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Clinical and molecular characteristics and long-term outcomes of pediatric intracranial meningiomas: a comprehensive analysis from a single neurosurgical center

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Abstract

Background Meningioma represents the most common intracranial tumor in adults. However, it is rare in pediatric patients. We aimed to demonstrate the clinicopathological characteristics and long-term outcome of pediatric meningiomas (PMs).

Method We enrolled 74 patients with intracranial PMs and analyzed their clinicopathological characteristics. Targeted next generation sequencing was used to detect alterations in meningioma relevant genes. Progression-free survival (PFS) was compared between PMs and adult meningiomas (AMs). Univariate and multivariate Cox analyses were employed to evaluate the predictive values of clinicopathological characteristics. A nomogram was constructed and its predictive accuracy evaluated.

Result 40 females (54.1%) and 34 males (45.9%) patients, with the gender ratio of 1.18:1, were identified. 9 (12.2%) cases were clinically diagnosed as NF2-related Schwannomatosis (NF2-SWN), while 65 (87.8%) were sporadic. Ventricular location was found in 16 patients (21.6%). 19 patients (25.7%) experienced recurrence during a median follow-up period of 33 months (range 2 -145.25 months). The 3-, 5-, and 8-year PFS rates was 74.74%, 74.74%, and 59.38%, respectively. The PFS of the PM and AM cohorts were not significantly different, with or without propensity score matching. *NF2* mutation was observed in 33 sporadic PMs (52.4%), whereas alterations in other genes (*AKT1*, *TRAF7*, *SMO*, *PIK3CA*, *KLF4*) frequently mutated in AMs, were not identified. The proportion of *NF2* mutation in PMs was significantly lower in the skull base than other locations ($p=0.02$). One anaplastic PM harbored *TERT* promoter mutation. Of note, in sporadic PMs, *NF2* mutations were not significantly associated with PFS ($p=0.434$) or overall survival (OS) ($p=0.60$). The multivariate Cox analysis showed NF2-SWN ($p<0.001$) and extent of resection ($p=0.013$) to be independently associated with the PFS of PMs. Our prognostic model showed predictive accuracy for long-term PFS in PMs as the 3-, 5- and 8-year Area Under the Curve (AUC) was 0.927, 0.930, and 0.870, respectively.

Conclusion PM was characterized by its relative male predominance, ventricular location, NF2-SWN, and *NF2* mutation. Of note, PMs had similar prognosis to AMs and *NF2* alteration was not significantly associated with PFS in PMs.

Keywords Meningioma, Pediatric, NF2-SWN, *NF2* mutation, Model

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Introduction

Meningioma is the most common primary intracranial tumor, which accounts for around 40.7% of all neoplasms in the central nervous system (CNS) [27]. According to the latest world health origination (WHO) classification of CNS tumors, meningiomas are classified into 3 grades and 15 subtypes [19]. The incidence of meningiomas increases with age [41]. Meningioma represents the most common intracranial tumor type in adult patients, while it only comprises 0.4–4.6% of the intracranial tumors in pediatric patients [15, 25, 26]. Adult meningiomas (AMs) are mostly presented as sporadic meningiomas. However, pediatric meningioma (PM) patients are commonly associated with radiation and various tumor predisposition syndromes [22, 35]. NF2-related Schwannomatosis (NF2-SWN) is the most common tumor predisposition syndrome found in PM patients. In PM patients with NF2-SWN, their tumors often show a more aggressive biological behavior [35, 36].

Meningioma is a highly heterogenous disease. Previous studies have demonstrated that PMs and AMs show distinct clinical characteristics [28, 29, 34]. It was reported that the gender distribution and the spectrum of histological variants are different between PMs and AMs [29]. In recent years, our knowledge on the molecular alterations in AMs has increased substantially. *NF2* mutations were identified in around 60% sporadic meningiomas, which is associated with reduced progression-free survival (PFS) in all grades [30, 44]. More recently, *SMO*, *KLF4*, *TRAF7*, *AKT1*, and *PIK3CA* alterations have been identified in non-*NF2* mutant meningiomas, and are associated with different clinical characteristics [1, 6, 44]. For PMs, recent studies reported that *NF2* mutations are also the most common alteration. However, other typical alterations found in AMs were absent [3, 14, 16]. Recently, *YAP1* fusions were identified in non-*NF2* PMs [37]. Kirches et al. [14] found loss of heterozygosity on chromosome 22 in 76% of PMs. They separated PM patients into three groups with different clinical characteristics and compared them with AM patients, showing that PM patients largely grouped separately.

Thus, meningiomas in different age groups display notable variations in clinicopathological characteristics and molecular alterations. However, the prognostic difference between PMs and AMs is unclear. Nowadays, models for the prediction of recurrence and survival status of AMs are rapidly increasing, while there has been no prognostic analysis of large cohorts and corresponding prediction models for PMs. In this study, we comprehensively demonstrated the clinicopathological and molecular characteristics as well as long-term outcome of PMs in a single neurosurgical center. A prognostic model with excellent performance was also constructed for the prediction of progression-free rates in PMs.

Materials and methods

Patient population and follow-up

The study cohort included 74 consecutive pediatric patients (age $\leq$ 20) with intracranial meningiomas managed in our center from 2010 to 2021. The inclusion criteria were as follows: 1) Pathological diagnosis of meningioma, 2) Complete clinical and follow-up information. Patients were followed up through outpatient services and phone communication after their operations. Postoperative complications, treatment and recurrent status were recorded. Patients lost to follow-up within the first year were excluded. Additionally, another 562 adult patients with intracranial meningiomas who underwent tumor resection in our hospital with complete follow-up information during the same period were also included for prognostic comparisons with PMs. This cohort consisted of 209 (37.2%) grade 1 meningiomas, 305 (54.3%) grade 2 meningiomas, and 48 (8.5%) WHO grade 3 meningiomas who has been regularly followed up in our center. These patients had standardized follow-up in our previously published study and were not consecutive [31, 32]. Progression-free survival (PFS) was defined as the time between surgery and tumor recurrence or progression, censored at the last follow-up visit or in the event of patient deaths from causes other than meningiomas.

