



Development and Validation of a Nomogram for Predicting Overall Survival in Pediatric Patients with Atypical Teratoid/Rhabdoid Tumors

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ABSTRACT

AIM: To construct a reliable prediction model for pediatric atypical teratoid/rhabdoid tumor (ATRT) patients.

MATERIAL and METHODS: Population-based data of patients diagnosed with intracranial ATRT were extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. These patients were randomly assigned into training and validation cohorts at a ratio of 2:1. Univariable and multivariable Cox analyses were conducted to determine independent factors of overall survival (OS). A nomogram was then developed using the covariates with the best prognostic value, and the predictive performance of the nomogram was assessed by calibration curves, concordance index, time-dependent receiver operating characteristic curve analysis, and decision curve analysis.

RESULTS: A total of 267 cases were included. The OS rates at 6 months, 1 year, and 3 years were 61.6%, 50.1%, and 35.4%, respectively. The results of multivariable Cox analysis showed that tumor extension, surgery type, radiotherapy, and chemotherapy were independent prognostic indicators. A nomogram integrating these factors was established to predict the 6-month, 1-year, and 3-year OS rates. This prediction model was validated in the validation cohort. The nomogram had favorable predictive performance and discrimination ability.

CONCLUSION: We developed and validated a novel nomogram with favorable discrimination ability to predict prognosis for newly diagnosed pediatric ATRT patients. Although additional validation is required, this may be a useful tool in clinical decision making.

KEYWORDS: Atypical teratoid/rhabdoid tumors, SEER program, Nomograms, Predict, Overall survival

ABBREVIATIONS: ATRT: Atypical teratoid/rhabdoid tumor, SEER: The National Cancer Institute's Surveillance, Epidemiology, and End Results, GT: Gross total resection, STR: Subtotal resection, OS: Overall survival, C-index: Concordance index, ROC: Receiver operating characteristic, DCA: Decision curve analysis

INTRODUCTION

Atypical teratoid/rhabdoid tumors (ATRTs), which are characterized by multilineage differentiation and pathologically primitive phenotypes, are embryonal central nervous system (CNS) malignancies that mainly occur in children younger than 3 years old. ATRTs rarely arise in teens and adults (3,14,16,18). Epidemiologically, ATRT only

accounts for 1-2% of all pediatric brain tumors; however, it is the most common CNS tumor in the first year of life (18). The age-standardized incidence rate for pediatric ATRTs is approximately 1.38 per 100,000 person years, and 14-21% of cases have metastatic tumor dissemination at initial diagnosis (2,3,25,27).

Despite recent advances in technologies and treatment strategies, the prognosis of ATRT is still dismal, with a reported median survival around 1 year (2,9). To date, trimodality therapy consisting of surgical resection, chemotherapy, and radiotherapy is recommended. However, radiation therapy for younger children remains controversial in consideration of its CNS toxicity (8). Given the diverse histopathological features of this disease and the lack of consensus on therapeutic strategies, the outcomes across individual patients are distinct, rendering it quite difficult to predict survival. Therefore, tools to accurately estimate the prognosis of patients with ATRT are greatly needed and can contribute to clinical management.

Nomograms, reliable visual calculations integrating independent-related variables identified by statistical methods to predict patient survival probability, have been widely applied in oncology (20,29-31). The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is a valuable resource for cancer research and has been advocated for tumor study. Therefore, in this study, we used this publicly accessible database to develop and validate a nomogram for survival prediction in pediatric ATRT patients in order to aid in clinical management for this disease.

■ MATERIAL and METHODS

The SEER database contains only anonymous data and is accessed publicly, no additional Institutional Review Board approval was required for the study.

Study Cohort

The population-based data of patients diagnosed with intracranial ATRT between 2000 and 2015 within 20 SEER registries were extracted. ATRT cases among pediatric patients (younger than 20 years) were identified according to anatomic site (C71.0-C71.9) and histology (9508/3) codes. We included only cases with histologically confirmed tumors; cases identified based on death certificate or autopsy were excluded. Cases with insufficient information on surgery type or tumor extension and those without a defined follow-up time or vital status were also excluded.

