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NLR、MLR、FAR与AIS患者静脉溶栓治疗预后关系的研究进展

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摘　要

NLR (中性粒细胞与淋巴细胞比值)、MLR (单核细胞与淋巴细胞比值)以及FAR (纤维蛋白原与白蛋白比值)作为新兴的炎症指标，与多种心脑血管疾病的发生、发展及其预后有关，已越来越多地应用于脑卒中患者发病及预后研究。但目前国内鲜有关于上述指标与AIS (急性缺血性脑卒中)患者静脉溶栓治疗预后关系相关研究，本文对NLR、MLR、FAR与AIS患者溶栓治疗预后相关性研究进行总结，以期为溶栓治疗患者不良预后早期干预提供参考。

关键词

中性粒细胞与淋巴细胞比值，血小板与淋巴细胞比值，纤维蛋白原与白蛋白比值，急性缺血性脑卒中，溶栓治疗预后，综述

Research Progress on the Relationship between NLR, MLR, FAR and Prognosis of AIS Patients Treated with Intravenous Thrombolytic Therapy

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Abstract

NLR (the ratio of neutrophils and lymphocytes), MLR (monocyte and lymphocyte ratio) and FAR

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(fibrinogen and albumin ratio) as indicators of inflammation of the emerging, are associated with many kinds of occurrence, development and prognosis of disease of heart head blood-vessel, and have been increasingly used in the study of pathogenesis and prognosis of patients with cerebral apoplexy. However, there are few domestic studies on the correlation between the above indicators and the prognosis of intravenous thrombolytic therapy in patients with AIS (acute ischemic stroke). In this paper, the studies on the correlation between the prognosis of thrombolytic therapy in patients with NLR, MLR, FAR and AIS were summarized, so as to provide reference for the early intervention of poor prognosis in patients with thrombolytic therapy.

Keywords

Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, Fibrinogen to Albumin Ratio, Acute Ischemic Stroke, Prognosis of Thrombolytic Therapy, Overview

1. 引言

急性缺血性脑卒中是世界上第三大致死和致残原因[1]，在我国，脑卒中是导致死亡和残疾的主要原因[2]，越来越多的证据表明炎症反应是一把双刃剑，它不仅加重了卒中急性期继发性脑损伤，而且有利于卒中后的脑恢复[3]。NLR (中性粒细胞与淋巴细胞比值)、MLR (单核细胞与淋巴细胞比值)以及 FAR (纤维蛋白原与白蛋白比值)均为近年来提出的复合炎性指标，具有快捷、简便、经济的优点，与脑血管事件严重程度及预后相关[4] [5]。急性缺血性卒中使用重组组织纤溶酶原激活剂溶栓旨在恢复受损的血流并防止进一步的神经元损伤[6]。研究表明，AIS 患者溶栓治疗后仍可出现出血转化(HT) [7]、早期神经功能恶化等多种不良结局。为探究新型预测指标，现就 NLR、MLR、FAR 与 AIS 患者静脉溶栓治疗预后关系的相关性研究进行综述。

2. NLR 与 AIS

2.1. NLR 与 AIS 机制

炎症在 AIS 等缺血性脑损伤的发病机制中起着重要作用。在各种类型的白细胞中，中性粒细胞是最先浸润缺血脑(局灶性脑缺血 30 分钟至数小时)，最先达到峰值(1~3 天)，然后随着时间消失或迅速减少的白细胞之一[3]。在亚急性期(数小时至数天)，浸润性白细胞释放细胞因子和趋化因子，特别是 ROS (活性氧)的过度产生和 MMP (基质金属蛋白酶) (主要是 MMP-9)的诱导/激活，通过引起更广泛的激活停留细胞和白细胞浸润，进一步放大脑炎症反应。最终导致血脑屏障的破坏、脑水肿、神经元死亡和出血性转化[8] [9]。淋巴细胞于卒中随着细胞亚型的不同而显示出不同的作用。越来越多的证据表明，B 细胞也可能在调节大脑功能方面发挥重要作用[10]。调节性 B 细胞已被证明在卒中发挥保护作用[11]，而在其他模型中发现了调节性 B 细胞的早期保护作用和 B 细胞的延迟有害作用[12]。在缺血大脑中大约 40%的浸润 T 细胞是 CD4+辅助性 T 细胞，而大约 30%是 CD8+阳性细胞毒性 T 细胞，通过耗竭抗体去除这些 T 细胞组分，可减少脑梗死体积[13]，有利于卒中结果。相比之下，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[14]，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，加剧了脑梗死后炎性反应程度。NLR 作为两者比值，可准确直观地反应出 AIS 炎症反应程度与继发脑损伤情况。