Clinical characteristics collection and pathological review

Clinical characteristics, including age at diagnosis, gender, systematic syndromes (mainly NF2-SWN), surgical history, and tumor location, were retrieved from the medical record. Simpson grades were extracted from the surgical record and confirmed by postoperative MRI. Extent of resection (EOR) was classified into gross-total resection (GTR, Simpson grades I–III) and subtotal resection (STR, Simpson grade IV-V). Tumor location was categorized as convexity, parasagittal, skull base, and ventricular. All the formalin-fixed tumor samples of patients were reviewed by two experienced pathologists (HX.C. and H.C.). Histopathological diagnosis was made according to the 2021 WHO Classification of the Central Nervous System Tumours. Immunohistochemical reviews, including Ki-67 index and progesterone receptor (PR), were performed as well.

Cohort matching

For the accuracy of prognostic comparisons between PMs and AMs, we performed propensity score matching (PSM) to minimize the possible confounding bias that

was caused by variables such as gender, tumor location, WHO grade, EOR, and postoperative radiotherapy [4]. The propensity score was calculated via logistic regression. We employed a 1:1 ratio to match patients in the PM and AM cohorts, and evaluated the quality of the match by considering p-value and absolute standardized difference (ASD). A successful match was defined as having $p > 0.05$ or $ASD < 0.2$.

Targeted sequencing

We utilized a custom-designed meningioma specified Next Generation Sequencing (NGS) panel to detect gene mutations in PMs [13]. The targeted NGS panel contained 184 genes reported to be frequently mutated in CNS tumors, including common pathological genes relevant in meningiomas as described previously, including *NF2, TRAF7, KLF4, AKT1, SMO, PIK3CA, SMARCE1, BAP1, CDKN2A/B, TERT-P, ARIDIA, SUFU, SMARCB1, POLR2A, DMD, and PBRM1*. The procedure of targeted sequencing was described previously [33].

Prognostic model construction

Univariate and multivariate Cox regression analyses were used to evaluate the relationship between clinicopathological characteristics and outcomes, aiming to identify independent predictors of tumor recurrence. Firstly, all clinicopathological characteristics were applied for univariate analysis. Secondly, the variables whose *p*-value being lower than 0.05 were evaluated via multivariate Cox analysis. Thirdly, the model was constructed by the backward step-down selection process with Akaike information criterion [9]. Finally, a nomogram for 3-, 5-, 8-year progression-free rate was created based on the model.

Statistical analysis

R software (Version 3.4.2) was used for statistical analysis. The R packages used for plotting and comparisons in the study included "survival, survminer, ggplot2, ggpubr, pheatmap, survivalROC, plotROC, regplot, survcomp, foreign, and tidyverse". PSM was performed using the R packages including "pacman, wakefield, knitr, and MatchIt". Continuous and categorical variables were compared through Student's t-test and Chi-square test, respectively. Maximally selected rank statistics was applied to determine the optimal cut-off for age at diagnosis and Ki-67 index. PFS was evaluated through Kaplan–Meier method and compared through the long-rank test. A two-sided P-value < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of PMs

In the PM cohort, 40 female (54.1%) and 34 male (45.9%) patients were identified, resulting in a gender ratio of 1.18:1. The mean age at diagnosis was 15.7 ± 4.33 years old (range: 2–20). 9 cases (12.2%) were diagnosed with NF2-SWN, while 65 (87.8%) were sporadic. 61 (82.4%) were de novo (newly diagnosed), while 13 (17.6%) were recurrent (with history of prior surgery). The most common tumor location was the convexity ($n = 29$, 39.2%, 20 frontal, 5 parietal, 2 temporal, and 2 occipital), followed by skull base ($n = 23$, 31.1%; 6 sphenoid ridge, 6 cerebellopontine angle, 4 sellar region, 3 petrous ridge, 2 foramen magnum, and 2 cerebellum,), ventricular ($n = 16$, 21.6%; 14 lateral ventricle and 2 fourth ventricle) and parasagittal ($n = 6$, 8.11%). Five cases with NF2 disease had multiple meningiomas. All the tumors received surgical removal; 56 patients (75.7%) underwent GTR, while 18 patients (24.3%) underwent STR. For meningiomas with STR, 14 (77.78%) were skull base or parasagittal located. Pathological review results showed that 61 tumors (82.4%) were diagnosed as WHO grade 1, 12 (16.2%) as WHO grade 2, and 1 (1.35%) as WHO grade 3 (anaplastic subtype). Immunohistochemical findings indicated that PR expression was positive in 29 patients (39.2%), negative in 26 patients (35.1%), and weakly positive in 19 patients (25.7%). The median Ki-67 index was 3% (range: 1–25%) (Table 1). Based on maximally selected rank statistics, the optimal cut-off of age at diagnosis and Ki-67 index were determined as 10 years old (See Additional Fig. 1A) and 2% (See Additional Fig. 1B), respectively.

Follow-up outcomes

The last follow-up was conducted on November 30, 2023, with a median follow-up period of 33 months (range 2 -145.25 months). In our cohort, postoperative radiotherapy indications in this study followed the EANO guidelines [10, 11]. Radiotherapy was recommended for WHO grade 2 and 3 meningiomas, while stereotactic radiosurgery (SRS) was suggested for subtotal resection tumors. The ultimate decision to proceed with radiotherapy rested with the patient. Among the PM patients, 13 (17.6%) received postoperative radiotherapy within 2–3 months after surgery. Of them, 10 (76.9%) patients with high grade meningioma received fractionated adjuvant radiotherapy with a mean dose of 42.5 ± 2.8 Gy (range: 15-45 Gy), and 3 (23.1%) patients with subtotal resected meningioma underwent stereotactic radiotherapy (Gamma Knife) with a mean dose of 13.2 ± 1.3 Gy (range: 12-16 Gy). During the follow-up period, 19 patients (25.7%) experienced recurrence, and 3 (4.1%) died of tumor progression. Analysis of the association of clinico-pathological parameters with

