Characterizing Prognostic Factors in Adult-Onset Neuroblastoma: A Population-Based Study.

Yao Zhang
Beijing Children's Hospital
Chenxuan Yang (yangcx13@foxmail.com)
Tsinghua University School of Medicine https://orcid.org/0000-0001-9064-9740

Research

Keywords: SEER, neuroblastoma, nomogram, adult-onset disease

Posted Date: February 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-198536/v1

Abstract

Background: Neuroblastoma (NB) is the most commonly diagnosed malignancy among pediatric patients with a high level of heterogeneity. NB is rarely seen in adult patients, yet adult-onset NB is associated with poor outcome and distinct clinical features from pediatric NB. Guidelines for the management of adult-onset NB are not yet defined and the treatment is largely dependent on the experience of corresponding oncologists. Previous reports on adult-onset NB have mostly been case reports or case series, without high-quality, population-based cohort study. Our study aims to provide new insights and promotes understanding of adult-onset NB using the data from Surveillance, Epidemiology and End Results (SEER) program.

Methods: We extracted data of primary NB patients diagnosed by positive histology during 1975-2016 from the SEER database, and grouped the patients according to the age of diagnosis. Competing-risk model and Kaplan-Meier plot were used to compare survival rates of adult-onset neuroblastoma with pediatric neuroblastoma. Cox proportional hazard regression model was used in univariate and multivariate analysis to identify prognostic factors affecting overall and cancer-specific survival rates in adult patients. A nomogram was developed according to the multivariate model and internally validated using receiver operator curve (ROC) and decision curve analysis (DCA).

Results: We found a worsened outcome (Median survival time 31 vs 70 months) and distinct clinical characteristics in adults compared with adolescents. Univariate analysis revealed that age (HR=1.7627, 95%CI: 1.1937-2.6027, p = 0.004), surgery (HR=0.3968, 95%CI: 0.2691-0.5852, p <0.0001), primary tumor site, histology type (HR=1.9792, 95%CI: 1.1159-3.5103, p = 0.0195), chemotherapy (HR=1.5723, 95%CI: 1.0284-2.4037, p = 0.0367) was significantly associated with prognosis. Upon multivariate Cox proportional hazard regression model, age, surgery, primary tumor site remained significant for cancer-specific survival. Using the multivariate regression model, we proposed a new nomogram for the prediction of 3-year and 5-year survival rate. The nomogram showed good performance on survival prediction and risk-group stratification in an internal validation cohort.

Conclusion: In conclusion, our study provided novel evidence on prognosis of adult-onset NB using large-scale populational database and identified surgical intervention as the most effective treatment toward adult-onset NB. Our nomogram can serve as potential prediction and risk-stratification tool in clinical practice.

Background

Neuroblastoma (NB) is a common malignant tumor for pediatric patients, the proportion of NB in all pediatric malignancy is 8-10% yet the mortality rate is around 15%(1). The median age of diagnosis is around 17 months(2). It is most commonly diagnosed in children aged from 0-1, accounting for 30% of total neuroblastoma incidence(3). NB arises from neural crest progenitor cells and is usually located at the adrenal glands or sympathetic ganglia, it is classified as an embryonal neuroendocrine tumor with a

high heterogeneity(4). Due to the variability in clinical manifestations, treatment, and prognosis on neuroblastoma are highly dependent on the nature of the tumor(5). Some patients showed remission or differentiation of the tumor without treatment, while others might have distant metastasis despite surgical intervention and systemic treatments(6).

Adult-onset neuroblastoma is a highly rare condition, the incidence is about 0.2 cases per million person-years(7). The prognosis of NB in adult patients is much worse than in pediatric patients. In most cases, patients suffer from continuous recurrence and result in cancer-specific mortality(8). It was reported in several cases that adult-onset NB had a poor response to chemotherapy or radiotherapy and potentially lead to local or distant recurrences(8-11). Molecular studies have also been conducted to identify that certain driver mutations are associated with later onsets of age, such as ATRX and TERT(12). However, ALK mutation or MYCN amplification, which are more commonly found in new-born NB, can also be detected in adults(13). Adult-onset NB also exhibits up-regulated maintenance of telomeres, which marks high risk and invasiveness of the tumor(14). Despite the studies, up until now, there is no widely accepted treatment guideline or risk prediction tool for adult-onset NB, and the clinical study of adult-onset NB has been based on case reports or older databases. Therefore, population-based, high-quality reports are needed to provide new evidence and insights into this disease.

To better understand the adult-onset NB from a large-scale, population-based cohort, we sought to characterize the clinical features and outcomes using the Surveillance, Epidemiology and End Results (SEER) database, which covers 18 geographic areas of the United States and represents about 30% of the population(15).

Methods

Data collection

The data of neuroblastoma patients was extracted from the Surveillance, Epidemiology, and End Results (SEER) database using the SEER*Stat program (version 8.3.8). The database of cancer incidence from 18 registries with additional treatment fields was chosen for the study, it was submitted on November 2018 and contains data from 1975 to 2016. The SEER database includes about 30% of the population in the United States and has excellent statistical power. The inclusion criteria for the study were defined as: 1. Any patient diagnosed with neuroblastoma by WHO classification from 1975 to 2016. 2. Diagnosis confirmed with positive histology by ICD-O-3. 3. Neuroblastoma was the first malignant tumor diagnosed for the patient. 4. There was only one primary site of the tumor. The exclusion criteria for the study were defined as: 1. Any patient with unknown follow-up or cause of death information. 2. Any patient with overall survival time of less than 1 month. According to the inclusion criteria, 4664 entries were extracted from the database, after exclusion of ineligible entries, 4561 patients were included for the study. The adult group and adolescent group were defined by the age of diagnosis (age > 19 for adults), and 193 patients were included in the adult group (Supplementary). Clinical characteristics including gender (male/female), age, race (white/black/other/unknown), primary site, tumor grade (grade I/II/III/IV),

histology subtype (neuroblastoma/ganglioneuroblastoma), surgery (yes/no/unknown), chemotherapy (yes/no/unknown), radiotherapy (yes/no/unknown), lymph node conditions (nodes removal, nodes positive), distant metastasis (bone, brain, liver ,lung), lymph-vascular invasion (yes/no/unknown) were retrospectively analyzed from the database. The continuous variables such as age were transformed as categorical variables by the database. The overall survival time was defined as the time from diagnosis to the date of death or lost to follow-up (censored). The cancer-specific survival time was defined as the time from diagnosis to the date of death specific to neuroblastoma.

Statistical analyses

Gender, race, tumor grade, primary site, histology type (ICD-O-3), surgery treatment, surgery type, lymph node removal, lymph node positivity, chemotherapy, radiotherapy was analyzed as potential prognostic factors. For comparison of proportions between the adult and adolescent group, chi-square test or Fisher's exact test was used to assess the difference. Survival rates of different groups were estimated by the Kaplan–Meier analyses and the log-rank test. The adult group was randomly separated into a training group and a validation group at a ratio of 4:1 (160 for the training group, 33 for the validation group) using the "caTools" package, the training group was used in the univariate and multivariate analysis and the validation group was used as internal validation. Univariate and multivariate Cox Proportional Hazard Regression Model was performed to estimate the impact of different factors on survival, presented as hazard ratio (HR) and corresponding 95 % confidential interval (CI) for every potential prognostic factor. The multivariate Cox regression was performed by the backward elimination method combined with manual adjustments according to established evidence. A p-value lower than 0.05 was deemed statistically significant for all analyses. The statistical analyses were carried out with R 3.6.1 with "survival" and "survminer" packages. A visualized nomogram was constructed based on the multivariate analysis of cancer-specific survival using the "rms" package. Accuracy of the prediction model in the validation group and the training group was evaluated by the receiver operator curve (ROC) using the area under the curve (AUC) as an indicator of the specificity and sensitivity, the plot was generated with "pROC" package in R. Calibration plot of the nomogram was used to determine the consistency of predicted value with the actual observed outcomes in the training group as well as the whole group. Decision curve analysis (DCA) is a method to evaluate the net benefit of using a certain diagnostic or prognostic tool by comparing the risk of intervention to the risk of the disease, the DCA plot was generated by "stdca" package to test for the clinical applicability of the newly constructed nomogram. R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses via RStudio software (version 1.1.456). The R code used for this study is available in supplementary files.

