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Original article

Nutritional status and inflammatory markers as survival predictors in pediatric central nervous system tumors

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SUMMARY

Background & aims: Central nervous system tumors (CNS) are the second most common malignancies in childhood. Inflammation and changes in nutritional status play an important role and can be used as prognostic markers. Thus, this study aimed to evaluate the predictive ability of nutritional status and inflammatory markers on overall survival (OS) of pediatric patients with CNS.

Methods: In this retrospective cohort study, 103 patients were followed for 5 years. Clinical, anthropometric, and hematological data were collected. Body mass index for age (BMI/A), neutrophil-to-lymphocyte ratio (NLR) and systemic inflammation response index (SIRI) were calculated. OS curves were calculated using the Kaplan Meier method and evaluated using the Log–Rank test. The Cox proportional hazards model was performed to identify independent variables associated with prognostic factors, generating hazard ratios (HR) and 95% confidence intervals (CI).

Results: Nutritional status did not significantly affect OS. However, patients with NLR ≥2.18 and SIRI ≥1249.18 had significantly lower OS in 5 years. Only treatment and high NLR were identified as independent prognostic factors for worse OS. Treatment with exclusive radiotherapy or chemotherapy (HR: 16.22, 95% CI: 2.19–120.07) and NLR (HR: 1.94, 95% CI: 1.02–3.69) were identified as independent prognostic factors for worse OS at 5 years.

Conclusion: High pretreatment NLR was shown to be an independent prognostic factor for OS in pediatric patients with CNS.

1. Introduction

Pediatric central nervous system tumors (CNS) are the second most common childhood malignancies after leukemia, accounting for about 26% of cases [1,2]. These neoplasms represent the most frequent solid tumors diagnosed in children and are the main cause of cancer mortality and morbidity in this age group [3–5]. In developed countries, studies have shown a 5-year survival rate of 72.5%–85.9% for these types of cancer [6–8] while in Brazil survival rates range from 42% to 77.2% [9,10].

In childhood cancer patients, nutritional status have a potential impact on disease progression and survival [11]. It has been suggested that malnutrition is linked with reduced overall survival (OS), reduced immune function, increased risk of toxicity, and decreased quality of life [12–14]. Moreover, obesity has been associated to reduced survival and increased toxicity-related mortality [15–17].

Besides, nutritional status impairment is associated with a pro-inflammatory environment, immunological depression, and poor prognosis [18,19]. Studies have already related that neutrophils, lymphocytes, and monocytes have prognostic value in patients with solid tumors, including pediatric cancer [20,21].

Neutrophil to lymphocyte ratio (NLR) was shown to be directly associated to malignant cancer [22]. Higher NLR values has been significantly correlated with poor survival in pediatric patients with solid tumors [23,24]. Likewise, high systemic inflammatory response index (SIRI) levels were associated with a poor prognosis in patients with cancer [25].

Abbreviations: AUC, Area under the curve; BMI/A, Body mass index/age; CI, Confidence intervals; CNS, Central nervous system tumors; HR, Hazard ratio; NLR, Neutrophil-to-lymphocyte ratio; OS, Overall survival; CT, Chemotherapy; ROC, Receiver operating characteristic; RT, Radiotherapy; SD, Standard deviation; SIRI, Systemic inflammation response index.

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However, data on the prognostic ability of inflammatory and nutritional markers in pediatric CNS tumors are scarce. Thus, this study aims to evaluate the predictive ability of nutritional status and inflammatory markers in the overall survival of pediatric patients with CNS.

2. Methods

2.1. Study design and patient selection

We performed a longitudinal retrospective cohort study with 230 pediatric patients with CNS aged ≤19 years, who were regularly enrolled in a National Referral Institute for Cancer treatment in Rio de Janeiro, Brazil between January 1st, 2010 to December 31st, 2015. Each patient's medical record was retrospectively screened to collect information on demographic, clinical, biochemical, and immunohistochemical characteristics, as well as treatment type and survival data.

Eligibility criteria were as follows: confirmation of the CNS tumor by imaging or immunohistochemical analysis; available data on weight, height or length, and complete blood parameters before any type of therapy. The exclusion criteria in the study were the presence of metastasis at the time of diagnosis, benign tumor of the central nervous system or unconfirmed diagnosis, treatment outside the institution or treatment abandonment, hematological disease, active infectious diseases, chronic inflammatory or autoimmune disease, use of immunomodulatory drugs (for example, corticosteroids), transfusion in the last 3 months and incomplete data. The study was approved by the Research Ethics Committee of the National Cancer Institute (CAAE: 43320821.7.0000.5274).