Table 1 The characteristics of meningiomas in pediatric patients

Clinical characteristics	[ALL] *N = 74*	No recurrence *N = 55*	Recurrence *N = 19*	P overall
Gender				1.000
Male	34 (45.9%)	25 (45.5%)	9 (47.4%)	
Female	40 (54.1%)	30 (54.5%)	10 (52.6%)	
Age (years)	Mean: 15.7 (Standard Deviation:4.33)	15.6 (4.36)	15.8 (4.37)	0.884
NF2-WNS				< 0.001
No	65 (87.8%)	54 (98.2%)	11 (57.9%)	
Yes	9 (12.2%)	1 (1.82%)	8 (42.1%)	
Surgical history				0.003
de novo	61 (82.4%)	50 (90.9%)	11 (57.9%)	
Recurrent	13 (17.6%)	5 (9.09%)	8 (42.1%)	
Tumor location				0.849
Convexity	29 (39.2%)	21 (38.2%)	8 (42.1%)	
Skull base	23 (31.1%)	16 (29.1%)	7 (36.8%)	
Ventricular	16 (21.6%)	13 (23.6%)	3 (15.8%)	
Parasagittal	6 (8.11%)	5 (9.09%)	1 (5.26%)	
EOR				0.012
GTR	56 (75.7%)	46 (83.6%)	10 (52.6%)	
STR	18 (24.3%)	9 (16.4%)	9 (47.4%)	
WHO grade				0.023
Grade 1	61 (82.4%)	49 (89.1%)	12 (63.2%)	
Fibrous	35 (42.3%)	28(50.9%)	7(36.8%)	
Meningothelial	23 (31.1%)	18(32.7%)	5(26.3%)	
Translational	2 (2.7%)	2(3.6%)	0(0.0%)	
Psammomatous	1 (1.4%)	1(1.8%)	0(0.0%)	
Grade 2	12 (16.2%)	6 (10.9%)	6 (31.6%)	
Atypical	10 (13.5%)	5(9.1%)	5(26.3%)	
Clear cell	1(1.4%)	0(0.0%)	1(5.3%)	
Chordoid	1(1.4%)	1(1.8%)	0(0.0%)	
Grade 3	1 (1.4%)	0 (0.0%)	1 (5.3%)	
Anaplastic	1 (1.4%)	0 (0.0%)	1 (5.3%)	
Ki-67 (%)	Median: 3.00 [Quartiles:2.00;5.00]	3.00 [2.00;5.00]	3.00 [3.00;6.00]	0.129
PR:				0.097
Positive	29 (39.2%)	18 (32.7%)	11 (57.9%)	Positive
Negative	26 (35.1%)	20 (36.4%)	6 (31.6%)	
Weak positive	19 (25.7%)	17 (30.9%)	2 (10.5%)	

NF2-SWN, NF2-related Schwannomatosis; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; PR, progesterone reception

recurrence revealed significant difference in NF2-SWN ($p < 0.001$), surgical history ($p = 0.003$), EOR ($p = 0.012$), and WHO grade ($p = 0.023$) between recurrent and stable patients. Patients who developed recurrence demonstrated a higher prevalence of NF2 disease and surgical history. Additionally, the proportion of STR and high-grade tumors was higher in the recurrence group than the non-recurrence group (Table 1). The survival analysis showed the median PFS of PMs was unavailable, and the 3-, 5-, and 8-year progression-free rate was 74.74%, 74.74%, and 59.38%, respectively. The median OS was unavailable, and the 3-, 5-, and 8-year survival rate was 97.15%, 97.15%, and 93.56%, respectively.

Clinical characteristics and outcome of the AM cohort

The AM cohort included 209 grade 1 (37.2%), 305 grade 2 (54.3%) and 48 grade 3 (8.5%) meningiomas, which were followed regularly at our center during the same

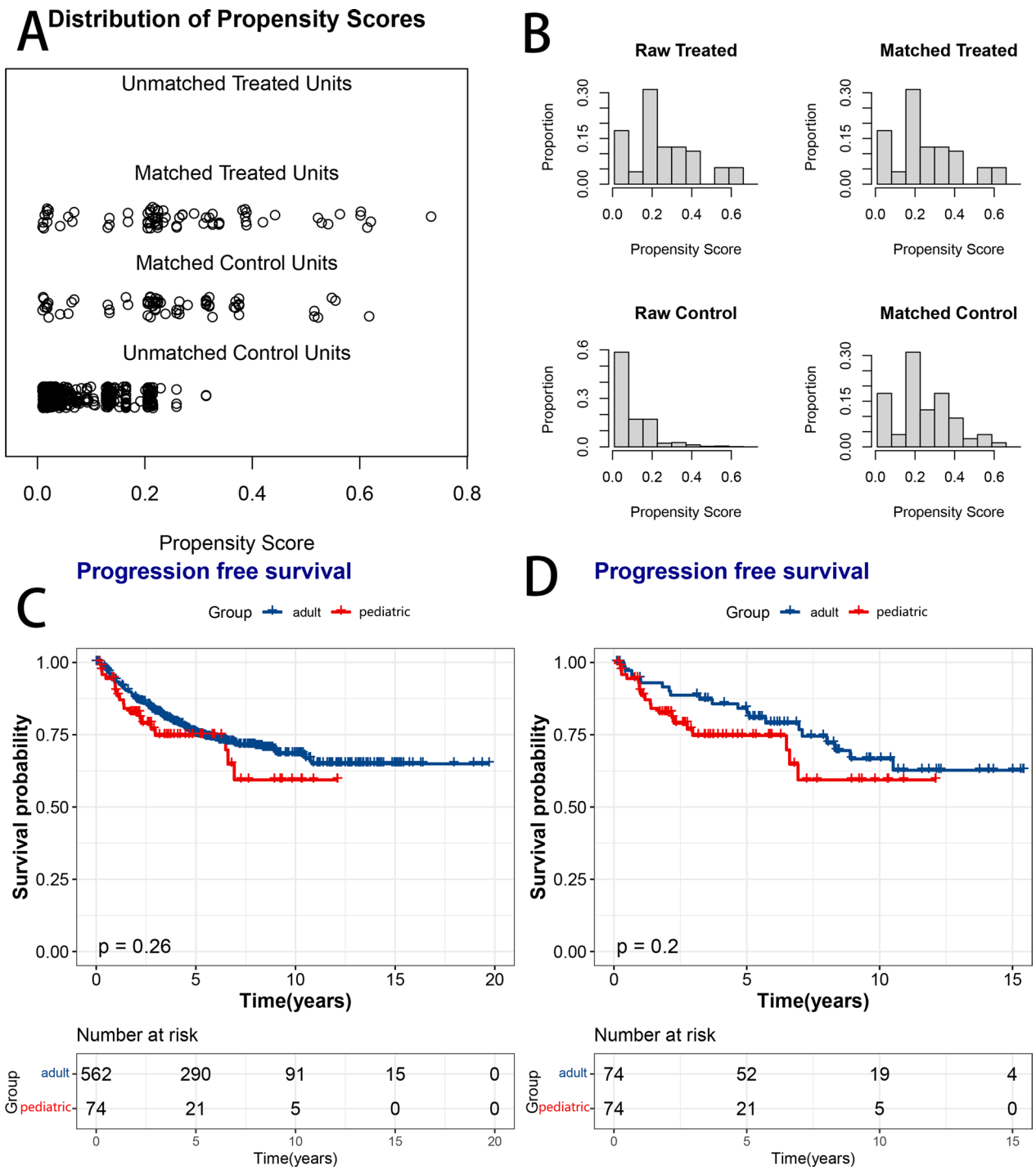

Fig. 1 Distribution of propensity scores and Kaplan–Meier survival curves of matched cohorts. **A**: Distribution of the matched samples in the PM (Treated Units) and AM (Control Units) cohorts. **B**: Distribution of propensity scores in the PM (Treated) and AM (Control) cohorts. **C**: Kaplan–Meier survival curves for PFS between the PM and AM cohorts before PSM. **D:** Kaplan–Meier survival curves for PFS between the PM and AM cohorts after PSM of the latter