2.2. NLR 与 AIS 及溶栓治疗预后

动脉粥样硬化是 AIS 的重要病理基础，其中颈动脉粥样硬化疾病占 30% [15]，无症状颈动脉狭窄患者每年发生脑卒中的风险小于 5%。症状性颈动脉狭窄导致卒中复发的风险更高，估计每年高达 15% [16]。斑块破裂、溃疡、血小板活化、血栓形成引起的动脉栓塞被认为颈动脉易损是 AIS 的发病机制，甚至在 AIS 中易损斑块破裂的风险比狭窄的严重程度更为重要[17]。NLR 是一种新的、有意义的生物标志物，与中国 AIS 患者颈动脉超声检测的颈动脉斑块易感性和存在易损斑块独立相关[18]，是颈动脉粥样硬化斑块存在和数量的强预测因子，它的使用可能有助于识别携带颈动脉斑块的风险[19]，高 NLR 是一般健康成年人缺血性卒中发病率的独立危险因素[20]。上述结果表明 NLR 可能是颈动脉斑块的独立危险因素，高 NLR 与 AIS 发生风险密切相关。大量证据显示 NLR 与 AIS 严重程度和不良预后相关：Huang LY 等[21]研究表明 NLR 与颅内动脉狭窄(ICAS)和缺血性卒中显著相关；Sun G 等[22]证实了作为炎症标志物，NLR 水平升高与颅内动脉夹层所致 AIS 3 个月预后不良相关；Nam KW 等[23]研究表明较高的 NLR 可预测急性缺血性卒中患者的卒中相关性肺炎；Zhang R 等[24]研究发现高 NLR 可以预测 AIS 患者的出血性转化和 3 个月死亡率。一项纳入了 3641 名患者的研究显示[25]，在接受 IVT 的 AIS 患者中，较高的 NLR 与出血性转化(HT)的风险增加(OR = 1.33, 95%CI = 1.14~1.56, P < 0.001)和较差的 3 个月功能结果(OR = 1.64, 95%CI = 1.38~1.94, P < 0.001)，这表明高 NLR 可成为接受 IVT 的 AIS 患者的 HT 发生风险和 3 个月功能预后不良的预测因素。