2.2. Anthropometry data

All parameters used to assess nutritional status, including body weight and height or length were obtained in medical records within a maximum interval of up to 15 days before any kind of treatment. Data such as weight loss percentage, arm circumference measurement, triceps skinfold, arm muscle circumference, pre-treatment serum levels of C-reactive protein, albumin, and prealbumin were not available and therefore could not be included in the study.

Children's body mass index for age (BMI/A) indicator was calculated by the *Anthro* software version 3.2.2 (World Health Organization, Geneva, SWI) for children <5 years old and *Anthro Plus* version 1.0.4 (World Health Organization, Geneva, SWI) for children over 5 years old and adolescents. Pre-treatment BMI/A was used as a nutritional predictor since it covers the entire pediatric age group, from 0 to 19 years.

Nutritional status was classified according to World Health Organization [26] reference as follow: nutritional risk, malnutrition and accentuated malnutrition - patients with z-score < −1 standard deviation (SD) of the mean BMI for age; eutrophic - patients between −1 SD and +1 SD of the mean BMI for age; and risk of overweight, overweight, obesity, severe obesity - patients with z-score > +1 SD of the mean BMI for age. After these classifications, the categories were grouped into nutritional risk (BMI z-scores < −1 SD of the mean BMI for age) and no nutritional risk (BMI z-scores ≥ −1 SD) for further analyses.

2.3. Inflammatory parameters

Neutrophils, lymphocytes and monocytes blood counts were also obtained in the medical records within a maximum interval of up to 15 days before any kind of treatment. The inflammatory markers was assessed using the neutrophil-to-lymphocyte ratio (NLR) and the systemic inflammation response index (SIRI). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The SIRI was defined as follows: SIRI = neutrophils × monocyes/lymphocytes [27].

2.4. Overall survival

The beginning of follow-up for OS was defined as the time, in years, from the disease histopathological diagnosis date until the death date. The follow-up for this study was performed for 5 years from the date of diagnosis.

2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of the variables. Categorical variables were expressed as absolute or relative frequencies and continuous variables as mean and standard deviation or median, minimum and maximum amplitude as appropriate.

To determine the ideal cut-off values according to death in 5 years and assess the sensitivity and specificity of the biomarkers studied, the time-dependent receiver operating characteristic (ROC) curve in conjunction with Youden's Index was used [28]. Moreover, overall survival curves were calculated using the Kaplan Meier method and evaluated by Log–Rank test.

The Cox proportional hazards model was performed to identify the most important subset of independent variables associated with prognostic factors, generating hazard ratios (HR) and 95% confidence intervals (CI). All factors with a p value < 0.250 in the univariate analysis were included in the multivariate [29].

We calculate the post hoc sampling power with the online tool: https://clincalc.com/Stats/Power.aspx. We set up the calculation for two independent groups, with dichotomous results and an alpha error rate of 0.01. The sample power was 96.9% and 98.2% for NLR and SIRI, respectively, in relation to registered deaths.

All statistical analyzes were conducted using IBM SPSS Statistics for Windows software, version 25 (IBM Corp., Armonk, NY, USA). The p-value <0.05 was considered statistically significant, with 95% CI. The STROBE Checklist quality criteria were used as a reference [30].

3. Results

3.1. Baseline clinical and characteristics

During the study period, 230 pediatric patients with central nervous system tumors were identified. One hundred and twenty-seven of these were excluded for not meeting the eligibility criteria. The remaining 103 patients were included in the analysis (Fig. 1). The median age at diagnosis was 64 months (range 2–169 months). Regarding sex, 42.7% of the patients were female and 57.3% male.

The most common diagnosis was astrocytomas or diffuse oligodendroglial (57.3%) followed by brainstem tumors (12.6%), neuroglial or mixed glial (6.8%), embryonal (6.8%), ependymal (5.8%), pineal region (4.8%), craniopharyngiomas (3.9%), germ cells (1.0%) and choroid plexus tumors (1.0%).

Regarding nutritional status, only 10.7% of patients were classified as nutritional risk, malnutrition or, accentuated malnutrition. Most patients were classified as eutrophic (42.7%) and risk of overweight, overweight or, obese (35.9%) according to BMI z-score. Other patient characteristics are shown in Table 1.