period as PMs. In this cohort, 325 females (57.8%) and 237 males (42.2%) were identified. The mean age at diagnosis was 53.8 ± 12.3 years old. The most common tumor location was convexity (248, 44.1%), followed by skull base (171, 30.4%), parasagittal (127, 22.6%) and ventricular (16, 2.8%). STR was achieved in 75 patients (13.3%). 206 patients (54.8%) received postoperative radiotherapy.

During the median follow-up of 65.5 months, 146 patients (26.0%) experienced tumor recurrence or progression. Prior to PSM, significant difference was observed in tumor location ($p < 0.001$), EOR ($p = 0.019$), radiotherapy ($p < 0.001$), and WHO grade ($p < 0.001$) between the PM and AM cohorts (Table 2).

Prognostic comparisons between PMs and AMs

PSM was conducted to minimize the influence of covariates between the PM and AM cohorts. Following the matching at a 1:1 ratio, 74 AM patients were selected to analyze prognostic differences with PMs (Fig. 1A). The propensity score of the matched AM cohort closely resembled that of the PM cohort (Fig. 1B). Differences in tumor location ($p = 0.794$), EOR ($p = 1.000$), radiotherapy ($p = 0.218$), and WHO grade ($p = 0.834$) were effectively minimized between the two cohorts. The results of ASDs also affirmed the well-balanced nature of differences between the two cohorts (Table 2). Kaplan–Meier analysis was employed to compare the prognostic differences between PMs and AMs. Prior to PSM, there was no significant difference in PFS between the two cohorts ($p = 0.26$) (Fig. 1C). Following PSM, the matched cohorts did not show a significant difference in PFS, either ($p = 0.2$) (Fig. 1D).

Prognostic factors for PFS in PMs

Univariate Cox regression analysis was employed to evaluate the predictive value of clinicopathological characteristics, including age at diagnosis, gender, tumor location, EOR, WHO grade, Ki-67, PR, and postoperative radiotherapy. The univariate analysis showed that WHO grade ($p = 0.003$), NF2-SWN ($p < 0.001$), surgical history ($p = 0.002$), EOR ($p = 0.031$), Ki-67 index ($p = 0.036$) were significantly associated with PFS (Fig. 2A). Specifically, GTR (Fig. 2B), low WHO grade (Fig. 2C), Ki-67 < 2% (Fig. 2D), no NF2-SWN (Fig. 2E), and no surgical history (Fig. 2F) were associated with significantly prolonged PFS. However, postoperative radiotherapy did not significantly prolong the PFS in our PM cohort (Fig. 3A). The Pearson Correlation Test indicated that the correlation coefficients between the 5 variables, i.e., WHO grade, NF2-SWN, surgical history, EOR, and Ki-67 index, identified with our Univariate Cox regression analysis, were below 0.3, suggesting their independence (Fig. 3B). Subsequently, we performed a multivariate Cox regression analysis of these factors, and demonstrated that NF2-SWN ($p < 0.001$, hazard ratio (HR) = 16.44, 95% confidence interval (CI) (5.05–53.55)) and EOR ($p = 0.013$, HR = 3.67, 95% CI (1.32–10.22)) were independent prognostic factors for the PFS of PM patients (Fig. 3C).

Table 2 The clinical characteristics differences of meningiomas patients before and after PSM

Clinical characteristics	Before PSM			After PSM			
	Adult 562	Pediatric 74	*P* value	Adult 74	Pediatric 74	*P* value	ASD
Surgical history = Yes (%)	89 (15.8)	13 (17.6)	0.831	8 (10.8)	13 (17.6)	0.346	0.177
Gender = female (%)	325 (57.8)	40 (54.1)	0.623	36 (48.6)	40 (54.1)	0.622	0.108
Location (%)			**0.001**			0.794	–0.056
Convexity	248 (44.1)	29 (39.2)		26 (35.1)	29 (39.2)		
Skull base	171 (30.4)	23 (31.3)		24 (32.4)	23 (31.3)		
Parasagittal	127 (22.6)	6 (8.1)		8 (10.8)	6 (8.1)		
Ventricular	16(2.8)	16 (21.6)		16(21.6)	16 (21.6)		
EOR = STR (%)	75 (13.3)	18 (24.3)	**0.019**	17 (23.0)	18 (24.3)	1.000	0.031
RT = Yes (%)	206 (54.8)	13 (17.6)	**< 0.001**	9 (31.0)	13 (17.6)	0.218	
WHO grade			**< 0.001**			0.834	–0.071
Grade 1	209 (37.2)	61 (82.4)		59 (79.7)	61(82.4)		
Grade 2	305 (54.3)	12 (16.2)		14 (18.9)	12 (16.2)		
Grade 3	48 (8.5)	1 (1.4)		1 (1.4)	1 (1.4)		
Ki-67 (mean)	5.21 (5.81)	4.24 (3.82)	0.163	5.15 (11.63)	4.24 (3.82)	0.526	–0.237
PR (%)			0.584			0.355	
Negative	211 (38.2)	26 (35.1)		32 (44.4)	26 (35.1)		
Weak positive	106 (19.2)	19 (25.7)		12 (16.7)	19 (25.7)		
Positive	235 (42.6)	29 (39.2)		28 (38.9)	29 (39.2)		

Statistically significant difference is given in bold

PSM, Propensity score matching; ASD, Absolute standardized difference; EOR, Extent of resection; STR, Subtotal resection; RT, Radiotherapy; PR, Progesterone receptor

