·论著·

中性粒细胞/淋巴细胞比值和血肿周围水肿体积是脑出血患者预后的独立预测因素

黄磊[1]，叶飞[2]，任思颖[2]，伍国锋[2]，王丽琨[2]

作者单位

1. 贵州医科大学临床医学院/贵州医科大学附属医院 贵阳 550004
2. 贵州医科大学附属医院急诊神经科 贵阳 550004

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通讯作者

王丽琨

769070308@qq.com

摘要　目的：探讨中性粒细胞/淋巴细胞比值（neutrophil-to-lymphocyte ratio，NLR）与脑出血（intracerebral hemorrhage，ICH）后血肿周围水肿（perihematomal edema，PHE）体积及预后的相关性。**方法：**回顾性收集ICH患者，根据随访出院后90 d改良Rankin量表（modified Rankin Scale，mRS）评分分为预后良好（mRS≤3分）组和预后不良（mRS＞3分）组。比较2组人口统计学、临床基线资料及影像学资料等。应用*Pearson*相关性分析NLR和PHE体积的相关性；多因素*Logistic*回归分析确定影响预后不良的独立危险因素；受试者工作特征（receiver operating characteristic，ROC）曲线评估NLR和发病第7天PHE体积对预后不良的预测价值。**结果：**根据纳入及排除标准共纳入177例ICH患者，其中预后良好105例，预后不良72例。单因素分析显示预后不良组ICH 24 h内PHE体积、第7天PHE体积、24 h内相对PHE体积、第7天相对PHE体积、NLR、PLR明显高于预后良好组，预后不良组脑疝比例高于预后良好组（$P<0.05$）。*Pearson*相关性分析显示，ICH 24 h内PHE体积与发病24 h内血肿体积及NLR呈正相关（$P<0.05$）；发病第7天PHE体积与NLR与发病24 h内血肿体积、发病第7天血肿体积、NLR呈正相关（$P<0.05$）。二元*Logistic*回归分析提示发病第7天PHE体积、NLR是ICH患者预后不良的独立危险因素（$P<0.05$）。ROC曲线发现发病第7天PHE体积曲线下面积为0.636（95% *CI* 0.54～0.73，$P=0.006$）；NLR曲线下面积为0.676（95% *CI* 0.585～0.768，$P<0.001$）。**结论：**入院时NLR水平较高的ICH患者，PHE越严重，入院时NLR升高和发病第7天PHE体积是ICH患者出院第90天预后不良的危险因素。

关键词　脑出血；中性粒细胞/淋巴细胞比值；血肿周围水肿；预后

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Neutrophil/Lymphocyte Ratio and Perihematoma Edema Volume Are Independent Prognostic Predictors of Patients with Intracerebral Haemorrhage

HUANG Lei[1], YE Fei[2], REN Siying[2], WU Guofeng[2], WANG Likun[2]. 1. School of Clinical Medicine, Guizhou Medical University, Guiyang 550004, China; 2. Emergency Department, Affiliated Hospital of Guizhou Medical University, Guiyang 550004, China

Abstract Objective: To investigate correlation between the neutrophil-to-lymphocyte ratio (NLR) and perihematomal edema (PHE) volume and prognosis after intracerebral hemorrhage (ICH). **Methods:** Patients with ICH were retrospectively enrolled and divided into good prognosis (mRS≤3) and poor prognosis (mRS>3) groups according to the Modified Rankin Scale (mRS) scores obtained 90 days after discharge from the hospital. Demographics, clinical baseline data and imaging data were compared between the two groups. Pearson correlation analysis was applied to determine the correlation between NLR and PHE volume. Multivariate *Logistic* regression analysis was used to determine independent risk factors affecting poor prognosis. Receiver operating characteristic (ROC) curves were used to assess the predictive value of NLR and PHE volume at day 7 from onset on poor prognosis. **Results:** A total of 177 patients with ICH were included according to the inclusion and exclusion criteria, including 105 patients withgood prognosis and 72 patients with poor prognosis. Univariate analysis showed that PHE volume at 24 h, PHE volume at day 7, relative PHE volume at 24 h, relative PHE volume at day 7, NLR and PLR were significantly higher in the poor prognosis group than in the good prognosis group, and the proportion of brain herniation was significantly higher in the poor prognosis group than in the good prognosis group ($P<0.05$). Pearson correlation analysis showed that PHE volume within 24 h of ICH was positively correlated with haematoma volume and NLR within 24 h from onset ($P<0.05$); PHE volume and NLR on day 7 from onset were positively correlated with hematoma volume within 24 h of onset, hematoma volume on day 7 from onset, and NLR ($P<0.05$). Binary Logistic regression analysis suggested that PHE volume at day 7 from onset and NLR were independent risk factors for poor prognosis in patients with ICH. ROC analysis domonstrated an area under curve of 0.636 (95% *CI* 0.54～0.73, $P=0.006$) for PHE volume on day 7 from onset and 0.676 (95% *CI* 0.585～0.768, $P<0.001$) for NLR. **Conclusion:** Higher NLR levels on admission correlated with more severe PHE. Elevated NLR on admission and PHE volume on day 7 from onset were risk factors for poor prognosis on day 90 post-discharge for patients with ICH.