Variable Selection

Patient and disease characteristics and treatment data were defined based on the SEER registry. Information regarding age at diagnosis (<1 year, 1-2 years, and ≥3 years), sex, race, tumor site, tumor size (<48 mm, ≥48 mm, and unknown), tumor extension, surgery type, and administration of radiotherapy and chemotherapy were also obtained. Tumor extension was classified into locoregional and distant spread according to the SEER coding guidelines. Surgery types were classified as no surgery, subtotal resection, and gross total resection (GTR). The primary outcome for our analysis was overall survival (OS).

First, we summarized characteristics of the included patients with frequencies and proportions. Then, these patients were randomly assigned into training and validation cohorts at a ratio of 2:1. Univariable and multivariable Cox proportional

hazards regression analyses were conducted to determine factors significantly associated with OS in the training set. We developed a survival prediction model using the nomogram method, incorporating predictive factors with the greatest prognostic value. The nomogram was further verified in the validation cohort. In addition, we employed concordance index (C-index) and time-dependent receiver operating characteristic (ROC) curve analyses to evaluate the discrimination ability of the model. The consistency of the nomogram-predicted survival with actual patient outcomes was assessed by calibration curves. Moreover, the clinical application value of the nomogram was analyzed via decision curve analysis (DCA).

Statistical Analysis

Chi-square tests were performed appropriately to compare across random sets. OS rates were estimated using the Kaplan-Meier method. The SEER*Stat software was used for patient data extraction, and R software was employed for all statistical analyses. A p value < 0.05 was defined as statistically significant.

■ RESULTS

Demographic and Clinicopathological Characteristics

From 2000 to 2015, a total of 267 patients met our inclusion criteria and were included in our study cohort. The demographic and clinical characteristics of pediatric patients with ATRT are presented in Table I. The majority of patients were younger than 3 years old, with 34.1% of patients being under the age of 1 year. More than half of the patients were male (53.2%), and 76.0% were white. Tumors most frequently occurred in the supratentorial location (41.6%) and had locoregional spread (75.7%). Additionally, most patients received surgery, with 41.2% of patients receiving GTR. Chemotherapy (73.0%) was the most common treatment type, whereas only 37.8% of patients were administered radiotherapy. The OS rates at 6 months, 1 year, and 3 years were 61.6%, 50.1%, and 35.4%, respectively. The baseline characteristics were comparable between the training and validation cohorts (Table I, all p>0.05).

Identification of Prognostic Factors

As shown in Table II, univariate Cox analysis revealed that age at diagnosis, tumor extension, surgery type, radiotherapy, and chemotherapy were significantly correlated with OS (all p<0.05). After adjusting for potential confounding factors, the results of multivariable Cox analysis showed that tumor extension (distant vs locoregional: hazard ratio [HR], 2.23, 95% confidence interval [CI] 1.43-3.48, p<0.001), surgery type (subtotal resection vs no surgery: HR, 0.26, p<0.001; GTR vs no surgery: HR 0.20, p<0.001), radiotherapy (yes vs no: HR 0.29, 95% CI 0.17-0.49, p<0.001), and chemotherapy (yes vs no: HR 0.54, 95% CI 0.32-0.89, p<0.001) remained independent prognostic factors of OS.

Nomogram Development and Performance Assessment

We next incorporated these prognostic factors into a nomogram for individual survival rate estimation. As presented in Figure 1, the nomogram was successfully established to predict the

