

## 外周血 MLR、NLR 与急性脑梗死的相关性研究进展

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**【摘要】** 急性缺血性脑卒中是危害我国人民生命和健康的最主要的疾病之一, 炎症反应与急性脑梗死密切相关, 炎症标志物水平的高低反映了炎症的严重程度, 尤其是外周血单核细胞与淋巴细胞比值(MLR)、中性粒细胞与淋巴细胞比值(NLR)作为近年来新兴的炎症指标, 受到了广泛的关注。现就外周血 MLR、NLR 与急性脑梗死发生、进展、预后等方面的相关性研究进行综述。

**【关键词】** 急性脑梗死; 单核细胞与淋巴细胞比值; 中性粒细胞与淋巴细胞比值; 综述

### Study on the correlation between MLR and NLR in peripheral blood and acute cerebral infarction

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**【Abstract】** Acute ischemic stroke is one of the major diseases which endanger the lives and health of people in China. Inflammatory reaction is closely associated with acute cerebral infarction, and the level of inflammatory markers reflects the severity of inflammation. Especially MLR (monocyte to lymphocyte ratio) and NLR (Neutrophil to lymphocyte ratio) in peripheral blood, as emerging indicators of inflammation in recent years, have been widely concerned. This article reviews the correlation between MLR and NLR in peripheral blood, and the occurrence, progression and prognosis of acute cerebral infarction.

**【Key words】** Acute cerebral infarction; Monocyte to lymphocyte ratio; Neutrophil to lymphocyte ratio; Review

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急性脑梗死是临床上一种常见的脑血管疾病,在我国具有高致残率、高复发率和高死亡率等特点<sup>[1]</sup>。炎症和免疫反应发生在急性脑梗死的各个阶段,急性脑梗死后的炎性反应在继发性脑损伤中发挥重要作用<sup>[2]</sup>。近年来,单核细胞与淋巴细胞比值(MLR)、中性粒细胞与淋巴细胞比值(NLR)被认为是新的炎性标志物进入了学者们的视野。首先,在临床血细胞分析验单中,单核细胞、中性粒细胞、淋巴细胞数值作为常规参数,容易获取且价格低廉;其次,MLR、NLR作为两个参数的比值,可排除单个参数受到脱水等因素的影响。因此,本文着重探讨外周血中MLR、NLR与急性脑梗死发生、进展、预后等方面的关系。

### 一、MLR与急性脑梗死

1. MLR与急性脑梗死机制: 颅内外大动脉粥样硬化是导致急性脑梗死的最常见原因,单核细胞是动脉粥样硬化过程的始动细胞与整个动脉粥样硬化过程密切相关。首先,内皮损伤学说可能是动脉粥样硬化发生、发展的重要机制之一。当动脉血管内皮细胞损伤时,单核细胞通过受损内皮细胞产生的多种促炎介质渗透和黏附于动脉壁的内侧,摄取低密度脂蛋白(LDL)和其他脂质引起炎症级联反应和泡沫细胞的形成,介导炎性介质与内皮细胞的相互作用<sup>[3]</sup>。单核细胞源性泡沫细胞在炎症或者动脉粥样硬化状态下表达高水平的组织因子,当组织因子与循环血液接触,容易形成血栓导致血管闭塞<sup>[4]</sup>。其次,巨噬细胞是单核细胞的衍生细胞,根据巨噬细胞表面抗体的表达分为M1和M2两种亚型。M1主要分泌与斑块不稳定性有关的炎性因子及蛋白酶,M2主要发挥免疫抗炎及组织修复作用<sup>[5]</sup>。目前的研究表明,不稳定斑块与薄纤维帽(少量纤维细胞、大量巨噬细胞)和大脂质核心有关<sup>[6]</sup>。凋亡的巨噬细胞会释放与坏死脂质核心密切相关的脂质及组织因子,单核细胞产生的多种溶解酶及基质金属蛋白酶(MMP)也促进了不稳定斑块的发生<sup>[7-8]</sup>。此外,炎性反应已被广泛认为是参与急性缺血性脑卒中病理生理过程的关键因素。急性脑梗死发生后,免疫细胞的浸润和促炎性因子的释放参与神经元损伤的继发性进展,从而加剧了血-脑脊液屏障的破坏。在急性脑梗死早期,大脑和外周血中可以检测到多种促炎性因子。单核细胞表面有许多可感知周围环境变化的受体,当机体组织受损或感染时,单核细胞可迅速募集到损伤或感染处并分化为巨噬细

胞或树突状细胞发挥作用。另一方面,淋巴细胞代表体内细胞和体液免疫水平,与动脉粥样硬化成反比,尤其是调节性T淋巴细胞具有显著的抗炎作用<sup>[9]</sup>。调节性T淋巴细胞是CD4 T淋巴细胞的一个亚类,在维持免疫稳态、预防自身免疫和炎症中起着重要作用。在急性脑梗死引发的相关炎性反应过程中,如果调节性T淋巴细胞功能受到抑制或缺如可能会加重炎性反应,并能够加重神经功能的缺损程度。急性脑梗死发生后,外周血中的淋巴细胞可能会通过破损的血-脑脊液屏障进入损伤的脑组织区域。所以,MLR值可间接反映急性脑梗死患者动脉粥样硬化及炎性反应的严重程度。

