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儿童神经母细胞瘤切除术后的生存预测因素

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摘　要

目的：探究术前中性粒细胞与淋巴细胞的比值(neutrophil to lymphocyte ratio, NLR)和血清C反应蛋白(c-reactive protein, CRP)与白蛋白(albumin, ALB)的比值(CRP/ALB ratio, CAR)对儿童神经母细胞瘤切除术后预后的预测价值。方法：利用受试者工作特征(ROC)曲线用于确定连续变量CAR与NLR的最佳截断值。并将患者分为三组：低NLR与低CAR被定义为NLR-CAR 0，高NLR与高CAR被定义为NLR-CAR 2，低NLR与高CAR或者高NLR与低CAR定义为NLR-CAR 1。Kaplan-Meier方法和Log-rank方法用于生存分析。采用单变量与多变量Cox比例风险回归来确定NB患者预后的独立因素。结果：根据ROC曲线，NLR的最佳截断值为2.49，CAR的最佳截断值为0.035。Kaplan-Meier方法显示，高NLR (>2.49)、高CAR (>0.035)以及NLR-CAR 2具有较差的总体生存期(P < 0.01)。单因素及多因素Cox回归分析显示，年龄(>18个月)、INSS分期(III-IV)以及NLR-CAR 2 (高NLR和高CAR)是NB患者预后的独立的危险因素(P < 0.05)。结论：NLR-CAR 2 (高NLR和高CAR)是NB患儿预后有价值的生物标志物。

关键词

神经母细胞瘤，手术，儿童，预后

Predictors of Survival after Resection of Children with Neuroblastoma

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Abstract

OBJECTIVE: To investigate the predictive value of preoperative neutrophil-to-lymphocyte ratio (NLR) and serum C-reactive protein to albumin ratio (CAR) on the prognosis after resection of neu-

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roblastoma in children. METHODS: Subject operating characteristic (ROC) curves were used to determine the optimal cut-off values for the continuous variable CAR versus NLR. And patients were divided into three groups: low NLR with low CAR was defined as NLR-CAR 0, high NLR with high CAR was defined as NLR-CAR 2, and low NLR with high CAR or high NLR with low CAR was defined as NLR-CAR 1. Kaplan-Meier method and Log-rank method were used for survival analysis. Univariate versus multivariate Cox proportional risk regression was used to determine independent factors of prognosis in NB patients. RESULTS: According to the ROC curve, the optimal cut-off value for NLR was 2.49 and for CAR was 0.035. Kaplan-Meier method showed that high NLR (>2.49), high CAR (>0.035) and NLR-CAR 2 had poorer overall survival (P < 0.01). Univariate and multifactorial Cox regression analysis showed that age (>18 months), INSS stage (III-IV), and NLR-CAR 2 (high NLR and high CAR) were independent risk factors for the prognosis of NB patients (P < 0.05). CONCLUSION: NLR-CAR 2 (high NLR and high CAR) is a valuable biomarker for the prognosis of children with NB.

Keywords

Neuroblastoma, Surgery, Children, Prognosis

1. 引言

神经母细胞瘤(Neuroblastoma, NB)是一种由未分化神经母细胞恶性增殖引起的儿童时期最常见的一种颅外实体瘤，约占儿童肿瘤的 6%~10%，死亡率约 15% [1]。NB 起病隐匿，大部分患儿在就诊时已进展为晚期，超过 50%的患者在就诊时已经出现骨骼或者远处的淋巴结转移，总体预后较差。尽管目前已有研究发现一些遗传学或分子生物学标志物如染色体 17/17q、PHOX2B 及 AEG-1 等表明与儿童 NB 的预后相关[2] [3] [4]，但其检测过程复杂、价格昂贵，对于普遍临床的预后价值不容乐观。