Table I: Patient Characteristics in the Study

Parameter	Total cohort, n (%)	Training cohort, n (%)	Validation cohort, n (%)	p-value
	267 (100)	178 (100)	89 (100)	
Age, year				0.959
<1	91 (34.1)	63 (35.4)	28 (31.5)	
1-2	114 (42.7)	73 (41.0)	41 (46.1)	
≥3	62 (23.2)	42 (23.6)	20 (22.5)	
Sex				0.965
Male	142 (53.2)	94 (52.8)	48 (53.9)	
Female	125 (46.8)	84 (47.2)	41 (46.1)	
Race				0.877
White	203 (76.0)	137 (77.0)	66 (74.2)	
Black	33 (12.4)	21 (11.8)	12 (13.5)	
Others/unknown	31 (11.6)	20 (11.2)	11 (12.4)	
Tumor site				0.493
Supratentorial	111 (41.6)	71 (39.9)	40 (44.9)	
Infratentorial	91 (34.1)	65 (36.5)	26 (29.2)	
Other/brain, NOS	65 (24.3)	42 (23.6)	23 (25.8)	
Tumor size				0.128
<48 mm	105 (39.3)	65 (36.5)	40 (44.9)	
≥48 mm	108 (40.4)	71 (39.9)	37 (41.6)	
Unknown	54 (20.2)	42 (23.6)	12 (13.5)	
Tumor extension				
Locoregional	202 (75.7)	134 (75.3)	68 (76.4)	
Distant	65 (24.3)	44 (24.7)	21 (23.6)	
Surgery				0.962
No surgery	21 (7.9)	14 (7.9)	7 (7.9)	
STR	136 (50.9)	91 (51.1)	45 (50.6)	
GTR	110 (41.2)	73 (41.0)	37 (41.6)	
Radiotherapy				0.824
No	166 (62.2)	112 (62.9)	54 (60.7)	
Yes	101 (37.8)	66 (37.1)	35 (39.3)	
Chemotherapy				0.661
No	72 (27.0)	50 (28.1)	22 (24.7)	
Yes	195 (73.0)	128 (71.9)	67 (75.3)	
6-month OS rate	61.60%	59.80%	65.30%	
1-year OS rate	50.10%	47.60%	55.20%	
3-year OS rate	35.40%	34.90%	36.40%	

STR: Subtotal resection, **GTR:** Gross total resection, **OS:** Overall survival.

Table II: Univariable and Multivariable Cox Analyses in the Training Cohort

Parameter	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, year				
<1	1[Reference]		1[Reference]	
1-2	0.63 (0.42-0.95)	0.029	0.93 (0.59-1.47)	0.744
≥3	0.42 (0.24-0.71)	0.001	0.85 (0.46-1.55)	0.591
Sex				
Male	1[Reference]		1[Reference]	
Female	1.19 (0.82-1.73)	0.359	1.12 (0.76-1.67)	0.561
Race				
White	1[Reference]		1[Reference]	
Black	1.57 (0.93-2.66)	0.092	1.29 (0.74-2.25)	0.373
Others/unknown	1.09 (0.60-2.01)	0.774	0.99 (0.52-1.88)	0.958
Tumor site				
Supratentorial	1[Reference]		1[Reference]	
Infratentorial	0.98 (0.63-1.52)	0.917	0.96 (0.59-1.58)	0.886
Others/brain, NOS	1.32 (0.82-2.10)	0.25	1.30 (0.80-2.12)	0.295
Tumor size				
<48 mm	1[Reference]		1[Reference]	
≥48 mm	1.17 (0.76-1.81)	0.465	0.74 (0.46-1.20)	0.224
Unknown	1.13 (0.68-1.86)	0.643	0.49 (0.27-0.87)	0.015
Tumor extension				
Locoregional	1[Reference]		1[Reference]	
Distant	2.10 (1.40-3.15)	<0.001	2.23 (1.43-3.48)	<0.001
Surgery				
No surgery	1[Reference]		1[Reference]	
STR	0.16 (0.09-0.30)	<0.001	0.26 (0.13-0.54)	<0.001
GTR	0.13 (0.07-0.25)	<0.001	0.20 (0.09-0.42)	<0.001
Radiotherapy				
No	Reference		Reference	
Yes	0.25 (0.16-0.40)	<0.001	0.29 (0.17-0.49)	<0.001
Chemotherapy				
No	1[Reference]		1[Reference]	
Yes	0.30 (0.20-0.45)	<0.001	0.54 (0.32-0.89)	0.017

STR: Subtotal resection, **GTR:** Gross total resection, **OS:** Overall survival.

