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Original Article

Predictive Role of the Prognostic Nutritional Index for the Prognosis of Pediatric High-grade Glioma Patients

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ABSTRACT

Aim: Pediatric high-grade glioma (pHGG) is a highly aggressive malignancy with poor prognosis. The role of nutritional status in pHGG prognosis is understudied. This study examined the prognostic value of the prognostic nutritional index (PNI) in pHGG patients.

Materials and Methods: This retrospective study analyzed data from 67 pediatric pHGG patients admitted to the Department of Neurosurgery at The 904th Hospital of the PLA between October 1st, 2016, and December 1st, 2022. The PNI was calculated at three time points: at admission, post-radiotherapy, and at 12 months. Clinical data including age, gender, Lansky performance status score, World Health Organization glioma grade, treatment, overall survival (OS), and time to progression were collected. Multivariate Cox regression analysis and Kaplan-Meier survival analysis were used to assess the correlation between PNI and the clinical outcomes.

Results: The median survival time was 15.3 months. PNI was highest post-radiotherapy and lowest at 12 months. Higher PNI scores at admission and at 12 months were associated with longer progression-free and OS. Multivariate analysis showed that Grade 3 glioma, isocitrate dehydrogenase mutation, and high PNI at admission were associated with delayed tumor progression and longer OS, while Grade 4 glioma and H3K27M mutation were associated with poorer outcomes.

Conclusion: The PNI is a valuable predictor of prognosis in pHGG patients. Higher PNI scores at admission and at 12 months are associated with better clinical outcomes. Nutritional support during the disease course may improve prognosis in pHGG patients.

Keywords: Prognostic nutritional index, pediatric, high-grade glioma, prognosis, survival

Introduction

Pediatric high-grade glioma (pHGG) is a highly aggressive malignant tumor of the central nervous system, predominantly affecting children and adolescents. While high-grade glioma (HGG) also occur in adults, pediatric cases differ substantially from adult gliomas in their biological characteristics, genetic mutations, and treatment responses, resulting in notably poorer outcomes in children and younger patients (1). The prognosis for pHGG remains grim, with an estimated 3-year event-free survival rate of only 10% and an overall survival rate of 20% in this timeframe's subtypes, with diffuse intrinsic pontine glioma (DIPG) presenting the worst prognosis: the average survival for patients with DIPG is less than a year, typically between 8 and 11 months, with only about 10% of patients surviving beyond two years and less than 2% reaching the five-year mark (2,3).

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The standard approaches for pHGG, namely surgical resection, radiotherapy, and chemotherapy, have limited efficacy in significantly improving long-term survival rates. Children with pHGG often present with early symptoms related to tumor-induced pressure, such as movement difficulties, strabismus, swallowing issues, and loss of appetite, which complicate daily care and the provision of adequate nutritional support. As the disease progresses, these often intensify, leading to a greater risk of malnutrition which can potentially impact patient outcomes (4,5). Despite the critical nature of these issues, the relationship between nutritional status and prognosis in pHGG patients remains understudied.

Thus, this study sought to explore this potential correlation through a detailed retrospective analysis, focusing on how nutritional status at various points during treatment might correlate with clinical outcomes in pediatric patients with HGGs.

Materials and Methods

Patients

This study included a retrospective analysis of pHGG patients admitted to the Department of Neurosurgery at The 904th Hospital of the PLA from October 1st, 2016 to December 1st, 2022. Ethical approval was not needed as it was a retrospective study without additional interventions or new data collection. Informed consent was obtained from the guardians of all participating children. This research was performed in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows: (1) aged between 1 and 18 years; (2) no gender restriction; (3) a diagnosis of pHGG [classified as World Health Organization (WHO) astrocytomas Grades III or IV) based on biopsy results; (4) the availability of relevant clinical data for analysis; and (5) a history of radiotherapy. The exclusion criteria included: (1) a lack of access to the required clinical data for the study; and (2) family refusal for follow-up or the provision of invalid contact information.