Results

Clinical characteristics and survival of Neuroblastoma in adults and adolescents

Of all the entries extracted according to the inclusion and exclusion criteria, a total number of 4561 patients were identified from the SEER database, with 4368 (95.8%) patients diagnosed before the age of 19 (adolescent group) and 193 (4.2%) diagnosed after the age of 19 (adult group) (Fig1.a). The median age of diagnosis for the adolescent group is 1-9 years old and 35-39 years old for the adult group. Most of the patients were diagnosed at the age of 1-9 (Fig1.b). There was no significant difference in the gender or race distribution between the adolescent and adult groups (Table 1). To compare the prognosis of neuroblastoma in adults and adolescents, Kaplan-Meier plot and log-rant test were used to determine the overall survival (OS) and cancer-specific survival (CSS) of the two groups. The adolescent group had a significantly better overall survival compared with the adult group ($p<0.0001$), the median survival time for the adult group was 31 months (95% CI: 24-45 months) while the median survival time for the adolescent group was 70 months (95% CI: 64-74 months) (Fig1.c). The cancer-specific survival was defined as the cause of death registered as neuroblastoma in the SEER database. Similarly, the adolescent group showed better cancer-specific survival compared with the adult group ($p<0.0001$) (Fig1.d). To further study the cancer-specific death caused by neuroblastoma in the two age groups, we used the competing risk model to test for the cumulative incidence of cancer-specific death. By considering other causes of death as competing risks, the model showed that adults were more susceptible to neuroblastoma-caused death compared with adolescents. Interestingly, adolescents had a significantly higher incidence of death by other causes (Fig1.e).

Table 1. Clinical characteristics of adult and adolescent neuroblastoma patients

	adolescents	percent	adults	percent	p-value
Total	4368		193		
Gender					0.7486
male	2292	52.5%	99	51.3%	
female	2076	47.5%	94	48.7%	
Race					0.6932
Black	555	12.7%	29	15.0%	0.3452
White	3429	78.5%	147	76.2%	0.44
Other	339	7.8%	16	8.3%	0.7882
Unknown	45	1.0%	1	0.5%	0.7423
Grade(differentiation)					
I(well-differentiated)	125	2.9%	1	0.5%	0.0855
II(moderately-differentiated)	43	1.0%	10	5.2%	<0.0001
III(poorly-differentiated)	1302	29.8%	28	14.5%	<0.0001
IV(undifferetiated)	424	9.7%	16	8.3%	0.5141
unknown	2474	56.6%	138	71.5%	<0.0001
Primary Site					
Brain	80	1.8%	50	25.9%	<0.0001
Retroperitoneum	528	12.1%	28	14.5%	0.3146

To determine whether there are significant differences between clinical characteristics in the two age groups, the chi-square test and Fisher's exact test were deployed to test frequencies of each category. The most common grade of differentiation was grade III (poorly-differentiated) in both age groups, with the proportion significantly higher in adolescents compared with adults (29.8% vs 14.5%, adolescents vs adults, $p<0.0001$). The inverse was true in grade II tumors, where the adult group had a higher proportion of patients (1.0% vs 5.2%, adolescents vs adults, $p<0.0001$). However, the grade information was not obtained or recorded in most cases (56.6% vs 71.5%, adolescents vs adults). The primary site of the tumor had distinct distribution in the two groups (Fig2), the most common primary sites in adult patients included brain, retroperitoneum, soft tissue, endocrine organs, nasopharynx area, and cranial nerves, while the most common primary sites in adolescent patients were endocrine organs, soft tissue, retroperitoneum, respiratory organs. In comparison, the adult group had a significantly higher incidence of neuroblastoma in the brain (25.9% vs 1.8%, adults vs adolescents, $p<0.0001$), nasopharynx area (8.3% vs 0.1%, adults vs adolescents, $p<0.0001$), and cranial nerves (7.8% vs 2.5%, adults vs adolescents,

p<0.0001). The adolescent group had significantly higher incidence in soft tissue (24.9% vs 13.5%, adolescents vs adults, p=0.0003) and endocrine organs (44.0% vs 10.9%, adolescents vs adults, p<0.0001). Histology type was also significantly different in the two age groups, adults had a higher proportion of ganglioneuroblastoma (23.8% vs 16.3%, adults vs adolescents, p=0.0056). Though contrary to the mortality rate, ganglioneuroblastoma is generally considered less aggressive than classic neuroblastoma, the results indicate that prognostic factors other than histology type might be stronger determinants of the prognosis of adult-onset neuroblastoma. The surgery rates were comparable between the two groups; however, the adolescent group had a higher resection rate (50.7% vs 36.3%, adolescents vs adults, p<0.0001), other forms of surgery include tumor destruction, tumor reduction, and explorative surgery with biopsy. The results suggest that although a similar proportion of patients underwent surgery in the two age groups, the adolescent patients were more likely to receive resection to achieve a better surgical outcome, this is possibly due to the nature of primary site locations and the complexity of surgery in adolescent patients. The adolescent group had a significantly more treatment rate of chemotherapy (66.2% vs 45.1%, adolescents vs adults, p<0.0001), but less treatment rate of radiology (19.2% vs 37.8%, adolescents vs adults, p<0.0001). The results are in line with the mortality rate since the current guideline for neuroblastoma treatment suggests that radiotherapy only applies to patients with recurrence after surgery or for palliative purposes, while chemotherapy is a common modality for low to mid-risk patients.

Univariate analysis of prognostic factors in adult patients.

To study the determinants of the worsened prognosis in adult patients, univariate analysis was performed using a Cox proportional hazard regression model (Cox regression model) in the adult group. For model development, the adult group was randomly separated into training and validation groups at a ratio of 4:1 for further analysis. Cox regression model on overall survival in the training group showed that gender and race were not associated with prognosis (Table 2). However, increased age was associated with a worse prognosis, the onset-age of more than 50 had a hazard ratio of 1.7627 (95%CI: 1.1937-2.6027, p = 0.004), indicating that even after stratification of age by adults and adolescents, it remains a strong determinant of prognosis. Another statistically significant prognostic factor for overall survival is the treatment by surgery, with a hazard ratio of 0.3968 (95%CI: 0.2691-0.5852, p <0.0001), suggesting that surgical intervention is still the most effective treatment for adult neuroblastoma patients. Considering that the overall survival does not fully reflect the characteristics of the tumor since other factors such as comorbidities and environmental exposure might affect the results, we also analyzed the cancer-specific survival using the Cox regression model. The cancer-specific survival analysis revealed that primary site of the nasopharynx and middle ear (HR=0.2547, 95%CI: 0.0749-0.8659, p = 0.0285), as well as cranial nerves and other nervous system organs (HR=0.2637, 95%CI: 0.0892-0.7798, p = 0.0160), had significantly better prognosis compared with other sites as reference. However, these areas of primary sites are less common than other sites such as the brain and retroperitoneum. Therefore, although more favorable to prognosis, they contribute less to the general survival rate of adult patients. Surgery remained a significant prognostic factor for better prognosis in the