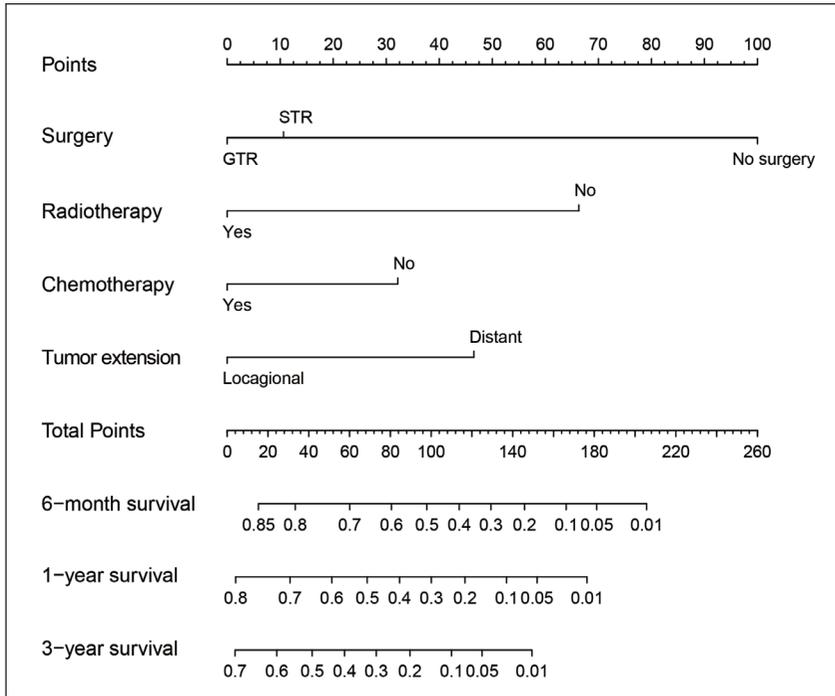


Figure 1: The novel-built nomogram predicting the 6-month, 1-year and 3-year overall survival for pediatric ATRT patients. **STR:** Subtotal resection, **GTR:** Gross total resection.

