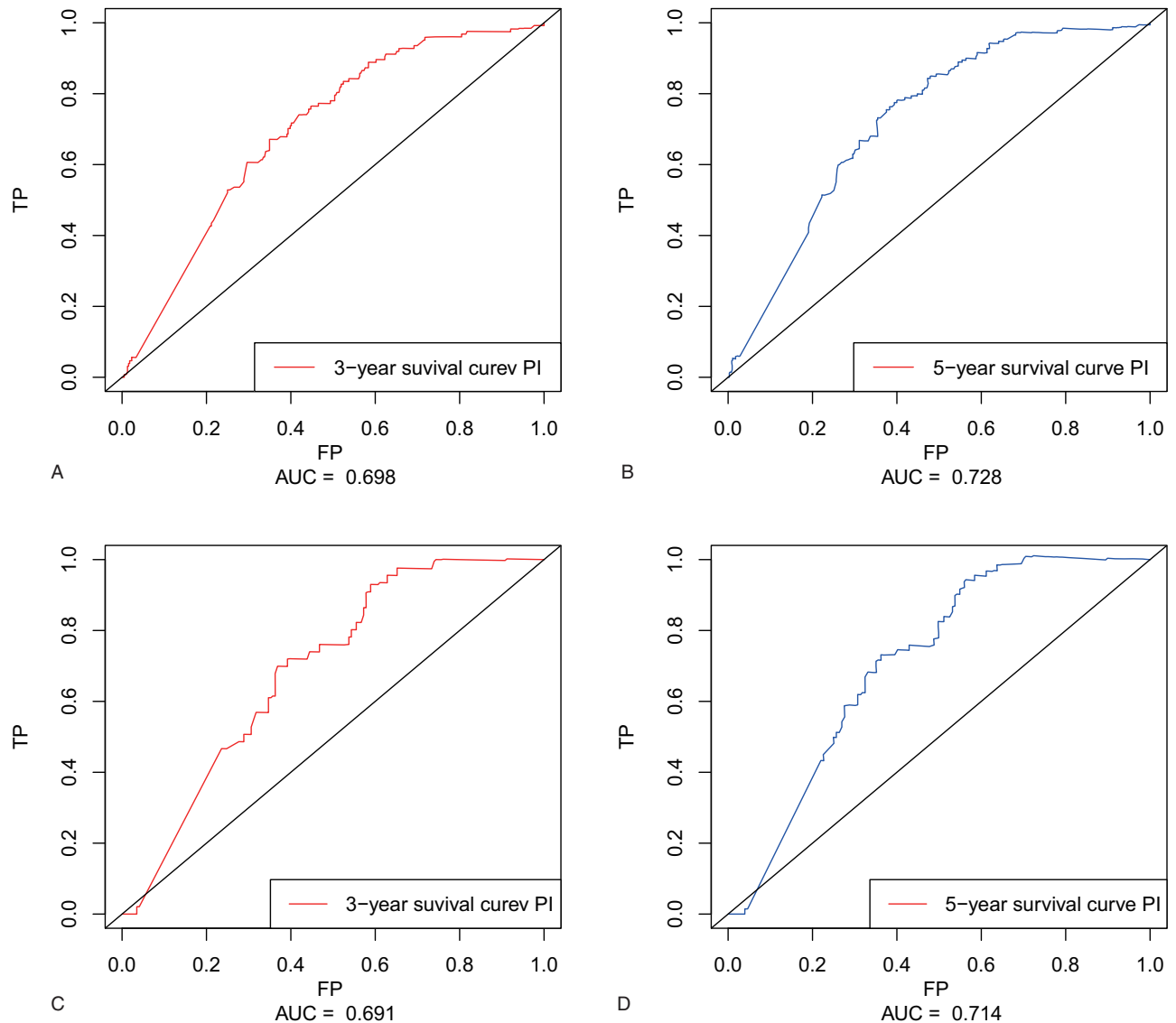


Figure 4. Performance of the nomogram derived PI in predicting the OS of neuroblastoma patients. Performance of the nomogram calculated PI in predicting the 3-year (A) and 5-year (B) OS in the development set. Performance of the nomogram calculated PI in predicting the 3-year (C) and 5-year (D) OS in the validation set.

compared with L2.^[10] Although there is some concordance of patients between the INRGSS and the INSS staging systems, the 2 systems differ in the sense that the INSS staging system contains inherent confounding of surgical treatment versus extent of the tumor, whereas INRGSS removes that confounding because it is assigned before surgery.^[10]

Recently, many other risk factors that influence the prognosis of neuroblastoma patients have been proposed, such as age,^[11] MYCN status,^[7,12] and gene expression profiles.^[7,10] Age at diagnosis is an important indicator of clinical course, with infants less than 18 months of age more likely to have a disease that spontaneously regresses or is successfully treated with surgery alone. In contrast, older children are more likely to have aggressive tumors that are resistant to multimodal and cytotoxic therapies.^[11] MYCN is an oncogene whose amplification places patients in higher-risk categories and translates to poor prognosis.^[12] Five genes have been screened as biomarkers of

prognosis for refractory neuroblastoma.^[7] Thus, we intended to combine these newly defined risk factors with the INSS staging system to predict the prognosis of the patients with neuroblastoma. From the public TARGET database, clinical features for neuroblastoma patients could be freely downloaded. These data included Survival time, Vital status, Gender, Race, Ethnicity, Age, INSS stage, MYCN status, Ploidy value, Histology, Grade, MKI, Diagnostic Category, and COG Risk Group. We proposed these factors might benefit stratifying neuroblastoma combined with INSS stage system. With these variates, a monogram for predicting the OS for neuroblastoma patients was developed and validated. In the initial nomogram based on the Cox regression with all the variates enrolled, the prediction score was less than 10 for Gender, Ethnicity, Age, MYCN status MKI and Diagnostic category. To simplify the prediction model, we excluded these variates with low scores from the model, although some variates were reported potent predictors for prognosis, such

