

## 急性前循环脑梗死机械取栓术后出血转化发生率及影响因素

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**【摘要】** 目的 探讨急性前循环大血管闭塞性(LVO)脑梗死机械取栓(MT)术后出血转化(HT)发生率及影响因素。方法 回顾性收集 107 例 2020-01—2021-12 序贯就诊于常德市第一人民医院神经内科确诊为急性前循环 LVO 脑梗死,并行急诊 MT 术患者临床资料,采用单因素和多因素 Logistic 回归分析 MT 术后 HT 发生影响因素,并行曲线拟合及阈值效益分析。结果 107 例急性前循环 LVO 脑梗死患者中 32 例术后发生 HT,占 29.91%,包括症状性 HT 13 例(12.15%)和非症状性 HT 19 例(17.76%)。多因素 Logistic 回归分析显示,术前侧支循环代偿程度低、术前急查外周中性粒细胞计数水平高、中性粒细胞/淋巴细胞比值(NLR)升高是急性前循环 LVO 脑梗死 MT 术后 HT 发生的独立危险因素( $P < 0.05$ )。应用平滑曲线拟合显示,术前急查 NLR 水平与急性前循环 LVO 脑梗死 MT 术后 HT 发生风险呈 J 型曲线关系,行阈值效应分析发现,曲线存在饱和效应值为 6.3。结论 术前侧支循环代偿程度低、术前急查外周中性粒细胞计数水平高、NLR 升高是急性前循环 LVO 脑梗死 MT 术后 HT 发生的独立危险因素。监测术前 NLR 变化可成为预测急性前循环 LVO 脑梗死 MT 术后 HT 发生风险的有效措施。

**【关键词】** 急性前循环大血管闭塞性脑梗死;机械取栓;出血转化;影响因素

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### Analysis of incidence and influencing factors of hemorrhagic transformation in patients with acute anterior circulation large vessel occlusive cerebral infarction after mechanical thrombolysis

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**【Abstract】** **Objective** To investigate the incidence and influencing factors of HT patients with acute anterior circulation LVO cerebral infarction after MT. **Methods** The clinical records of 107 patients with acute anterior circulation LVO cerebral infarction and underwent MT admitted to the first people's hospital of Changde city from January 2020 to December 2021 were reviewed retrospectively. Univariate and multivariate logistic regression were used to analyze the risk factors, curve fitting and threshold benefit analysis were performed to further assess the association between the risk factors and HT. **Results** Among 107 patients with ACI, 32 cases (29.91%) developed HT after MT, including 13 cases of symptomatic HT (12.15%) and 19 cases of non-symptomatic HT (17.76%). Multivariate logistic regression analysis illustrated that lower preoperative compensatory degree of collateral circulation, higher peripheral neutrophil count and higher preoperative NLR level were independent risk factors for HT after MT. Smooth curve fitting showed that the relationship between preoperative NLR level and HT occurrence after MT presented a J-shaped curve. Further threshold benefit

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analysis showed that when  $NLR < 6.3$ , The risk of HT after MT was positively correlated with NLR level.

**Conclusion** lower preoperative compensatory degree of collateral circulation, higher peripheral neutrophil count and higher preoperative NLR level were independent risk factors for HT after MT. Monitoring preoperative NLR changes can be an effective measure to predict the risk of HT after MT in acute anterior circulation LVO cerebral infarction.

**【Key words】** Acute large vessel occlusive cerebral infarction; Mechanical thrombolysis; Hemorrhagic transformation; Influencing factors

急性缺血性脑梗死 (acute cerebral infarction, ACI) 是一类因脑动脉闭塞造成脑供血、供氧不足, 从而出现一系列神经功能缺损症状的严重疾病, 其中大血管闭塞性 (large vessel occlusion, LVO) 脑梗死占全部 ACI 的 1/3 以上<sup>[1]</sup>, 因具有高致死、致残率及高复发率等特点, 已成为经济及社会发展的沉重负担。机械取栓 (mechanical thrombectomy, MT) 作为一项近年来兴起的血管内介入治疗措施, 已被多项研究证实能延长 ACI 超早期治疗时间窗, 显著提供血管再通率, 从而改善患者临床预后<sup>[2-3]</sup>。随着 MT 技术的积极开展, 其术后并发症亦被广泛关注, 如血管痉挛、血管再闭塞、血栓逃逸引发新部位梗死、颅脑高灌注损伤、术后出血转化 (hemorrhagic transformation, HT) 等<sup>[4]</sup>。其中, 术后 HT 是 MT 最常见、最严重的并发症, 发生率在 10%~49.5%<sup>[5-7]</sup>。据报道<sup>[8]</sup> 术后 HT 发生可显著增加患者病死率, 与 LVO 脑梗死预后不良密切相关。因此, 探寻 MT 术后 HT 的独立影响因素及有效预测因子, 对 LVO 脑梗死超早期治疗决策的精准指导十分有益。本研究旨在回顾性收集 107 例经急诊 MT 治疗的急性前循环 LVO 脑梗死患者临床资料, 统计分析 MT 术后 HT 的发生率及影响因素, 为指导急性前循环 LVO 脑梗死超早期治疗决策提供精准化依据。