3. MLR 与 AIS

3.1. MLR 与 AIS 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。急性缺血性卒中(AIS)后，外周血单核细胞在 24 h 内浸润病灶部位，3~7 天达到高峰，并分化为巨噬细胞。传统上，单核细胞/巨噬细胞(MMs)被认为在 AIS 中扮演有害的角色，急性期减少 MMs 可减轻缺血引起的脑损伤。然而，多项研究表明 MMs 具有抗炎作用，参与血管生成，吞噬坏死神经元，促进神经血管修复[26]。单核细胞趋化蛋白(MCP-1, CCL2)及其受体 CCR2 也参与了脑缺血损伤后的炎症反应[27] [28]，且 CCL2/CCR2 轴在单核细胞募集到缺血脑中起关键作用[29] [30] [31]，中枢神经系统损伤环境中 CCR2 依赖的炎症单核细胞早期募集并随后分化为非炎症吞噬细胞是脑缺血后炎症与修复的关键机制[32]。脑卒中后，MMs 对脑缺血灶的浸润减少，脑卒中体积减少，神经元凋亡减少[33] [34] [35]，血脑屏障损伤和脑水肿减少[29]，这些研究表明 MMs 对缺血性脑卒中有一定的危害作用。然而，其他研究得出了相反的结论。有研究采用 CCR2 敲除小鼠或 CCR2 拮抗剂抑制 Ly6ChighCCR2+单核细胞进入缺血灶，导致梗死体积增大，神经功能障碍加重[10] [16] [36] [37] [38] [39] [40]，梗死后出血[32]。CXCR4 消融减少了瞬时 MCAO(短暂大脑中动脉阻断)后单核细胞浸润，这与第 3 天[41]时更高的神经功能缺损和病变体积增加有关。这表明 MMs 在缺血性脑梗死中具有有益作用。MMs 在缺血早期和恢复期的不同时间点也有不同的作用。CCR2 依赖的 MMs 被发现在急性期加重脑损伤，而在 MCAO 后的后期促进神经功能[36]。卒中后 5 天，PPARγ 驱动的巨噬细胞开始过度表达相关基因参与神经血管重建(包括血管生成和轴突再生)，促进轴突再生和脑修复[42]，这表明巨噬细胞可能在脑卒中后启动脑修复中起重要作用。因此，巨噬细胞在缺血性脑卒中后死亡神经元的吞噬和清除中发挥重要作用，促进脑炎症的解决、脑修复和神经功能的恢复。然而，MMs 也会在缺血性卒中后损伤神经元[26]。有报道称 MMs 可在缺血后损伤髓鞘。去除 MMs 可减少同侧纹状体髓鞘损伤，提示 MMs 可增加缺血后髓鞘损伤[34]，通过产生促炎细胞因子、趋化因子、活性氧和谷氨酸，浸润 MMs 会加重髓鞘损伤[43]。同时，

外周 MMs 可促进缺血后血管生成，保护缺血区域新生微血管，减少血管破裂引起的脑出血转化。因此，MMs 在缺血脑组织中可能具有双重作用，其保护作用或有害作用可能取决于损伤程度、损伤后时间和微环境。

3.2. MLR 与 AIS 及溶栓治疗预后

颈动脉狭窄主要是由颈动脉粥样硬化引起的，是缺血性脑卒中的主要发病机制，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。一项回顾性分 395 名缺血性卒中参与者的研究[44]发现，MLR 是颈动脉狭窄的独立危险因素(OR: 9.74, 95%CI: 1.16~81.54)，在 ROC 曲线分析中，MLR 的截断值 0.20 预测了颈动脉狭窄的严重程度，其敏感性为 80.40%，特异性为 26.40% (ROC 曲线下面积：0.598, 95% CI: 0.53~0.67, p = 0.004)。这表明 MLR 在缺血性脑卒中患者颈动脉狭窄中起重要作用，是颈动脉狭窄严重程度的独立危险因素。Liu H 等[45]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，且 MLR 值 > 0.1958 是 AIS 发生的独立预测因子。在 AIS 预后方面，Ren H 等[46]证实 AIS 患者入院时较低的 LMR 与 AIS 患者严重中风和 3 个月不良预后独立相关；Song Q 等[47]发现在 AIS 患者中，低 LMR 与高 HT 风险独立相关，入院 LMR 可作为 HT 的预测因素之一。另外，有证据表明，AIS 患者高 MLR 与 SAP(卒中相关性肺炎)显著相关[48]，且高 MLR 是 SAP 患者发生重症肺炎的独立危险因素[49]，对 SAP 患者发生重症肺炎具有预测价值。此外，高 MLR 与卒中后抑郁(PSD)和 PSD 严重程度增加独立相关[50]。既往研究表明，溶栓后早期神经功能预后，包括溶栓后早期神经功能恶化(END)和溶栓后早期神经功能改善(ENI)与静脉溶栓患者的预后相关[51] [52]，溶栓前 MLR 与溶栓后 END 相关[53]。一项顾性纳入 108 例接受溶栓治疗患者的研究[54]发现 LMR 值与神经功能损害程度呈负相关($r = -0.372$, $P < 0.001$)。这说明低的 MLR 值是不良预后的独立保护因素，高 MLR 值是 AIS 溶栓治疗不良预后的独立预测指标。所以，高 MLR 可能是 AIS 患者颈动脉狭窄的独立危险因素，也可能成为 AIS 患者及其溶栓治疗不良预后的独立预测因子。

