

Prognostic Value of Inflammation Biomarkers for Survival of Patients with Neuroblastoma

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Chen Zheng*
Shuaibin Liu*
Jiexiong Feng
Xiang Zhao 

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, People's Republic of China

*These authors contributed equally to this work

Purpose: The prognostic significance of inflammation-based biomarkers for neuroblastoma (NB) has not been investigated before. The aim of this study was to evaluate the prognostic value of pre-treatment inflammation biomarkers in children patients with NB.

Patients and Methods: Patients diagnosed with NB from 2008 to 2016 in our institution were enrolled in this study. The clinical data and survival outcomes were retrospectively reviewed. Inflammation biomarkers or scores including C-reactive protein (CRP), albumin (ALB), Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), high-sensitivity modified Glasgow Prognostic Score (Hs-mGPS), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and system inflammation index (SII) were tested in this study. Univariate and multivariate survival analyses were performed to assess the prognostic value of these inflammation indicators for overall survival (OS) of children with NB. Kaplan–Meier survival curves were also conducted.

Results: A total of 70 children diagnosed with neuroblastoma were enrolled in this study. NLR, PLR, LMR and SII were found to be not predictive of OS for NB patients. However, CRP, ALB, GPS and CAR were significantly associated with OS of NB patients. Multivariate analysis adjusting for age, sex, histology, tumor size, tumor stage and metastasis revealed that ALB, CAR, GPS and Hs-mGPS were significantly associated with OS of NB patients. Receiver operating characteristic (ROC) curves and Akaike Information Criterion (AIC) analyses revealed that Hs-mGPS is superior to other inflammation biomarkers in predicting OS of NB patients. Subgroup survival analysis for immature NB patients revealed similar results.

Conclusion: Hs-mGPS is an effective prognostic factor for OS of patients with NB and is promising to be used as a factor for risk stratification and an indicator for more aggressive therapy.

Keywords: inflammation, neuroblastoma, biomarker, Glasgow Prognostic Score, survival

Introduction

The links between inflammation and cancer are well established nowadays. Increasing evidences suggested that not only inflammations can cause cancers but also cancers can cause inflammations.¹ Cancer-related inflammation may lead to alteration of the cancer biology and tumor-microenvironment and contribute to the progression of malignancy through multiple mechanisms including promotion of proliferation, inhibition of apoptosis, induction of angiogenesis, facilitating metastasis, immunosuppression, and resistance to chemotherapeutic drugs.^{1–3} Researchers are also beginning to focus on anti-inflammatory agents as new approaches for cancer prevention and treatment.^{1,2}

The association between inflammation and cancer also promoted the investigation of the prognostic role of inflammation-based biomarkers for cancer patients. In

Correspondence: Xiang Zhao
Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, People's Republic of China
Email zhaoxiang8609@163.com

recent years, several blood inflammation biomarkers or inflammation-based scores have been found to be predictive of survival for multiple types of cancers. These potential prognostic inflammation indicators include C-reactive protein (CRP), albumin (ALB), Glasgow Prognostic Score (GPS), C-reactive protein to albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and systemic immune-inflammation index (SII).^{4–30}

Neuroblastomas (NBs) are the most common extracranial solid malignancy in childhood.³¹ NBs are a heterogeneous group of tumors composed of cellular aggregates with different degrees of differentiation, from mature ganglioneuroma (GN) to less mature ganglioneuroblastoma (GNB) to immature neuroblastoma (NB).^{31,32} Although the overall survival (OS) rate for NB increased during the past several decades, the 5-year OS is only about 71% for all children diagnosed with NB.³¹ Improvement of the risk stratification factor and therapeutic methods for NB is still required.

Numerous evidences also revealed that inflammatory molecules and inflammatory cells play important roles in the progression and metastasis of NB.^{33–43} However, the prognostic significance of inflammation biomarkers in the blood for the survival of NB patients has not been investigated before. Therefore, we conducted the current retrospective study to investigate the prognostic significance of pre-treatment blood inflammation biomarkers or scores for the OS of the patients with NB in our institution. The results showed that NLR, PLR, LMR, and SII were not predictive of OS, while CAR and Hs-mGPS were significantly associated with OS of NB patients in both univariate model and multivariate model survival analysis.

Materials and Methods

Patients

Between January 2008 to December 2016, 86 consecutive patients pathologically diagnosed with neuroblastic tumors at Tongji Hospital of Huazhong University of Science and Technology were retrospectively reviewed. The inclusion criteria were as follows: (1) patients pathologically diagnosed with GN, GNB, or NB; (2) patients with complete follow-up data and clear end points; (3) patients with complete data of laboratory test of pre-treatment inflammation biomarkers. The exclusion criteria were as follows: (1) Patients with evidence of infectious disease or other inflammatory conditions; (2) patients with incomplete clinical data

or incomplete survival data. Finally, 70 children patients with complete data were enrolled in this study.