cancer-specific survival (HR=0.3513, 95%CI: 0.2188-0.5639, p<0.0001) while tumor resection showed significant better prognosis compared with other forms of surgery (HR=0.3556, 95%CI: 0.1595-0.7928, p = 0.0115). Histology type of neuroblastoma was associated with worsened prognosis (HR=1.9792, 95%CI: 1.1159-3.5103, p = 0.0195), in line with the more aggressive nature of classic neuroblastoma. Interestingly, patients who received chemotherapy had worse survival (HR=1.5723, 95%CI: 1.0284-2.4037, p = 0.0367), this is probably because chemotherapy is more commonly used in patients with higher risk level or nonresectable tumor as replacement therapy, thus these patients generally have a more advanced stage of the tumor. We also tested the lymph node removal and positive lymph nodes by biopsy in the Cox regression model, however, these factors did not have a significant impact on survival. To further validate the Cox regression results, we plotted the overall survival and cancer-specific survival in the whole adult group stratified by different prognostic factors, all showed statistical significance (Fig.3 a-e).

Table 2. Univariate analysis of prognostic factors in adult-onset neuroblastoma patients

	OS			CSS		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender						
Female	1.0000			1.0000		
Male	0.9446	0.6885 - 1.296	0.724	0.9443	0.6184 - 1.4417	0.7905
Race						
White	1.0000			1.0000		
Black	0.9467	0.6094 - 1.4708	0.8075	0.92	0.5172 - 1.6363	0.7765
Other	0.754	0.4138 - 1.3739	0.3563	0.7066	0.2838 - 1.7595	0.4557
Unknown	1.0155	0.1413 - 7.3	0.9878	N/A	N/A	N/A
Age						
20-29	1.0000			1.0000		
30-39	1.2115	0.7936 - 1.8494	0.3741	1.4088	0.8032 - 2.4709	0.2319
40-49	1.5794	0.9124 - 2.734	0.1026	1.5366	0.7474 - 3.1591	0.2427
50+	1.7627	1.1937 - 2.6027	0.0044	1.5497	0.9148 - 2.6253	0.1033
Grade(differentiation)						
I(well-differentiated)	1.0000			1.0000		
II(moderately-differentiated)	0.8961	0.3933 - 2.0417	0.794	0.527	0.1289 - 2.155	0.3727
III(poorly-differentiated)	1.4453	0.9028 - 2.3138	0.125	1.1367	0.5984 - 2.1589	0.6956
IV(undifferetiated)	1.2453	0.7135 - 2.1734	0.4402	1.4669	0.753 - 2.8576	0.2601
unknown	N/A	N/A	N/A	N/A	N/A	N/A

Primary Site						
Others	1.0000			1.0000		
Brain	0.7881	0.4784 - 1.2983	0.3499	0.6383	0.3422 - 1.1908	0.1583
Cranial Nerves Other Nervous System	0.7778	0.4087 - 1.4802	0.444	0.2637	0.0892 - 0.7798	0.016
Nose, Nasal Cavity and Middle Ear	0.6117	0.2925 - 1.2793	0.1917	0.2547	0.0749 - 0.8659	0.0285
Other Endocrine including Thymus	0.9207	0.4993 - 1.6977	0.7913	0.5957	0.2744 - 1.2932	0.1903
Retroperitoneum	1.1726	0.6668 - 2.062	0.5804	0.8646	0.435 - 1.7187	0.6782
Soft Tissue including Heart	1.0032	0.5644 - 1.7831	0.9913	0.6889	0.3317 - 1.4305	0.3175
Trachea, Mediastinum and Other Respiratory Organs	0.6191	0.2364 - 1.6214	0.329	0.6171	0.1815 - 2.098	0.4394
Histology type						
Ganglioneuroblastoma	1.0000					
Neuroblastoma	1.2055	0.8424 - 1.7249	0.3067	1.9792	1.1159 - 3.5103	0.0195
Surgery						
No	1.0000					
Yes	0.3968	0.2691 - 0.5852	<0.0001	0.3513	0.2188 - 0.5639	<0.0001
Tumor resection						
No/other surgery type	1.0000					
Yes	0.6157	0.3478 - 1.0899	0.096	0.3556	0.1595 - 0.7928	0.0115
Nodes removal						
No	1.0000					
Yes	0.553	0.243 -	0.1581	0.4946	0.1095	0.3601

		1.2587			- 2.2335	
Nodes positive						
No	1.0000					
Yes	2.3586	0.6339 - 8.7765	0.2006	N/A	N/A	N/A
Chemotherapy						
No	1.0000					
Yes	1.2275	0.893 - 1.6873	0.2067	1.5723	1.0284 - 2.4037	0.0367
Radiology + Surgery						
No	1.0000					
Yes	0.8993	0.6504 - 1.2434	0.5208	0.9844	0.6408 - 1.5123	0.9429

Multivariate analysis of prognostic factors in adult patients.

To adjust for different confounding factors and assess the adjusted significance of the prognostic factors for adult-onset neuroblastoma, we performed multivariate Cox regression on the training group to test for previously identified factors as well as the established confounding or prognostic factors. Factors highly correlated with each other were removed to avoid multicollinearity. Age and surgery treatment were identified as significant prognostic factors for overall survival after adjustment (Table2). Higher age of onset was associated with worsened prognosis while surgery was an important factor for better prognosis with a hazard ratio of 0.2966 (95%CI: 0.1796-0.4900, p<0.0001). Cancer-specific survival was also analyzed by the multivariate Cox regression model. Likewise, age was significantly associated with worsened prognosis, patients who were diagnosed at the age of 40-49 had the highest hazard ratio of 2.1865 (95%CI: 1.0028-4.6742, p=0.0436) as compared with the age group of 20-29 for reference. Surgery remained the most important factor for improved prognosis (HR=0.3412, 95%CI: 0.1951-0.5970, p<0.0001). The primary site was also a significant factor for the outcome after adjustment, patients who had primary tumor located at cranial nerves or nervous system other than the brain had a better survival (HR=0.2635, 95%CI: 0.0867-0.8004, p=0.0186), so did those with the primary site at nasopharynx and middle ear (HR=0.2717, 95%CI: 0.0769-0.9602, p=0.0431). Finally, the histology type of classic neuroblastoma was significantly associated with increased cancer-specific mortality (HR=2.0346, 95%CI:

1.0612-3.9011, p=0.0325). Chemotherapy was not significant in multivariate analysis, indicating that it should only be applied to a certain subset of patients.