目前，越来越多的研究表明炎症在肿瘤的发生发展中起到了重要的作用[5] [6]。有研究报道，在高风险的 NB 中，炎症能够驱动染色体 11q 缺失，导致不良的预后[7]，在转移性 MYCN 非扩增 NB 中，肿瘤相关的巨噬细胞与患者不良预后相关[8]。在 NB 的小鼠模型中，抗炎药能够抑制肿瘤的生长[9]。这些研究表明炎症参与了 NB 的发展。基于炎症相关的血液指标可以预测不同肿瘤的预后[10] [11] [12] [13] [14]。中性粒细胞与淋巴细胞的比值(neutrophil to lymphocyte ratio, NLR)，是根据全血细胞计数的中心粒细胞与淋巴细胞计数之间的比率计算得来，已被认为作为多种肿瘤的有效预后标志物[15] [16] [17]。C 反应蛋白(c-reactive protein, CRP)是肝脏在全身炎症状态下产生的蛋白，血清白蛋白(albumin, ALB)一直被视为全身的营养状态指标，CAR (CRP/ALB ratio, CAR)作为 C 反应蛋白与血清白蛋白的比值，因此 CAR 可以准确反应个体的炎症营养状态[18]，可作为食管癌[19]、胰腺癌[17]、胃癌[20]以及肝癌[21]等预后的危险因素。

然而，目前还没有报道联合 NLR 和 CAR 预测儿童 NB 的总体生存期。在本研究中，我们的研究目的旨在结合术前炎症标志物 NLR 和 CAR 探究其对儿童 NB 的预后预测价值。

2. 资料与方法

2.1. 一般资料

本研究回顾性分析从 2010 年 1 月到 2020 年 12 月青岛大学收治的神经母细胞瘤患儿的临床资料。这项回顾性研究得到了青岛大学附属医院伦理委员会的批准，并按照赫尔辛基宣言进行。所有患儿均签署

了知情同意书。通过门诊定期复诊检查或电话随访等方式对 NB 患儿进行随访。NB 患儿随访中位时间 32 个月。总生存期(OS)定义为从手术到死亡或者最后一次随访时间。收集 NB 患者的临床特征包括年龄、性别、INSS 分期、肿瘤的大小、化疗以及原发部位。诊断时的年龄大于 18 个月通常与 NB 患儿的不良预后相关，因此我们按照(年龄 ≤18 个月和年龄 >18 个月)进行分组[22]。按照 INSS 分期标准将儿童 NB 临床分期为 I-IV 期，其中 III-IV 期为进展期[23]。

2.2. 纳入和排除标准

本研究的纳入标准：1) 经手术后病理学诊断为神经母细胞瘤；2) 年龄小于或等于 14 岁；3) 接受规范化治疗且临床资料完整。本研究的排除标准：1) 伴有其他恶性肿瘤或者影响患者生存的疾病；2) 随访过程中失访或临床资料不完整。根据纳入和排除标准，共有 61 名 NB 患儿纳入研究。

2.3. 外周血的采集

在患儿进行手术前 1 周内进行血液检测。NB 患儿禁食 6 小时，并在 07:00 到 07:30 之间用无菌 EDTA 管进行采血，收集血液样本。NLR=外周血中性粒细胞计数/外周淋巴细胞计数；CAR = C 反应蛋白/白蛋白计数。

2.4. 统计学方法

所有的统计分析均采用 SPSS 26.0 (SPSS Company, Chicago, IL, USA)和 GraphPad Prism 9.0 (GraphPad Software, CA, USA)。绘制受试者工作特征(receiver operating characteristic, ROC)曲线，计算曲线下面积(area under the curve, AUC)以评估预测指标价值，计算出 NLR 与 CAR 的最佳截断值，使用卡方检验或 Fisher 精确检验比较分类变量。采用 Kaplan-Meier 方法估算生存曲线，并利用 Log-rank 检验进行生存曲线的差异性分析。为确定 NB 患儿的独立预后因素，对单变量 Cox 回归分析中 $P < 0.05$ 的变量进行多变量 Cox 回归分析。统计分析均为双侧检验，$P < 0.05$ 为差异有统计学意义。

3. 结果

评估 NLR、CAR 的临界值：根据 ROC 曲线，术前 NLR 与 CAR 的最佳截断值分别为 2.49 和 0.035。NLR 的 ROC 曲线下的面积是 0.7364 (95% CI 为 0.6576 到 0.8349)，CAR 的曲线下面积是 0.69 (95% CI 为 0.5963 到 0.7837)。根据 ROC 曲线的最佳截断值，将 NLR 和 CAR 分为高 NLR 组(>2.49)和低 NLR 组(≤2.49)，CAR 分为高 CAR 组(>0.035)和低 CAR 组(≤0.035)。详见图 1。