Research Content and Methods

The primary objective of this study was to assess the nutritional status of patients using the prognostic nutritional index (PNI) and, in turn, to evaluate any correlation between nutritional status and prognosis in pHGG patients. The peripheral blood albumin level and lymphocyte counts at three stages: at admission (prior to biopsy); within one week after the end of radiotherapy; and at 12 months were used to calculate the PNI in order to assess the patient's nutritional status.

The secondary objective of this study was to analyze the following clinical data with respect to the patients' outcome: age, gender, Lansky performance status (LPS) score, WHO grade, treatment, time to progression [from diagnosis, verified by T2 phase magnetic resonance imaging (MRI) scan and neurological deficiency] and gene mutation.

The formula for calculating PNI was as follows: PNI=10 × serum albumin (g/L) + 0.005 × peripheral blood lymphocyte count (/mm^3).

Statistical Analysis

Statistical analysis was performed using R 4.1.1. Multivariate Cox regression analyses were conducted in order to identify factors influencing treatment outcomes and prognosis in pHGG patients. OS was measured and compared by Kaplan-Meier (KM) survival analysis. The cut-off value for PNI was determined based on previous studies. A cut-off value of 40 was selected to categorize patients into high PNI (PNI≥40) and low PNI (PNI<40) groups which had been used in previous studies for PNI (6-8).

Results

Clinical Characteristics of Patients

A total of 86 patients admitted to The 904th Hospital of the PLA between October 1st, 2016 and December 1st, 2022 were screened (Figure 1). Among them, 14 patients had incomplete records for the primary endpoints, and the families of 5 patients declined to participate in the follow-up. Finally, this study retrospectively analyzed 67 pediatric patients, all of whom were diagnosed with pHGG by MRI scan and their pathological results from biopsies. Table I presents the clinical characteristics of these 67 patients, with a mean age of 10.1±5.2 years, with 47.8% of them being female. Regarding the LPS scores, 3 patients scored 40, 14 patients scored 50, 17 patients scored 60, 25 patients scored 70, and 8 patients scored 80. All patients received radiotherapy; 12 patients underwent chemotherapy, and 5 received conventional treatment. According to the WHO 2021 classification system for brain tumors, 27 patients were classified as Grade 3, and 40 patients were classified as Grade 4. Regarding genetic mutations, 15 patients had an isocitrate dehydrogenase (IDH) mutation, 57 patients had a H3K27M mutation, 4 patients had a BRAF V600E mutation, and all patients had a p53 mutation.

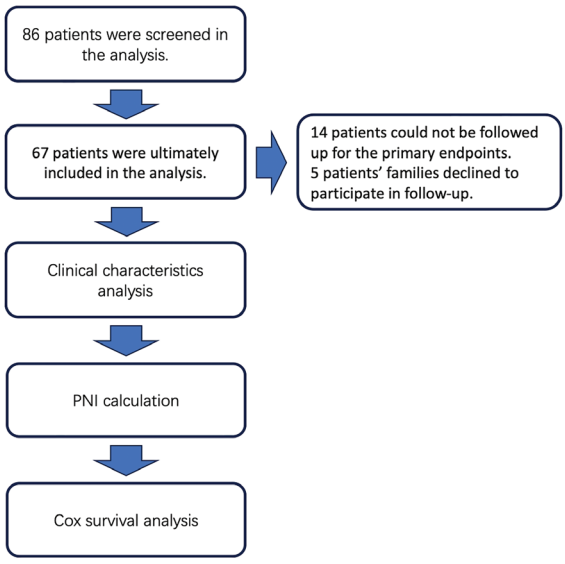

Figure 1. This flowchart illustrates the patient screening and analysis process in this clinical study. A total of 86 patients were initially screened for inclusion in this analysis. Out of these, 67 patients were ultimately included in this analysis. Fourteen patients could not be followed up for the primary endpoints, and 5 patients' families declined to participate in the follow-up. The analysis began with an assessment of the clinical characteristics of the included patients. Next, a prognostic nutritional index calculation was conducted. Finally, Cox survival analysis was performed in order to evaluate survival outcomes

