Prognostic Nomogram in Children and Adolescents With Central Nervous System Germ Cell Tumors

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Abstract

**Background:** The prognostic risk factors for primary central nervous system (CNS) germ cell tumors (GCTs) in children and adolescents remain controversial. This study aimed to develop and validate a nomogram that predicts 5- and 10-year survival rates for CNS GCTs in children and adolescents.

**Methods:** Pediatric with intracranial GCTs in the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2018 were analyzed. All GCTs children were randomly divided into the development group (70%) and the validation group (30%). The least absolute shrinkage and selection operator (LASSO) was used to screen the characteristic variables, and the 5- and 10-year survival probability nomogram was constructed. The accuracy of the nomogram was evaluated by consistency index (C-index), calibration plot, receiver operating characteristic curve (ROC), decision curve analysis (DCA) and survival curve.

**Results:** We identified 819 cases of CNS GCTs in children. Three variables (histology, site and size) were selected by lasso regression to construct the nomogram. The C-index of the development group and verification group is 0.744 and 0.759. According to the time points of 5 and 10 years, the area under the curve of the development group is 0.753 and 0.696, and the verification set is 0.787 and 0.718. The results show that the prognostic nomogram developed by us has good accuracy.

**Conclusions:** This is the first prognostic nomogram of CNS GCTs in children and adolescents. It can effectively predict the 5- and 10-year survival probability of children. It provides a useful prediction tool for clinicians.

Background

Germ cell tumors (GCTs) originate from pluripotent embryonic germ cells during embryonic development and central nervous system (CNS) GCTs are one of the most common primary sites.\(^1\,^2\) CNS GCTs mostly occur in the deep part of the midline structures, and about 50% occur in the pineal gland.\(^3\) Primary CNS GCTs are rare, with an incidence of approximately 0.1/100,000 in the United States, accounting for less than 5% of all CNS tumors.\(^4\) Intracranial CNS GCTs mainly occur in children and adolescent males and are almost all malignant tumors (except benign teratoma).\(^5\) According to the histological features of intracranial GCTs, it can be divided into two categories: germinomatous GCTs (GGCTs) and nongerminomatous GCTs (NGGCTs\).\(^3\) The histomorphological characteristics of GGCTs are similar to those of spermatogonia of the testis in males or ovary dysgerminoma in females. In addition, heterogeneous NGGCTs are composed of a variety of mixed germ cell components (such as teratoma, choriocarcinoma and embryonal carcinoma, etc.), which have a very poor prognosis.\(^6\)

The prognosis of GCTs is influenced by age, race, histological type, tumor location, tumor size, chemoradiotherapy, treatment and other risk factors.\(^7\,^8\,^9\) Denyer et al. found in their study that germinoma patients with radiotherapy alone had a better prognosis than surgical resection.\(^8\) In addition, the impact
of different treatment methods on prognosis is also controversial. Unfortunately, there is no effective way to evaluate the prognosis of CNS GCTs in children and adolescents. Therefore, it is necessary to develop a clinically practical prediction model to predict the survival probability of germinoma of the central nervous system in children. The nomogram can use multivariate regression analysis, integrate multiple prediction indexes, and use line segments with scales to predict individual prognosis. It can also transform complex regression equations into visual images, making the results of predictive models more readable and easier to evaluate for patients.\(^{10,11}\)

The Surveillance, Epidemiology and End Results (SEER) database is the largest clinical information collection platform in the United States, including demographic data, incidence rate, histology, treatment data and follow-up information. We conducted a prognostic study based on the SEER database in order to identify the characteristic variables that influence prognostic factors and predict the prognosis of intracranial GCTs in children and adolescents. In addition, we developed a nomogram model which can accurately predict the prognosis combined with characteristic variables and carried out internal validation.