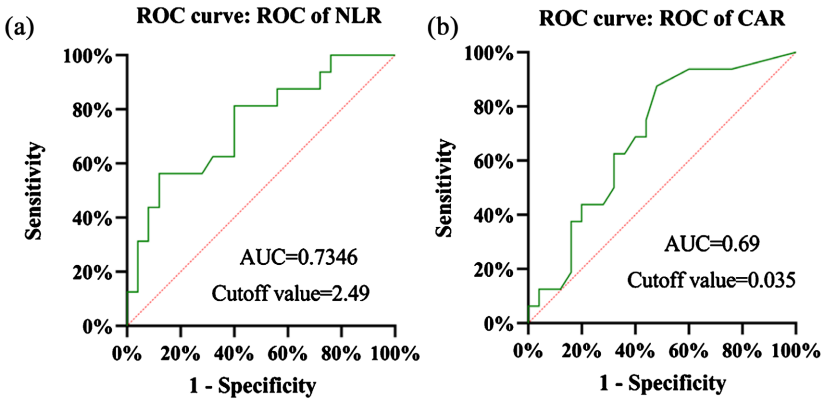

Figure 1. ROC curves of NLR and CAR in children with neuroblastoma
图 1. NB 患儿 NLR、CAR 的 ROC 曲线

NB 患儿临床基线特征比较：共有 61 例 NB 患儿符合条件并纳入了我们的研究。其中男性 33 例(45.9%)，女性 28 例(54.1%)。NB 患儿的年龄中位数为 32 个月。根据 NLR 分组，年龄、LDH、WBC、肿瘤大小和 INSS 分期有显著的差异($P < 0.05$)；根据 CAR 分组，年龄、ALB、LDH、肿瘤的大小和肿瘤的部位有显著的差异($P < 0.05$)。具体详见表 1。

Table 1. Comparison of clinical baseline information of children with NB according to NLR, CAR grouping
表 1. 根据 NLR、CAR 分组的 NB 患儿的临床基线资料比较

Variables	NLR		P value	CAR		P value
	High	Low		High	Low	
Sex						
Female	10 (35.7%)	18 (64.3%)	0.958	16 (57.1%)	12 (42.9%)	0.973
Male	21 (63.3%)	12 (36.4%)		19 (57.6%)	14 (42.4%)	
Age						
≤18 months	1 (4.0%)	24 (96.0%)	0.000	6 (24.0%)	19 (76.0%)	0.000
>18 months	21 (58.3%)	15 (41.7%)		29 (80.6%)	7 (19.4%)	
ALB						
≥35 g/L	20 (43.5%)	26 (56.5%)	0.035	29 (63.0%)	17 (37.0%)	0.117
<35 g/L	2 (13.3%)	13 (86.7%)		6 (40.0%)	9 (60.0%)	
LDH						
≤400 U/L	7 (17.9%)	32 (82.1%)	0.000	16 (41.0%)	23 (59.0%)	0.001
>400 U/L	15 (68.2%)	7 (31.8%)		19 (86.4%)	3 (13.6%)	
WBC						
$\leq 10 \times 10^9$/L	6 (15.8%)	32 (84.2%)	0.000	18 (47.4%)	20 (52.6%)	0.042
$>10 \times 10^9$/L	16 (69.6%)	7 (30.4%)		17 (73.9%)	6 (26.1%)	
Tumor size						
≤5 cm	1 (4.3%)	22 (95.7%)	0.000	5 (21.7%)	18 (78.3%)	0.000
>5 cm	21 (55.3%)	17 (44.7%)		30 (78.9%)	8 (21.1%)	
Site						
Non-Adrenal	6 (33.3%)	12 (66.7%)	0.774	12 (66.7%)	6 (33.3%)	0.343
Adrenal	16 (37.2%)	27 (62.8%)		23 (53.5%)	20 (46.5%)	
Chemotherapy						
Yes	15 (34.1%)	29 (65.9%)	0.605	24 (54.5%)	20 (45.5%)	0.472
No	7 (41.2%)	10 (58.8%)		11 (64.7%)	6 (35.3%)	
INSS Stage						
I-II	3 (11.5%)	23 (88.5%)	0.001	9 (34.6%)	17 (65.4%)	0.002
III-IV	19 (54.3%)	16 (45.7%)		26 (74.3%)	9 (25.7%)	