Survival Analysis

According to the KM survival curve, the median survival time was 15.3 months (Figure 2). Median progression time was 14.4 months (Table II). Thirty-eight patients survived over 12 months. We used multivariate Cox survival analysis in order to assess the relationships between the patients' clinical characteristics, tumor progression time and their survival time. The results indicated that age, sex, LPS score, chemotherapy or conventional treatment, BRAF V600E mutation, and the PNI value after radiotherapy had no significant association with tumor progression time after radiotherapy (Figure 3A). However, those patients with Grade 3 glioma, *IDH* mutation, and high PNI at admission experienced delayed tumor progression. In contrast, Grade 4 glioma and H3K27M mutation were associated with faster progression. Regarding OS, there was no significant correlation between age, sex, chemotherapy, conventional treatment, BRAF V600E mutation, and PNI after radiotherapy with OS (Figure 3B). However, higher LPS scores, Grade 3 glioma, IDH mutation, high PNI at admission and at 12 months, and longer progression times were associated with longer OS. Conversely, Grade 4 glioma and H3K27M mutation were associated with shorter survival times.

Table I. Clinical characteristics of patients

N	67
Age (y)	10.1±5.2
Gender (female)	32 (47.8%)
LPS	
40	3 (4.5%)
50	14 (20.9%)
60	17 (25.4%)
70	25 (37.3%)
80	8 (11.9%)
Treatment	
Radiotherapy	67 (100%)
Chemotherapy	12 (17.9%)
Traditional therapy	5 (7.5%)
WHO grade	
Grade 3	27 (40.3%)
Grade 4	40 (59.7%)
Gene mutation	
IDH mut	15 (22.4%)
H3K27M	57 (85.1%)
BRAF V600E	4 (6.0%)
p53	67 (100%)

Numeric variables were expressed in mean ± standard deviation or median (minimum-maximum), and typed variables were expressed in n (n%)
LPS: Lansky performance status, WHO: World Health Organization, IDH: Isocitrate dehydrogenase

PNI Changes for Outcome

We attempted to deepen our understanding of how different levels of the PNI relate to patient prognosis by analyzing OS outcomes. By examining PNI values at three key time points, at admission, at one week post-radiotherapy, and at 12 months, we observed that PNI was highest shortly after radiotherapy but decreased significantly by the 12-month mark, showing marked differences compared to admission and post-radiotherapy levels (Figure 4A).

To further clarify the role of PNI in prognosis, we selected a PNI cut-off of 40, categorizing patients with a PNI ≥40 as having a high PNI and those with a PNI <40 as having a low PNI. We then conducted a KM survival analysis in order to compare OS between these two groups. Our findings revealed that an early high PNI was associated with a significantly better prognosis, suggesting that nutritional

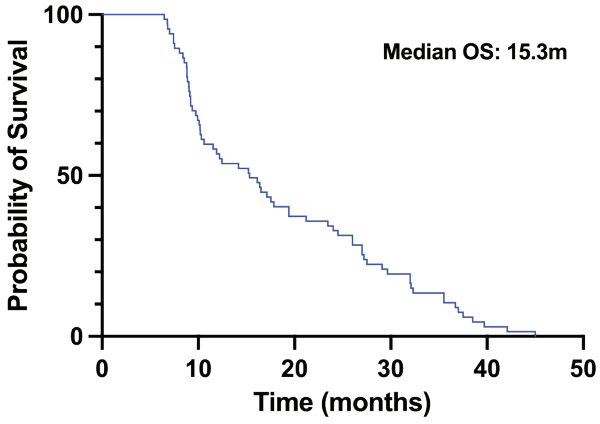

Figure 2. The Kaplan-Meier survival curve for all patients, the median survival was 15.3 months
OS: Overall survival

Table II. Patients outcome	
Progression time (m)	14.4 (2.1-32.3)
Survival at 12 months after onset	38 (56.7%)
Overall survival (m)	15.3 (6.5-45.0)
PNI	
PNI at admission	42.1±5.7
PNI after radiotherapy	45.1±6.1
PNI at 12 months (n=38)	40.1±3.4
Numeric variables were expressed in mean ± standard deviation or median (minimum-maximum), and typed variables were expressed in n (n%) PNI: Prognostic nutritional index	

status at the outset may play a critical role in patient survival (Figure 4B). This positive association, however, was less pronounced immediately following radiotherapy, possibly reflecting transient treatment effects on nutritional status and immune response (Figure 4C).

