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·临床研究·

术前预后营养指数、中性粒细胞与淋巴细胞比值及血小板与淋巴细胞比值对脑胶质瘤患者术后预后的评估价值研究*

陈莉莉 李 鑫△ 康晓慧 秦 玥 魏文艳

（首都医科大学附属北京天坛医院国际部 北京 100070）

摘要 目的:探讨术前预后营养指数(PNI)、中性粒细胞与淋巴细胞比值(NLR)及血小板与淋巴细胞比值(PLR)对脑胶质瘤患者术后预后的评估价值。**方法:**回顾性分析2016年2月至2019年2月我院收治的131例脑胶质瘤患者(脑胶质瘤组)的临床资料,另选择同期86例于门诊健康体检的志愿者为对照组，收集相关资料计算PNI、NLR、PLR。比较脑胶质瘤患者不同临床病理特征PNI、NLR、PLR的差异,Kaplan-Meier法绘制不同PNI、NLR、PLR水平脑胶质瘤患者的生存曲线,单因素和多因素COX回归分析影响脑胶质瘤患者预后的相关因素,受试者工作特征曲线(ROC)分析术前PNI、NLR、PLR预测脑胶质瘤患者预后的价值。**结果:**脑胶质瘤组NLR、PLR高于对照组($P<0.05$),PNI低于对照组($P<0.05$)。世界卫生组织(WHO)分级Ⅲ级患者NLR、PLR高于WHO分级Ⅰ～Ⅱ级患者($P<0.05$),PNI低于WHO分级Ⅰ～Ⅱ级患者($P<0.05$)。高NLR组、高PLR组3年生存率低于低NLR组、低PLR组($P<0.05$),低PNI组3年生存率低于高PNI组($P<0.05$)。WHOⅢ级、NLR(较高)、PLR(较高)是脑胶质瘤患者预后不良的危险因素($P<0.05$),PNI(较高)是保护因素($P<0.05$)。术前PNI、NLR、PLR联合预测脑胶质瘤患者预后的曲线下面积为0.849,高于单独指标预测的0.703、0.706、0.704。**结论:**脑胶质瘤患者术前PNI降低,NLR、PLR均升高,且与预后不良有关,术前PNI、NLR、PLR可作为脑胶质瘤患者预后评估的参考指标。

关键词:脑胶质瘤;预后营养指数;中性粒细胞与淋巴细胞比值;血小板与淋巴细胞比值;预后

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Evaluation Value Study of Preoperative Prognostic Nutritional Index, Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio on Postoperative Prognosis of Patients with Brain Glioma*

CHEN Li-li, LI Xin△, KANG Xiao-hui, QIN Yue, WEI Wen-yan

(International Department of Beijing Tiantan Hospital Affiliated to Capital Medical University, Beijing, 100070, China)

ABSTRACT Objective: To investigate the value of preoperative prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in the evaluation of postoperative prognosis in patients with brain glioma. **Methods:** The clinical data of 131 patients with brain glioma (brain glioma group) who were admitted to our hospital from February 2016 to February 2019 were retrospectively analyzed, and 86 healthy volunteers who underwent physical examination in the outpatient department during the same period were selected as the control group. The relevant data were collected and PNI, NLR and PLR were calculated. The differences of PNI, NLR and PLR in patients with brain glioma with different clinicopathological characteristics were compared. Kaplan-Meier method was used to draw the survival curves of patients with brain glioma with different levels of PNI, NLR and PLR. Univariate and multivariate COX regression analysis was used to analyze the related factors affecting the prognosis of patients with brain glioma. Receiver operating characteristic curve (ROC) was used to analyze the value of preoperative PNI, NLR and PLR in predicting the prognosis of patients with brain glioma. **Results:** The NLR and PLR in the brain glioma group were higher than those in the control group ($P<0.05$), and PNI was lower than that in the control group ($P<0.05$). The NLR and PLR of patients with World Health Organization (WHO) grade Ⅲ were higher than those of patients with WHO grade Ⅰ～Ⅱ ($P<0.05$), and the PNI was lower than that of patients with WHO grade Ⅰ～Ⅱ ($P<0.05$). The 3-year survival rate of high NLR group and high PLR group were lower than those of low NLR group and low PLR group ($P<0.05$), and the 3-year survival rate of low PNI group was lower than that of high PNI group ($P<0.05$). WHO grade Ⅲ, NLR (higher) and PLR (higher) were risk factors for poor prognosis in patients with brain glioma ($P<0.05$), and PNI (higher) was a protective