NLR 和 CAR 与 NB 患儿总体生存率的关系：Kaplan-Meier 生存分析显示，高 NLR 组的 OS 水平显著低于 NLR 组(图 2(a)，$P < 0.0001$)，高 CAR 组的 OS 水平显著低于低 CAR 组(图 2(b)，$P = 0.0016$)。

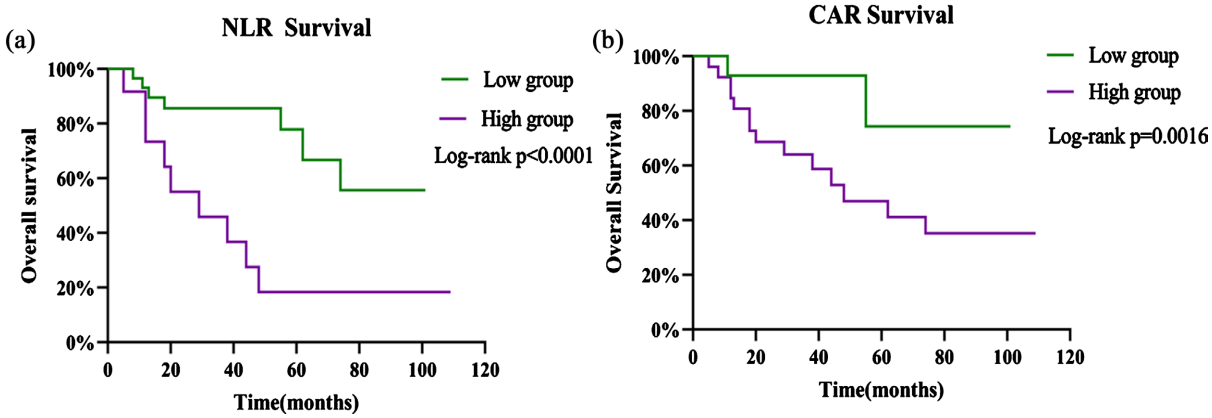

Figure 2. Relationship between NLR and CAR levels and prognosis
图 2. NLR 与 CAR 水平与预后的关系

NLR-CAR 分组与 NB 患儿临床基线资料之间的相关性：根据 NLR 和 CAR 水平分为三组：高 NLR 和高 CAR 定义为 NLR-CAR 2 组，低 NLR 和低 CAR 定义为 NLR-CAR 0 组，高 NLR 和低 CAR 或低 NLR 和高 CAR 定义为 NLR-CAR 1 组。根据 NLR-CAR 组，年龄、ALB、LDH、肿瘤的大小和肿瘤的位置有显著差异($P < 0.05$)。详见表 2。

Table 2. Comparison of clinical baseline information of children with NB according to NLR-CAR grouping
表 2. 根据 NLR-CAR 分组 NB 患儿的临床基线资料比较

Variables	NLR-CAR 0	NLR-CAR 1	NLR-CAR 2	P value
Sex				
Female	11 (39.3%)	8 (28.6%)	9 (32.1%)	0.799
Male	14 (42.1%)	7 (21.1%)	12 (36.4%)	
Age				
≤18 months	19 (76.0%)	5 (20.0%)	1 (4.0%)	0.000
>18 months	6 (16.7%)	10 (27.8%)	20 (55.6%)	
ALB				
<35 g/L	9 (60.0%)	4 (26.7%)	2 (13.3%)	0.104
≥35 g/L	16 (34.8%)	11 (23.9%)	19 (41.3%)	
LDH				
≤400 U/L	22 (56.4%)	11 (28.2%)	6 (15.4%)	0.000
>400 U/L	3 (13.6%)	4 (18.2%)	15 (68.2%)	
WBC				
≤10 × 10^9/L	20 (52.6%)	12 (31.6%)	6 (15.8%)	0.000
>10 × 10^9/L	5 (21.7%)	3 (13.0%)	15 (65.2%)	
Tumor size				
≤5 cm	18 (78.3%)	4 (17.4%)	1 (4.3%)	0.000
>5 cm	7 (18.4%)	11 (28.9%)	20 (52.6%)	