Keywords intracerebral hemorrhage; neutrophil/lymphocyte ratio; perihematoma edema; prognosis

自发性脑出血（intracerebral hemorrhage，ICH）是发病率和致死率极高的卒中亚型，约70%幸存患者发病后6个月内会遗留不同程度的肢体瘫痪[1]。发病后血肿不仅直接造成机械性原发损伤，还导致继发性血肿周围水肿（perihematomal edema，PHE）形成，而PHE的发生与发展与炎症反应密切相关[2]，两者均与患者神经功能恶化和临床预后不良明显相关[3,4]。

外周血中性粒细胞/淋巴细胞比值（neutrophil-to-lymphocyte ratio，NLR）、血小板与淋巴细胞比值（platelet-to-lymphocyte ratio，PLR）可以提示患者全身炎症反应状态[5]，且能作为ICH患者预后的独立预测因素[6,7]。ICH后全身炎症反应会导致患者临床预后变差[8]，随血液循环的中性粒细胞迅速介导全身及血肿周围炎症反应，还可引起短暂性免疫抑制，从而导致外周淋巴细胞减少[9]，而淋巴细胞减少可增加患者的感染风险[10]。因此，NLR的动态变化可快速反映炎症水平。PHE是指脑实质内血肿附近脑组织中水分含量增加，是ICH后继发炎性损伤的重要体现[11]，与炎症反应、凝血酶活化、血脑屏障（blood-brain barrier，BBB）破坏及血红蛋白的细胞毒性相关[12]。ICH后PHE的自然演变长达14 d甚至更久，发病数小时内PHE逐渐形成，3～7 d左右达到峰值，导致患者神经功能持续恶化[3]。

PHE形成机制及炎症反应与ICH患者的预后相关。有研究报道了NLR可评估ICH后脑水肿分级及发病后30 d预后情况[13]。本文使用半自动量化软件将PHE体积量化，并分析入院时NLR与PHE的相关性，同时联合两者对出院后90 d预后进行评估，从而探讨ICH发病NLR和PHE体积与出院后90 d预后的相关性。

1 资料与方法

1.1 一般资料

回顾性纳入2020年1月至2022年5月在贵州医科大学附属医院急诊神经科诊断为ICH的患者177例。纳入标准：根据中国脑出血诊治指南（2019），经头颅CT证实为ICH；头颅CT显示为幕上出血（包括基底节、丘脑、脑叶）；体积＜60 mL。排除标准：多发性颅内出血；头颅CT显示幕下出血；血肿体积＞60 mL；颅内肿瘤、动脉瘤、外伤、梗死或其他病变所致颅内出血；凝血功能障碍或有服用抗凝药物史；入院时患有可能影响炎症反应的疾病，如感染性脑膜炎、全身感染等；既往有严重心、肾、肝、肺功能障碍史；既往遗留神经功能障碍的卒中患者；临床资料不完整。所有患者均接受基于高血压脑出血管理指南的相同治疗方案，部分患者由经验丰富的神经科医师进行评估行立体定向微创血肿清除术治疗，通过电话随访出院第90天患者预后情况，根据改良Rankin量表（Modified Rankin Scale，mRS）将这些患者分为预后良好（mRS≤3分）组和预后不良（mRS＞3分）组[14]，见图1。本研究已通过贵州医科大学附属医院医学科学伦理委员会审批（审批编号：2022伦审第92号），且获得所有患者及家属知情同意。