## 1 资料与方法

**1.1 研究对象** 回顾性收集 107 例 2020-01—2021-12 序贯就诊于常德市第一人民医院神经内科首次确诊为急性前循环 LVO 脑梗死, 并行急诊 MT 术的患者临床资料。纳入标准: (1) 发病至入院时间 < 24 h, 年龄 > 18 岁, 经头颅影像学评估证实存在新发责任梗死灶, 且符合 2018 版中国急性缺血性脑卒中诊治指南诊断标准<sup>[9]</sup>; (2) 根据重建计算机断层血管造影 (computed tomography angiography, CTA) 进行判读, 证实为前循环 LVO (颈内动脉颅内段、大脑中动脉 M1 段或 M2 段), 并进行急诊 MT 术; (3) 术后 24~72 h 内完成头颅双能量计算机断层扫描 (Computed tomography, CT); (4) 患者及家属知情, 自愿并签署知

情同意书。排除标准: (1) 头颅 CT 或磁共振成像 (magnetic resonance imaging, MRI) 提示为脑实质出血、脑室出血或蛛网膜下腔出血者; (2) 既往有脑梗死病史或头颅影像学评估提示存在陈旧性梗死病灶; (3) 既往有颅内出血、动脉瘤、动静脉畸形、凝血机制障碍等易导致颅内出血发生病史; (4) 合并严重的心、肝、肺、肾功能不全等终末期疾病等不宜行急诊手术者。本研究经院伦理委员会审核通过。

**1.2 临床处理方法** 本研究所涉及手术操作均由同一介入团队实施完成。根据患者术前配合程度及全身一般状况, 选择局部麻醉、局部麻醉+镇静或全身麻醉等不同麻醉方式, 选择桡动脉或股动脉进行数字减影血管造影 (digital subtraction angiography, DSA) 并评估侧支循环代偿, 侧支循环评价系统使用 2013 年由美国介入放射学学会提出的 ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology, ASITN/SIR) 评分。DSA 完成后即刻进行 MT 术, 单次取栓效果不佳时, 可视情况多次操作, 最多不超过 5 次, 若仍未能实现血管再通, 可采取球囊扩张、支架置入、导管内注入替罗非班等补救措施, 依据改良脑梗死血栓溶解 (modified thrombolysis in cerebral infarction, mTICI) 分级造影评价血管再通情况, 如 mTICI 分级为 2b 或 3 级时视为血管开通成功, 手术结束。术后立即复查头颅双能量 CT 并转入神经内科重症监护室, 视情况予抗栓、稳定斑块、控制血压、稳定血糖等处理, 术后 24~72 h 再次复查头颅双能量 CT, 待病情平稳后转回普通病房继续治疗。

**1.3 临床资料收集** (1) 一般人口统计学信息及临床资料, 包括性别、年龄、入院基线血压、入院基线美国国立卫生院卒中量表 (National Institute of Health stroke scale, NIHSS) 评分、入院基线改良 Rankin 量表 (modified Rankin scale, mRS) 评分、术前侧支循环评估 ASITN/SIR 评分, 发病至再灌注时间 (onset to reperfusion time, ORT), 并依据急性卒中治疗 Org10172 试验 (Trial of Org 10172 in Acute Stroke Treatment, TOAST) 统计脑梗死病因; (2) 既往史, 包

括高血压、糖尿病及心房纤颤史；(3)生化指标：术前急查外周静脉血，检测血常规、高密度脂蛋白、低密度脂蛋白、肾功能、同型半胱氨酸、血浆 D-二聚体水平。MT 术后 HT 定义：患者 MT 术后 24~72 h 复查头颅双能量 CT，显示在原有低密度梗死区或其他脑组织区出现局限性或扩散性高密度信号（CT 值在 50~80 Hu）则考虑为 HT，如诊断结果存在争议，则由另 2 名神经科副主任及以上职称医师共同商议讨论得出。