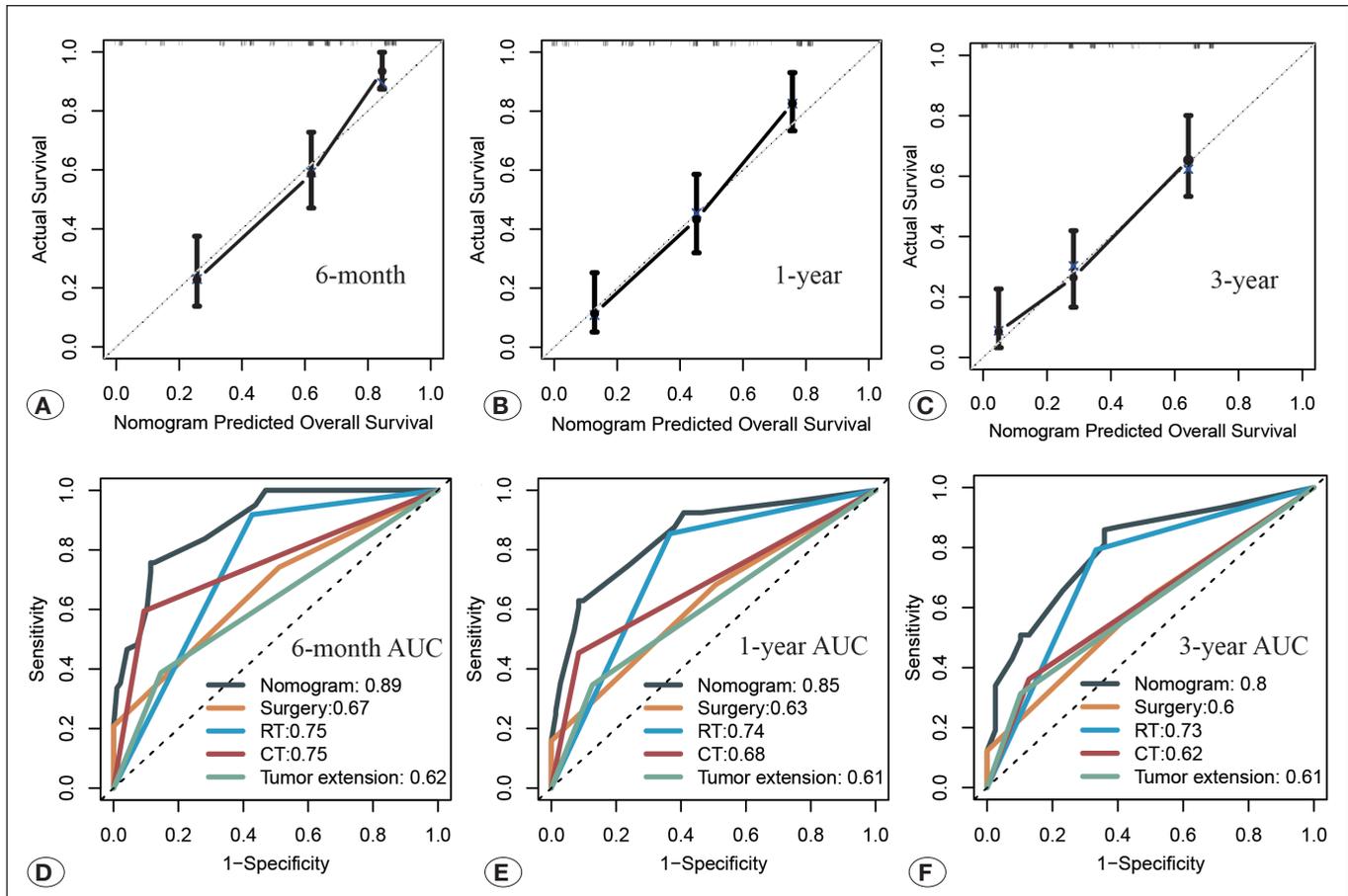


Figure 2: Calibration curves and ROC curves of the nomogram in the training cohort. Calibration plots describing **A)** 6-month, **B)** 1-year and **C)** 3-year OS; ROC curves predicting **D)** 6-month, **E)** 1-year and **F)** 3-year OS. **ROC:** Receiver operating characteristic, **OS:** Overall survival.

6-month, 1-year, and 3-year OS rates in the training cohort. The calibration curves in both the training and validation datasets demonstrated good consistency between the observed and predicted outcomes (Figure 2A-C and Figure 3A-C). Favorable discrimination performance of the nomogram was also indicated by the C-index (0.799) and ROC curve analysis, which showed areas under the curve (AUCs) at 6 months, 1 year, and 3 years of 0.89, 0.85, and 0.80, respectively, in the training cohort (Figure 2D-F). The C-index in the validation cohort was 0.756, and the AUCs at 6 months, 1 year, and 3 years were 0.86, 0.83, and 0.76, respectively (Figure 3D-F). These validated the good predictive ability of the nomogram. We further compared the indicative prognostic power of this novel prediction model with other scoring systems for ATRT, and we found that the nomogram had the best performance with the highest AUC. Finally, DCA showed that our model was of great clinical value in both the training and validation groups (Figure 4A-F).

DISCUSSION

The importance of survival prediction is increasingly recognized in current clinical practice. Owing to the relative rarity of ATRT,

there is, to our knowledge, no prognostic prediction model for these patients. Here, we used the SEER database, which provided a pediatric ATRT cohort with a relatively large sample size, to build a nomogram for OS estimation, thereby aiding in individualized management decision-making. We also verified the greater predictive performance of the model by comparing it with traditional scoring systems for ATRT in both the training and validation cohorts. Our nomogram had the highest AUC, indicating its better predictive ability. The clinical utility of the predictive model was further proved by DCA.