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作者简介:陈莉莉(1990-),女,硕士研究生,研究方向:神经疾病诊治,E-mail: chenlili2211@163.com

△ 通讯作者:李鑫(1984-),女,本科,主任医师,研究方向:老年疾病诊治,E-mail: lixinlx2019@163.com

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factor (P<0.05). The area under curve of preoperative PNI, NLR and PLR combined to predict the prognosis of patients with brain glioma was 0.849, which was higher than the prediction of 0.703, 0.706 and 0.704 by single indicator. **Conclusion:** Preoperative PNI is decreased, NLR and PLR are increased in patients with brain glioma, which are related to poor prognosis. Preoperative PNI, NLR and PLR can be used as reference indicators for prognosis assessment of patients with brain glioma.

Key words: Brain glioma; Prognostic nutritional index; Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio; Prognosis

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前言

脑胶质瘤是恶性程度最高,最具侵袭性的脑肿瘤[1]。尽管近年来手术切除、放疗和化疗等标准治疗取得了较大进展,但高级别脑胶质瘤患者治疗效果并不理想,治疗后易出现肿瘤复发和恶性进展[2]。脑胶质瘤发病与营养和炎症存在密切关系[3,4],预后营养指数(PNI)是一种基于炎症的营养评分[5],可有效评估癌症患者的营养和免疫状态进而预测生存结果,是癌症患者预后预测的简单可靠指标[6]。中性粒细胞与淋巴细胞比值(NLR)是全身炎症反应的标志物,研究显示 NLR 值增加与各种癌症总生存期降低相关,被认为是癌症不良预后因素[7]。血小板与淋巴细胞比值(PLR)可反映急性炎症和血栓前状态,PLR 值在非小细胞肺癌、胃癌、结直肠癌等多种恶性肿瘤中升高,且与癌细胞转移和不良预后发生有关[8-10]。本研究拟分析术前 PNI、NLR、PLR 对脑胶质瘤患者术后预后的预测价值,以期为临床脑胶质患者预后分析提供参考。

1 资料与方法

1.1 临床资料

回顾性分析 2016 年 2 月 -2019 年 2 月我院收治的 131 例脑胶质瘤患者(脑胶质瘤组)的临床资料,纳入标准:① 符合《中国中枢神经系统胶质瘤诊断与治疗指南(2015)》[11]诊断标准;② 经术后病理学证实为脑胶质瘤;③ 年龄 18 周岁以上。排除标准:① 其它部位原发恶性肿瘤;② 自身免疫性疾病、血液系统疾病、严重感染患者;③ 临床资料不完整者。患者资料:男 73 例,女 58 例,年龄 52～71 岁,平均(65.23± 4.05)岁;肿瘤直径 1～5 cm,平均(3.51± 0.62)cm;世界卫生组织(WHO)分级[12]:Ⅰ级 35 例,Ⅱ级 46 例,Ⅲ级 50 例;术前卡氏功能状态(KPS)评分 60～90 分,平均(75.12± 10.08)分。另选择同期 86 例于门诊健康体检的志愿者为对照组,男 49 例,女 37 例,年龄 51～70 岁,平均(64.23± 4.07)岁。两组年龄、性别比较差异无统计学意义(P>0.05),具有可比性。