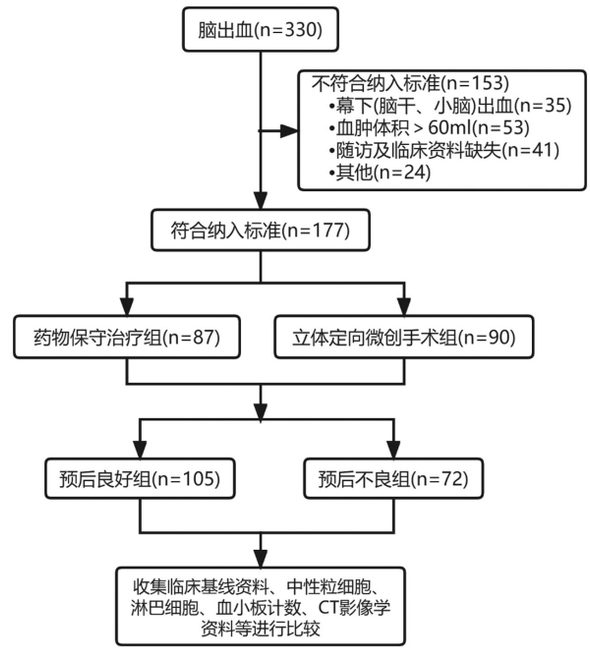


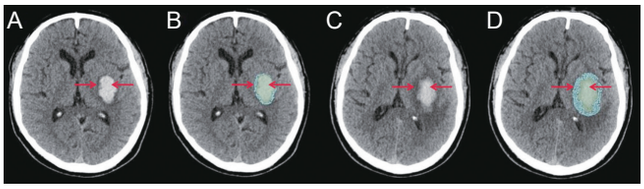
图1 ICH数据收集流程

1.2 方法

1.2.1 临床基线资料收集 据入院病例记录一般资料及基础疾病，包括性别、年龄、既往病史及服药史、血压、吸烟史、饮酒史、高血压病史、糖尿病史、高脂血症史等。

1.2.2 影像学处理 在影像科下载患者发病24 h内、发病第7天颅脑CT影像资料，利用3D Slicer软件导入颅脑CT DICOM格式，使用辅助软件半自动切割法来测量ICH和PHE体积，血肿阈值设定为44～100 HU之间，PHE阈值设定为3～33 HU之间[15]，通过软件自动导出血肿及PHE体积，见图2。将PHE体积除以对应血肿体积得到相对PHE体积。

1.2.3 指标检测 发病后24 h内对所有研究对象采集外周静脉血，完成血常规、血生化等检测，根据检测结果的血小板、中性粒细胞、淋巴细胞计数计算NLR、



注：A：ICH发病24 h内颅脑CT扫描血肿；B：经3D Slicer测量后对应示意图，绿色区域为血肿（约12 mL），蓝色区域为血肿周围水肿（约3 mL）；C：发病第7天头颅CT扫描显示血肿较前吸收且血肿周围水肿明显加重；D：3D Slicer测量后提示绿色区域较前稍减少（约9 mL），蓝色区域较前明显增大（约11 mL）。

图2 头颅CT扫描及3D Slicer处理后血肿及血肿周围水肿

PLR数值。

1.2.4 预后评估 对患者出院后第90天预后进行随访，通过有经验神经科医师电话联系评估患者mRS评分，以mRS≤3分为预后良好，mRS＞3分为预后不良。

1.3 统计学处理

应用*SPSS* 26.0软件进行统计分析。计量资料运用*Kolmogorov-Smirnov*检验正态性，符合正态分布的计量资料以（$\bar{x}\pm s$）表示，2组均数间比较采用两独立样本*t*检验；非正态分布的计量资料以M(Q1～Q3)表示，2组间比较采用*Mann-Whitney*检验；计数资料采用χ^2检验；*Pearson*相关性分析检测NLR与PHE相关性；运用多因素二元*Logistic*回归分析影响ICH患者短期预后不良的危险因素。通过受试者工作特征（Receiver operating characteristic，ROC）曲线评价入院时NLR、第7天水肿体积对预后的预测能力，以*Youden*指数最大确定诊断最佳截断值。*P*＜0.05为差异有统计学意义。