In our investigation, four factors, tumor extension, surgery type, radiotherapy, and chemotherapy, were identified as independent prognostic indicators and were integrated into our prediction model. Similarly, Yamasaki et al., in a study including 38 ATRT patients, found that metastasis stage and GTR were prognostic factors for progression-free survival, whereas high-dose chemotherapy was significantly related to OS (28). However, no benefit of postoperative radiotherapy was observed in their cohort, which might be attributable to selection bias and the small sample size of their study (20). Several studies have also indicated that younger age, distant metastasis, and delayed initiation of radiotherapy

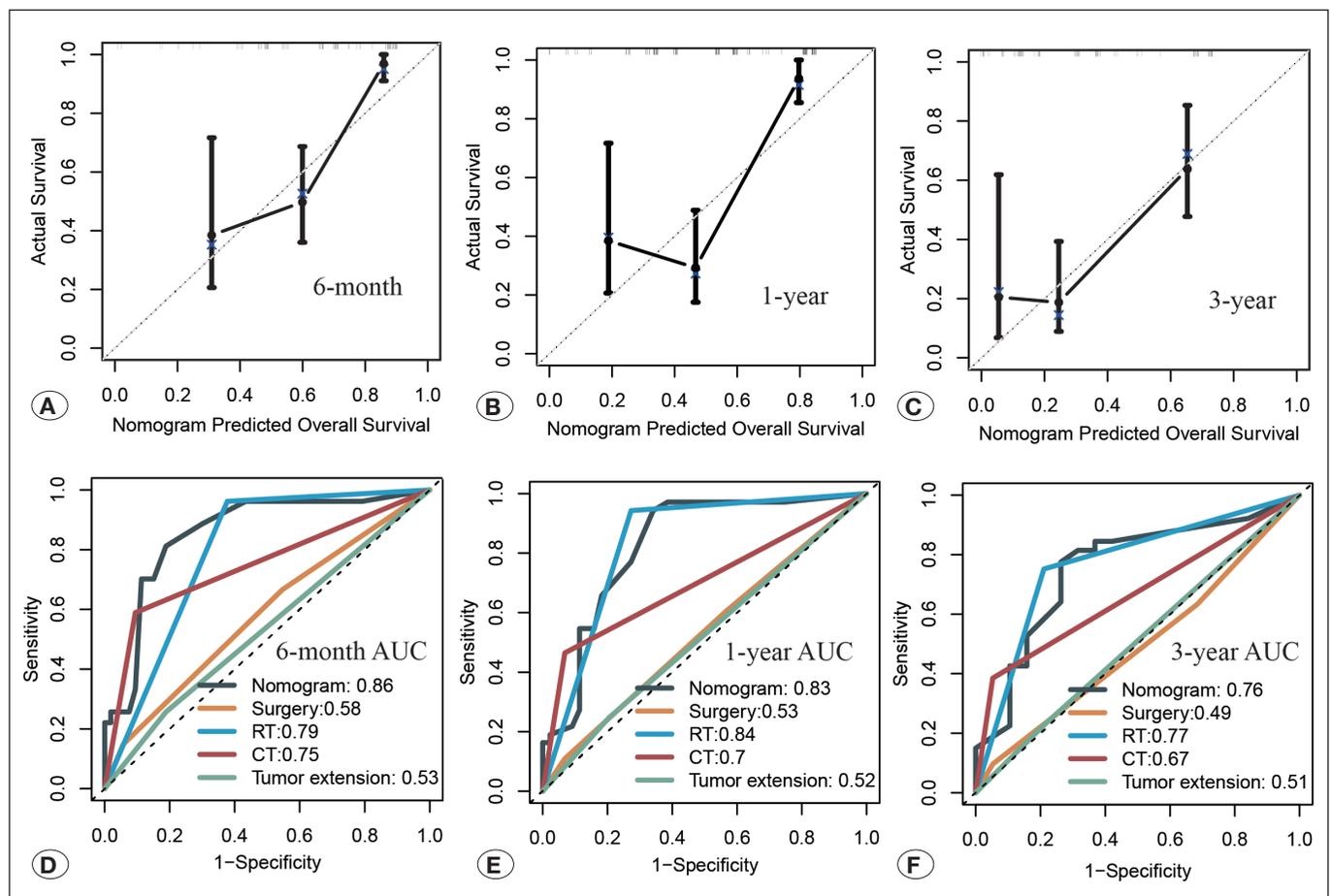


Figure 3: Calibration curves and ROC curves of the nomogram in the validation cohort. Calibration plots describing **A)** 6-month, **B)** 1-year and **C)** 3-year OS; ROC curves predicting **D)** 6-month, **E)** 1-year and **F)** 3-year OS. **ROC:** Receiver operating characteristic; **OS:** Overall survival.