2. MLR与急性脑梗死发生风险: MLR值对急性脑梗死发生风险及颈动脉狭窄程度的评估具有重要价值。Liu等<sup>[10]</sup>对253例急性脑梗死患者和211例健康体检者进行回顾性分析,发现缺血性脑卒中患者的MLR值明显高于对照组。MLR值 $> 0.1958$ 是急性脑梗死发生的独立预测因子,且高水平的MLR值可能还是严重颈动脉狭窄的独立危险因素。所以,MLR值可能是诊断急性脑梗死患者颈动脉狭窄的一个潜在指标<sup>[9]</sup>。

3. MLR值与急性脑梗死的严重程度及预后: MLR值可能与急性脑梗死的严重程度及出血转化风险呈正相关<sup>[11-12]</sup>。Ren等<sup>[13]</sup>对108例接受溶栓的急性脑梗死患者进行回顾性分析,根据入院时LMR值(淋巴细胞与单核细胞比值)分为3组(第1组LMR值 $> 4.34$ ,第2组LMR值 $2.79 \sim 4.34$ ,第3组LMR值 $< 2.79$ )。结果显示,第3组患者淋巴细胞计数低于对照组( $P < 0.001$ ),单核细胞计数高于对照组( $P < 0.05$ ),LMR值与神经功能缺损程度呈负相关( $r = -0.372, P < 0.001$ )。ROC提示LMR值预测预后的敏感性(71.6%)和特异性(80.5%)中等,最佳截断点为3.48,较低水平LMR值也是急性脑梗死患者静脉溶栓后预后不良的独立预测因子。在急性脑梗死的血管内治疗方面,Lux等<sup>[14]</sup>收集了121例接受血管内治疗的急性脑梗死患者术前和术后24h的淋巴细胞和单核细胞计数等临床和实验室资料,采用多变量Logistic回归分析探讨LMR值与功能结局的关系,发现在3个月时,入院时的LMR值与预后无明显相关性;而术后24h LMR值判别不良预后的最佳临界值为2.0(80%敏感性和50%特异性),术后24h低水平LMR值是3个月功能预后不良的独立预测因子。

## 二、NLR与急性脑梗死

1. NLR与急性脑梗死相关机制:急性脑梗死可在数分钟内触发炎症反应,并持续数天到数周,甚至持续更长时间<sup>[15]</sup>。梗死区域内脑细胞的死亡导致促炎性因子的释放和免疫细胞的快速浸润。急性脑梗死早期可能会伴随着血-脑脊液屏障的破坏,使外周血中的白细胞渗入到缺血的脑组织间隙中<sup>[16]</sup>。其中,中性粒细胞已经被证明参与急性脑梗死的炎症反应<sup>[17-18]</sup>,而且是急性脑梗死后进入大脑的第一批细胞,脑梗死发生后,血源性中性粒细胞立即迁移,甚至逆着血流方向迁移,到达缺血坏死的脑组织区域<sup>[19]</sup>。目前有几种假说,中性粒细胞可能在微血管网中造成物理性堵塞,导致缺血组织血供进一步减少;另外中性粒细胞释放一系列炎症因子可导致脑损伤进一步加重<sup>[20-21]</sup>。除此之外,中性粒细胞还可能通过不同的机制促进血栓形成,包括涉及中性粒细胞胞外网络(NET)的形成、释放蛋白酶以及与小血小板的相互作用。这种血栓形成过程可能增加缺血性脑卒中的风险,并且可能在急性期进一步促进血栓形成。虽然淋巴细胞在炎症反应中发挥着重要作用,但确切地说,淋巴细胞的作用取决于淋巴细胞的亚型,B淋巴细胞在急性脑梗死造成的脑损伤中具有神经保护作用<sup>[22]</sup>。也有研究表明,部分亚型的T淋巴细胞在急性脑梗死造成的脑损伤中具有消极作用<sup>[23-24]</sup>,例如Th17细胞,在急性脑梗死发生后,Th17淋巴细胞的比例和数量显著增加,加剧了脑梗死后炎症反应程度;而NLR作为两者的比值,可以更为准确地反映急性脑梗死后继发性脑损伤及炎症反应程度。

2. NLR值与急性脑梗死发生风险:NLR值水平可能与急性脑梗死发生风险、颈动脉狭窄程度及颈动脉斑块稳定性呈正相关,并且有助于对急性脑梗死与短暂性脑缺血发作进行鉴别诊断。较高的NLR值不仅与急性脑梗死发生的高风险相关<sup>[27]</sup>,可能还是严重颈动脉狭窄的独立预测因子<sup>[25]</sup>。NLR值在预测颈动脉斑块稳定性方面也有重要的意义。Yüksel等<sup>[26]</sup>纳入了139例颈动脉狭窄(50%~70%)的无症状患者,根据颈动脉多普勒超声和CT血管造影将颈动脉斑块分为钙化组和非钙化组,对钙化斑块组( $n=73$ )和非钙化斑块组( $n=66$ )的NLR值进行比较,发现非钙化斑块组的NLR值明显高于钙化斑块组(非钙化斑块组和非钙化斑块组的NLR值分别为2.6、2.1),差异有统计学意义( $P < 0.001$ ),提示NLR