Table 3. Multivariate analysis of adjusted prognostic factors in adult-onset neuroblastoma patients

	OS			CSS		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender						
Female	1.0000			1.0000		
Male	0.9996	0.651-1.5348	0.9984	0.9817	0.6237-1.5452	0.9363
Age						
20-29	1.0000			1.0000		
30-39	2.0547	1.1361-3.7162	0.0172	2.0132	1.05-3.8599	0.0351
40-49	1.6448	0.7964-3.3971	0.1787	2.1865	1.0228-4.6742	0.0436
50+	1.821	1.0673-3.1068	0.0279	1.8995	1.1063-3.2614	0.02
Surgery						
No	1.0000			1.0000		
Yes	0.2966	0.1796-0.4900	<0.0001	0.3412	0.1951-0.597	<0.0001
Unknown	1.6873	0.6973-4.0827	0.2459	1.8420	0.7000-4.8469	0.2159
Primary Site						
Others				1.0000		
Brain				0.8188	0.4207-1.5934	0.5562
Cranial Nerves Other Nervous System				0.2635	0.0867-0.8004	0.0186
Nose, Nasal Cavity and Middle Ear				0.2717	0.0769-0.9602	0.0431
Other Endocrine including Thymus				1.1988	0.5228-2.7489	0.6686
Retroperitoneum				0.9036	0.4329-1.8862	0.7872
Soft Tissue including Heart				0.8875	0.4111-1.9159	0.7612
Trachea, Mediastinum and Other				0.6867	0.1862-	0.5723

Respiratory Organs		2.5317	
Histology type			
Ganglioneuroblastoma	1.0000		
Neuroblastoma	2.0346	1.0612-3.9011	0.0325

Development and validation of a nomogram to predict cancer-specific survival

Next, to make the model more suitable for clinical application, we developed a nomogram based on the multivariate Cox regression model for cancer-specific survival. The 3-year and 5-year estimated survival rate was calculated from the model as readouts (Fig.4). By adding up the points generated by different prognostic factors and vertically refer the total points to the survival rate, one can easily generate the prognostic information for a certain patient. The nomogram was tested for the prognostic power using the ROC plot. In the training group, AUC for 5-year survival rate prediction was 0.726, 3-year survival rate prediction was 0.701. In the validation group, the nomogram also generated robust predictive power, with an AUC for a 5-year survival rate prediction of 0.698 and a 3-year survival rate prediction of 0.724 (Fig.5 a-b). The calibration plot also showed good consistency between nomogram predictions and actual observations (Fig.5 c-d, Supplementary). Finally, the DCA curve was plotted to ascertain that the nomogram was useful in clinical decision-making (Fig.5 e-f, Supplementary). The results in the 3-year and 5-year survival predictions both showed that the nomogram had good clinical applicability due to the increased net benefit and a wide range of threshold probabilities.

Stratification of high and low-risk patients according to the nomogram points.

Finally, we sought to find the cut-off value of the total points generated by the nomogram to achieve the best discriminating power of high-risk and low-risk patients. Multiple testing was conducted to identify the cut-off value of 178.3 (80% percentile). Kaplan-Meier plot and log-rank test were performed to validate the stratification of patients by the cut-off value. Both the validation group and the whole adult group showed significant separation of patients on the overall survival and cancer-specific survival (Fig.6 a-d). Therefore, apart from the prediction of survival rate, our nomogram also had an excellent performance in identifying high-risk patients from low-risk patients.

Discussion

Adult-onset neuroblastoma is a rare disease with a low prevalence and incidence worldwide(14). Our study identified 193 adult-onset neuroblastoma patients and 4368 adolescent neuroblastoma patients using the large cohort data from the SEER program to provide novel insights into the disease. Previous studies and census data estimated an incidence of adult-onset neuroblastoma at around 5%(16), our study showed that the proportion of adult patients was 4.2% in the SEER cohort, representing 30% of the total population in the US. The median age of diagnosis in our study lay within the age group of 35-39, consistent with previous cases reporting that most of the patients with adult-onset neuroblastoma were diagnosed before the age of 40(17). Through Kaplan-Meier plot and log-rank analysis, we confirmed that adult-onset neuroblastoma exhibited significantly worse outcomes, both in overall survival and in cancer-specific survival, as was reported by various previous studies(11, 18, 19). It was of note that by using the competing risk model, we found more adolescent neuroblastoma patients died of causes other than the tumor (cardiovascular disease, sepsis, suicide, etc.)(20). This was not the case for adult patients, who had significantly higher mortality due to neuroblastoma than other causes. This suggests that apart from cancer itself, other factors such as comorbidities and psychological counseling should also be considered during the treatment of neuroblastoma.

Analyses of the clinical characteristics revealed that the adult and adolescent groups did not differ in gender or race distribution. Although most entries did not include grade information, the data showed that both groups had a majority of patients with grade III (poorly differentiated) cancer at the time of diagnosis. This result indicates that differentiation might not be the potential factor for the worsened prognosis in adults, neuroblastoma with similar differentiation might behave differently in adults and adolescents, based on other molecular or genetic factors(12). Comparison of primary sites generated the most important distinction between adult and adolescent groups. The most common primary site for adolescent patients was endocrine organs, namely the adrenal glands, which can be rather safely resected by laparoscopic or robotic surgeries(21). However, the most common primary site for adult patients is brain neuroblastoma, a rather unfavorable site for any tumors. The other common primary sites for the two groups were similar, both including retroperitoneum and soft tissues. Interestingly, there was a rather large proportion of adolescent patients with neuroblastoma located in the respiratory organs, whereas such primary site was rare in adult patients.

Identification of prognostic factors using the univariate and multivariate Cox regression model revealed that age and surgery were good predictors for the overall survival in adult-onset neuroblastoma patients. Age, surgery, primary site, and histology type were significant predictors for cancer-specific survival. Higher age at diagnosis was associated with a worsened survival, as aging determines physiological status, treatment outcome, and the nature of the tumor(22). Surgery was the most effective way of treating adult-onset neuroblastoma, shown by a low hazard ratio in both overall survival and cancer-specific survival. Chemotherapy and radiotherapy were not significantly associated with prognosis. However, this could be because that these treatments are usually applied to the more advanced tumor or for palliative purposes(23), and thus the corresponding population is different from the rest in terms of tumor staging(10, 13, 24, 25). Moreover, some patients who received chemotherapy or radiotherapy outside the SEER registered facilities were defined as unknown in the database, this could also lead to

inaccuracy in the analysis. The primary site was significantly associated with prognosis, tumors located at the nasopharynx area and cranial nerves had better prognosis shown by low hazard ratios. This could be explained by advances in the pediatric and ENT surgical approaches of endonasal and endoscopic resection and reconstruction to achieve good local control of these tumors(17, 26, 27). Histology type also determines the clinical outcomes, which was consistent with previous guidelines(28).

By using the prognostic factors identified in the Cox regression model, we constructed and proposed a novel clinical nomogram for the prediction of 3-year and 5-year survival of adult-onset neuroblastoma patients. The nomogram was also useful in stratifying patients into high-risk and low-risk groups based on the total points. Currently, there are ongoing studies on immune-based or cell-death-based therapies for neuroblastoma patients(23, 29, 30), future studies or clinical trials can utilize the nomogram and stratification strategy as potential criteria for enrolling high-risk patients for further development of new treatments.

The current study was not without limitations. The population examined in the study was registered in the database over a long span of time, therefore the potential changes in guidelines and medical technologies could shift the prognosis and generate heterogeneity for the population studied. Although data filtering and feature selection measures were taken, the missing and unknown entries in the database can also lead to bias in the analysis as they are not completely missing at random. Lastly, despite the vast population covered by the SEER program, adult-onset neuroblastoma patients remained a rather small cohort and therefore limiting the statistical power for any analysis performed.

Conclusions

In conclusion, considering the low incidence of adult-onset neuroblastoma and the scarcity of large-scale study, the characteristics of this disease has been rather poorly understood. The current study is the first to provide population-based evidence and comprehensive insights into the characteristics of adult-onset neuroblastoma and factors associated with the poor outcome of this disease. Our study can serve as the very first step in understanding and demystifying the disease for further more detailed studies.

Declarations

Ethics approval and consent to participate: Ethical approval and consent were waived for this study, due to the fact that patients in the SEER database could not be identified by any data extracted. Access to the database was approved by signing the data-use agreement from SEER administration (http://seer.cancer.gov/data/sample-dua.html).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analysed during the current study are available in the SEER repository, http://seer.cancer.gov. All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests: the authors declare that they have no competing interests

Funding: This research received no external funding.