The patients were routinely followed up every 3 months during the first 3 years after initial treatment and every 6 months subsequently. The last follow-up date was November 2019. Clinical characteristics of the patients including age at diagnosis, sex, INSS (International Neuroblastoma Staging System) stage, metastasis status at diagnosis and tumor size were extracted. Since age at diagnosis younger than 18 months usually associated with good survival of NB patients, the age status was categorized accordingly (age ≤ 18 months versus age > 18 months).³¹

Ethical Approval

This study was approved by the Ethics Committee of Tongji Hospital of Huazhong University of Science and Technology. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all the participants' legal guardians.

Inflammation-Based Biomarkers or Scores

The blood test for CRP level, ALB level, neutrophil counts, lymphocyte counts, monocyte counts, and platelet counts were obtained 1 to 7 days before surgery or any other treatment was carried out. Three types of GPS score were calculated as previously reported: (1) traditional GPS, which is derived by allocating 1 point each for elevated CRP (> 10 mg/L) and hypoalbuminemia (serum albumin < 35 g/L), so that patients with both, one, or none of these conditions would have scores of 2, 1, or 0; (2) modified GPS (mGPS), in which hypoalbuminemia was assigned a score of 0 in the absence of an elevated CRP; (3) high-sensitivity modified GPS (Hs-mGPS), in which 3 mg/L (rather than 10 mg/L) is used as the CRP cut-off value.⁴⁴ CAR was calculated as CRP to ALB ratio. NLR was calculated as neutrophil counts to lymphocyte counts ratio. PLR was platelet counts to lymphocyte counts ratio. LMR was lymphocyte counts to monocyte counts ratio. SII was calculated as platelet counts \times neutrophil counts/lymphocyte counts.^{20–22}

Statistical Analysis

Univariate and multivariate survival analyses were performed by Cox proportional hazards model to estimate

the hazard ratios (HR) with 95% confidence intervals (CI). An observed HR > 1 indicated worse outcomes for the tested biomarkers. The time-dependent receiver operating characteristic (ROC) curve and area under curve (AUC) analyses were used to evaluate the sensitivity and specificity of the investigated biomarkers. The optimal cutoff values for continuous variables were determined by Youden's index (sensitivity + specificity - 1), and the value which has the highest Youden's index was chosen as the optimal cut-off value. Akaike Information Criterion (AIC) analysis was also performed to compare the discriminative ability of different biomarkers. Survival curves were constructed using the Kaplan–Meier method and evaluated by Log-rank test. The difference between groups was evaluated by the Mantel–Haenszel chi-square test. Statistical analyses were carried out using the SPSS Statistics software version 18 (IBM Corporation, USA). AIC analyses were performed by STATA statistical software package version 15.0 (Stata Corporation, College Station, USA). All statistical tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Patients Characteristics

A total of 70 patients pathologically diagnosed with neuroblastoma were enrolled in the current study, with 31 female patients and 39 male patients. Twenty-one patients were diagnosed under the age of 18 months, and 49 were diagnosed older than 18 months. Twenty-two cases were categorized as INSS 1, eight cases were INSS 2, 14 cases were INSS 3, and 26 cases were INSS 4. The histology subtypes include GN ($n=1$), GNB ($n=13$) and NB ($n=56$). Twenty-three patients received surgery followed by observation, 35 patients received surgery followed by routine chemotherapy, 9 patients received neoadjuvant chemotherapy and followed by surgery and routine chemotherapy, and three patients received only chemotherapy after surgical biopsy. Twenty-six cases were with a tumor size less than 5 cm (diameter) and 44 cases were with a tumor size larger than 5 cm (diameter). The average follow-up time is 53.1 months.

Survival Analysis for Overall Neuroblastoma Patients

Univariate survival analysis (Table 1) revealed that clinical characteristics including age (HR=3.31; 95% CI=1.15–9.53; $p=0.026$), INSS stage (HR=4.22; 95% CI=1.71–10.39; $p=0.002$), tumor size (HR=2.85; 95% CI=1.16–7.00;

$p=0.023$), and metastasis (HR=4.49; 95% CI=2.10–9.62; $p<0.001$) were significantly associated with OS of the patients. As for the inflammation biomarkers, CRP (HR=3.96; 95% CI=1.88–8.35; $p<0.001$), ALB (HR=2.67; 95% CI=1.18–6.03; $p=0.019$), GPS (HR=4.74; 95% CI=2.19–10.25; $p<0.001$), mGPS (HR=3.96; 95% CI=1.89–8.25; $p<0.001$), Hs-mGPS (HR=8.80; 95% CI=3.55–21.8; $p<0.001$), and CAR (HR=8.74; 95% CI=2.07–36.80; $p=0.003$) were significantly associated with OS of the patients. However, NLR, PLR, LMR and SII have no predictive value for OS of NB patients.

Multivariate survival analyses (Table 1) for the inflammation biomarkers were performed by adjusting for clinical characteristics including age, sex, INSS stage, histology, tumor size and metastasis. The results of the multivariate analyses showed that ALB (HR=3.32; 95% CI=1.38–7.99; $p=0.007$), GPS (HR=2.96; 95% CI=1.16–7.56; $p=0.023$), Hs-mGPS (HR=6.18; 95% CI=2.21–17.27; $p=0.001$) and CAR (HR=6.75; 95% CI=1.48–30.82; $p=0.014$) were significantly associated with OS of NB patients.