1.2 检测方法

收集患者术前和对照组体检时的血常规和常规生化检测结果,包括血清白蛋白、淋巴细胞计数、中性粒细胞计数、血小板计数。血液标本采集和检测方法:采集空腹肘静脉血 5 mL,2 mL 注入 EDTA 抗凝试管混匀,采用 LH750 全自动血细胞分析仪(美国贝克曼库尔特公司)检测淋巴细胞计数、中性粒细胞计数、血小板计数,3 mL 注入干燥试管室温下静置取上层液离心(3 000 rpm,半径 10 cm,时间 5 min)分离血清,采用 AU480 全自动生化分析仪(美国贝克曼库尔特公司)检测血清白蛋白水平。淋巴细胞计数正常值:2× 10^9/L～4× 10^9/L,中性粒细胞计数正常值:1.8× 10^9/L～6.3× 10^9/L,血小板计数正常值:100× 10^9/L～300× 10^9/L,白蛋白:35 g/L～50 g/L。计算 PNI= 血清白蛋白(g/L)+5× 淋巴细胞计数(10^9/L),NLR= 中性粒细胞计数 / 淋巴细胞计数,PLR= 血小板计数 / 淋巴细胞计数。

1.3 随访

脑胶质瘤患者出院后电话随访 3 年,随访期间定期门诊复查,统计随访期间患者总生存情况,随访截止时间为 2022 年 2月。

1.4 统计学分析

以 SPSS 25.00 录入和分析数据,Kolmogorov-Smirnov 法检验计量资料符合正态分布以($\bar{x}\pm s$)表示,采用独立样本 t 检验。以率(%)表示计数资料再采用 x^2 检验。Kaplan-Meier 绘制脑胶质瘤患者生存曲线,Log-Rank x^2 检验差异性。单因素和多因素 COX 回归分析影响脑胶质瘤患者术后预后的因素。受试者工作特征曲线(ROC)分析 PNI、NLR、PLR 预测脑胶质瘤患者预后的价值。检验水准 α=0.05。

2 结果

2.1 两组 PNI、NLR、PLR 比较

脑胶质瘤组 NLR、PLR 高于对照组(P<0.05),PNI 低于对照组(P<0.05),见表 1。

表 1 脑胶质瘤组和对照组 PNI、NLR、PLR 差异($\bar{x}\pm s$)

Table 1 Differences in PNI, NLR and PLR between brain glioma group and control group($\bar{x}\pm s$)

Groups	n	PNI	NLR	PLR
Brain glioma group	131	41.02± 4.18	3.68± 0.71	139.81± 20.42
Control group	86	59.51± 6.79	1.29± 0.40	56.16± 9.45
t		-24.829	28.386	35.551
P		0.000	0.000	0.000

2.2 脑胶质瘤患者不同临床病理特征 PNI、NLR、PLR 比较

WHO 分级Ⅲ级患者 NLR、PLR 高于 WHO 分级Ⅰ～Ⅱ级

患者(P<0.05),PNI 低于 WHO 分级Ⅰ～Ⅱ级患者(P<0.05),不同年龄、性别、肿瘤直径、术前 KPS 评分的 PNI、NLR、PLR 比较差异无统计学意义(P>0.05),见表 2。

表 2 脑胶质瘤患者不同临床病理特征 PNI、NLR、PLR 的差异($\bar{x}\pm s$)

Table 2 Differences in PNI, NLR and PLR of patients with brain glioma with different clinicopathological characteristics($\bar{x}\pm s$)