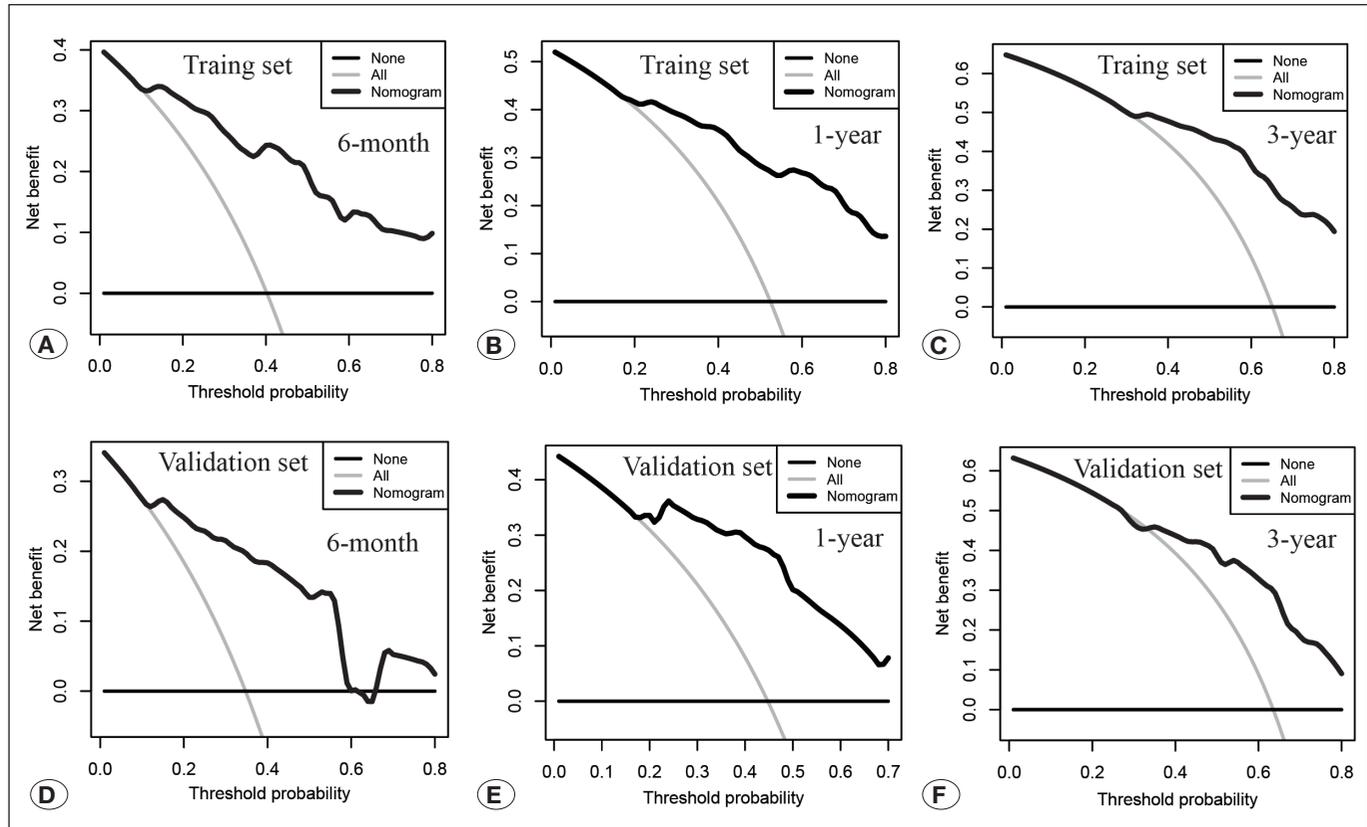


Figure 4: DCA curves of the nomogram for **A)** 6-month, **B)** 1-year and **C)** 3-year OS in training cohort and for **D)** 6-month, **E)** 1-year and **F)** 3-year OS in validation cohorts. **DCA:** Decision curve analysis; **OS:** Overall survival.

have a negative impact on OS (9,12,19,26). Additionally, supratentorial tumor location tends to lead to a better outcome (2). Nevertheless, in our large study, patient age and tumor location had only marginal effects on survival. In order to simplify our model for ease of use, these two factors were excluded from our nomogram.

Despite the high heterogeneity in tumor location, treatment response, and disease stage in ATRT patients, ATRTs also almost universally exhibit loss of SMARCB1, which may contribute to clinical heterogeneity (12). Recent transcription and methylation profiling studies also suggest the existence of molecular subgroups among ATRTs (11). This molecular heterogeneity should be further explored to aid in developing novel therapeutic strategies for ATRT patients.

To date, the role of radiotherapy in pediatric patients with ATRT remains controversial, especially for children younger than 3 years old, because the toxicity of radiation therapy to the developing CNS can lead to long-term sequelae. Nevertheless, a number of studies have demonstrated a clinical benefit of radiotherapy with regard to survival (1,4,5,7,10,13,15,17,22,24,25). Recently, Quinn et al. conducted a propensity score-matched analysis to robustly evaluate the role of radiotherapy in a cohort of 190 pediatric ATRT patients. They found that trimodality therapy could achieve better survival than surgery and chemotherapy without radiotherapy, and the benefit of radiotherapy was more significant in infants and toddlers (22). Park

et al. found in their multicenter study that high-dose chemotherapy and adjuvant radiotherapy remained significant prognostic factors for progression-free survival in ATRT patients younger than 3 years old (21). Recently, the first ATRT-specific cooperative group trial, ACNS0333, was designed to evaluate the efficacy and safety of intensive