Authors' contributions: YZ collected the data, performed data analysis, investigation and visualization, and wrote the manuscript. CY Conceptualized the study, performed data analysis and investigation, and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements: We thank Xiaoli Ma for advice on manuscript writing.

References

1. Maris JM. Recent advances in neuroblastoma. N Engl J Med. 2010;362(23):2202-11.
2. London WB, Castleberry RP, Matthay KK, Look AT, Seeger RC, Shimada H, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(27):6459-65.
3. Stiller CA, Parkin DM. International variations in the incidence of neuroblastoma. International journal of cancer. 1992;52(4):538-43.
4. Hoehner JC, Gestblom C, Hedborg F, Sandstedt B, Olsen L, Påhlman S. A developmental model of neuroblastoma: differentiating stroma-poor tumors' progress along an extra-adrenal chromaffin lineage. Lab Invest. 1996;75(5):659-75.
5. Esposito MR, Aveic S, Seydel A, Tonini GP. Neuroblastoma treatment in the post-genomic era. J Biomed Sci. 2017;24(1):14.
6. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(2):298-303.
7. Esiashvili N, Goodman M, Ward K, Marcus RB, Johnstone PAS. Neuroblastoma in adults: Incidence and survival analysis based on SEER data. Pediatric blood & cancer. 2007;49(1):41-6.
8. Rogowitz E, Babiker HM, Kanaan M, Millius RA, Ringenberg QS, Bishop M. Neuroblastoma of the elderly, an oncologist's nightmare: case presentation, literature review and SEER database analysis. Exp Hematol Oncol. 2014;3:20.
9. König M, Osnes T, Jebsen P, Evensen JF, Meling TR. Olfactory neuroblastoma: a single-center experience. Neurosurg Rev. 2018;41(1):323-31.
10. Schipper MH, van Duinen SG, Taphoorn MJ, Kloet A, Walchenbach R, Wiggenraad RG, et al. Cerebral ganglioneuroblastoma of adult onset: two patients and a review of the literature. Clin Neurol Neurosurg. 2012;114(6):529-34.
11. Allan SG, Cornbleet MA, Carmichael J, Arnott SJ, Smyth JF. Adult neuroblastoma. Report of three cases and review of the literature. Cancer. 1986;57(12):2419-21.

12. Brady SW, Liu Y, Ma X, Gout AM, Hagiwara K, Zhou X, et al. Pan-neuroblastoma analysis reveals age- and signature-associated driver alterations. Nat Commun. 2020;11(1):5183.
13. Suzuki M, Kushner BH, Kramer K, Basu EM, Roberts SS, Hammond WJ, et al. Treatment and outcome of adult-onset neuroblastoma. International journal of cancer. 2018;143(5):1249-58.
14. Duan K, Dickson BC, Marrano P, Thorner PS, Chung CT. Adult-onset neuroblastoma: Report of seven cases with molecular genetic characterization. Genes Chromosomes Cancer. 2020;59(4):240-8.
15. Surveillance E, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying) - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.
16. Cheung N-KV, Zhang J, Lu C, Parker M, Bahrami A, Tickoo SK, et al. Association of age at diagnosis and genetic mutations in patients with neuroblastoma. JAMA. 2012;307(10):1062-71.
17. Matthay KK, Maris JM, Schleiermacher G, Nakagawara A, Mackall CL, Diller L, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078.
18. Nzegwu MA, Aghaji A. Neuroblastoma occurring in a 38-year old Nigerian man: a rare finding. Rare Tumors. 2009;1(1):e15.
19. Aleshire SL, Glick AD, Cruz VE, Bradley CA, Parl FF. Neuroblastoma in adults. Pathologic findings and clinical outcome. Arch Pathol Lab Med. 1985;109(4):352-6.
20. Horn SR, Stoltzfus KC, Mackley HB, Lehrer EJ, Zhou S, Dandekar SC, et al. Long-term causes of death among pediatric patients with cancer. Cancer. 2020;126(13):3102-13.
21. Russo AE, Untch BR, Kris MG, Chou JF, Capanu M, Coit DG, et al. Adrenal Metastasectomy in the Presence and Absence of Extraadrenal Metastatic Disease. Ann Surg. 2019;270(2):373-7.
22. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol. 2018;19(6):e305-e16.
23. Garrovillo K, Garrett J, Bollin K, Nasraty F, Sikand H. Dinutuximab in adult-onset chemotherapy refractory high-risk neuroblastoma. J Oncol Pharm Pract. 2020;26(8):2058-65.
24. Zhao Q, Liu Y, Zhang Y, Meng L, Wei J, Wang B, et al. Role and toxicity of radiation therapy in neuroblastoma patients: A literature review. Crit Rev Oncol Hematol. 2020;149:102924.
25. Jrebi NY, Iqbal CW, Joliat G-R, Sebo TJ, Farley DR. Review of our experience with neuroblastoma and ganglioneuroblastoma in adults. World journal of surgery. 2014;38(11):2871-4.
26. Abdelmeguid AS. Olfactory Neuroblastoma. Curr Oncol Rep. 2018;20(1):7.
27. Logrono R, Futoran RM, Hartig G, Inhorn SL. Olfactory neuroblastoma (esthesioneuroblastoma): appearance on fine-needle aspiration: report of a case. Diagnostic cytopathology. 1997;17(3):205-8.
28. Lonergan GJ, Schwab CM, Suarez ES, Carlson CL. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics. 2002;22(4):911-34.

29. Park JA, Cheung N-KV. Targets and Antibody Formats for Immunotherapy of Neuroblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(16):1836-48.
30. Valter K, Zhivotovsky B, Gogvadze V. Cell death-based treatment of neuroblastoma. Cell Death Dis. 2018;9(2):113.