**1.4 统计学分析** 运用 Empower Stats 与 R2.2 软件进行数据分析。所有计量资料首先需进行正态性检验，以均数±标准差( $\bar{x}\pm s$ )表示符合正态分布计量资料，以方差分析(analysis of variance, ANOVA)进行组间差异比较，以中位数(四分位数间距)表示非正态分布计量资料，以 Kruskal-Wallis 秩和检验进行组间差异比较。计数资料及等级资料均采用频数(构成比)表示，以卡方检验( $\chi^2$  test)或 Fisher 精确检验进行组间差异比较。首先运用单因素及多因素 Logistic 回归模型分析急性前循环 LVO 脑梗死 MT 术后 HT 发生的影响因素，随后应用曲线拟合及阈值效益分析术前急查中性粒细胞/淋巴细胞比值(neutrophil-lymphocyte ratio, NLR)与 MT 术后 HT 发生风险的相关性。所有统计检验结果以  $P < 0.05$  为差异具有统计学意义。

## 2 结果

**2.1 临床一般资料及生化指标组间分析** 本研究共收集经急诊 MT 术治疗的急性前循环 LVO 脑梗死患者 107 例，年龄(64.66±12.94)岁，其中男 58 例，占 54.21%。观察患者 MT 术后 24~72 h 内 HT 发生情况，其中 32 例患者术后发生 HT，占 29.91%，包括症状性 HT 13 例(12.15%)和非症状性 HT 19 例(17.76%)，记为出血组，其余患者记为非出血组。2 组性别、年龄基线资料均衡可比( $P > 0.05$ )。出血组入院基线 mRS 评分明显高于非出血组，而术前侧支循环代偿评估分级明显低于非出血组，2 组间差异具有统计学意义( $P < 0.05$ )；入院基线 NIHSS 评分、高血压史、糖尿病史、心房纤颤史、TOAST 分型、入院基线血压、ORT 等因素占比(或数值)在 2 组间显示差异无统计学意义( $P > 0.05$ )，见表 1。出血组术前急查外周血中性粒细胞计数、NLR 明显高于非出血组( $P < 0.05$ )，而术前急查外周淋巴细胞计数、血红蛋白、高密度脂蛋白、低密度脂蛋白、血浆 D 二聚体、同型半胱氨酸、肌酐、尿酸等生化指标数值在 2 组间显示差异无统计学意义( $P > 0.05$ )，见表 2。

表 1 出血组和未出血组患者临床基线资料比较

Table 1 Comparison of clinical baseline data between bleeding group and non-bleeding group

资料	未出血组 (n=75)	出血组 (n=32)	P 值
年龄/岁	64.75±13.17	64.47±12.61	0.920
男[n(%)]	41(54.67)	17(53.12)	0.883
基线 NIHSS 评分/分	14.89±5.00	16.09±5.01	0.259
基线 mRS 评分/分	4.32±0.47	4.53±0.51	0.040*
既往史			
高血压[n(%)]	39(52.00)	13(40.62)	0.281
糖尿病[n(%)]	16(21.33)	7(21.88)	0.950
心房纤颤[n(%)]	31(41.33)	15(46.88)	0.596
TOAST 分型[n(%)]			0.991
大动脉粥样硬化型	38(50.67)	16(50.00)	
心源性栓塞型	35(46.67)	15(46.88)	
其他病因型	2(2.67)	1(3.12)	
入院时收缩压/mmHg	160.41±19.04	158.71±23.25	0.718
入院时舒张压/mmHg	87.85±12.09	87.84±15.57	0.996
ORT/min	447.05±238.22	443.62±160.68	0.941
分级[n(%)]			<0.001**
0 级	18(24.00)	15(46.88)	
1 级	9(12.00)	12(37.50)	
2 级	8(10.67)	3(9.38)	
3 级	24(32.00)	1(3.12)	
4 级	16(21.33)	1(3.12)	