**Methods**

**Study Population**

This study complied with the use requirements of the ‘Surveillance, Epidemiology, and End Results Program Data Use Agreement’ database and was approved by the SEER institutional (user name: 10901-November 2020). All studies were conducted according to the Helsinki Guidelines. The SEER database is the largest cancer database in the United States, covering about one-third of the U.S. population. Data for clinical information on pediatric patients with intracranial germinoma were submitted in November 2020 from 18 registries. Criteria for inclusion included: (1) Age 0-19 years; (2) Diagnose GGCT or NGGCT; (3) The primary site is located in the intracranial; (4) Confirmed by microscopic histological examination. Patients with incomplete clinical information were excluded. The histological type of GGCTs was the International Classification of Diseases for Oncology, third edition (ICD-O-3) 9064 (Germinoma).\(^3\) Histological ICD-O-3 numbers for NGGTs include 9065 (Germ cell tumor), 9070 (Embryonal carcinoma), 9071 (Yolk sac tumor), 9080 (Teratoma), 9082 (Malignant teratoma), 9085 (Mixed germ cell tumor), 9100 (Choriocarcinoma), and 9101 (Choriocarcinoma combined with other germ cell elements).\(^3\) The primary site ICD-O-3 of the tumor is encoded as follows: C70.0–C70.9, C71.0–C71.9, C72.2–C72.5, C72.8–C72.9, C75.3 (Pineal gland), C75.1 (Pituitary gland), C75.2 (Craniopharyngeal duct).\(^2\) 70% of the children with germinoma meeting the criteria were randomly selected and assigned to the development group, and the rest were assigned to the validation group. Figure 1 shows the flow chart of screening children with intracranial germinomas from the SEER database in this study.

**Study design**

Clinical cancer patient statistics were collected for age, sex, and race at the time of diagnosis. Histological characteristics of cancer include histology, primary tumor site, tumor size, and surgery. Based
on previous studies, the ages of children and adolescents were divided into 0-9 years old and 10-19 years old.\textsuperscript{9} Demographic and racial information classification: white, black and other races. Acharya et al. classified germinoma into GGCTs and NGGCTs in their study.\textsuperscript{3} The primary sites of tumors were the pineal gland, pituitary gland/ craniopharyngeal duct, and others. Germinoma sizes were less than 5cm (<5cm), greater than or equal to 5cm (5cm+), and unknown. Surgery includes surgical sets (codes 20, 21, 22, 25, 27,30, 40, 50, 55, 60, 90) and nonsurgical or unknown sets (codes 00, 99). Survival time for cancer patients is measured by the number of months of survival or the time of the last follow-up, and survival status includes alive or death.

Development and validation of a nomogram

Using the development-set data of children with germinoma obtained above, least absolute shrinkage and selection operator (LASSO) regression were used to screen the best predictive variable data.\textsuperscript{12} These indexes were used to construct a nomogram model of 5- and 10-year survival probability of germinoma in children. The stability and accuracy of the nomogram model were verified by C-index, calibration plot, receiver operating characteristic curve (ROC) and survival curve. In addition, the net benefit was predicted by the model is tested with decision curve analysis (DCA).\textsuperscript{13}

Statistical analysis

The "caret" package was used to randomly select 70% of all patients as the model development population and 30% as the validation sample. Through “glmnet” and “survival” packages, LASSO regression was used to screen out the variables for constructing the nomogram, which was used to predict the 5- and 10-year survival probability of children germinoma. C-index is an assessment of how likely a model is to predict the patient's ability to have the event.\textsuperscript{14} The calibration plot can be used to evaluate the accuracy of the model, which is the difference between the probability of the event predicted by the model and the actual event. In addition, the "rms", "foreign" and "survival" packages were used for internal validation of the model using bootstrapping technique on the basis of 1000 samples. The DCA curve of the multivariate COX regression model was plotted using the "ggDCA" package. The net benefit of the nomogram to children with germ cell tumor was evaluated the clinical practicability of the model at 5- and 10-year timepoint. The "survivalROC" package was used to draw the ROC curve of the 5- and 10-year survival probability prediction model for children with germinoma. The prognostic index (PI) was constructed using the variables obtained from the above screening, and the best cut-off value was calculated. We divided PI into a high-risk group and low-risk group based on the best cutoff point and plotted the survival curve of the development group and verification group by "Kaplan-Meier" method. P<0.05 was considered statistically significant. SEER*Stat software version 8.3.9 (https://seer.cancer.gov/seerstat/) was used to extract clinical data in patients with intracranial germ cell tumors. R software 4.0.5 (https://www.r-project.org) was used for statistical analysis and image production.