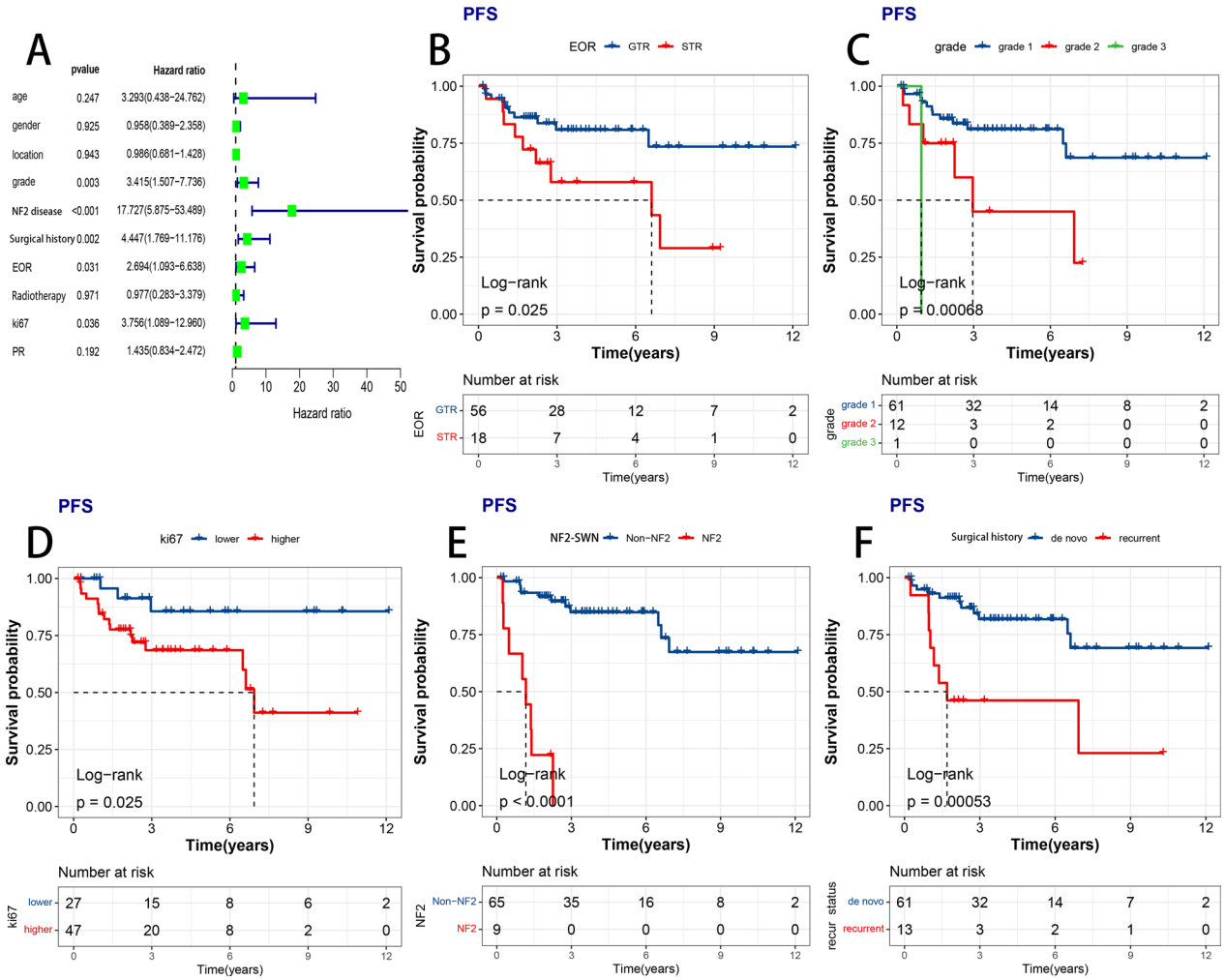

Fig. 2 The univariate Cox analysis of clinicopathological factors. **A**: The forest plot of univariate Cox analysis result. **B**: The Kaplan–Meier curves of EOR. **C**: The Kaplan–Meier curves of WHO grade. **D**: The Kaplan–Meier curves of Ki-67 index. **E**: The Kaplan–Meier curves of NF2-SWN. **F**: The Kaplan–Meier curves of surgical history

Molecular alterations in PMs

To understand genetic alterations in PMs and their potential impact on prognosis, we performed targeted gene sequencing in 63 of 65 patients with sporadic PMs (Two samples failed the quality inspection). The results showed that 33 tumors (52.38%) had *NF2* mutations and 1 anaplastic tumor (1.59%) had *TERT* promoter mutation. However, mutations in other meningioma-associated genes such as *AKT1, KLF4*, and *TRAF7* were not found in PMs (See Additional Table 1). We further analyzed the correlation between *NF2* mutations and clinical characteristics. There were no significant differences in gender ($p=0.40$) and WHO grade ($p=0.26$) between *NF2* wild-type and *NF2* mutant sporadic PMs (Fig. 4A). 17 of 25 (68.0%) sporadic PMs located in convexity harbored *NF2* mutations, whereas only 4 of 18 (22.2%) PMs located in skull base harbored *NF2* mutations. Statistical analysis revealed that *NF2* mutations were significantly predominant in non-skull base tumors (Fig. 4B, $p=0.02$). We found 11 patients (11/14, 78.6%) with ventricular PMs were female and 7 (63.6%) of them had *NF2* mutations (Fig. 4B). Unexpectedly, the recurrence rate of patients with *NF2* mutations (18.2%) was similar to that of *NF2* wild-type (13.3%) (Fig. 4C, $p=0.74$). Kaplan–Meier analysis showed that *NF2* mutation status was not associated with PFS (Fig. 4D, $p=0.43$) or OS (Fig. 4E, $p=0.60$) in sporadic PMs.