In those patients who survived beyond 12 months, a high PNI was again linked to longer OS, reinforcing the importance of sustained nutritional and immune health in improving long-term survival (Figure 4D). Collectively, these findings indicate that a high PNI, particularly in the early and later stages (12 months), may serve as a useful predictor of overall survival, highlighting the value of monitoring and supporting nutritional health as part of long-term management in those patients with HGGs.

According to the results of this study, PNI levels at admission and at 12 months have a more significant impact on survival rates. Specifically, those patients with higher PNI at admission tended to have better prognoses. This may be because a good nutritional status provides a

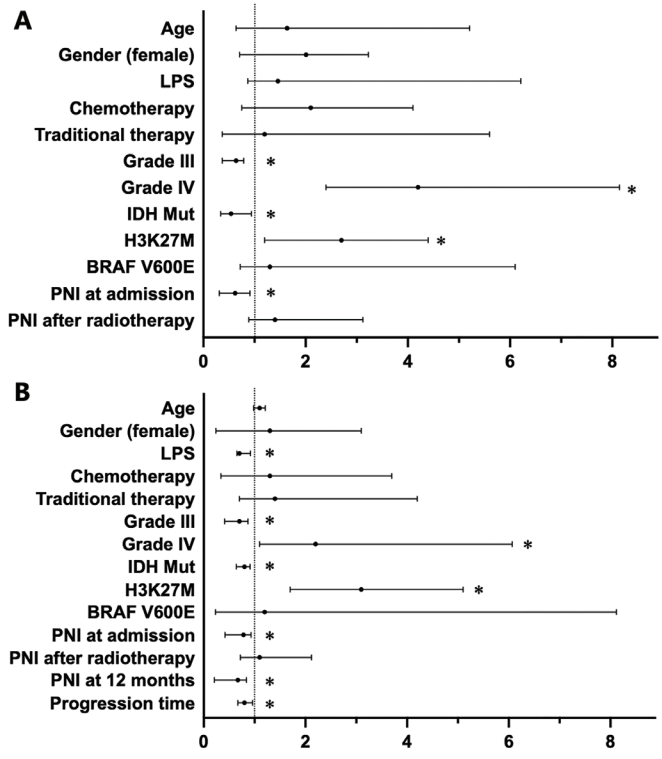

Figure 3. This tree map shows the clinical factors with respect to patient outcomes analyzed by multivariate COX survival analysis (•: Indicates the coef value, the bar represents the 95% confidence interval, and *: Represents p<0.05) (A) This panel primarily illustrates the relationship between clinical characteristics and progression time. The Grade 3 tumor, IDH mutation and high PNI at admission indicated later progression. Grade 4 tumor and H3K27M mutation indicated earlier progression. (B) This panel primarily illustrates the relationship between clinical characteristics and overall survival. High LPS at admission, Grade 3 tumor, IDH mutation, high PNI score at admission and 12 months and later progression were associated with longer survival times. Grade 4 tumor and H3K27M were associated with poorer outcomes
IDH: Isocitrate dehydrogenase, PNI: Prognostic nutritional index, LPS: Lansky performance status

better foundation for subsequent treatments, helping to enhance the body's immune system and tolerance, thereby delaying tumor progression and improving survival rates to some extent. At 12 months, those patients with higher PNI levels also showed longer survival times, indicating that maintaining good nutritional status throughout the disease process is crucial for long-term survival. In contrast, although PNI levels one week after radiotherapy can also reflect the patient's nutritional status to some extent, the correlation with survival rates was relatively weaker. This was likely because radiotherapy itself may have certain effects on the patient's nutritional status and immune function.