Results
Demographic characteristics

A total of 819 germinoma patients who met the inclusion criteria were enrolled and divided into the training set (575 patients) and the validation set (244 patients). Most of the patients with intracranial germ cell tumors in the validation set and the test set were male children, accounting for 76.0% (437/575 patients) and 75.4% (184/244 patients) respectively. The histological diagnosis of GGCT was 73.4% (422/575 patients) in the development group and 73.0%(178/244 patients) in the validation group, respectively. The primary site of intracranial tumors was mainly in the pineal gland, with development set accounting for 46.1% (265/575 patients) and verification set accounting for 53.3% (130/244 patients). Univariate Cox regression analysis: age (HR = 0.81; 95% CI, 0.46 to 1.43, P =0.474), gender (HR = 1.37; 95% CI, 0.81 to 2.31, P =0.244), race (HR = 0.96; 95% CI, 0.71 to 1.30, P =0.797), histological (HR = 4.47; 95% CI, 2.75 to 7.25, P < 0.001), site (HR = 1.25; 95% CI, 0.97 to 1.62, P =0.087), size (HR = 1.72; 95% CI, 1.30 to 2.28, P < 0.001), surgery (HR = 0.82; 95% CI, 0.51 to 1.33, P = 0.423). Table 1 summarizes the detailed demographic information and clinical histological characteristics of the cohort studies.
Table 1
Baseline characteristics of intracranial germ cell tumors in children from the SEER database.

| Characteristics | All patients N=819 (%) | Training set N=575 (%) | Validation set N=244 (%) | P value |
|-----------------|------------------------|------------------------|--------------------------|---------|
| Age(years)      |                        |                        |                          | 0.474   |
| 0-9             | 188 (23.0)             | 131 (22.8)             | 57 (23.4)                |         |
| 10-19           | 631 (77.0)             | 444 (77.2)             | 187 (76.6)               |         |
| Gender          |                        |                        |                          | 0.244   |
| Male            | 621 (75.8)             | 437 (76.0)             | 184 (75.4)               |         |
| Female          | 198 (24.2)             | 138 (24.0)             | 60 (24.6)                |         |
| Race            |                        |                        |                          | 0.797   |
| White           | 590 (72.0)             | 395 (68.7)             | 195 (79.9)               |         |
| Black           | 73 (8.9)               | 57 (9.9)               | 16 (6.6)                 |         |
| Other           | 156 (19.0)             | 123 (21.4)             | 33 (13.5)                |         |
| Histological    |                        |                        |                          | P<0.001 |
| GGCTs           | 600 (73.3)             | 422 (73.4)             | 178 (73.0)               |         |
| NGGCTs          | 219 (26.7)             | 153 (26.6)             | 66 (27.0)                |         |
| Site            |                        |                        |                          | 0.087   |
| Pineal gland    | 395 (48.2)             | 265 (46.1)             | 130 (53.3)               |         |
| Pit/Cra gland   | 73 (8.9)               | 52 (9.0)               | 21 (8.6)                 |         |
| Other           | 351 (42.9)             | 258 (44.9)             | 93 (38.1)                |         |
| Size (cm)       |                        |                        |                          | P<0.001 |
| <5cm            | 369 (45.1)             | 264 (45.9)             | 105 (43.0)               |         |
| 5cm+            | 155 (18.9)             | 107 (18.6)             | 48 (19.7)                |         |
| Unknown         | 295 (36.0)             | 204 (35.5)             | 91 (37.3)                |         |
| Surgery         |                        |                        |                          | 0.423   |
| Yes             | 411 (50.2)             | 279 (48.5)             | 132 (54.1)               |         |
| No/Unknown      | 408 (49.8)             | 296 (51.5)             | 112 (45.9)               |         |

GGCTs: Germinomatous germ cell tumors; NGGCTs: Nongerminomatous germ cell tumors; Pit/Cra gland: Pituitary gland/ Craniopharyngeal duct.
Feature selection and construction of the nomogram

Data from children with an intracranial germinoma in the development group were used to screen out three characteristic variables as predictors of the construction of the prognostic nomogram by LASSO regression: histological (coefficient 1.20), site (coefficient 0.02), and size (coefficient 0.34). (Figure 2) A nomogram prognostic model was constructed based on LASSO regression results of the development data set. We used this prognostic model to predict 5- and 10-year survival rate in children with germ cell tumors. (Figure 3) The score of the nomogram is shown in Supplementary Table 1.