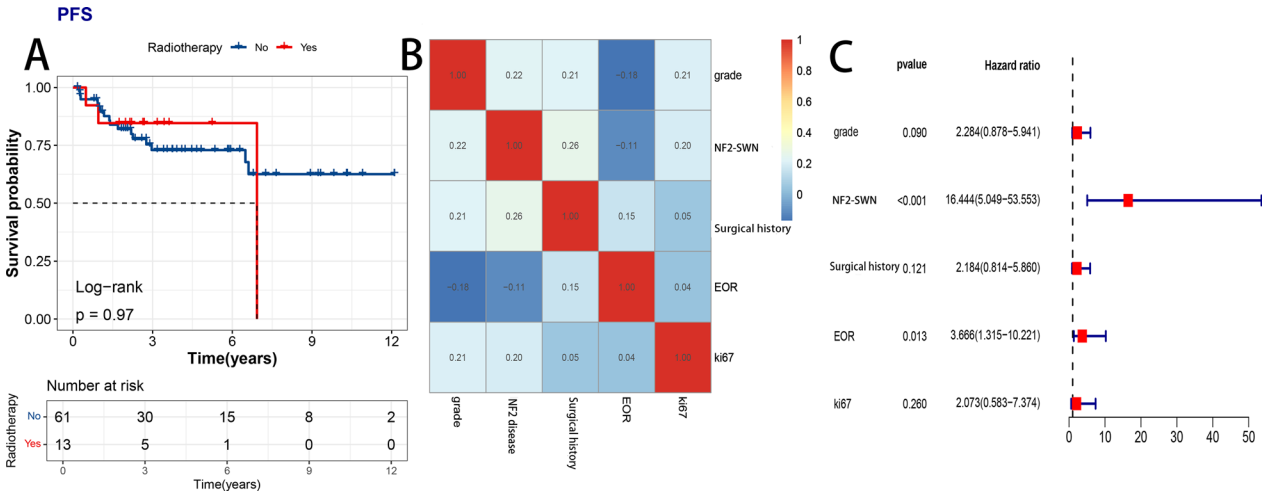

Fig. 3 The multivariate Cox analysis in pediatric meningioma. **A**: The Kaplan–Meier curves of postoperative radiotherapy. **B**: The correlation coefficient plot between EOR, WHO grade, Ki-67 index, NF2-SWN and surgical history. **C**: The forest plot of multivariate Cox analysis result

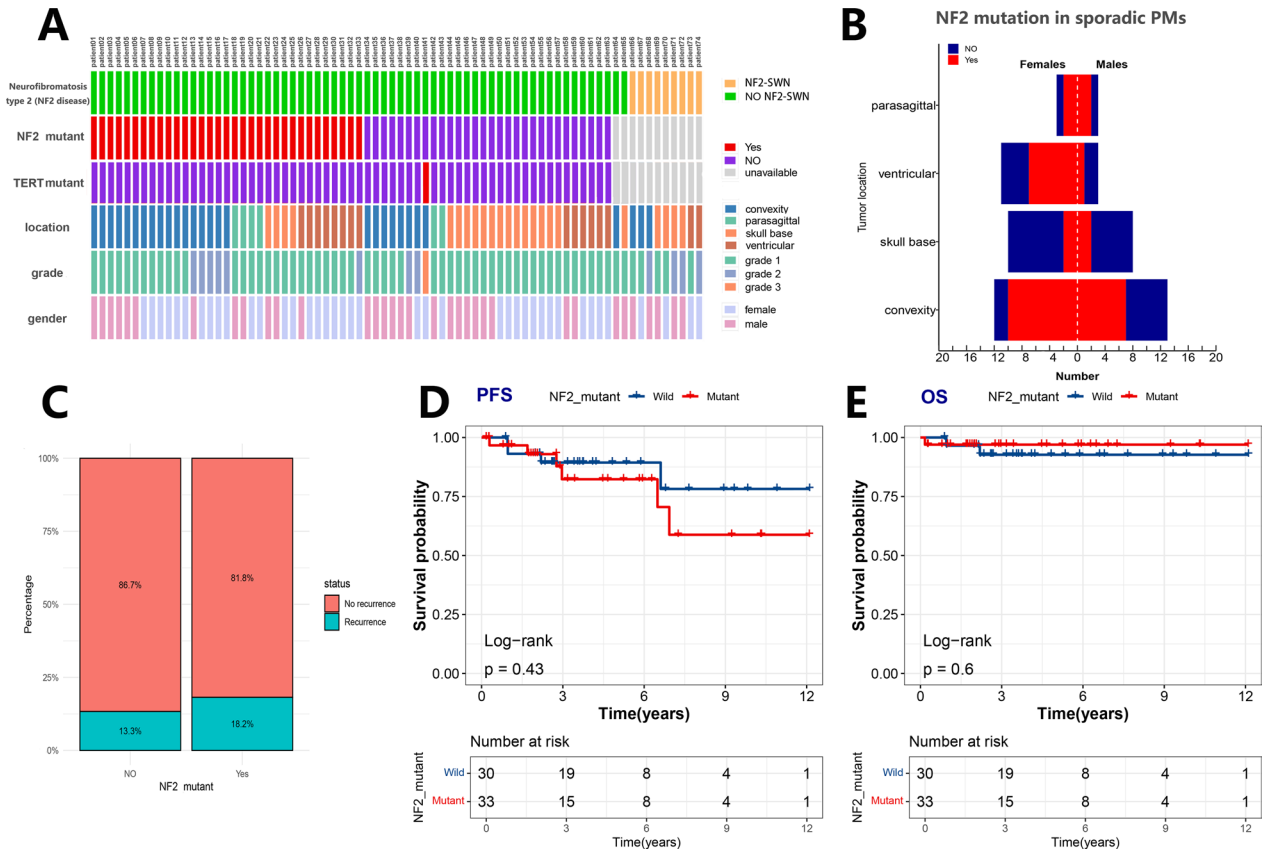

Fig. 4 Genomic analysis and impact of *NF2* status on survival. **A**: Genomic mutation and relevant clinical characteristics of PM patients. **B**: the number of *NF2* mutation in different tumor location. **C**: the recurrence rate comparison between *NF2* wild-type and mutant PM patients. **D**: The Kaplan–Meier curves of *NF2* mutation for PFS. **E**: The Kaplan–Meier curves of *NF2* mutation for OS

Construction of a nomogram for prediction of recurrence in PM patients

To assist identification of high-risk PM patients prone to recurrence in clinical practice, we developed a prognostic model by the backward step-down selection process in multivariate Cox analysis. The 3-, 5- and 8-year Area Under the Curve (AUC) of the model was 0.927, 0.930, 0.870, respectively (Fig. 5A), indicating its superior predictive accuracy for long-term PFS. The risk score of the prognostic model was calculated as follows: risk score = 0.9033 * grade + 2.9232 * NF2-SWN + 0.7719 * surgical history + 1.4083 * EOR. Utilizing maximally selected rank statistics, we determined the optimal cut-offs of the risk score as 3.45. Based on this cut-off, PM patients were categorized into high-risk and low-risk groups, displaying a striking significant difference in PFS ($p < 0.0001$) (Fig. 5B). Furthermore, we constructed a nomogram based on the model to predict the progression-free rates of PM patients at 3, 5, and 8 years following surgical intervention (Fig. 5C). The calibration curve demonstrated great agreement between observation and prediction of PFS (Fig. 5D). The 3-year (See Additional Fig. 2A), 5-year (See Additional Fig. 2B), and 8-year (See Additional Fig. 2C) decision curve analysis underscored the nomogram as a very effective tool for predicting the likelihood of tumor recurrence. This predictive tool for long-term prognosis can guide physicians to personalized management strategies to optimize long-term outcomes.