2 结果

2.1 入组情况基线资料对比

330例ICH患者中，男123例（69.5%），年龄（59.0±13.8）岁，预后良好105例，预后不良72例。单因素分析显示预后不良组发病24 h内PHE体积、发病第7天PHE体积、发病24 h内相对PHE体积、发病第7天相对PHE体积、NLR、PLR明显高于预后良好组，预后不良组脑疝比例显著高于预后良好组（*P*＜0.05），见表1。

2.2 发病24 h内、发病第7天血肿及PHE体积比较

患者发病第7天血肿体积明显低于入院24 h内血肿体积（*P*＜0.01），发病第7天PHE体积较发病24 h内

表1 预后良好与预后不良组患者临床资料对比

组别	例数	年龄/（岁，$\bar{x}\pm s$）	男性/[例(%)]	高血压史/[例(%)]	糖尿病史/[例(%)]	吸烟史/[例(%)]	饮酒史/[例(%)]	出血部位/[例(%)]		
								基底节	丘脑	脑叶
预后良好组	105	58.4±13.6	77(73.3)	98(93.3)	14(13.3)	59(56.2)	31(29.5)	68(64.8)	13(12.4)	24(22.9)
预后不良组	72	59.9±14.0	46(63.9)	67(93.1)	6(8.3)	30(41.7)	22(30.6)	54(75.0)	9(12.5)	9(12.5)
Z/*F*/χ^2值		0.073	1.797	0.005	1.065	3.604	0.022	3.107		
*P*值		0.485	0.180	0.942	0.302	0.058	0.883	0.211		

组别	出血破入脑室/[例(%)]	脑疝/[例(%)]	血肿扩大/[例(%)]	收缩压/(mmHg, IQR)	舒张压/(mmHg, IQR)	甘油三酯/(mmol/L, IQR)	总胆固醇/(mmol/L, IQR)
预后良好组	35(33.7)	6(5.7)	3(2.9)	161.0(147.5～181.5)	97.0(88.5～109.0)	1.1(0.8～1.9)	4.2±1.1
预后不良组	23(31.9)	11(15.3)	7(9.7)	171.0(153.5～192.0)	100.0(89.0～115.8)	1.2(0.9～1.9)	4.3±1.0
Z/*F*/χ^2值	0.056	4.499	5.355	−1.637	−1.334	−0.828	0.314
*P*值	0.812	0.034	0.069	0.102	0.182	0.407	0.427

组别	高密度脂蛋白/(mmol/L, IQR)	低密度脂蛋白/(mmol/L, IQR)	NLR/(IQR)	PLR/(IQR)	发病24 h内血肿体积/(mL, IQR)	发病24 h内PHE体积/(mL, IQR)	发病24 h内相对PHE体积/(mL, IQR)
预后良好组	1.1(0.9～1.4)	2.6±0.9	4.8(3.2～6.9)	159.1(114.1～210.3)	13.5(6.1～23.2)	3.9(1.9～9.1)	0.3(0.2～0.5)
预后不良组	1.1(0.9～1.4)	2.8±0.9	6.7(4.4～14.9)	186.9(130.3～255.5)	18.6(10.4～27.5)	7.1(4.1～16.1)	0.5(0.3～0.9)
Z/*F*/χ^2值	−0.512	0.450	−3.246	−2.338	−1.850	−4.131	−4.720
*P*值	0.608	0.314	0.001	0.019	0.064	＜0.001	＜0.001