注：\* $P < 0.05$ ，\*\* $P < 0.001$

## 2.2 急性前循环 LVO 脑梗死 MT 术后 HT 的影响因素分析

**2.2.1 单因素及多因素 Logistic 回归分析：**运用 Empower Stats 软件中单因素分析模块，以是否发生 HT 为因变量 Y 筛选，结果显示，术前侧支循环代偿程度低、入院基线 mRS 评分高、术前急查外周中性粒细胞计数水平高、NLR 升高是急性前循环 LVO 脑梗死 MT 术后 HT 发生的危险因素( $P < 0.05$ )，见表 3。运用 Empower Stats 软件中多个回归方程模块，对单因素分析筛选出来的自变量进行多因素 Logistic 回归分析，结果显示，术前侧支循环代偿程度低、术前急查外周中性粒细胞计数水平高、NLR 升高是急性前循环 LVO 脑梗死 MT 术后 HT 发生的独立危险因素( $P < 0.05$ ，表 3)。此外，为检验结果趋势稳定性，还将连续变量术前急查外周血中性粒细胞计数、NLR 按低、中、高三等分进行分组，再次进行多因素 Logistic 回归分析，结果显示急性前循环 LVO 脑梗死 MT 术后 HT 的效应值 OR 随术前急查外周血中性粒细胞计数、NLR 水平上升而升高，提示结果趋势稳定

存在( $P < 0.05$ , 表 3)。

2.2.2 平滑曲线拟合及阈值效应分析:为进一步探讨术前急查 NLR 水平与急性前循环 LVO 脑梗死 MT

术后 HT 发生风险的相关性,调整了可能影响二者关系的混杂因素后,对其进行平滑曲线拟合,结果显示术前急查 NLR 水平与急性前循环 LVO 脑梗死 MT 术后 HT 发生呈 J 型曲线关系(图 1);行阈值效应分析发现,曲线的饱和效应点为 6.3,当  $NLR < 6.3$  时,急性前循环 LVO 脑梗死 MT 术后 HT 发生风险随 NLR 水平上升而上升( $OR=2.2, 95\% CI 1.2\sim 3.8, P=0.007$ ),当  $NLR \geq 6.3$  时,急性前循环 LVO 脑梗死 MT 术后 HT 发生风险不再上升( $OR=1.0, 95\% CI 0.9\sim 1.2, P=0.446$ )。见图 1、表 4。

表 2 出血组和对照组患者临床生化指标比较  
Table 2 Comparison of clinical biochemical indexes between bleeding group and control group

生化指标	未出血组 (n=75)	出血组 (n=32)	P 值
外周中性粒细胞计数/ $(\times 10^9$ 个/L)	6.75±2.73	9.46±2.34	<0.001**
外周淋巴细胞计数/ $(\times 10^9$ 个/L)	1.38±1.69	1.03±0.42	0.247
NLR	7.06±5.06	11.12±5.93	<0.001**
外周血红蛋白/(g/L)	126.44±18.84	128.91±19.04	0.538
低密度脂蛋白/(mmol/L)	2.50±0.89	2.19±0.77	0.082
高密度脂蛋白/(mmol/L)	1.13±0.32	1.13±0.33	0.927
同型半胱氨酸/ $(\mu\text{mol/L})$	12.90±5.78	17.37±28.41	0.193
血浆 D 二聚体/(ng/L)	3.19±4.94	2.21±2.02	0.284
肌酐/ $(\mu\text{mol/L})$	72.87±22.73	78.16±28.79	0.312
尿酸/ $(\mu\text{mol/L})$	312.29±117.82	316.41±107.74	0.866

注:NLR:中性粒细胞-淋巴细胞比率,\* $P < 0.05$ ,\*\* $P < 0.001$

### 3 讨论

MT 术能延长急性 LVO 脑梗死超早期治疗时间窗,显著提高血管再通率,改善患者预后,已成为目前一线治疗方案,术后 HT 并发症发生限制了 MT 术发展。据报道,MT 术后 HT 发生率在 10%~49.5%<sup>[5-7]</sup>,其中症状性 HT 发生率约为 16.0%<sup>[10]</sup>,本研究显示 HT 发生率为 29.91%,其中症状性 HT 为 12.15%,与既往报道结果基本一致。MT 术后复查头颅 CT 显示高密度信号是一种常见现象,但对于区分是造影剂外渗还是 HT,存在一定难度。双能量 CT 是能区分二者的有效手段,它通过双能量三物质分离技术对碘进行识别,获得碘图及不含碘对比剂 CT 平扫模拟图,

表 3 急性前循环 LVO 脑梗死 MT 术后出血转化单因素及多因素 Logistic 回归分析

Table 3 Univariate and multivariate Logistic regression analysis of hemorrhagic transformation after MT in acute anterior circulation LVO cerebral infarction