Continued

Site				
Adrenal	6 (33.3%)	6 (33.3%)	6 (33.3%)	0.536
Non-Adrenal	19 (44.2%)	9 (20.9%)	15 (34.9%)	
Chemotherapy				
Yes	19 (43.2%)	11 (25.0%)	14 (31.8%)	0.772
No	6 (35.3%)	4 (23.5%)	7 (41.2%)	
INSS Stage				
I-II	17 (65.4%)	6 (23.1%)	3 (11.5%)	0.001
III-IV	8 (22.9%)	9 (25.7%)	18 (51.4%)	

NLR-CAR 与总体生存率的关系：Kaplan-Meier 生存分析显示，相比于其他两组，NLR-CAR 2 组的总体生存率最差(P < 0.0001)。如图 3。

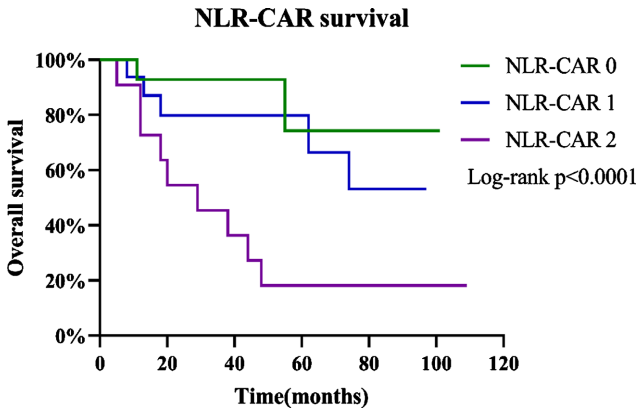

Figure 3. Effect of NLR-CAR on overall survival
图 3. NLR-CAR 对总体生存率的影响

单变量和多变量 Cox 回归分析：单变量分析显示，年龄(>18 个月) (HR 4.614; 95% CI = 1.959~10.866; P = 0.000)、ALB ≥ 35 g/L (HR 0.441; 95% CI = 0.228~0.855; P = 0.015)、化疗(HR 0.422; 95% CI = 0.233~0.764; P = 0.004)、INSS 分期(HR 3.788; 95% CI = 1.941~7.392; P = 0.000)和 NLR-CAR 2 (HR 6.122; 95% CI = 2.518~14.882; P = 0.000)与总体生存率显著相关。在多变量分析显示，年龄>18 个月(HR 3.593; 95% CI = 1.379~9.358; P = 0.009)、INSS 分期(HR 3.854; 95% CI = 1.700~8.738; P = 0.001)以及 NLR-CAR 2 (HR 3.237; 95% CI = 1.192~8.789; P = 0.021)是 NB 患者预后的独立的危险因素(P < 0.05)。见表 3。

Table 3. Univariate and multivariate Cox regression analysis of prognostic factors for OS in children with NB
表 3. NB 患儿 OS 预后因素的单变量和多变量 Cox 回归分析

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Female	1.00 (reference)	0.418		
Male	1.393 (0.625~3.109)			

Continued

Age				
≤18 months	1.00 (reference)	0.033	1.00 (reference)	0.009
>18 months	2.726 (1.085~6.849)		3.593 (1.379~9.358)	
ALB				
<35 g/L	1.00 (reference)	0.702		
≥35 g/L	0.847 (0.362~1.984)			
LDH				
≤400 U/L	1.00 (reference)	0.147		
>400 U/L	1.542 (0.859~2.767)			
WBC				
≤10 × 10^9/L	1.00 (reference)	0.303		
>10 × 10^9/L	1.388 (0.744~2.592)			
Tumor size				
≤5 cm	1.00 (reference)	0.054		
>5 cm	2.051 (0.987~4.263))			
Site				
Non-Adrenal	1.00 (reference)	0.056		
Adrenal	2.311 (0.979~5.455)			
Chemotherapy				
No	1.00 (reference)	0.004		
Yes	0.422 (0.233~0.764)			
INSS Stage				
I-II	1.00 (reference)	0.005	1.00 (reference)	0.001
III-IV	3.680 (1.485~9.124)		3.854 (1.700~8.738)	
NLR-CAR		0.000		0.001
NLR-CAR 0	1.00 (reference)		1.00 (reference)	
NLR-CAR 1	1.958 (0.754~5.087)	0.168	1.073 (0.370~3.108)	0.879
NLR-CAR 2	6.122 (2.518~14.882)	0.000	3.237 (1.192~8.789)	0.021