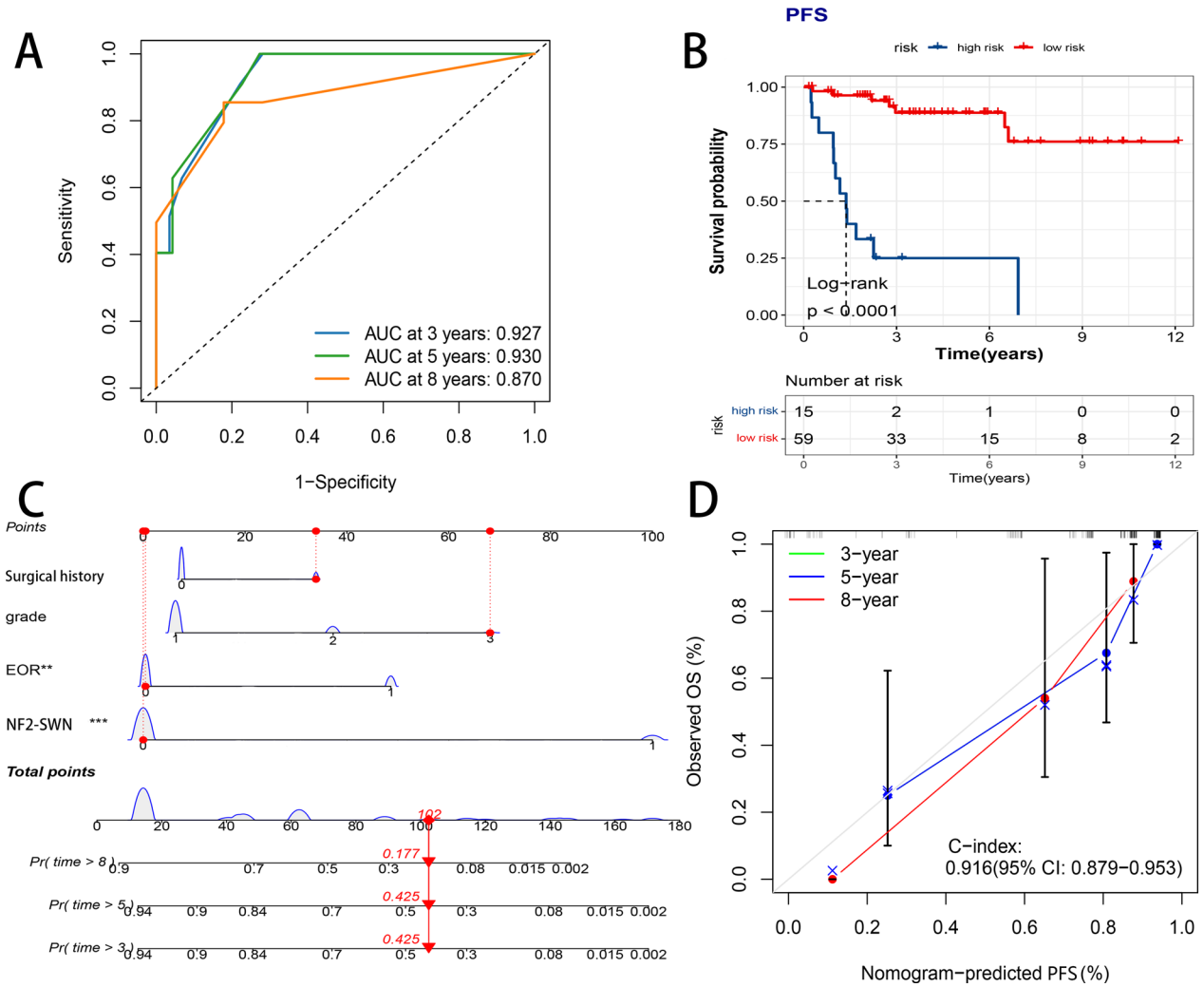

Fig. 5 The prediction performance of the prognostic model. **A**: The time-independent ROC curves and AUC values of the prognostic model. **B**: The Kaplan–Meier curves for PFS of the high and low risk groups divided by the cut-off 3.45. **C**: The nomogram to predict the 3-year, 5-year, and 8-year PFS rate of PM patients. Red shows an example for a total point calculation. **D**: The calibration curved of the nomogram

Discussion

Our PM cohort was comprised of 40 females (54.1%) and 34 males (45.9%), with the gender ratio of 1.18:1. Similar to prior studies, female predominance was very modest among PMs as opposed to AMs that show a clearer female predominance [17, 35]. A recent review reported PMs with a male-to-female ratio of 40:60 [24]. This discrepancy may be attributed to hormonal influences, specifically progesterone and estrogen, which play a role in modulating the growth of a significant proportion of meningiomas. The variation in sex distribution between AM and PM patients could be attributed to differences in sex hormone levels between these two populations [20].

In our PM cohort, 9 individuals (12.2%) were diagnosed with NF2-SWN, while 65 (87.8%) were sporadic cases. Previous studies indicate that PMs often show associations with NF2-SWN and other tumor predisposition syndromes. NF2-SWN was frequently reported in PMs where the incidence ranged widely from 3.7 to 50% [17, 22, 35, 40]. A literature review involving 99 patients from 32 different authors indicated that 13% of PM patients (13 out of 99) had a prior diagnosis of NF2-SWN, highlighting a significant co-occurrence of NF2-SWN in PM patients [24]. The prevalence of NF2 distinguishes pediatric patients from their adult counterparts, which may contribute to the uncertainty surrounding the biological behavior and treatment guidelines in PMs [39]. Notably, ventricular tumors accounted for 21.6% (16/74) of PMs in our study. Previous studies reported that intraventricular meningiomas are relatively common in pediatric cases, particularly in the lateral ventricle, compared with relative rarity of adult intraventricular meningiomas [22, 24, 38]. Opoku et al. [24] found that ventricular meningiomas represented 50% of their PM patients. In contrast, a series involving 675 AM patients reported that intraventricular meningiomas comprised only 3.7% of the cases [18].