组别	发病第7天血肿体积/(mL, IQR)	发病第7天PHE体积/(mL, IQR)	发病第7天相对PHE体积/(mL, IQR)	肺部感染/[例(%)]	消化道出血/[例(%)]	低钾血症/[例(%)]	高脂血症/[例(%)]	住院天数/(d, IQR)
预后良好组	6.9(3.9～11.2)	3.5(2.1～5.9)	0.5(0.3～0.8)	54(51.4)	16(15.2)	40(38.1)	33(31.4)	10.0(8.0～14.0)
预后不良组	6.7(3.7～12.8)	6.9(2.2～14.5)	0.7(0.4～1.4)	44(61.1)	16(22.2)	38(53.5)	25(34.7)	12.0(9.0～17.0)
Z/*F*/χ^2值	−0.139	−2.776	−2.601	1.620	1.407	5.046	3.958	−1.574
*P*值	0.889	0.006	0.009	0.203	0.236	0.800	0.138	0.115

PHE体积差异无统计学意义（*P*=0.084），见表2。

2.3 NLR与PHE体积的*Pearson*相关性分析

*Pearson*相关性分析显示，发病24 h内PHE体积与发病24 h内血肿体积及NLR成正相关（*r*=0.619，*P*<0.001；*r*=0.227，*P*=0.030），与PLR无相关性（*r*=0.022，*P*=0.769）；发病第7天PHE体积与发病24 h内血肿体积、发病第7天血肿体积和NLR成正相关（*r*=0.238，*P*=0.004；*r*=0.457，*P*<0.001；*r*=0.199，*P*=0.016），与PLR无相关性（*r*=0.024，*P*=0.774）。

2.4 影响ICH患者预后不良多因素二元*Logistics*回归分析

将单因素分析中PHE体积、NLR和PLR为自变量进行多因素二元*Logistics*回归，以出院90 d不良预后作为因变量，将上述对ICH患者预后有影响因素纳入，结果提示，发病第7天PHE体积、NLR是ICH患者预后不良的独立危险因素（*P*<0.05），发病24 h内PHE体积、PLR、脑疝与预后无关（*P*>0.05），见表3。

2.5 NLR和发病第7天PHE体积对预后不良的预测价值分析

绘制ROC曲线评估发病第7天PHE体积与NLR对ICH预后的预测价值，以0.50作为ROC曲线下面积的参考值，发病第7天PHE体积曲线下面积为0.636（95% *CI* 0.54～0.73，*P*=0.006），当第7天PHE体积截断值为6.95时，对应的敏感性为50.8%，特异性为82.4%，约登指数0.332；当NLR曲线下面积为0.676（95% *CI* 0.585～0.768，*P*<0.001），对应的敏感性为52.5%，特异性为78.8%，约登指数0.313，见图3。

3 讨论

本研究结果显示，ICH后入院时高水平的NLR和PHE体积与患者的预后不良有关，NLR和PHE体积呈正相关，且入院时NLR、发病第7天PHE体积能作为出院90 d预后不良的独立危险因素。因此，早期对NLR及PHE的监测能对预后起到较好的预测价值。

先前研究发现，入院时NLR升高是ICH患者发病90 d临床结局不良的预测指标，该研究还指出与ICH评分相比，NLR在预测不良结局方面更敏感，但特异性较低[16]。本研究与先前的研究结果一致，得出NLR升高能作为ICH患者出院90 d预后不良的独立危险因素。同样在接受手术治疗患者中，NLR升高与血肿清除后90 d的不良预后独立相关[7]。且有研究发现NLR升高能独立预测ICH患者神经功能恶化[17]，较高NLR水平与患者短期高死亡率及发病90 d的高致残率显著相关[18]。Zhang等[19]将随访时间调整至180 d，仍发现NLR升高能独立预测ICH患者不良结局。

对预后有影响的单因素分析中，为减少血肿体积对预后的干扰，本研究对血肿体积进行限制，同时取PHE的相对体积进行预后间比较，结果均提示预后不良组拥有更高的PHE水平。PHE也是导致患者神经功能恶化和临床预后不良的原因之一，PHE峰值体积能作为90 d临床不良结局的独立预测因素[20]。据报道出血后7 d左右PHE进展达到高峰[21]，本研究以发病第7天PHE体积为峰值代表，比较发病24 h内PHE体积，结果提示第7天PHE体积对预后预测意义更大，结果符合前述研究。还有研究发现患者24 h内PHE体积与深部和大叶性脑出血的死亡率相关，且72 h内PHE体积与深部ICH后功能结局不良有关[22]，遗憾的是此次未能纳入72 h内PHE进行比较分析，也未对死亡率进行归纳，但Marchina等[23]也指出72 h内的PHE体积对患者临床结局和死亡率影响较弱。本研究明确的是幕上ICH患者发病第7天PHE体积能作为90 d预后不良的独立危险因素。虽然比较发病24 h内和第7天PHE体积仅有轻微增加，但部分患者接受微创手术治疗后血肿明显减少，进而PHE进展得到缓解，患者预后也能