值与非钙化斑块的破裂风险呈正相关。同时,NLR值也有助于急性脑梗死与其他疾病进行鉴别,短暂性脑缺血发作患者外周血NLR值明显低于急性脑梗死患者<sup>[27]</sup>。这些证据均表明较高的NLR值为急性脑梗死的早期诊断提供了重要线索。

3. NLR值与急性脑梗死早期功能恶化及严重程度:NLR值与急性脑梗死患者的早期功能恶化及病情严重程度密切相关。较高的NLR值在预测大动脉粥样硬化型脑梗死及静脉溶栓患者的早期功能恶化方面具有重要意义<sup>[28-29]</sup>,并且与大面积脑梗死患者恶性脑水肿的风险增加有关<sup>[30]</sup>。这些临床证据有助于对早期功能恶化的高危患者进行评估和早期干预。Xue等<sup>[31]</sup>选择了280例急性缺血性脑卒中患者纳入研究,根据NLR值( $NLR < 2$ ,  $NLR=2 \sim 3$ ,  $NLR > 3$ )分为3组,采用NIHSS评分评估患者的病情严重程度,在调整潜在混杂因素后,发现入院时NLR值与卒中的严重程度相关,提示入院时的NLR值与急性缺血性卒中患者的严重程度有关。在与脑梗死体积的关系方面,NLR值可能与急性前循环脑梗死体积呈正相关,而与后循环脑梗死体积无关<sup>[32]</sup>。

4. NLR值与急性脑梗死预后:NLR值对急性脑梗死预后的预测也引起了学者们的关注,较高的NLR值可能是大面积脑梗死患者住院期死亡率的独立预测因子<sup>[33]</sup>。Ying等<sup>[34]</sup>选择了208例接受静脉溶栓治疗的急性缺血性脑卒中患者,随访3个月,分别于入院时、静脉滴注重组组织型纤溶酶原激活剂(r-tPA)后、24 h和7 d采血检测中性粒细胞和淋巴细胞计数,采用Logistic回归分析NLR值升高与脑实质出血或3个月不良预后的关系,发现NLR值的动态升高可以预测脑实质出血风险及3个月的功能预后,并且NLR值可能与伴有活动性癌症的隐源性卒中患者的预后呈负相关<sup>[35]</sup>,与接受血管内治疗的急性脑梗死患者再灌注程度也呈负相关<sup>[36]</sup>。在预测接受血管内治疗的急性脑梗死患者3个月预后方面,入院时NLR值与功能预后无明显相关性,而术后24 h高水平NLR值是预后不良的独立预测因子<sup>[14]</sup>。感染是急性脑梗死最常见的并发症之一,较高的NLR值可以预测急性脑梗死后感染的发生<sup>[37]</sup>,早期对高危人群(如高龄、长期卧床者、基础疾病多者)感染进行干预可能有效改善急性脑梗死的预后。

## 三、MLR、NLR与冠心病

截至目前,学者对MLR值、NLR值与冠状动脉病变的关系也进行了大规模的研究。Chen等<sup>[38]</sup>对

963例接受冠状动脉造影的非ST段抬高心肌梗死患者[年龄为(60.77±11.34)岁,男性758例]进行分析和随访,采用多元线性回归分析MLR与冠状动脉病变严重程度相关性,结论为MLR与冠状动脉病变严重程度独立相关,在反映冠状动脉病变严重程度方面优于NLR。循环MLR值水平也对稳定型心绞痛易损斑块的鉴别有潜在价值<sup>[39]</sup>。但在神经领域,相对于NLR值,对MLR的研究相对较少,并且目前国内外鲜有学者对两者进行敏感性及其特异性差异的研究。

#### 四、小结与展望

外周血MLR、NLR作为近年来新兴的炎性指标,与急性脑梗死的发生、发展和预后等方面密切相关。但在急性脑梗死发生时和发生后,一方面外周血MLR、NLR水平受诸多因素影响(侧支循环、应激程度及对炎症敏感性的个体化差异等);另一方面根据急性脑梗死病因的不同,MLR、NLR与其发生、发展和预后的相关性也有所不同。所以,MLR、NLR在预测急性脑梗死的发生、发展和预后等方面具有一定的局限性,且目前鲜有学者研究过MLR与颈动脉斑块稳定性的关系及两者在预测急性脑梗死发生风险、脑梗死严重程度及预后方面的敏感性及其特异性差异。所以,仍需学者们进行进一步的研究,为指导急性缺血性脑卒中的预防、高危人群的筛选及干预等临床工作做出贡献。

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