Our targeted DNA sequencing of sporadic PMs revealed that 33 patients harbored *NF2* mutations and 1 patient harbored *TERTp* mutation, while other typical mutations involving AKT1, KLF4, TRAF7 were absent. These findings were consistent with previous studies [3, 14]. Perry et al. [29] conducted a detailed analysis of *NF2* mutations in PM patients, finding mutations in 86% of those with NF2-SWN and 70% in those without NF2-SWN, which aligns with our findings. However, Kirches et al. [14] found *NF2* mutation in only 24% PM patients. We attribute this proportion difference primarily to the varying distribution of WHO grades. In Kirches' cohort, 30% of tumors were grade 1, 57% were grade 2, and 14% were grade 3 meningiomas. In contrast, our cohort comprised 82.4% grade 1, 16.2% grade 2, and 1.4% grade 3 meningiomas. To investigate further, we reviewed the recent literature review by Arnault et al. [40], which included 56 studies and 498 cases of PMs. This reported that 67% of tumors were grade I, 23% were grade II, and 10% were grade III, a distribution more similar to our cohort. In addition, the proportion of *NF2* mutations in non-skull base PMs was significantly higher than that in skull base PMs, which is similar to the genetic mutation characteristics of AMs [6]. Notably, our survival analysis showed *NF2* mutation was not a significant factor affecting PFS of PMs, unlike the results found in AMs [45]. Recently, *YAP1* fusions was reported in some non-*NF2* PMs [37]. *YAP1* is a transcriptional coactivator of the *HIPPO* pathway and acts downstream of the *HIPPO* pathway through the TEAD family transcription factors [47, 48]. The *NF2* gene product merlin protein acts upstream of the HIPPO pathway [46]. *YAP1* fusion and *NF2* mutation are mutually exclusive, so Sievers P et al. [37] speculated that *YAP1* fusion could be an alternative to *NF2* mutation. In addition, increasing evidence suggests the functional relationship between *YAP1*, *NF2*, and *HIPPO* pathway activation [2]. *YAP1* fusions, which our target sequencing method was unable to detect, may contribute to the similar prognosis found in *NF2* mutant and wild-type PMs, since no other typical mutations were detected in non-*NF2* PMs.

In this study, no significant differences were observed in PFS between the PM and AM cohorts, even after PSM. Previous studies indicated that the prognosis for PMs remains favorable despite aggressive characteristics. Rochat et al. [34] followed up PM patients for a long period and found that 20 out of 22 meningiomas were benign. Remarkably, two patients diagnosed with anaplastic meningiomas were still alive after 17- and 18-year-follow-ups. Dudley et al. [8] also found that PM patients had similar outcomes and were treated identically to AM patients. Our multivariate Cox analysis showed that NF2-SWN ($p < 0.001$) and EOR ($p = 0.013$) were independently associated with the PFS of PM patients. In PM patients with NF2-SWN, their tumors often show a more aggressive biological behavior, a tendency to grow rapidly, a higher likelihood of recurrence shortly after initial treatment, and an inclination towards malignancy [35, 36]. These biological characteristics contribute to an overall unfavorable prognosis [36]. A meta-analysis involving 677 patients with meningiomas indicated that patients with NF2-SWN experienced a worse PFS compared to those without NF2-SWN [16]. Therefore, PM patients with NF2-SWN face a heightened risk of developing progressive and recurrent tumors, necessitating an extended postoperative follow-up period [5, 7]. Additionally, previous studies demonstrated that surgical intervention is the preferred treatment for PM patients and the EOR plays a crucial role in influencing the recurrence of tumors [42].

PMs are a heterogeneous group of tumors. It is crucial to identify meningiomas with high risk of recurrence to implement early intervention. In this study, we constructed a prognostic model with the 3-, 5- and 8-year AUC of 0.927, 0.930, 0.870, respectively. This is the first model for the prediction of PM recurrence with excellent performance. For pediatric patients experiencing recurrence, opting for a second-look surgery proves more effective than resorting to radiotherapy. Prior research has emphasized the recommendation of radiotherapy exclusively in cases of recurrence, high-grade tumors, or when surgical accessibility is limited [5, 23, 43]. Grade 2 meningiomas in children may undergo radiotherapy upon reaching 8 years of age. For WHO Grade 3 meningiomas, fractionated radiotherapy is advised for children aged 3 years and older [12, 23]. In instances of inaccessible tumors or histologically aggressive neoplasms, stereotactic radiosurgery (SRS) presents a viable alternative. Notably, Horiba et al. [12] highlighted the feasibility of SRS in a 2-year-old patient. Minniti et al. [21] reported a significant intracranial tumor control rate, ranging from 85 to 97%, at the 5-year follow-up after SRS.

Conclusion

PMs are characterized by their atypicality of relative male predominance, ventricular location, NF2-SWN and *NF2* mutation. Of note, PMs had similar outcome to AMs and there was no significant association between *NF2* mutation status and PFS in PMs.

Limitation

Firstly, selection bias and recall bias may exist due to the retrospective nature of the study. Secondly, some patients were lost during the long-term follow-up period. Thirdly, molecular genomic data was only available for the genes known to be relevant in CNS tumors such as *NF2*, *AKT1*, *KLF4*, *TRAF7*, *TERT*, and *CDKN2A/B*. Whole-exome sequencing should be performed in PMs and may detect novel driver mutations in future studies. Finally, the nomogram developed was based on a limited sample size and remains unvalidated. Future studies are needed to validate it and enhance its applicability.

Abbreviations

AM	Adult meningioma
AUC	Area under the curve
ASD	Absolute standardized difference
CI	Confidence interval
CNS	Central nervous system
EOR	Extent of resection
GTR	Gross-total resection
HR	Hazard ratio
NF2-SWN	NF2-related Schwannomatosis
NGS	Next Generation Sequencing
OS	Overall survival
PM	Pediatric meningioma
PFS	Progression-free survival
PR	Progesterone receptor
PSM	Propensity score matching
STR	Subtotal resection
WHO	World health origination

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

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Author contributions

LHR provided the design concept of this study, LHR, JJD and LYH drafted the manuscript. LHR, JJD and QX collected, processed and analyzed the data. LHR completed the drawing of the figures. HW, YG and LYH completed the revision of the manuscript. All authors contributed to this article and read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study used publicly available datasets and the ethics approval and consent to participate was not applicable.

Consent for publication

The authors consent for publication.

Competing interests

The authors declare no competing interests.

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