Clinicopathological characteristics	n	PNI	t/P	NLR	t/P	PLR	t/P
Age							
≥60 years	68	40.59± 2.03	-1.831/0.070	3.71± 0.35	0.844/0.400	142.02± 18.35	1.385/0.168
<60 years	63	41.48± 3.41		3.65± 0.46		137.42± 19.66	
Gender							
Male	73	41.13± 2.09	0.722/0.479	3.70± 0.32	0.913/0.363	141.85± 18.74	1.389/0.167
Female	58	40.88± 1.89		3.65± 0.30		137.24± 19.03	
Tumor diameter							
≥3 cm	72	40.75± 1.95	1.801/0.074	3.70± 0.41	0.503/0.616	141.99± 18.08	1.451/0.149
<3 cm	59	41.35± 1.83		3.66± 0.50		137.15± 20.06	
WHO grade							
Ⅰ～Ⅱ grade	81	41.95± 2.01	7.458/0.000	3.43± 0.25	-17.265/0.000	133.51± 10.06	-10.046/0.000
Ⅲ grade	50	39.52± 1.43		4.09± 0.13		150.02± 7.39	
Preoperative KPS score							
≥75 scores	69	41.25± 3.01	1.080/0.282	3.62± 0.35	-1.831/0.069	138.36± 18.35	-0.921/0.359
<75 scores	62	40.76± 2.03		3.75± 0.46		141.42± 19.66	

2.3 不同 PNI、NLR、PLR 水平脑胶质瘤患者的术后预后情况

随访期间死亡 65 例，根据 PNI、NLR、PLR 均值将脑胶质瘤患者分为高 PNI 组(≥41.02,64 例)和低 PNI 组(<41.02,67 例);高 NLR 组(≥3.68,68 例)和低 NLR 组(<3.68,63 例);高 PLR 组(≥139.81,66 例)和低 PLR 组(<139.81,65 例)。绘制 Kaplan-Meier 曲线,高 NLR 组、高 PLR 组 3 年生存率分别低于低 NLR 组、低 PLR 组 [36.76% (25/68)Vs 65.08%(41/63);39.39% (26/66)Vs 61.54%(40/65),Log-Rank x^2=9.564、5.697,P<0.05],低 PNI 组 3 年生存率低于高 PNI 组(38.81%(26/67)Vs 62.50%(40/64),Log-Rank x^2=7.794,P<0.05),见图 1。

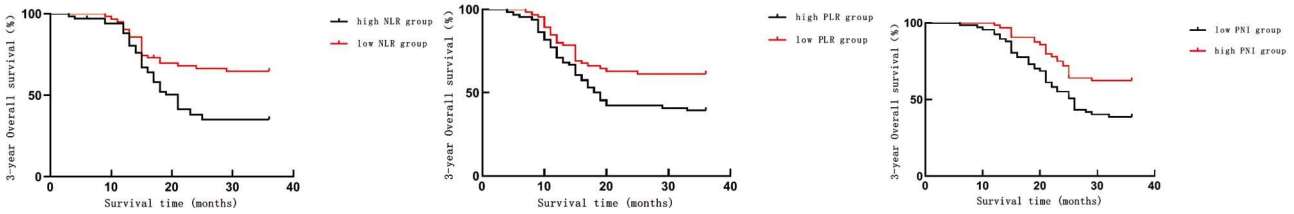

图 1 不同 PNI、NLR、PLR 水平脑胶质瘤患者的生存曲线

Fig.1 Survival curves of patients with brain glioma with different levels of PNI, NLR and PLR

2.4 影响脑胶质瘤患者预后的因素分析

单因素 COX 回归分析结果显示肿瘤直径≥3 cm、WHO 分级Ⅲ级、NLR、PLR、PNI 与脑胶质瘤患者预后不良有关(P<0.05),多因素 COX 回归分析结果显示 WHOⅢ级、NLR(较高)、PLR(较高)是脑胶质瘤患者预后不良的危险因素(P<0.05),PNI(较高)是保护因素(P<0.05),见表 3。

2.5 PNI、NLR、PLR 预测脑胶质瘤患者预后的价值分析

PNI、NLR、PLR 预测脑胶质瘤患者预后的曲线下面积为 0.703、0.706、0.704,联合 PNI、NLR、PLR 预测脑胶质瘤患者预后的曲线下面积为 0.849,高于单独指标预测效能,见表 4 和图2。