ROC Curve and AIC Analysis

The ROC curve and AUC analyses were performed to determine the optimal cutoff values for CAR and the value which has the highest Youden's index was chosen as the optimal cut-off value (0.0959). Since NLR, PLR, LMR, and SII were not shown to be predictive of OS by univariate Cox proportional model survival analysis, no further analysis was conducted for these biomarkers.

ROC curves and AUC analyses were also performed to evaluate the discriminatory ability of those inflammation biomarkers (Figure 1A and Table 2). The results revealed that Hs-mGPS has the highest AUC level (AUC=0.881; 95%=0.702–0.920; $p<0.001$) in predicting OS. AIC analyses also revealed that Hs-mGPS has the lowest AIC level (206.0429) in predicting OS (Table 2). These results suggested that Hs-mGPS is superior to other inflammation biomarkers in predicting OS of NB patients.

Kaplan–Meier Survival Curves

The survival curves of the prognostic inflammation biomarkers for patients with neuroblastoma were generated by the Kaplan–Meier method as is shown in Figure 2. Patients with elevated CRP level had significantly worse OS than those with normal CRP level (Figure 2A, $p < 0.001$). Patients with hypoalbuminemia had significantly worse OS than those with normal ALB level (Figure 2B, $p = 0.014$). Patients with higher CAR value had significantly worse OS than

Table 1 Univariate and Multivariate Cox Regression Analyses for Overall Survival of Patients with Neuroblastoma

Variables		Total No. (Death No.)	Univariate Analysis		Multivariate Analysis ^a	
			HR(95% CI)	P value	HR(95% CI)	P value
Sex	Female	31 (15)	1 (Ref.)			
	Male	39 (14)	0.62 (0.30–1.29)	0.202		
Age	≤ 18 months	21 (4)	1 (Ref.)			
	> 18 months	49 (25)	3.31 (1.15–9.53)	0.026		
INSS stage	1/2	30 (6)	1 (Ref.)			
	3/4	40 (23)	4.22 (1.71–10.39)	0.002		
Histology	GN/GNB	14 (4)	1 (Ref.)			
	NB	56 (25)	1.86 (0.65–5.35)	0.246		
Tumor size	≤ 5cm	26 (6)	1 (Ref.)			
	> 5cm	44 (23)	2.85 (1.16–7.00)	0.023		
Metastasis	Without metastasis	44 (11)	1 (Ref.)			
	With metastasis	26 (18)	4.49 (2.10–9.62)	< 0.001		
NLR	Continuous variable	70 (29)	1.14 (0.95–1.43)	0.139		
PLR	Continuous variable	70 (29)	1.001 (0.997–1.005)	0.694		
LMR	Continuous variable	70 (29)	0.91 (0.80–1.03)	0.122		
SII	Continuous variable	70 (29)	1.000 (1.000–1.001)	0.102		
CAR	Continuous variable	70 (29)	1.63 (1.33–2.01)	< 0.001	1.41 (1.12–1.78)	0.003
CRP	≤ 10mg/L	47 (12)	1 (Ref.)		1 (Ref.)	
	> 10mg/L	23 (17)	3.96 (1.88–8.35)	< 0.001	2.13 (0.87–5.22)	0.098
ALB	≥ 35g/L	59 (21)	1 (Ref.)		1 (Ref.)	
	< 35g/L	11 (8)	2.67 (1.18–6.03)	0.019	3.32 (1.38–7.99)	0.007
GPS	0	44 (10)	1 (Ref.)		1 (Ref.)	
	1/2	26 (19)	4.74 (2.19–10.25)	< 0.001	2.96 (1.16–7.56)	0.023
mGPS	0	47 (12)	1 (Ref.)		1 (Ref.)	
	1/2	23 (17)	3.96 (1.89–8.25)	< 0.001	2.13 (0.87–5.22)	0.098
Hs-mGPS	0	41 (6)	1 (Ref.)		1 (Ref.)	
	1/2	39 (23)	8.80 (3.55–21.80)	< 0.001	6.18 (2.21–17.27)	0.001
CAR	< 0.0959	22 (2)	1 (Ref.)		1 (Ref.)	
	> 0.0959	48 (27)	8.74 (2.07–36.80)	0.003	6.75 (1.48–30.82)	0.014

Notes: ^aMultivariate analyses were adjusted by sex, age, INSS stage, histology, tumor size and metastasis.

Abbreviations: HR, hazard ratio; CI, confidence interval; INSS, International Neuroblastoma Staging System; GN, ganglioneuroma; GNB, ganglioneuroblastoma; NB, neuroblastoma; CAR, C-reactive protein to albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, system inflammation index; CRP, C-reactive protein; ALB, albumin; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS; Ref., reference.

those with lower CAR value (Figure 2C, $p < 0.001$). Patients with elevated GPS score (GPS, mGPS or Hs-mGPS) had significantly worse OS than those with normal GPS score (Figure 2D–F; $p < 0.001$, respectively).