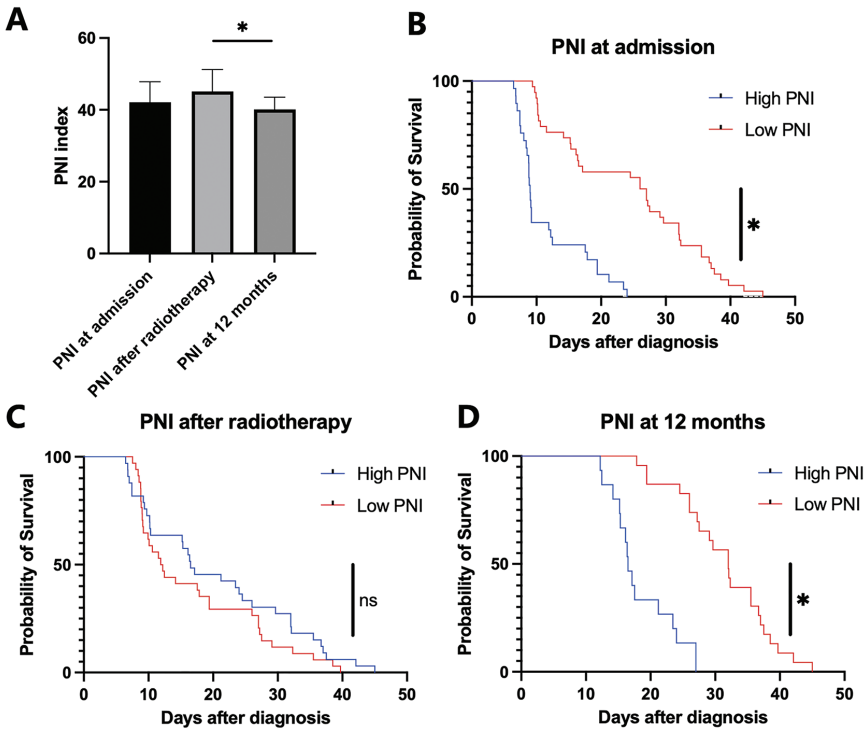

Figure 4. This figure illustrates the relationship between the prognostic nutritional index and survival outcomes across different time points in this clinical study (*: Indicates p<0.05) (A) A bar graph showing changes in PNI at three different time points: at admission, after radiotherapy, and at 12 months. (B) A Kaplan-Meier (KM) survival curve depicting the probability of survival based on PNI at admission. Patients with a high PNI have significantly better survival probabilities compared to those with a low PNI. (C) A KM survival curve showing survival probabilities based on PNI levels after radiotherapy. No significant difference was observed between high and low PNI groups at this time point. (D) A KM survival curve displaying survival probabilities based on PNI at 12 months. High PNI was associated with a significantly better survival rate than low PNI
PNI: Prognostic nutritional index

Discussion

pHGG is the most common malignant brain tumor in children, with a high mortality rate and limited effective treatment options (9). Currently, for pHGG, the concept of multidisciplinary collaboration is indispensable. It is no longer a task which can be accomplished by a single discipline (10). Appropriate and continuous nutritional support is also crucial for a positive patient prognosis (11). pHGG have distinct characteristics compared to adult gliomas. For instance, patients often face inadequate nutritional intake in the early stage. In addition to decreased oral intake, tumor-related cachexia, reduced digestive capacity, gastrointestinal dysfunction, increased catabolism, and the side effects of radiotherapy and chemotherapy all exacerbate the deterioration of the patients' nutritional status (12,13).

In this study, we used PNI to assess patients' nutritional status at onset, after radiotherapy, and at the 12-month mark. Compared to previous single nutritional indicators, PNI incorporates serum protein levels and has greater prognostic value for glioma patients, which has been confirmed by several studies (14). Among the three time points measured, PNI was lowest at 12 months, indicating a decline in nutritional status later in the disease course. This decline is multifactorial, with decreased appetite in the late stage of pHGG, and reluctance among guardians for invasive nutritional support measures (such as gastrointestinal tubes), which further complicates nutritional support. Additionally, most families lack sufficient experience in long-term care and nutritional support, highlighting the importance of continuously providing caregivers with adequate guidance throughout the treatment. Among the three periods, the PNI was highest following radiotherapy,

which may be related to symptomatic relief after radiation therapy, thus improving nutritional intake. We suggest that this period is an opportune time for nutritional intervention.