Figures

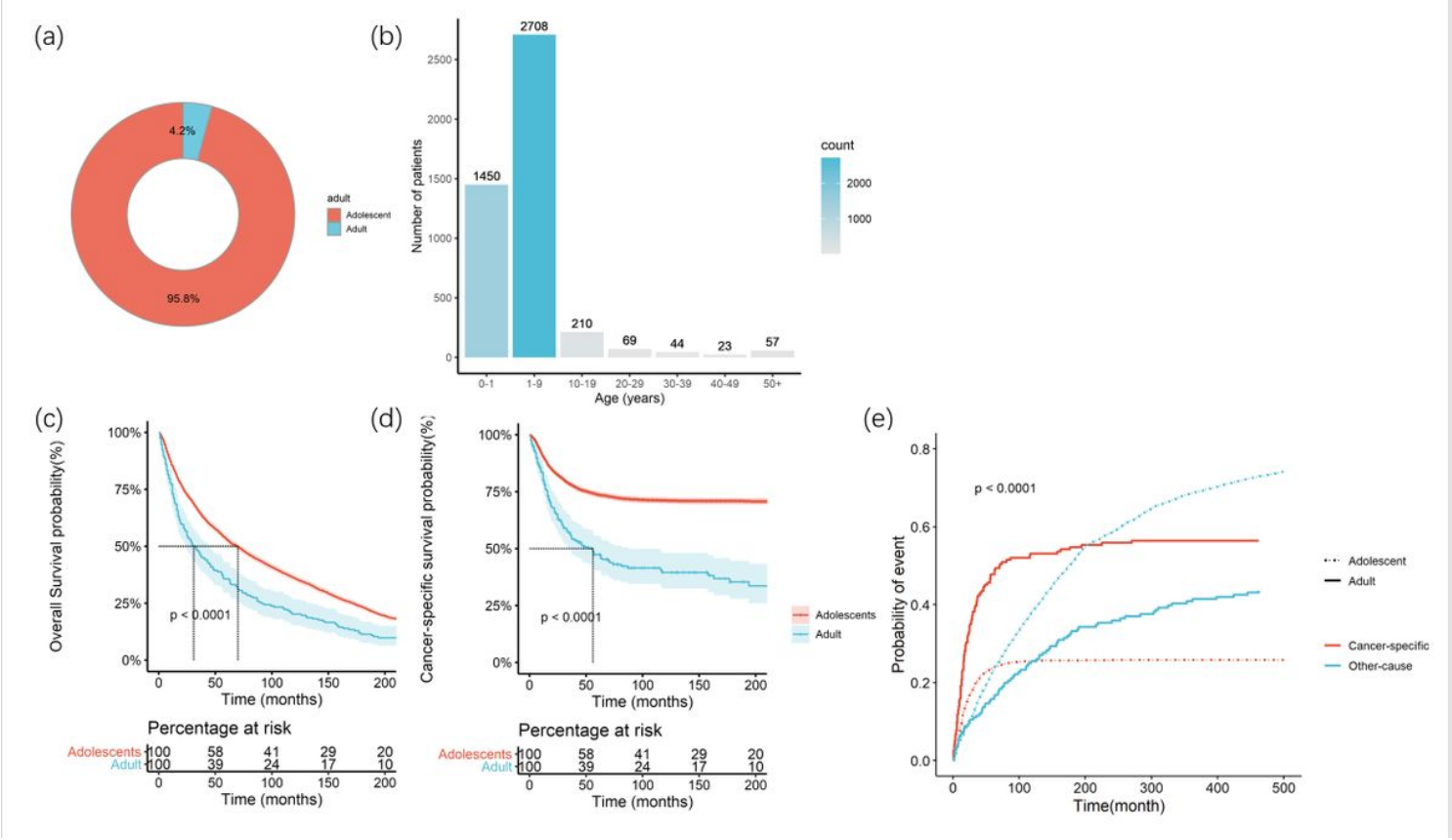

Figure 1

(a, b) Proportions and the age distributions of 4561 adult and adolescent patients diagnosed with neuroblastoma during 1975 to 2016 registered in the SEER database; (c, d) Kaplan-Meier plot of overall and cancer-specific survival of adult and adolescent neuroblastoma patients; (e) Competing risk model of adult and adolescent patients comparing the cancer-specific death and death by other causes.

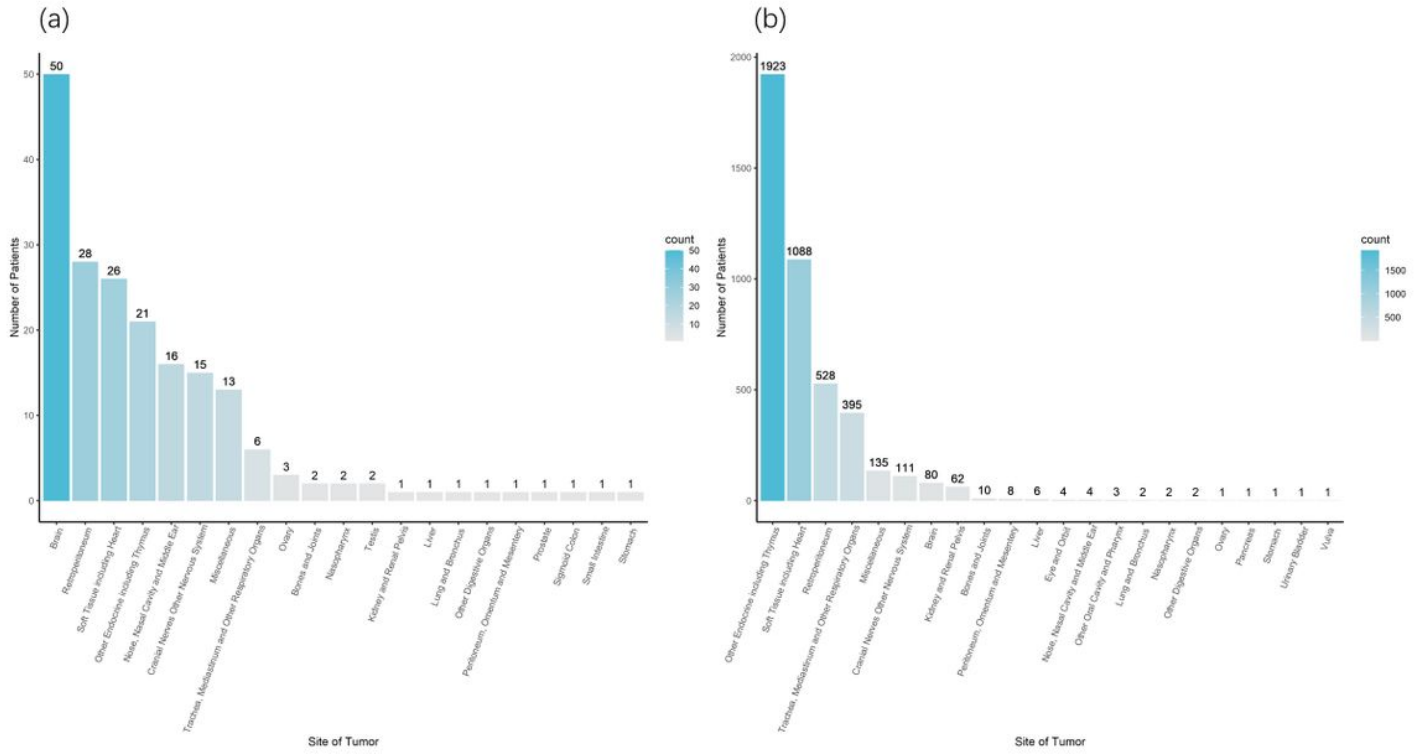

Figure 2

(a) Distribution of tumor primary sites in adult-onset neuroblastoma patients ranked by the number of patients. (b) Distribution of tumor primary sites in adolescent-onset neuroblastoma patients ranked by the number of patients