变量	单因素分析		调整模式 I		调整模式 II	
	OR(95% CI)	P 值	OR(95% CI)	P 值	OR(95% CI)	P 值
基线 mRS 评分	2.41(1.03, 5.62)	0.042 0	2.41(1.03, 5.64)	0.041 6	2.40(0.98, 5.89)	0.055 3
术前侧支循环代偿程度						
差(0~1 级)	1.0		1.0		1.0	
中(2~3 级)	0.12(0.04, 0.40)	0.000 5	0.11(0.03, 0.38)	0.000 4	0.10(0.03, 0.34)	0.000 2
好(4 级)	0.06(0.01, 0.51)	0.009 3	0.06(0.01, 0.50)	0.009 1	0.07(0.01, 0.61)	0.015 9
外周中性粒细胞计数	1.50(1.23, 1.83)	<0.000 1	1.56(1.26, 1.94)	<0.000 1	1.58(1.26, 1.97)	<0.000 1
外周中性粒细胞三分组						
低中性粒细胞组	1.0		1.0		1.0	
中中性粒细胞组	5.04(1.27, 20.05)	0.021 6	5.57(1.37, 22.68)	0.016 6	5.56(1.32, 23.36)	0.019 1
高中性粒细胞组	11.00(2.85, 42.45)	0.000 5	14.42(3.45, 60.26)	0.000 3	14.63(3.42, 62.63)	0.000 3
NLR	1.14(1.05, 1.24)	0.001 8	1.15(1.05, 1.25)	0.001 5	1.15(1.06, 1.25)	0.001 5
NLR 三分组						
低	1.0		1.0		1.0	
中	5.74(1.45, 22.64)	0.012 6	5.78(1.44, 23.20)	0.013 4	6.11(1.49, 25.04)	0.011 9
高	9.84(2.55, 38.00)	0.000 9	10.21(2.62, 39.86)	0.000 8	11.58(2.87, 46.66)	0.000 6

注:调整模式 I 调整变量性别、年龄,调整模式 II 调整变量性别、年龄、高血压、糖尿病、心房纤颤、基线 NIHSS 评分、ORT

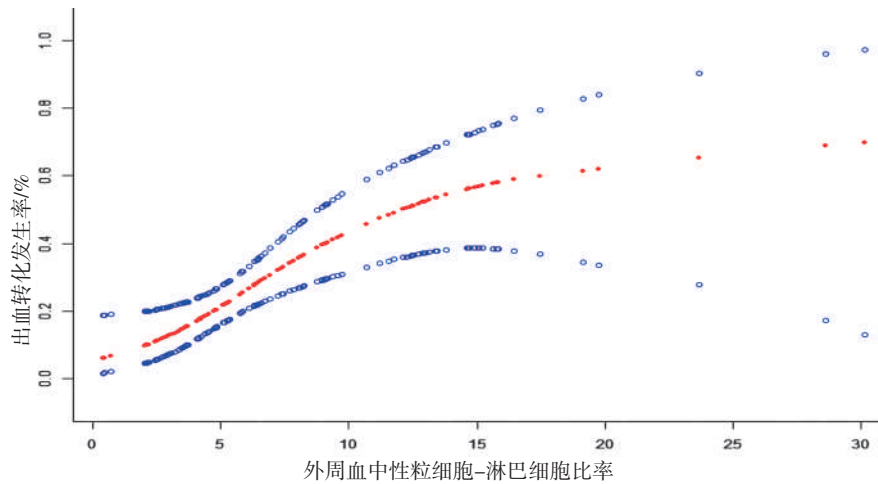


图1 术前急查NLR水平与急性前循环LVO脑梗死MT术后HT发生率的关系  
Figure 1 The relationship between the NLR level in the preoperative emergency investigation and the incidence of HT after acute anterior circulation LVO cerebral infarction after MT

表4 急性前循环LVO脑梗死NLR水平与MT术后HT相关性阈值效应分析

NLR水平拐点	OR(95% CI)	P值
模型 I	1.2(1.1, 1.3)	0.001
一条直线效应		
模型 II		
< 6.3 效应 1	2.2(1.2, 3.8)	0.007
≥ 6.3 效应 2	1.0(0.9, 1.2)	0.446
2 与 1 的效应差	0.5(0.3, 0.9)	0.019
对数似然比检验		0.007

从而实现碘化造影剂外渗和HT的鉴别<sup>[11]</sup>。据此,本研究为更真实判别HT发生,对患者术后24~72 h内均采用双能量CT复查。当前,国内外已有多项研究对ACI患者MT术后HT相关影响因素进行分析,但因纳入研究人群同质性不足、混杂因素比较单一、样本量小等问题,尚缺乏一致结论。而本研究限定研究人群为首次发病24 h内并行急诊MT术的急性前循环LVO脑梗死患者,且纳入术前、术中、术后多种可能影响因素进行分析,对术前高危人群筛选、术后用药指导、远期预后判别均有重要指导意义。