Subgroup Analysis for Immature Neuroblastoma Patients

Univariate survival analysis (Table 3) revealed that clinical characteristics including age (HR=4.25; 95% CI=1.45–12.40;

$p=0.008$), INSS stage (HR=3.44; 95% CI=1.29–9.19; $p=0.014$), tumor size (HR=2.92; 95% CI=1.16–7.31; $p=0.023$), and metastasis (HR=3.93; 95% CI=1.72–8.99; $p=0.001$) were significantly associated with OS of patients with immature NB. As for the inflammation biomarkers, CRP (HR=3.27; 95% CI=1.46–7.31; $p=0.004$), GPS (HR=4.03; 95% CI=1.73–9.40; $p=0.001$), mGPS (HR=3.27; 95% CI=1.46–7.31; $p=0.004$), Hs-mGPS (HR=8.94; 95% CI=3.05–26.26; $p < 0.001$), and CAR (HR=15.35; 95%

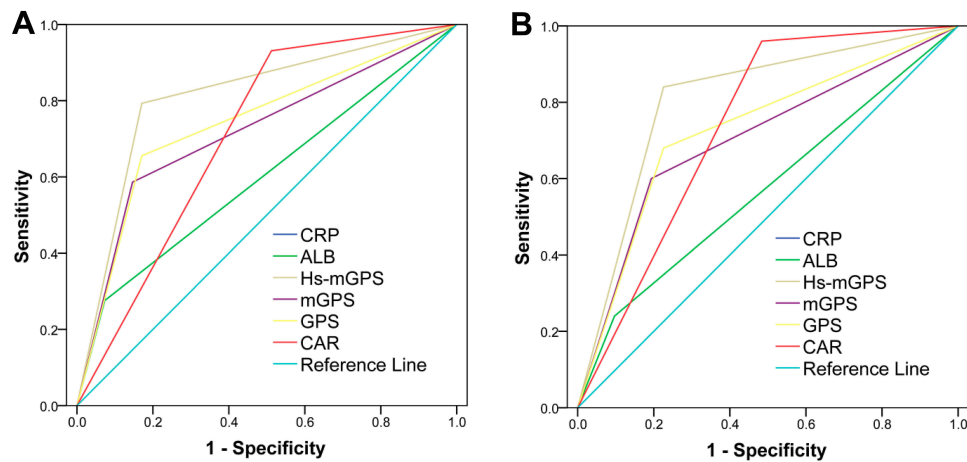


Figure 1 The receiver operating characteristic (ROC) curves and area under curve (AUC) analyses for the prognostic role of the inflammation biomarkers in (A) total 70 patients with neuroblastoma and (B) 56 patients with immature neuroblastoma.

Abbreviations: CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein to albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS.

CI=2.07–113.71; $p=0.008$) were significantly associated with OS of patients with immature NB. However, NLR, PLR, LMR and SII have no predictive value for OS.

Multivariate survival analyses (Table 3) adjusted for clinical characteristics including age, sex, INSS stage, tumor size and metastasis showed that ALB (HR=2.81; 95% CI=1.03–7.68; $p=0.044$), Hs-mGPS (HR=6.01; 95% CI=1.84–19.57; $p=0.003$) and CAR (HR=12.52; 95% CI=1.57–100.02; $p=0.017$) were significantly associated with OS of the patients with immature NB.

ROC Curve and AIC Analysis

ROC curves and AUC analyses revealed that Hs-mGPS has the highest AUC level (AUC=0.807; 95% CI=0.687–0.927; $p<0.001$) in predicting OS for patients with immature NB (Figure 1B and Table 4). AIC analyses also revealed that Hs-

mGPS has the lowest AIC level (167.7397) in predicting OS for patients with immature NB (Table 4). These results suggested that Hs-mGPS is also superior to other inflammation biomarkers in predicting OS for patients with immature NB.

Kaplan–Meier Survival Curves

The survival curves of the prognostic inflammation biomarkers for NB patients were generated by Kaplan–Meier method as is shown in Figure 3. Patients with elevated CRP level had significantly worse OS than those with normal CRP level (Figure 3A, $p = 0.002$). Serum ALB level could not significantly stratify NB patients into two different survival groups (Figure 3B, $p = 0.1$). Patients with higher CAR value had significantly worse OS than those with lower CAR value (Figure 3C, $p < 0.001$). Patients with elevated GPS score had significantly worse OS than those with normal GPS score ($p = 0.001$, $p = 0.009$ and $p < 0.001$ for GPS, mGPS and Hs-mGPS, respectively) (Figure 3D–F).