Effect verification of nomogram

We internally verified the model. The C-index of the development group was 0.744, and that of the verification group was 0.759. The 5- and 10-year survival prognostic models of intracranial germinoma in children showed good accuracy in the calibration plots in both the training cohort and the validation cohort (Figure 4A and B). The net benefit of the predictive model for germinoma children was demonstrated by DCA. The X-axis represents the risk threshold probability and the Y-axis represents the clinical net benefit. As shown in Figure 4C and D, our 5- and 10-year survival probability prognostic models for the children with intracranial germinoma showed good net benefits.

ROC and survival curve

A multivariate COX regression model was established with germinoma histology, site and size as variables. The area under curve (AUC) values of the 5- and 10-year overall survival of the development group were 0.753 and 0.696, and the AUC values of the validation set were 0.787 and 0.718. (Figure 5A and B). The continuous variable PI is calculated using the three variables (histological, site, size). In the development set, the best cutoff point of PI is calculated with the 5- and 10-year survival time as the cutoff point is 0.85. The cut-off point of 5- and 10-year survival time in the validation set was 1.27. The population was divided into high-risk group and low-risk group according to the optimal cutoff point of the variable PI and the survival curve was plotted. Median follow-up time in children with intracranial germinoma development set was 92 months (1-227 months) and verification set was 80 months (1-227 months). The 5-year survival rates were 96.5% and 80.9%, and the 10-year survival rates were 95.3% and 76.5%, respectively, in the low-risk and high-risk children in the development set. The 5-year survival rates were 95.1% and 74.6%, and the 10-year survival rates were 92.6% and 70.5%, respectively, in the low-risk and high-risk children in the validation group. Survival curve analysis (Figure 5C and D) showed that children with low-risk germinoma lived longer than those with high-risk germinoma in both the development and validation sets (P <0.0001).

Discussion
In this retrospective cohort study based on SEER database, we developed and verified a new prognostic model based on three clinical variables (histology, site, size) for the first time. Compared with clinical risk factors, our model can improve the prediction ability of prognosis in children and adolescents with CNS GCTs.

Our results show that GCTs histology, tumor site and size may be important predictors of CNS GCTs survival in children and adolescents. In addition, we also established a nomogram based on high-risk factors to predict the 5- and 10-year survival probability of children CNS GCTs, and verified the stability of the model through internal validation.

Consistent with other cancers, the histological type of intracranial germinoma has a significant influence on the prognosis of children. In our study, it was found that NGGCTs scored 76 points in the nomogram constructed based on multivariate regression analysis, which was significantly higher than GGCTs. Compared with other germ cell tumors, NGGCTs have higher invasiveness and malignancy, and poor prognosis. This is consistent with the findings of Matsutani et al., that germinoma with different histological characteristics has a significant impact on the prognosis of patients. In addition, the clinical treatment of NGGCTs generally requires the combination of surgery and postoperative radiotherapy and chemotherapy, and the treatment complications are also prognostic factors that cannot be ignored, which can be further explored in future studies.

In this study, the site of intracranial germinoma was only screened in LASSO regression but was not statistically significant in univariate COX regression (P=0.087). This may be related to the incomplete statistics of the SEER database itself, as some tumors are present in multiple intracranial sites simultaneously. Intracranial germinoma usually occurs in the sellar region, pineal gland, basal ganglia and other parts. In our study, the number of germinomas in the pineal region was 48.2%, and Acharya et al. also reported that about half of CNS GCTs occurred in the pineal region. We found that tumor location was also an important factor affecting the prognosis of children. This may be due to the fact that the pineal region is located in an important intracranial anatomical site, which may cause increased intracranial pressure, diabetes insipidus, sleepiness and other changes in consciousness. In addition, because the pineal region is located deep in the brain, it is difficult to treat, resulting in a poor prognosis of tumors in this region.