本研究显示,患者术前侧支循环代偿程度低是术后HT发生的独立危险因素。郝永刚等<sup>[10]</sup>在2017年国内一项多中心前循环LVO脑梗死MT术后HT危险因素研究中亦有类似发现,术前侧支循环评估ASITN/SIR评分<2分可增加MT术后HT发生风险。WUFUER等<sup>[12]</sup>通过系统回顾和荟萃分析研究侧

支循环状态对ACI患者溶栓结局的影响,结果显示良好的侧支循环可降低ACI患者HT发生风险。良好的侧支循环有利于维持缺血半暗带区血供,减少核心梗死区体积进一步扩大,减少缺血脑细胞诱发的血-脑屏障破坏、炎症因子释放等一系列级联反应,进而降低梗死后HT风险,改善远期预后并降低卒中再发风险等<sup>[13-14]</sup>。脑侧支循环评估方法众多,DSA因其空间分辨率高,且能动态评估侧支循环的优点,为现阶段评估侧支循环的金标准。本研究采用基于DSA的侧支循环评价系统

ASITN/SIR评分,结果显示,随着术前侧支循环开放级别提升,急性LVO脑梗死MT术后HT发生风险明显下降。因此,术前及时采取头颅MRA、CTA或DSA等措施评估侧支循环开发程度,对术前高危人群筛选、规避术后不良事件发生十分有益。

本研究表明,术前急查外周中性粒细胞计数水平高、NLR升高是急性前循环LVO脑梗死MT术后HT发生的独立危险因素,进一步曲线拟合及阈值效应分析发现,术前急查NLR水平与急性前循环LVO脑梗死MT术后HT发生风险呈J型曲线关系,且存在饱和效应点为6.3。近年来,NLR作为一种新型复合炎症标志物,已被发现与多种炎症相关疾病的病死率及不良预后密切相关,包括各种癌症、心血管疾病、败血症及代谢综合征等<sup>[15-16]</sup>。随着研究不断深入,NLR与脑卒中之间的密切关系亦被广泛关注。ZHANG等<sup>[17]</sup>研究发现,NLR对原发性脑干出血患者的90 d的不良临床结局具有重要的预测价值,且最佳预测截止点为6.65。PIKIJA等<sup>[18]</sup>研究也发现NLR是LVO脑梗死患者MT术后HT发生率和90 d病死率的独立预测因素。尽管NLR对卒中相关不良事件及临床结局的预测价值至今尚无统一论,但炎症反应在脑卒中病理生理中的关键作用能部分解释这一结论。

NLR主要由外周血中性粒细胞计数与外周血淋巴细胞计数相比换算而来,是动态反映机体先天性及获得性免疫状态的复合炎症指标<sup>[19-25]</sup>。脑卒中发生后血流停止即刻诱发炎症级联反应<sup>[20,26-30]</sup>,随着促炎症因子、趋化因子、自由基等释放,大量先天免疫细胞被招募至缺血脑组织区以触发炎症反应,中性

粒细胞通常是第一个由外周血招募至颅内的先天免疫细胞<sup>[21,31-36]</sup>,通过多种途径介导的神经毒性作用,包括分泌细胞毒性介质和促炎细胞因子,加剧氧化应激和血-脑屏障损伤,破坏神经元完整性,导致取栓后 HT 及其他不良结局发生<sup>[22,37-40]</sup>。淋巴细胞是免疫系统的主要调节因子,在宿主对病原体防御中起着关键作用。卒中后诱发的免疫抑制可使淋巴细胞计数进一步下降并发感染,进一步加重炎症反应<sup>[41-48]</sup>。因此,监测术前 NLR 变化可成为预测 MT 术后 HT 发生风险的有效措施。

本研究证实,术前侧支循环代偿程度低、术前急查外周中性粒细胞计数水平高、NLR 升高是急性前循环 LVO 脑梗死 MT 术后 HT 发生的独立危险因素,对存在上述危险因素的患者术前应充分评估及识别。另外,NLR 是临床上经济且易获得的生物学指标,可成为 MT 术后 HT 发生的有效预测因子,对精准筛查术前高危人群、术后用药指导、远期预后判别均有重要指导意义。

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