Table 2 ROC Curves and AIC Analyses for the Predictive Ability of the Inflammation Biomarkers in Patients with Neuroblastoma

Biomarkers	AIC	ROC		
		AUC	95% CI	P value
CRP	221.7524	0.720	0.593–0.874	0.002
ALB	230.2184	0.601	0.463–0.740	0.151
Hs-mGPS	206.0429	0.811	0.702–0.920	< 0.001
GPS	218.2753	0.742	0.619–0.865	0.001
mGPS	221.7524	0.720	0.593–0.847	0.002
CAR	218.9109	0.709	0.589–0.830	0.003

Abbreviations: AIC, Akaike Information Criterion; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval; CRP, C-reactive protein; ALB, albumin; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS; CAR, C-reactive protein to albumin ratio.

Discussion

Numerous studies have confirmed the links between inflammation and neuroblastoma.³⁶ For example, high expression of Chemokine receptor-4 (CXCR4) was found in NB tumors with high-stage and in NB patients with bone or bone marrow metastasis; NB patients with tumors highly expressing CXCR4 also had a significantly bad survival outcome.^{36,38} Pro-inflammatory transcription factor NF- κ B is constitutively activated in S-type neuroblastoma and is required for the survival of tumor cell.^{36,40} NB cells metastasized to the bone marrow could stimulate the

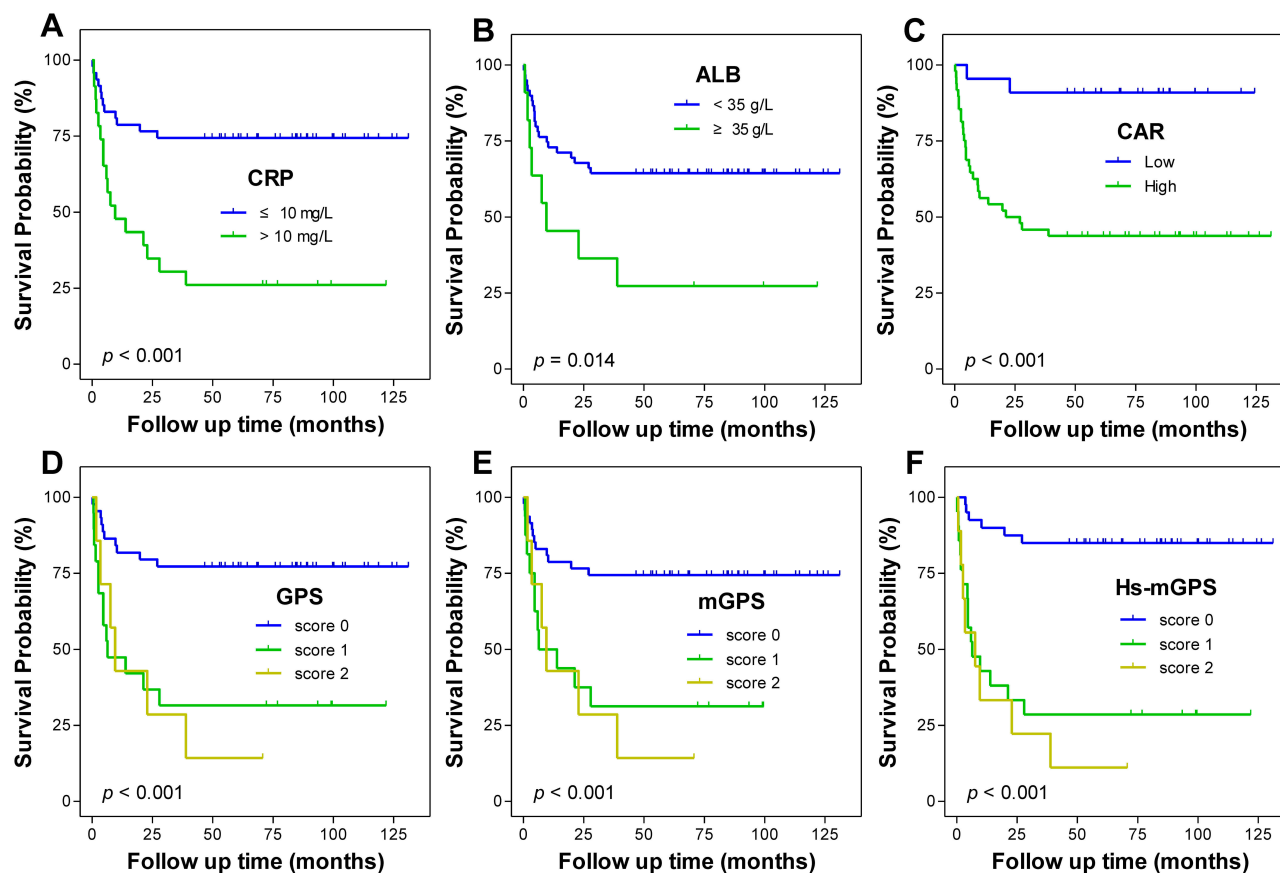


Figure 2 Kaplan–Meier survival curves for overall survival in total 70 patients with neuroblastoma according to (A) CRP, (B) ALB, (C) CAR, (D) GPS, (E) mGPS, (F) Hs-mGPS.