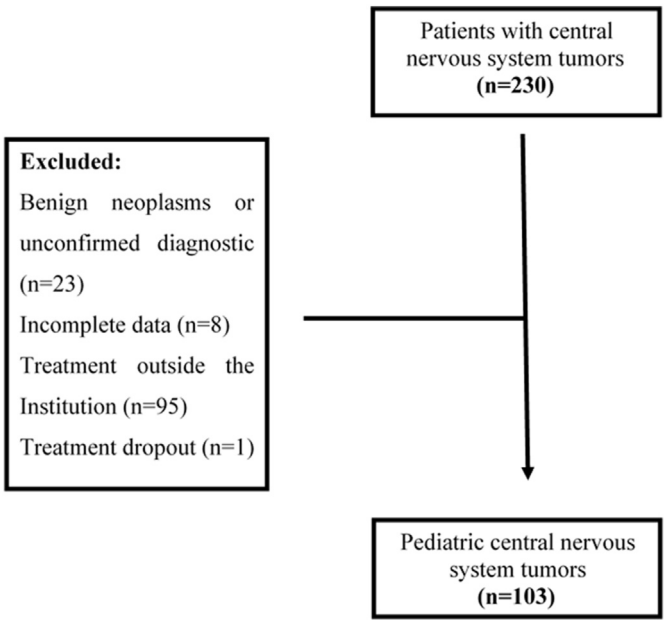

Fig. 1. Patient selection flow diagram. Note: N= Number of patients.

Table 1
Characteristics of the pediatric patients with central nervous system tumors (n = 103).

Variables	Categories	N	%
Age (months)[a]		64	2–169
Sex	Female	44	42.7
	Male	59	57.3
Tumor location	Astrocytic and diffuse oligodendroglial	59	57.3
	Ependymal	6	5.8
	Choroid plexus	1	1.0
	Neuronal and mixed glial	7	6.8
	Pineal region	5	4.8
	Brain stem	13	12.6
	Embryonal	7	6.8
	Germ cells	1	1.0
	Craniopharyngioma	4	3.9
Metastasis	No	95	92.2
	Yes	8	7.8
Residual disease	No	81	78.6
	Yes	22	21.4
Disease recurrence	No	96	93.2
	Yes	7	6.8
BMI z-score[b]	Nutritional risk/malnutrition/ accentuated malnutrition	11	10.7
	Eutrophic	44	42.7
	Risk of overweight/ overweight/obese	37	35.9
Treatment[b]	Expectant conduct	11	10.7
	Surgery	20	19.4
	Surgery + Adjuvant or Neoadjuvant treatment	29	28.2
	Exclusive radiotherapy or chemotherapy	38	36.9
	Radiotherapy + immunotherapy	1	1.0
Death within 5 years	No	58	56.3
	Yes	45	43.7
NLR[a]		2.08	0.42–22.31
SIRI[a]		1556.12	213.67–29455.75

SIRI = Systemic inflammation response index; NLR = Neutrophil-to-lymphocyte ratio; N= Number of observations; BMI z-score = Body mass index z-score.
[a] Median (minimum and maximum).
[b] Variable with missing.

3.2. Ideal cut-off values of pretreatment inflammatory markers for estimating prognosis

We analyzed the optimal cut-off values calculated by the ROC analysis. The ROC curves were presented in Fig. 2. The optimal cut-off values were 2.18 (AUC: 0.639, 95% CI: 0.539–0.731), and 1249.18 (AUC: 0.622, 95% CI: 0.521–0.716) for NLR, and SIRI, respectively. Values greater than or equal to the cutoff of NLR and SIRI were associated to a worse prognosis.

3.3. Kaplan–meier curves of BMI, NLR, and SIRI

In our cohort, nutritional status (BMI z-score) did not significantly affect OS in the period evaluated (5-year) (Fig. 3A). However, patients with NLR ≥2.18 and SIRI ≥1249.18 had significantly lower 5-year overall survival ($p = 0.003$ and $p = 0.012$, respectively) (Fig. 3B and C).

3.4. Predictive factors associated with CNS patient's prognosis

Treatment, metastasis, residual disease, high preoperative NLR and high preoperative SIRI were significantly associated with worse OS in 5 years in univariate Cox regression analysis (Table 2).