postoperative chemotherapy and focal radiation for treatment of ATRTs. The results showed that intensive multimodal therapy could significantly improve outcomes for ATRT patients (23). Another prospective multi-institutional trial also indicated that an intensive multimodality regimen could prolong both progression-free survival and OS in these patients (6). Similarly, our study also demonstrated improvement in survival with radiotherapy in the multi-variable Cox analysis. Further randomized controlled trials are required to verify the effect of radiotherapy in pediatric ATRT patients younger than 3 years.

Some limitations should be noted. First, although the SEER database can provide a large study cohort, it is dependent on accurate data coding and reporting, which might cause some bias. Second, information on target volumes, dose, and fractionation are unavailable for patients treated with radiotherapy, and detailed regimens of chemotherapy are also unknown. In addition, with great advances in molecular biology, a number of genomic markers associated with ATRT occurrence and progression have been identified; however, because the SEER database fails to provide genomic data, we

were unable to analyze these factors and integrate them into our model. Finally, our prediction model needs to be evaluated carefully in other cohorts.

CONCLUSION

In our study, a novel nomogram with favorable discrimination ability was successfully constructed and validated to predict the 6-month, 1-year, and 3-year survival probabilities for newly diagnosed pediatric ATRT patients. This nomogram can promote doctor-patient communication and assist in clinical decision-making. This model could also be used to estimate significant prognostic factors in ATRTs.

AUTHORSHIP CONTRIBUTION

Study conception and design: TZ

Data collection: YL

Analysis and interpretation of results: TZ, XP

Draft manuscript preparation: YL

Critical revision of the article: TZ

Other (study supervision, fundings, materials, etc.): YL, XP, TZ

All authors (YL, XP, TZ) reviewed the results and approved the final version of the manuscript.

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