表2 不同时间点血肿及PHE体积比较（mL，$\bar{x}\pm s$）

	发病24 h内	发病第7天	*Z*值	*P*值
血肿体积	18.5±13.5	9.9±11.3	−6.981	<0.001
PHE体积	9.1±10.7	9.5±14.3	−1.726	0.084

表3 影响ICH患者预后不良多因素二元*Logistic*回归分析

	B	标准误差	瓦尔德	*P*	*OR*	95% *CI*	
						下限	上限
发病24 h内PHE体积	0.031	0.024	1.703	0.192	1.032	0.985	1.081
发病第7天PHE体积	0.04	0.02	4.008	0.045	1.041	1.001	1.082
NLR	0.105	0.046	5.187	0.023	1.111	1.015	1.216
PLR	0.002	0.002	1.002	0.317	1.002	0.998	1.007
脑疝	0.116	0.667	0.03	0.862	1.123	0.304	4.152
常量	−2.208	0.508	18.884	0	0.110		

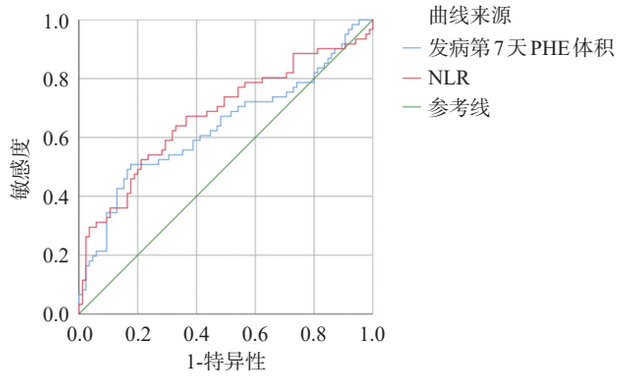


图 3 发病第7天PHE体积及NLR预测脑出血患者预后不良的ROC曲线

得到改善[24]。

本研究的创新点在于可反映入院NLR与PHE呈正相关，以及两者对出院90 d预后的预测价值。尽管前期已有有关NLR、PHE及预后两两间的报道，但将三者间联系到一起的研究却很少。先前Kashiwazaki等[25]发现发病24～72 h PHE体积变化量与NLR呈正相关，但未分析预后。Volbers等[20]发现峰值PHE体积能独立预测第90天临床不良结局，且峰值PHE体积和发病第6天NLR相关，该研究并未回答NLR水平和PHE的因果关系。本研究与前面提到一项研究[13]相似，相同点在于均发现NLR与PHE的相关性，本研究更新的点在于：①使用3D Slicer软件取得更加精准的PHE体积，前述仅对脑水肿范围与大脑半球位置关系进行分级处理；②发现入院时NLR指标能作为预后不良的独立危险因素；③相比评估发病30 d预后，本研究将随访时间延长至患者出院第90天；④本研究除评估24 h内PHE体积外，增加了对发病第7天PHE体积的评估，动态掌握了PHE变化情况。本研究在上述研究基础上发现入院时NLR能作为预后的预测指标，发病第7天相比24 h内PHE体积对预后预测价值更大，还发现发病24 h内及第7天PHE随NLR升高而加重。因此，本研究认为NLR升高是引起PHE的原因之一，同时也能反映PHE的恶化。

综上所述，通过本研究可推测，ICH后除入院时NLR升高导致的不良结局外，NLR诱导PHE的发生和发展也可造成预后不良。本研究存在局限性：为控制血肿体积的影响将其纳入标准控制在60 mL以下，不排除存在选择偏倚；患者住院期间随访NLR次数较少，未能动态跟踪NLR与PHE之间的相关性。

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