Abbreviations: CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein to albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS.

expression of interleukin-6 (IL-6), whereas IL-6 could also increase the proliferation of IL-6-R-positive NB cells and protect the tumor cell from etoposide-induced apoptosis; NB patients with bone metastasis were also found to have an elevated level of IL-6 in the serum.^{36,41} There was also evidences revealed that interactions between NB tumor and inflammatory cells promote the progression and metastasis of NB.^{36,39,42,43} Metastatic neuroblastoma was shown to have higher infiltration of tumor-associated macrophages (TAMs) than locoregional tumors.³⁹ Bone marrow-derived mesenchymal stem cells (BM-MSCs) and peripheral blood mononuclear cell (PBMC)-derived macrophages could be recruited to the tumor site and activated into TAMs and cancer-associated fibroblast (CAF), and then promote the progression of neuroblastoma by forming a favorable environment.⁴² Tumor-infiltrating T lymphocytes (TILs) were shown to have an influence on the behavior of neuroblastoma and might be important for the treatment of NB patients.⁴³

The relationship between blood inflammation biomarkers and the prognosis of NB patients has not been investigated before. In the present study, we for the first time demonstrated that two serum-tested inflammation-based scores (CAR and Hs-mGPS) were significantly associated with OS of NB patients in both univariate survival analysis and multivariate survival analysis adjusted by clinical risk factors. The ROC curve and AIC analysis revealed that Hs-mGPS was superior to other inflammation biomarkers in the discriminative ability of predicting OS of NB patients. A number of studies have also found similar results for the prognostic role CAR or GPS in various types of cancers.^{7–9,45–62} This highlighted the general prognostic role of these two inflammation-based scores in malignancies.

It has to be mentioned that both of the two composite inflammation scores were based on serum CRP and ALB levels. CRP is a non-specific serum biomarker of acute-phase inflammatory response, while Low serum ALB is often used

Table 3 Univariate and Multivariate Cox Regression Survival Analyses for Overall Survival of Patients with Immature Neuroblastoma

Variables		Total No. (Death No.)	Univariate Analysis		Multivariate Analysis ^a	
			HR(95% CI)	P value	HR(95% CI)	P value
Sex	Female	25 (13)	1 (Ref.)			
	Male	31 (12)	0.63 (0.29–1.37)	0.241		
Age	≤ 18 months	21 (4)	1 (Ref.)			
	> 18 months	35 (21)	4.25 (1.45–12.40)	0.008		
INSS stage	1/2	21 (5)	1 (Ref.)			
	3/4	35 (20)	3.44(1.29–9.19)	0.014		
Tumor size	≤ 5cm	23 (6)	1 (Ref.)			
	> 5cm	33 (19)	2.92 (1.16–7.31)	0.023		
Metastasis	Without metastasis	33 (9)	1 (Ref.)			
	With metastasis	23 (16)	3.93 (1.72–8.99)	0.001		
NLR	Continuous variable	56 (25)	1.16 (0.95–1.42)	0.146		
PLR	Continuous variable	56 (25)	1.000 (0.996–1.004)	0.939		
LMR	Continuous variable	56 (25)	0.93 (0.82–1.06)	0.294		
SII	Continuous variable	56 (25)	1.000 (1.000–1.001)	0.186		
CAR	Continuous variable	56 (25)	1.55 (1.25–1.92)	< 0.001	1.35 (1.07–1.71)	0.012
CRP	≤ 10mg/L	35 (10)	1 (Ref.)		1 (Ref.)	
	> 10mg/L	21 (15)	3.27 (1.46–7.31)	0.004	1.71 (0.67–4.36)	0.263
ALB	≥ 35g/L	47 (19)	1 (Ref.)		1 (Ref.)	
	< 35g/L	9 (6)	2.12 (0.85–5.32)	0.109	2.81 (1.03–7.68)	0.044
GPS	0	32 (8)	1 (Ref.)		1 (Ref.)	
	1/2	24 (17)	4.03 (1.73–9.40)	0.001	2.42 (0.89–6.56)	0.083
mGPS	0	35 (10)	1 (Ref.)		1 (Ref.)	
	1/2	21 (15)	3.27 (1.46–7.31)	0.004	1.71 (0.67–4.36)	0.263
Hs-mGPS	0	28 (4)	1 (Ref.)		1 (Ref.)	
	1/2	28 (21)	8.94 (3.05–26.26)	< 0.001	6.01 (1.84–19.57)	0.003
CAR	< 0.0959	17 (1)	1 (Ref.)		1 (Ref.)	
	> 0.0959	39 (24)	15.35 (2.07–113.71)	0.008	12.52 (1.57–100.02)	0.017

Notes: ^aMultivariate analyses were adjusted by sex, age, INSS stage, tumor size and metastasis.