3 讨论

脑胶质瘤是中枢神经系统中最常见的原发性恶性肿瘤,主要由胶质细胞或前体细胞恶变引起,其标准临床治疗是手术以及术后放疗或辅以替莫唑胺为基础的化疗,尽管治疗方法和技术取得进展,但胶质瘤患者的总生存率并没有显著提高,因此,迫切需要寻找与脑胶质瘤患者预后相关的生物学标志物[13,14]。

营养和免疫与恶性肿瘤进展存在密切关系,营养缺乏可降低机体对抗肿瘤治疗的耐受性，增加抗肿瘤治疗不良反应风险,降低患者生存率[15],营养不良还可导致免疫细胞代谢障碍

表 3 影响脑胶质瘤患者预后的单因素和多因素 COX 回归分析

Table 3 Univariate and multivariate COX regression analysis of affecting the prognosis of patients with brain glioma

Factors	Assignment	Univariate COX regression analysis		Multivariate COX regression analysis	
		HR(95%CI)	*P*	HR(95%CI)	*P*
Constant term	-	-	0.000	-	-
Age	0=≥60 years, 1=<60 years	1.257(0.858～1.843)	0.758	-	-
Gender	0=female, 1=male	1.033(0.983～1.084)	0.523	-	-
Tumor diameter	0=<3 cm, 1=≥3 cm	1.582(1.045～2.393)	0.012	1.025(0.869～1.357)	0.256
WHO grade	0=Ⅰ～Ⅱ grade, 1=Ⅲ grade	1.808(1.298～2.517)	0.000	1.652(1.224～2.230)	0.000
KPS score	0=≥75 scores, 1=<75 scores	1.343(0.833～2.167)	0.719	-	-
PNI	Substitution of original value	0.532(0.375～0.753)	0.000	0.552(0.385～0.791)	0.000
NLR	Substitution of original value	1.640(1.208～2.227)	0.000	1.540(1.155～2.055)	0.002
PLR	Substitution of original value	1.654(1.206～2.267)	0.003	1.645(1.212～2.234)	0.000

表 4 PNI、NLR、PLR 预测脑胶质瘤患者预后的效能

Table 4 Efficacy of PNI, NLR and PLR in predicting the prognosis of patients with brain glioma

Factors	Area under curve (95%CI)	Critical value	Sensitivity(%)	Specificity(%)	Jordan index
PNI	0.703(0.608～0.797)	35.16	69.41	65.22	0.3463
NLR	0.706(0.612～0.800)	3.85	71.76	63.04	0.3480
PLR	0.704(0.607～0.801)	146.28	72.94	69.57	0.4251
Combine	0.849(0.772～0.925)	-	85.88	86.96	0.7284

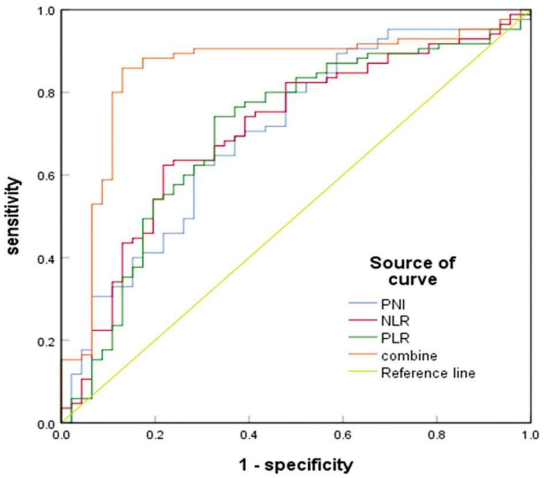

图 2 PNI、NLR、PLR 预测脑胶质瘤患者预后的 ROC 曲线图

Fig.2 ROC curve of PNI, NLR and PLR predicting prognosis of patients with brain glioma