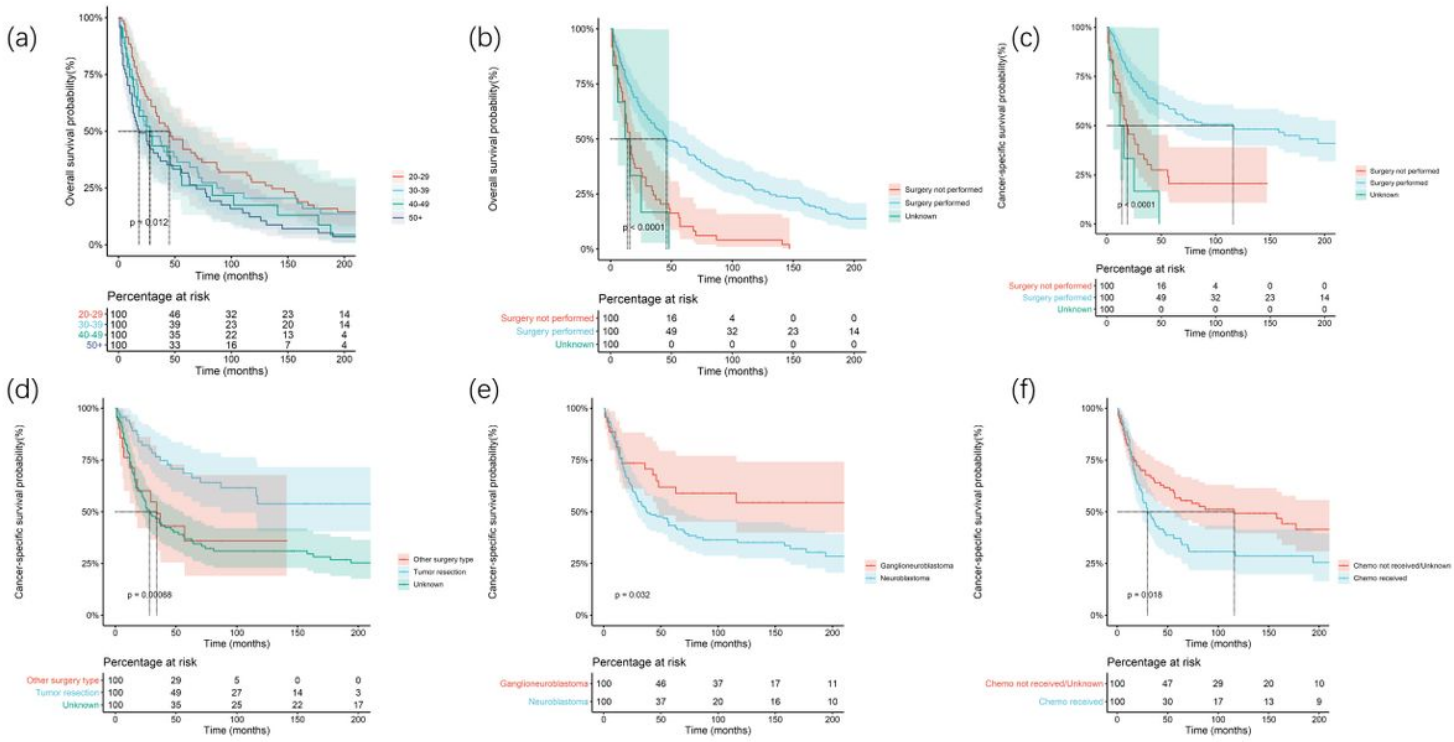

Figure 3

(a) Kaplan-Meier plot of the overall survival of adult-onset neuroblastoma patients grouped by age of diagnosis. (b) Kaplan-Meier plot of the overall survival of adult-onset neuroblastoma patients grouped by surgery status. (c) Kaplan-Meier plot of the cancer-specific survival of adult-onset neuroblastoma patients grouped by surgery status. (d) Kaplan-Meier plot of the cancer-specific survival of adult-onset neuroblastoma patients grouped by type of surgery performed. (e) Kaplan-Meier plot of the cancer-specific survival of adult-onset neuroblastoma patients grouped by histology type. (f) Kaplan-Meier plot of the cancer-specific survival of adult-onset neuroblastoma patients grouped by chemotherapy.

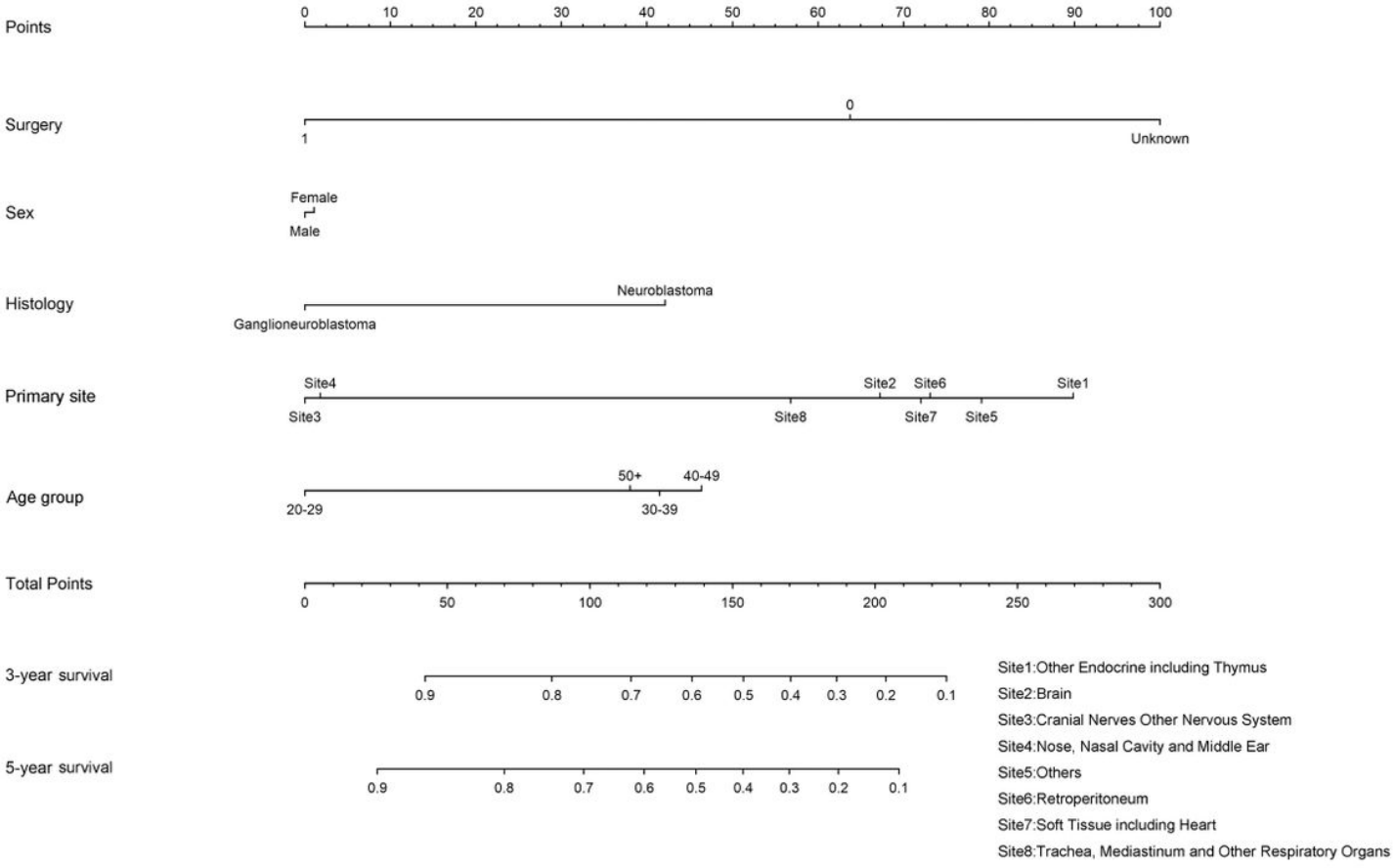

Figure 4

Clinical nomogram of adult-onset neuroblastoma patients to predict 3-year and 5-year survival rates.