Abbreviations: HR, hazard ratio; CI, confidence interval; INSS, International Neuroblastoma Staging System; CAR, C-reactive protein to albumin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, system inflammation index; CRP, C-reactive protein; ALB, albumin; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS; Ref., reference.

as an indicator for malnutrition, inflammation activity and disease progression in clinical practice.^{4,63} Either elevated serum CRP level or low serum ALB level has been shown to be associated with poor survival in multiple types of cancer patients.^{4,6,23-30} Taken together with the prognostic role GPS and CAR for cancer patients, these evidences highlight the importance of serum CRP and ALB level in the prediction of survival for malignancies. Elevated CRP level or low ALB level might represent an inherent aggressive propensity of the cancers including neuroblastoma. In the present study, we also identified that elevated CRP level or low ALB level was

significantly associated with poor OS of patients with neuroblastoma in the univariate analysis, but not in the multivariate analysis adjusted by clinical risk factor. However, the combined use of CRP and ALB into CAR or Hs-mGPS revealed really good results in both univariate model and multivariate model survival analysis. It is very interesting that a high serum CRP level has also been linked to PD-L1 (programmed death-ligand 1) positivity in patients with non-small cell lung cancer.^{4,64} Since PD-1 (programmed death 1) and PD-L1 are also involved with neuroblastoma,³⁶ elevated serum CRP level might also be

Table 4 ROC Curves and AIC Analyses for the Predictive Ability of the Inflammation Biomarkers in Patients with Immature Neuroblastoma

Biomarkers	AIC	ROC		
		AUC	95% CI	P value
CRP	182.1524	0.703	0.562–0.845	0.009
ALB	188.4158	0.572	0.418–0.725	0.360
Hs-mGPS	167.7397	0.807	0.687–0.927	< 0.001
GPS	179.205	0.727	0.590–0.865	0.004
mGPS	182.1524	0.703	0.562–0.845	0.009
CAR	173.6069	0.738	0.607–0.869	0.002

Abbreviations: AIC, Akaike Information Criterion; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval; CRP, C-reactive protein; ALB, albumin; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS; CAR, C-reactive protein to albumin ratio.

a potential indicator for immune checkpoint blockade therapy with anti-PD-1 antibodies for NB patients.

Surprisingly, we did not find any role of NLR, PLR, LMR or SII in predicting the survival of NB patients. This

result is contrary to previous studies focusing on other types of malignancies, while a number of studies found a positive result for NLR, PLR, LMR or SII in the role of predicting the survival for cancer patients.^{5,10-13,16-22} In fact, these markers also have their theoretical foundations for predicting the survival of cancer patients. For example, neutrophils could produce various factors that could promote tumor cell proliferation and invasion; lymphocytes could mediate cytotoxic cell death and inhibiting tumor cell proliferation and metastasis; monocytes in the peripheral blood reflect the status of TAM in patients, while TAM derived from monocytes inhibit immune response and promote tumor growth; elevated platelet counts could stimulate tumor angiogenesis and promote tumor metastasis.^{21,65,66} As we have mentioned above, TAMs or TILs also have an influence on the behavior of NB. However, we did not find any association between NLR, LMR, PLR or SII with the survival of NB patients. We think one possible reason responsible for this discrepancy