和能量供应缺乏，引起免疫功能下降[16]，最终加速肿瘤进展。PNI 基于血清白蛋白浓度和淋巴细胞计数反映免疫营养状况，与不同恶性肿瘤患者的临床结局相关，研究显示 PNI 水平增高与接受雄激素剥夺治疗的前列腺癌患者无进展生存期、癌症特异性生存期和总生存期延长有关[17]，PNI 降低与头颈癌患者总生存率降低有关[18]。本研究结果显示脑胶质瘤患者 PNI 降低，低 PNI 与 WHO 分级增加和低生存率有关，PNI 预测脑胶质瘤预后的曲线下面积达 0.703，提示 PNI 可作为脑胶质瘤患者预后的标志物。PNI 较高导致预后良好的可能原因为 PNI 升高反映了营养良好状态和淋巴细胞介导的抗肿瘤免疫反应增强，这两者可抑制外周血循环肿瘤细胞增殖和转移，抑制机体炎症反应，降低肿瘤复发的风险[17,19]。

炎症在肿瘤发生和进展中发挥关键作用，机体慢性炎症反应可促使细胞癌变、存活、增殖、侵袭、血管生成和转移，与各类肿瘤预后不良有关[20]。中性粒细胞、淋巴细胞、血小板等血液学炎症参数均可反映炎症状态，对肿瘤预后有重要的预测价值[21]，其中 NLR 是中性粒细胞计数和淋巴细胞计数的比值，PLR 是血小板计数和淋巴细胞计数的比值，NLR 值升高提示机体过度炎症反应和免疫功能低下，PLR 值升高提示免疫炎症反应和血液高凝状态[22,23]。本研究发现脑胶质瘤患者 PLR 和 NLR 异常升高，且与 WHO 分级增加和低生存率有关。分析原因为：首先，中性粒细胞主要通过诱导炎症反应，产生和释放活性氧诱导癌前上皮细胞中基因突变导致脱氧核糖核酸（DNA）损伤和癌变，释放生长因子促使血管生成，癌细胞增殖、侵袭和迁移等途径导致癌症的发生和进展[24,25]。其次，表达促凋亡配体的肿瘤细胞可诱导淋巴细胞的破坏和数量减少，肿瘤细胞上表达的程序性死亡配体 1 可能会导致肿瘤浸润淋巴细胞增殖和存活率降低，淋巴细胞减少影响 T 或 B 淋巴细胞亚群功能，降低机体抗肿瘤免疫功能，进而导致肿瘤进展[26,27]。第三，恶性血栓形成是癌症患者最常见的临床表现之一，并且与较差的生存率有关[28]，癌细胞可分泌凝血酶，激活凝血因子 V、VIII、XI 和 XIII 以及血小板蛋白酶激活（PAR）受体促使血小板活化和聚集，启动凝血级联反应[29]，而活化血小板可诱导环氧合酶 2 表达激活肿瘤基质细胞和上皮细胞的旁分泌信号，增强癌细胞侵袭性[30]，另外血小板 α 颗粒中储存转化生长因子 β、血管内皮生长因子和血小板衍生生长因子等大量生长因子，在血小板激活后释放

出来并与癌细胞直接接触,诱导肿瘤细胞生长和肿瘤新生血管形成[31]。因此,NLR 值和 PLR 值升高与脑胶质瘤患者预后不良发生风险有关。

ROC 曲线分析结果显示 PNI、NLR、PLR 对脑胶质瘤患者预后的预测均具有一定价值,联合三者可提高预后的预测效能,提示 NLR、PLR 可作为脑胶质瘤患者预后的标志物,联合 PNI、NLR、PLR 可提高对胶质瘤患者预后预测的效能。COX 回归分析结果显示 WHO Ⅲ级与脑胶质瘤患者预后不良也存在密切关系,这与以往报道的高级别脑胶质瘤患者预后较差的结果一致[32]。

综上,脑胶质瘤患者 PNI 降低,NLR、PLR 均升高,低 PNI 和高 NLR、PLR 与脑胶质瘤 WHO 分级增加和低生存率有关,具有作为脑胶质瘤预后标志物的潜能。

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