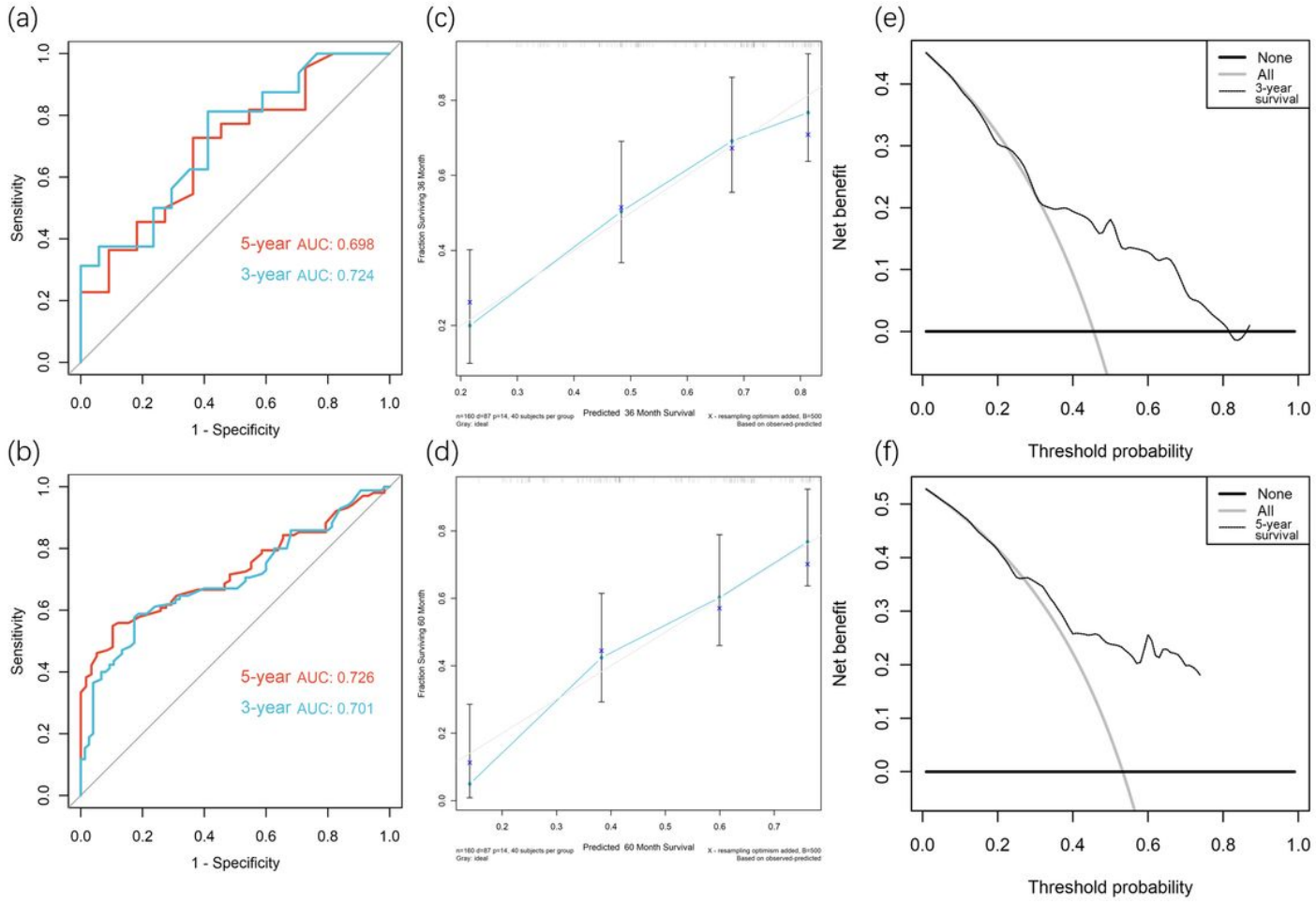

Figure 5

(a, b) Receiver operator curve (ROC) of nomogram-predicted 3-year and 5-year survival in the training group and the validation group. (c, d) Calibration plot of the 3-year and 5-year nomogram predictions versus the actual observations in the training group. (e, f) Decision curve analysis (DCA) of the 3-year and 5-year nomogram predictions and the net benefit of decision in the training group.

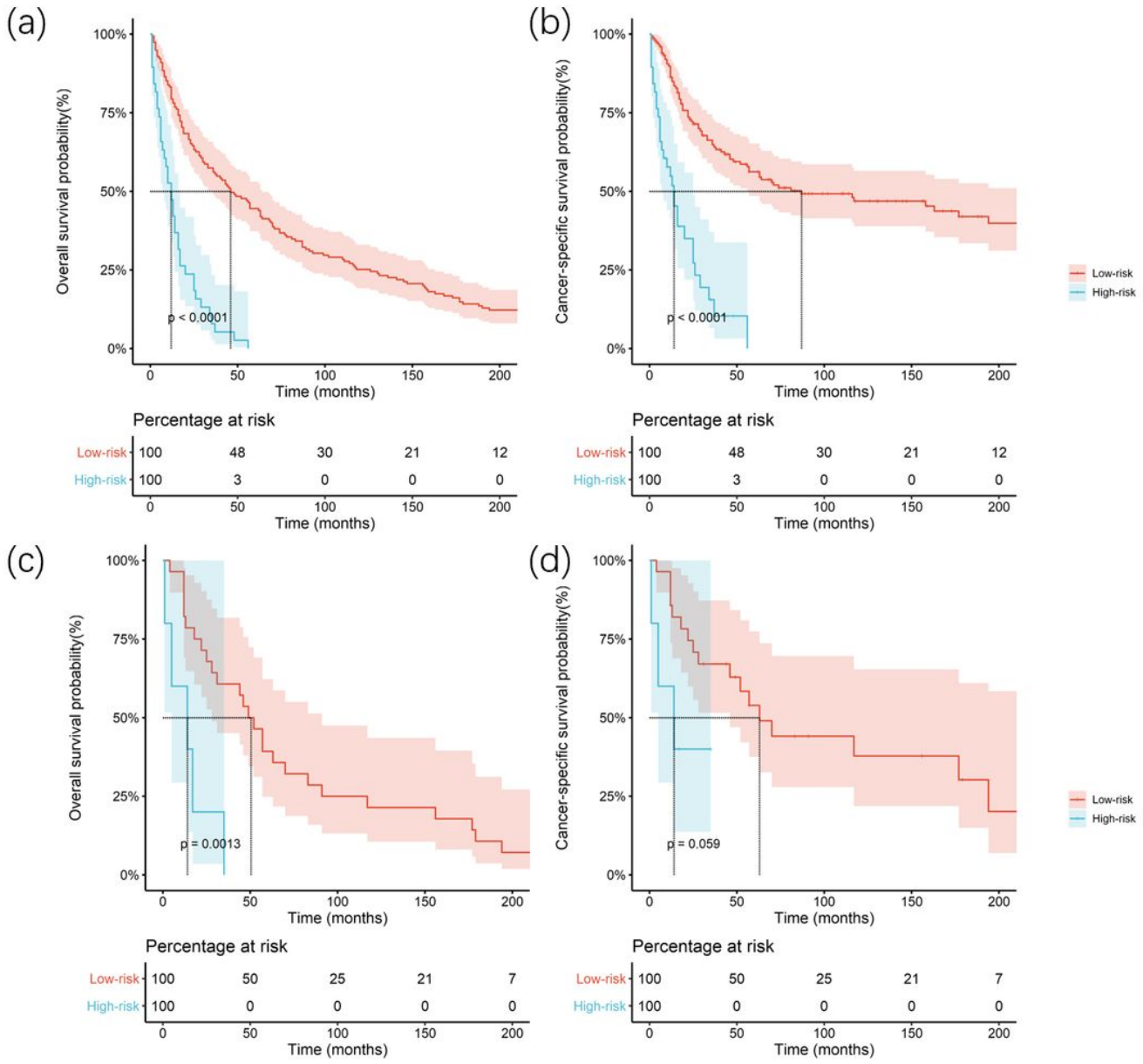

Figure 6

(a, b) Kaplan-Meier plot of overall and cancer-specific survival of high-risk and low-risk patients stratified by the nomogram score in the total 193 patients. (c, d) Kaplan-Meier plot of overall and cancer-specific survival of high-risk and low-risk patients stratified by the nomogram score in validation group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.jpg
- SupplementaryFigure2.jpg

- SupplementaryFigure3.jpg
- SupplementaryFigure4.jpg
- Supplementaryfiles.docx