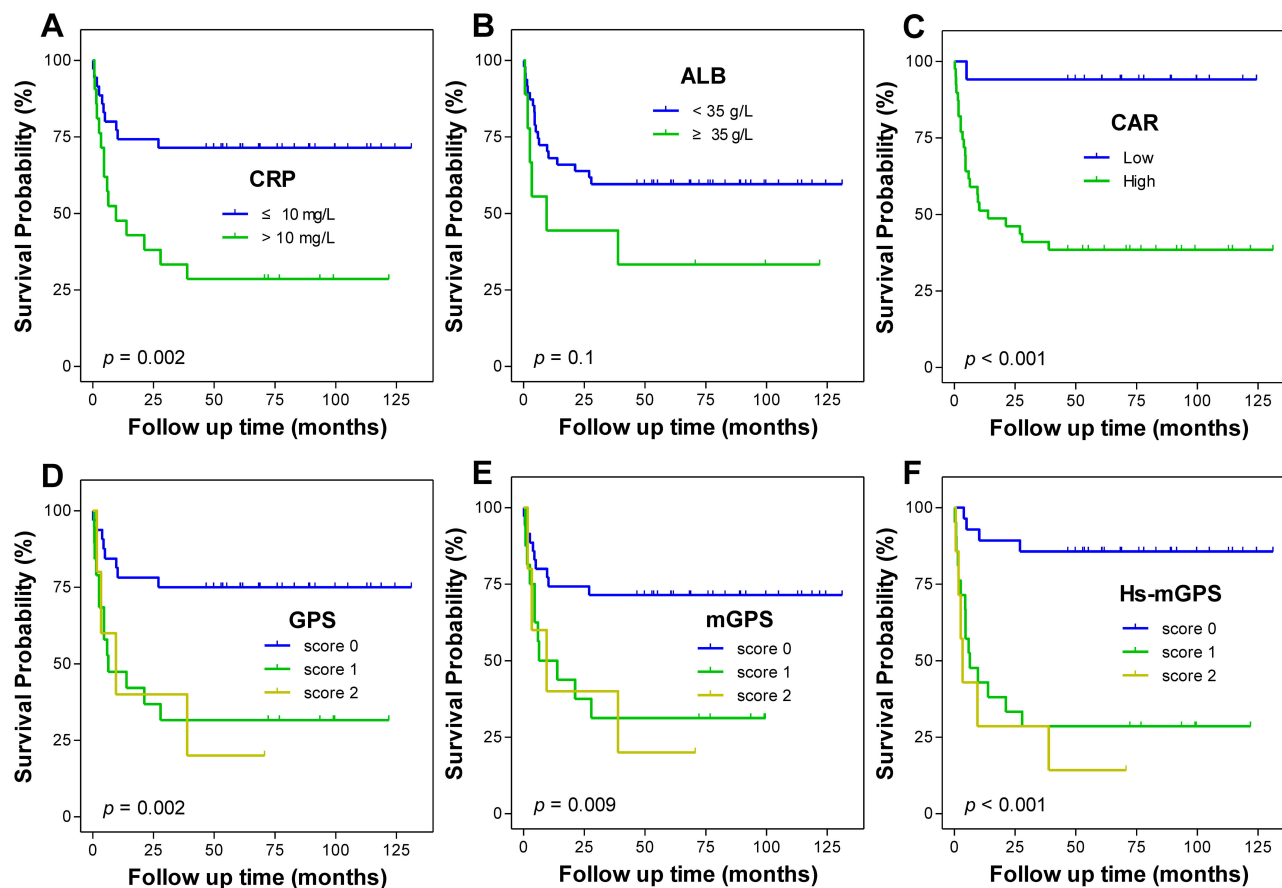


Figure 3 Kaplan–Meier survival curves for overall survival in 56 patients with immature neuroblastoma according to (A) CRP, (B) ALB, (C) CAR, (D) GPS, (E) mGPS, (F) Hs-mGPS.

Abbreviations: CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein to albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified GPS; Hs-mGPS, high-sensitivity modified GPS.

is that the normal level of blood neutrophil counts, lymphocyte counts and monocytes counts vary among children with different age group, so that those markers based on these blood cell counts lose their prognostic function in children patients.

Since three subtypes of GPS (traditional GPS, mGPS and Hs-mGPS) have been reported in previous studies, we investigated the prognostic value of all the three subtypes of GPS in our study. The results revealed that all of the three subtypes of GPS are significantly associated with the survival of NB patients in the univariate model survival analysis. However, in the multivariate analysis adjusted by clinical risk factors, only Hs-mGPS was shown to be significantly associated with OS for patients with immature NB. Hs-mGPS was also shown to be superior to the other two kinds of GPS in the ROC curve analysis and AIC analyses both in the total cohort and in the immature NB subgroup. Different from GPS and mGPS, 3 mg/L (rather than 10 mg/L) is used as the CRP cut-off value in Hs-mGPS. We think that one reason for the superior of Hs-mGPS might be that children rarely have concomitant conditions that could affect serum CRP level, such as cardiovascular disease or rheumatic diseases. The level of serum CRP in healthy children is supposed to be less than 3 mg/L, while adults with sub-clinical cardiovascular disease would have a CRP level larger than 3 mg/L.

CAR is another promising biomarker calculated by the ratio of CRP level to ALB level as demonstrated in previous studies.^{7,8} In the present study, we also find that CAR is significantly associated with the survival of NB patients either in univariate model or multivariate model survival analysis. However, the determination of the optimal cut-off value for CAR holds back its clinical use as a convenient indicator. The optimal cut-off value may vary among different studies. As we have shown in one previous study, the optimal cut-off value for CAR varies from 0.1035 to 1.5 among 4 studies investigating the prognostic role of CAR for sarcoma.⁴⁴

There are some limitations to the present study. Firstly, this is a retrospective study, and only a small number of patients were enrolled, the results should be undoubtedly interpreted with caution. Secondly, the patients in this study are all Chinese children; the results may not be applicable for patients in other districts of the world. Thirdly, the MYCN amplification status, which is one of the most important risk factors for NB, is unavailable for most of the patients in this study. In the early days, the MYCN status was not detected in our institution due to

technical reasons. We recommend future studies including the MYCN amplification status as covariate when investigate the independent prognostic role of these inflammation biomarkers. Prospective studies with larger sample size are also required to verify the conclusion of this study.

Conclusion

In this retrospective study, we identified that NLR, PLR, LMR, and SII were not predictive of OS for patients with NB. However, Hs-mGPS and CAR were shown to be significantly associated with OS of NB patients in both univariate analysis and multivariate analysis adjusted by clinical risk factors. The prognostic role of Hs-mGPS is superior to other inflammation biomarkers. Elevated Hs-mGPS might represent an aggressive propensity of neuroblastoma. Since CRP and ALB are both readily accessible and cheap laboratory parameters widely used in clinical routine, it is promising for Hs-mGPS to be used as a factor of risk stratification and indicator for more aggressive therapy for NB patients.

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Disclosure

The authors report no conflicts of interest in this work.

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