Given the difficulties in providing nutritional support in the later stages, we recommend implementing personalized interventions in order to support immune functions and overall metabolic health. These interventions may include a high-protein diet to prevent muscle wasting and to maintain lean body mass, which are essential for immune function (15). Additionally, ensuring a sufficient intake of omega-3 fatty acids, vitamins (such as vitamin D and B vitamins), and minerals (such as zinc and selenium) can help modulate inflammation and support tissue repair (16). For patients struggling with oral intake, nutritional supplementation or enteral nutrition may be necessary to meet caloric and protein needs (17,18). Close monitoring of nutritional status throughout the treatment is also critical in order to allow timely adjustments to the intervention plan, although further clinical trials are needed to confirm the effectiveness of these interventions.

The mechanisms by which nutritional status affects the prognosis of children with pHGG are diverse. Improved nutritional status may impact pHGG outcomes through several potential mechanisms. One key area is the role of nutrition in supporting the immune system. A well-nourished state may enhance immune surveillance and response to therapies, including immunotherapy, which is particularly relevant to our research focus (19). Additionally, certain nutrients may influence inflammation, which has been shown to affect tumor progression and treatment response. For instance, omega-3 fatty acids are known to regulate inflammatory pathways which could impact the tumor microenvironment (20). Another potential mechanism involves energy metabolism. Nutritional status can alter metabolic pathways, which could affect cancer cell proliferation, particularly in fast-growing tumors such as DIPG (21). These biological processes and pathways are worth further investigation in the context of DIPG and nutritional interventions.

In order to investigate the relationship with patient prognosis, we conducted a multivariate Cox survival analysis on multiple clinical indicators. Relative to lower-grade gliomas (Grade 3), IDH mutation, and higher PNI (at the early stage of the disease) were associated with a relatively longer progression-free survival and overall survival, consistent with other research findings regarding these clinical features and prognosis. Additionally, the 12-month PNI also indicated a longer survival period for patients. However, both the Cox survival analysis and KM survival curve analysis suggest that the prognostic predictive value of PNI after radiotherapy appears to be smaller than at the other two time points. This may be due to the direct impact of radiotherapy on PNI. Overall, we conclude that maintaining nutritional support throughout the disease course is crucial for patient prognosis.

Currently, studies on the prognostic value of PNI in pediatric tumors are relatively limited. For instance, a study on medulloblastoma patients undergoing surgical resection found that PNI could play a predictive role in overall survival, with an optimal cut-off value of 56.5 (22). Another study on pineal region tumors found that the hemoglobin, albumin, lymphocyte, and platelet score, which includes PNI, was positively associated with survival chances (23). These studies, although not specifically focused on pHGGs, provide a broader context for understanding the potential prognostic value of PNI in pediatric tumors. Our study uniquely contributes to the field by focusing on the temporal dynamics of PNI at admission and at 12 months, demonstrating its significant impact on survival rates in pHGG patients. This detailed temporal analysis is a novel aspect which differentiates our work from previous studies, offering new insights into the importance of sustained nutritional support throughout the disease course (23).

Study Limitations

This study has several limitations. Firstly, we were unable to conduct a prospective cohort study to verify the effectiveness of nutritional interventions, so further validation is needed. Secondly, the low incidence of pHGG makes follow-up challenging. The sample size of this study was small, introducing a degree of sample bias. Additionally, differences in direct therapeutic interventions for each patient may have led to variability in prognosis.

Conclusion

This study conducted a retrospective analysis of the relationship between PNI at different time points and prognosis in pHGG patients. Our results showed that a favorable early PNI level and a high PNI level 12 months post-onset are associated with better prognosis. Therefore, nutritional support during the course of the disease in children with pHGG is essential.

Ethics

Ethics Committee Approval: This study involved a retrospective follow-up analysis of previously collected data and was granted an exemption from the ethic committee of The 904th Hospital of the PLA.

Informed Consent: This study obtained written consent from the guardians of all participants.

Footnotes

Authorship Contributions

Concept: L.S., Y.W., Design: L.S., Y.W., Data Collection or Processing: N.S., Y.S., S.W., L.S., Y.W., Analysis or Interpretation: N.S., Y.S., S.W., L.S., Y.W., Literature Search: N.S., Y.S., S.W., L.S., Y.W., Writing: N.S., Y.S.

Conflict of Interest: All authors declare no conflict of interest.

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