Tumor size is known to be an important prognostic factor in many solid tumors. The variables screened by us through LASSO also included tumor size, indicating that the prognosis of CNS GCTs was significantly correlated with it. We found that the poor prognosis of CNS GCTs in children and adolescents was associated with tumor size, and the prognosis was worse as the number of tumors increased. This may be associated with a large germ cell tumor infiltrating the surrounding tissue and requiring craniotomy and postoperative chemoradiotherapy. And the treatment of small tumors is only simple chemoradiotherapy. It is worth noting that craniotomy itself can cause great collateral damage to children, especially deep brain tumors. Therefore, in future studies, the size of the tumor needs to be further refined. Unlike previous studies, we did not find a correlation between age, sex, race, or treatment
and the outcome of intracranial germinoma in children. This may be caused by a difference in the way we classify variables.

Currently, the impact of risk factors related to CNS GCTs on prognosis remains controversial. In addition, independent prognostic factors may be difficult to predict the prognosis of germinoma. A variable PI was calculated using the three risk factors, and the children were classified into high-risk and low-risk groups. The survival curve (Figure 5, C and D) showed that there was a significant difference in survival time between the high-risk group and the low-risk group, and the difference between the development group and the validation group was statistically significant (P<0.0001). We tested the stability and accuracy of the new prognostic nomogram model. The consistency index of the model in the development group and the validation group was 0.744 and 0.759, indicating that the model has the good predictive ability and can be used in clinical practice. In summary, the prediction model constructed by multiple factors has a more significant effect on prognosis than that of a single factor, and it is a very promising method for predicting prognosis in the future.

There are still limitations to the study. First, the SEER database is retrospective data with limited clinical information of patients, and there may be selection bias in inpatient data. Future randomized controlled trials are needed to validate prognostic risk factors for germinoma. Second, the current prognostic model is only validated based on internal data, and external validation is needed in the future. Nevertheless, our nomogram helps predict the prognosis of CNS germinoma in children with good accuracy.

**Conclusion**

To our knowledge, this is the first study to develop a prognostic model for CNS GCTs in children and adolescents based on large sample size. Our results suggest that the nomogram can effectively predict 5- and 10-year survival probability in children and adolescents with CNS GCTs, thus providing clinicians with a useful prognostic tool.

**Abbreviations**

GCTs: germ cell tumors; CNS: central nervous system; GGCTs: germinomatous germ cell tumors; NGGCTs: nongerminomatous germ cell tumors; SEER: Surveillance, Epidemiology and End Results; LASSO: least absolute shrinkage and selection operator; ROC: operating characteristic curve; DCA: decision curve analysis; PI: prognostic index;

**Declarations**

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**Author contributions**
Conception and design: ZTJ, YQY; Collection and assembly of data: ZTJ;
Data analysis and interpretation: ZTJ
Manuscript writing: All authors;
Final approval of manuscript: All authors;
Accountable for all aspects of the work: All authors

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The authors declare no competing interests.

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Data availability statement
SEER is an open access database (https://seer.cancer.gov/). All data is freely available in the SEER*Stat software.

Ethical approval statement
The study was approved by the SEER Ethics Committee and provided account access. All participants had informed consent. Details are available at https://seer.cancer.gov. The study was carried out in accordance with the Declaration of Helsinki.

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**Figures**
Figure 1

Flowchart of participant inclusion and exclusion GGCTs: Germinomatous germ cell tumors; NGGCTs: Nongerminomatous germ cell tumors;
Figure 2

LASSO regression model was used to select characteristic impact factors. (A) LASSO coefficients of 3 features; (B) Selection of tuning parameter ($\lambda$) for LASSO model

Figure 3
Nomograms predicting 5- and 10-year survival probability. Pit/Cra gland: Pituitary gland/Cranioopharyngeal duct; GGCTs: Germinomatous germ cell tumors; NGGCTs: Nongerminomatous germ cell tumors

Figure 4

(A) 5- and 10-year calibration plot of the development group; (B) 5- and 10-year calibration plot of the validation group; (C) 5- and 10-year DCA of the development group; (D) 5- and 10-year DCA of the validation group.
Figure 5

(A) 5- and 10-year ROC of the development group; (B) 5- and 10-year ROC of the validation group (C) Survival curve of development group based on prognosis index; (D) Survival curve of validation group based on prognosis index

Supplementary Files

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- Additionalfile1.docx
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- Additionalfile3.csv