On the other hand, in the multivariate Cox regression analysis, only treatment with exclusive radiotherapy or chemotherapy (RT or CT) and high NLR values were identified as an independent prognostic factors for poor OS. Treatment with RT or CT (HR: 16.22, 95% CI: 2.19–120.07; $p = 0.006$) and high NLR (HR: 1.94, 95% CI: 1.02–3.69; $p = 0.043$) demonstrated to be predictive prognostic factors for OS in 5-year (Table 2).

4. Discussion

Our main finding showed that pretreatment NLR is an independent prognostic factor for overall survival in pediatric patients with central nervous system tumors. However, the exact mechanism about the role of preoperative NLR in the prognosis of pediatric tumors is poorly understood.

High NLR may reflects a systemic inflammatory state and the imbalance between tumor growth promotion and control [31,32]. Neutrophils are able to promote proliferation, tumor cell invasion and metastasis through the production of cytokines, resulting in immune escape of cancer cells and treatment resistance. In contrast, lymphocytes are responsible for generating specific immune responses to control tumor growth [33,34].

Previous studies have already founded that an elevated NLR have a prognostic significance for pediatric cancer [35–37]. Flores-Bustamante et al. [38] demonstrated that high NLR values was a prognostic factor for worse OS in pediatric patients with CNS that undergoing to surgical resection. Also, Jing Zhang et al. [39] also found that craniopharyngioma patients with high NLR had worse OS and, life quality. In addition, Nayak et al. [24] considered NLR as, potentially, an universal prognostic factor for worse outcomes for pediatric patients with solid tumors.

Regarding SIRI, studies have shown positive results of this inflammatory marker in predicting overall survival for different types of cancer [25,39,40]. SIRI has the potential to demonstrate the possible interactions between monocytes, neutrophils, and lymphocytes and their influences on the tumor microenvironment, which increases its prognostic value [41–43]. Nevertheless, in our study, SIRI was not found as an independent prognostic factor for overall survival.

Cancer treatment is widely recognized as one of the factors involved in overall survival. Here, treatment based on exclusive RT

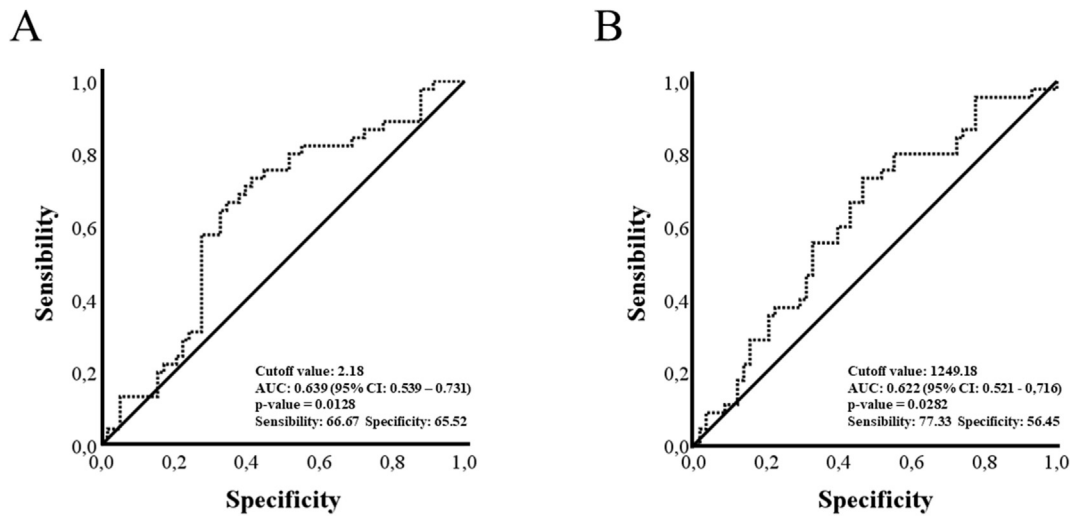

Fig. 2. Area under the receiver operating characteristics curves (AUC): NLR = 0.639 (95% CI: 0.539–0.731, p = 0.0128); SIRI = 0.622 (95% CI: 0.521–0,716, p = 0,0282). Note: SIRI= Systemic inflammation response index; NLR= Neutrophil-to-lymphocyte ratio.