4. 讨论

目前，越来越多的研究表明肿瘤微环境在神经母细胞瘤的进展中发挥重要的调节作用[24]。肿瘤局部的炎症反应可通过炎症细胞释放各种炎症介质、上调各种细胞因子等改变肿瘤微环境从而促进肿瘤进展，因此微环境中的炎症细胞一直被认为是肿瘤进展的关键因素[8]。有研究表明，患者的营养状态影响癌症患者远期预后[25]。NLR 和 CAR 可以直观地反映机体的炎症状态和营养状态，同时，他们作为血清标志物，在临床上容易获取，也一直被认为是肿瘤预后的理想标志物。

NLR 是一种炎症和免疫相关的标志物，与多种肿瘤的预后相关[15] [16] [17]。值得注意的是，大多数的研究都认为高 NLR 的患者预后较差，但具体的机制尚不清楚。有研究认为，中性粒细胞不仅可以产

生与肿瘤相关的细胞因子，还能抑制细胞毒性 T 细胞的活性，从而促进肿瘤的进展[26] [27]。在我们的研究中，我们通过 ROC 曲线确定 NLR 最佳的截断值为 2.49，通过分组发现，高 NLR 组的总体生存率显著低于NLR组，这与之前的研究一致[28]。高NLR意味着中性粒细胞的增多通常伴有相对的淋巴细胞减少，而中性粒细胞的增加促进了肿瘤的血管生成以及协助肿瘤细胞的侵袭[29]，淋巴细胞的减少则提示机体对肿瘤免疫反应不足[30]，这可能是高 NLR 组的 NB 患儿预后差的原因。

C 反应蛋白(CRP)是肝脏合成的急性期非特异性的血清标志物。目前，CRP 已被证实与多种肿瘤的不良预后相关[31]。血清白蛋白(ALB)是一种能够反映机体营养状态的血清蛋白，低 ALB 可以影响多种肿瘤的预后[32] [33]。CAR 作为 CRP 与 ALB 的比值，高 CAR 的肿瘤患者预后更差[18] [34] [35] [36]。Chen Zheng 等人通过对 70 例 NB 患儿进行分析，通过 ROC 曲线确定最佳临界值为 0.0959，高 CAR 组的预后生存差[37]。然而在我们研究中，通过 ROC 曲线确定了 CAR 的最佳临界值为 0.036，这与他们的最佳临界值不同，我们认为造成最佳临界值的差异可能由于样本量的不同以及纳入的标准不同造成的。在不同的肿瘤中，CAR 的最佳临界值差异更大[38]，因此，如何准确地判断 CAR 的最佳临界值值得我们探究。但值得注意的是，Kaplan-Meier 生存分析显示，高 CAR 组的 NB 患儿的总体生存率更低，这与先前的研究一致[37]。

我们的研究表明，NLR-CAR 2 (高 NLR 和高 CAR)的 NB 患儿预后最差，单因素和多因素 Cox 回归分析提示NLR与CAR均高的组(NLR-CAR 2)是NB患儿预后的独立危险因素。本研究首次将NLR与CAR联合分析，NLR 反映的是机体的炎症状态，而 CAR 反映了机体的营养状态，将两者联合分析，起到相互补充的作用[38]。在结肠癌中，全身炎症反应是决定晚期患者血清白蛋白的浓度的主要原因[39]，这也提示了 NLR 与 CAR 之间的相互的联系。总而言之，将 NLR 与 CAR 联合分析，从炎症、免疫和营养三个方面进行全面的分析，因此在预后预测中实现更好的诊断性能。

不可否认的是，我们的研究存在一些局限性。首先，这项研究是基于单个医疗机构的小样本回顾性分析，因而可能有潜在的选择偏倚。其次，我们的研究缺乏外部验证。我们期待未来有大样本、多中心、前瞻性的合作研究进一步证明我们研究的结论。

总之，NLR-CAR 2 (高 NLR 和高 CAR)可作为 NB 患儿独立的预后危险因素。

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