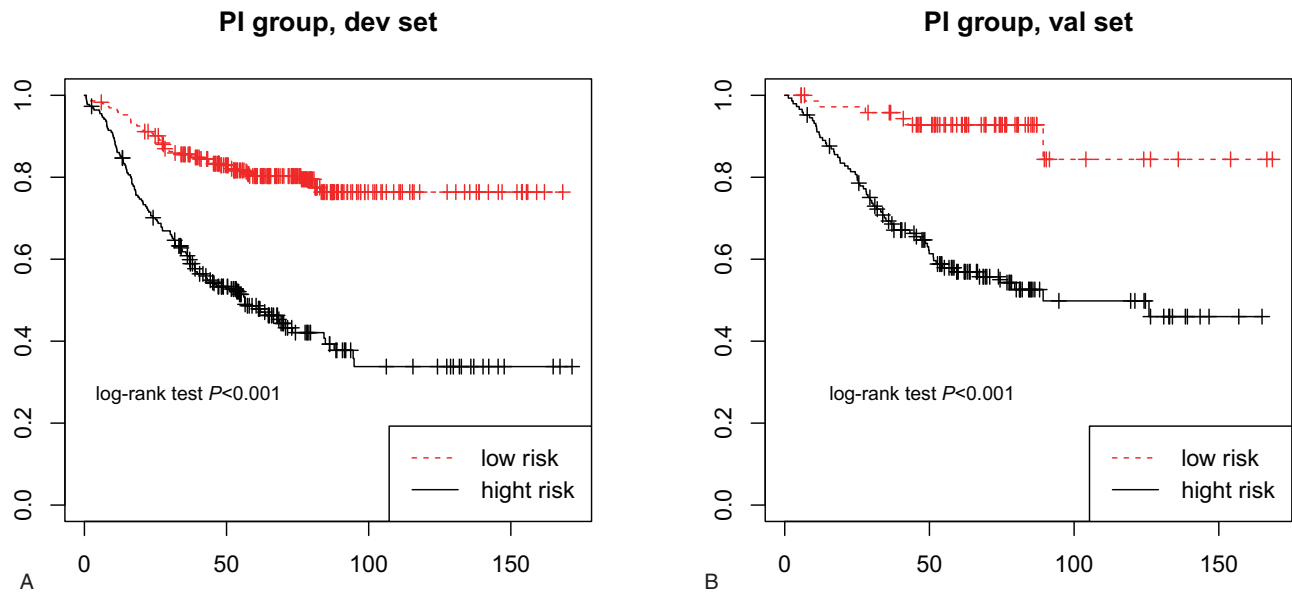


Figure 5. Survival analysis of the nomogram derived PI discriminated subgroups for patients with neuroblastoma. The survival curves were compared between the nomogram derived PI discriminated low and high-risk subgroups in the development (A) and validation (B) sets.

as age^[11] and *MYCN*^[13] amplification status. This discrepancy may come from the case selection bias and the collinearity of the variates enrolled in this study. Variates of Race, INSS stage, Ploidy value, Histology, Grade, and COG risk group were taken into the final nomogram model. In this manuscript, our nomogram demonstrated reasonable discrimination and calibration capacity. In both the development and validation sets, the OSs between the nomogram predicted high and low-risk subgroups were significantly different. These results may aid the stratification of this highly heterogeneous disease.

The prediction model in this study was presented as a nomogram, other than the traditional Cox regression model. The nomogram-based statistical method has been widely implemented in prognosis-associated clinical studies with comparable results, and it can enable specifically individual survival scores by dynamically incorporating clinical variables with technical feasibility and reproducibility.^[14] The easy comprehension and application make nomogram an ideal presentation for prediction models.

5. Limitations

There are some limitations to this study. First, although image-defined risk factors have been adopted by the INRGSS, these variates were not supplied by this database, and not enrolled in the final nomogram. Second, to pursue the simplicity of the nomogram, only variates with a score larger than 10 were enrolled in the final nomogram, and some well-documented risk factors such as age and *MYCN* status were omitted. This may hamper the precision of the model. A larger patient cohort was needed to further elucidate the role of these well-defined risk factors for neuroblastoma. Third, the involvement of the INSS staging system in this nomogram brought all the shortcomings of INSS into the nomogram, as mentioned in the previous report.^[10] Fourth, some recently defined predictors such as anaplastic lymphoma kinase and TrkB status were not included in the TARGET database and absent for analysis.^[12]

6. Conclusions

Although limitations, conclusions still can be derived from this study. Some newly defined risk factors should be considered for aiding the risk stratification of neuroblastoma in combination with INSS or INRGSS. Our nomogram can be considered for predicting the prognosis of patients with neuroblastoma.

Author contributions

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Software: Qinglin Liu.

Supervision: Wandong Su.

Validation: Hao Xue.

Writing – original draft: Qinglin Liu.

Writing – review & editing: Qinglin Liu.

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