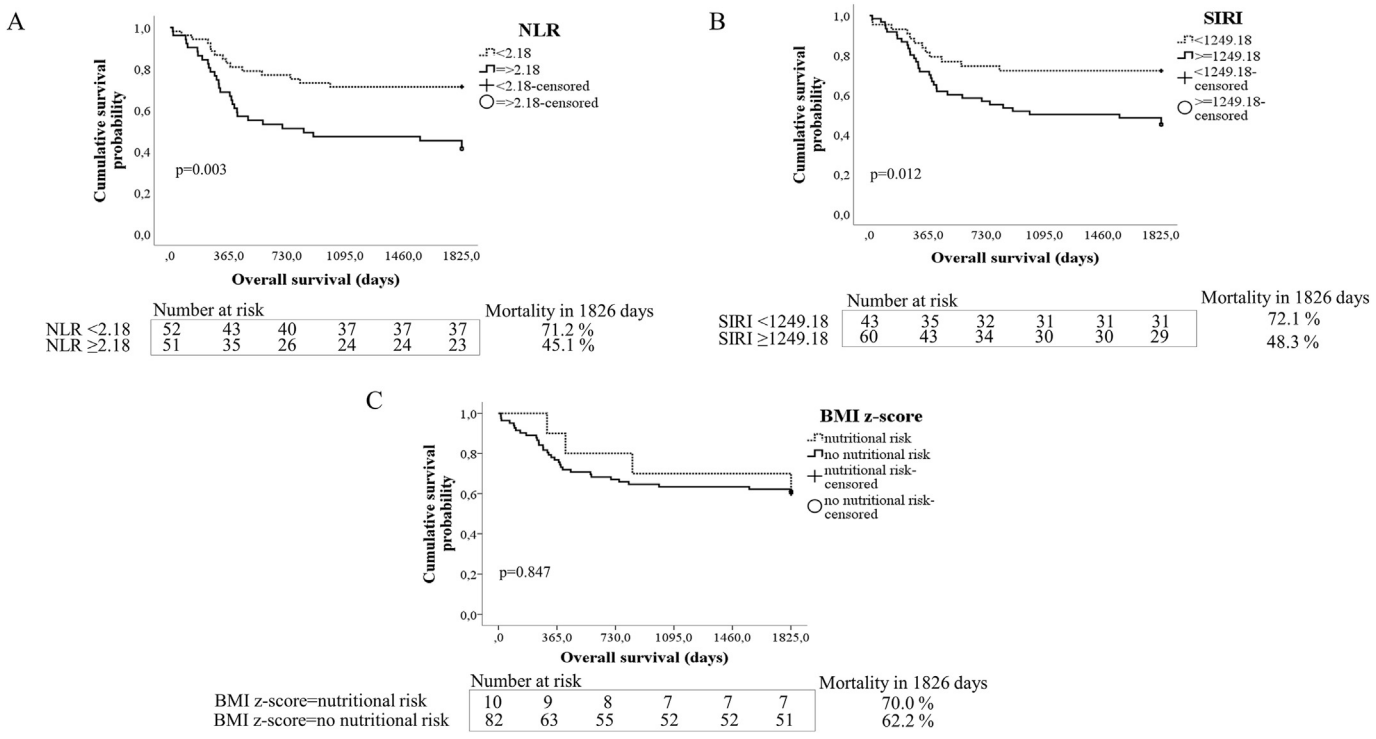

Fig. 3. Kaplan–Meier 5-years overall survival (OS) curves plus log-rank p-values for pediatric central nervous system tumors. (A) OS curves stratified according NLR cutoff values. (B) OS curves stratified according to SIRI cutoff values. (C) OS curves stratified according to BMI z-score. Note: SIRI = Systemic inflammation response index; NLR = Neutrophil-to-lymphocyte ratio; N= Number of observations; BMI z-score = Body mass index z-score.

or CT was the main therapeutic intervention that independently increased the risk of death at 5 years. Baliga et al. [44] also demonstrated that prolonged RT is associated with a decrease in OS, especially in patients with high-risk medulloblastoma. Similarly, Parsons et al. [45] found worse survival for pediatric and adults patients diagnosed with pilocytic astrocytoma who received exclusive RT or CT.

The increased risk of death observed with exclusive RT or CT is probably due to differences between patients. Generally, only the group of patients considered to be at high risk for recurrence, with current recurrences, those with a worse evolution, or with the impossibility of surgical resection are submitted to this type of treatment.

The literature highlights malnutrition as an important factor in the poor prognosis, increasing morbidity and mortality risk, and negatively impacting the cancer treatment course [11,46,47]. However, in our study, nutritional status did not significantly affect overall survival when assessed by the BMI/A z-score and was not identified as an independent prognostic factor for survival in pediatric patients with CNS. In our cohort, most patients were

Table 2
Predictive factors associated with overall survival in univariate and multivariate analysis.

Variables	Categories	Univariate analysis			Multivariate analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Age (months)[a]	<64	1	–	–			
	≥64	0.98	0.54–1.75	0.938			
Sex	Female	1	–	–			
	Male	1.20	0.66–2.18	0.550			
Metastasis	No	1	–	–	1	–	–
	Yes	2.36	0.99–5.61	**0.052**[a]	0.64	0.26–1.57	0.333
Residual disease	No	1	–	–	1	–	–
	Yes	0.27	0.09–0.77	**0.014**[a]	0.45	0.16–1.30	0.142
Disease recurrence	No	1	–	–			
	Yes	0.53	0.13–2.18	0.379			
Treatment	Expectant conduct	1	–	–	1	–	–
	Surgery	–	–	–	–	–	–
	Surgery + Adjuvant or Neoadjuvant	4.75	0.61–36.80	**0.136**[a]	5.29	0.67–41.88	0.115
	Exclusive radiotherapy or chemotherapy	15.30	2.08–112.71	**0.007**[a]	16.22	2.19–120.07	**0.006**[b]
	Radiotherapy + immunotherapy	15.20	0.94–245.84	**0.055**[a]	15.42	0.95–249.67	0.054
BMI z-score	No nutritional risk	1	–	–			
	Nutritional risk	0.903	0.32–2.55	0.847			
NLR[b]	<2.18	1	–	–	1	–	–
	≥2.18	2.51	1.35–4.67	**0.004**[a]	1.94	1.02–3.69	**0.043**[b]
SIRI[b]	<1249.18	1	–	–	1	–	–
	≥1.249.18	2.29	1.18–4.43	**0.014**[a]	1.75	0.89–3.45	0.107

CI = Confidence interval; HR = Hazard ratio; NLR = Neutrophil-to-lymphocyte ratio; SIRI = Systemic inflammation response index; BMI z-score = Body Mass Index z-score.
[a] $p < 0.250$.
[b] HR for multivariate analyses adjusted by metastasis, residual disease, treatment, NLR and, SIRI. NLR and SIRI were tested separately due to collinearity.

classified as eutrophic, but a high percentage were at risk of overweight, overweight or, obesity according to the BMI/A z-score. Tsutsumi & Speridião [48] and Lopes [49] had already found the same results regarding the nutritional status distribution in patients with brain tumors and patients with solid tumors, including CNS, respectively.

Interestingly, Iniesta et al. [50] also demonstrated a higher prevalence of overweight and obesity in pediatric patients with CNS when compared to other cancer types. We highlight that our study included only pediatric patients with CNS, while other studies that identified a higher prevalence of malnutrition or nutritional risk included children and adolescents with different types of neoplasms, which could explain the difference in results [51,52].

Similarly, Pedrosa et al. [53] found no relationship between nutritional status and overall survival of pediatric patients with leukemia and solid tumors. Viani et al. [54] also demonstrated that malnutrition at diagnosis classified by BMI/A did not significantly impact the overall survival of pediatric patients with solid and hematological tumors. Additionality, Small et al. [55] showed that there was also no association between nutritional status determined by BMI/A and survival in patients with neuroblastoma.

The present study has some limitations that should be considered when interpreting the findings. This was a retrospective study, making the potential for selection bias unavoidable. The limitations of the BMI/A z-score in the diagnosis of nutritional status in pediatric cancer patients, the small sample size, and the different types of treatment included in this study are other important factors. However, this is a new focus for the use of NLR exclusively for pediatric patients with CNS cancer. Larger prospective studies are needed to implement the cutoffs and verify the conclusion of this study.

In conclusion, our results demonstrated that high preoperative NLR was an independent prognostic factor for OS in pediatric patients with CNS cancer. Thereby, NLR is an inflammatory marker that can be used in clinical practice as a risk stratification factor in order to guide the therapeutic plan of pediatric patients with CNS cancer.

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Author contributions

LDM is the coordinating investigator and conceptualized the study. ICLS, GSVS and LBM contributed to the study conception and performed the statistical analysis. ICLS drafted and edited the manuscript.

All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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