4. FAR 与 AIS

4.1. FAR 与 AIS 机制

纤维蛋白原是凝血级联反应的关键组成部分，其循环水平的变化可能导致血栓性疾病，例如静脉血栓栓塞(VTE)和缺血性卒中(AIS) [55]。纤维蛋白原是脑中已知的促炎因子[56]，高纤维蛋白原是 AIS 的危险因素[57]，也是脑卒中后预后不良的因素[58] [59] [60]。这可能与 AIS 时血脑屏障通透性的增加[61] [62]，不同类型的血浆蛋白外渗到脑实质，纤维蛋白原硝基酪氨酸反应增强[63]引起凝块不稳定性增加，增加了微栓子的潜在风险[64]有关。总之，纤维蛋白原，特别是硝基纤维蛋白原，在脑卒中缺血半暗区脑组织损伤的进展中发挥了相关作用，并且决定了最终损伤的程度[63]。另一方面，大量证据表明，氧化应激介导缺氧缺血动物模型中的神经元死亡[65]，白蛋白(HSA)氧化在 AIS 患者中增加。氧化白蛋白水平与神经指标如 NIHSS 评分呈正相关[65]，AIS 患者相对较高的 HSA 水平可以降低不良预后的风险[66]，这表明脑脊液中 HSA 的氧化不仅可以作为提供氧化应激状态信息的生物标志物，而且还可能与 AIS 患者神经功能缺损严重程度以及预后相关。因此，FAR 值可间接反映 AIS 患者严重程度及预后情况。

4.2. FAR 与 AIS 及溶栓治疗预后

在缺血性卒中的发病机制中，血管内皮的变化和血小板的活化起着重要作用。这一过程导致动脉粥样硬化血栓并发症，从而导致脑梗死[67]。高血浆纤维蛋白原与总卒中风险增加相关[57] [68]。高纤维蛋白原血症已被确认为静脉和动脉血栓形成的独立危险因素，可能有助于动脉粥样硬化斑块的形成和进展

[69]。急性缺血性脑卒中后纤维蛋白原水平的升高也与脑卒中后更差的神经预后[70]和溶栓疗效降低相关[58] [59] [60]。研究表明，高纤维蛋白原水平与脑卒中后出血转化(HT) [71]、情绪障碍[72]、抑郁和认知障碍[72]、青年患者(<50 岁)较差的长期认知[73]等不良预后相关。Shi J 等[74]的研究结果表明，溶栓治疗后纤维蛋白原水平的动态增加预示着治疗后 3 个月内死亡或严重残疾的风险增加，表明血浆纤维蛋白原水平作为接受溶栓治疗的急性缺血性卒中患者短期不良预后的预测标志物具有潜在作用。低 HSA 浓度与全脑卒中、缺血性卒中、缺血性卒中亚型和脑出血的风险增加有关[75]。低 HSA 水平可能是 AIS 患者肺炎的独立预测因素[76]，是 AIS 患者静脉溶栓后 HT 的独立影响因素[77]及预测因素[78]，可预测 AIS 或 TIA 患者的功能预后和死亡率[79]，增加急性缺血性脑卒中患者的复发风险[80]。提示 HSA 水平可作为 AIS 患者溶栓治疗的预后及 HT、SAP 等预测因子。因此，FAR 作为两者比值，有理由认为 FAR 与 AIS 发生与复发风险、不良预后及溶栓治疗预后包括 HT、PSD、SAP 等有关。

5. 小结与展望

急性脑卒中是单病种致残率最高的疾病，其高发病率、高死亡率和高致残率给社会、家庭和患者带来沉重的负担和巨大的痛苦，早期采取有针对性的治疗对改善卒中患者预后具有重要意义。外周血 NLR、MLR、FAR 作为简单、可靠、易获取的炎性标志物，可能与 AIS 患者溶栓治疗的预后及 HT、PSD、SAP 等发生有关，但相关机制尚未明确。相信随着相关研究的深入，NLR、MLR、FAR 将用于预测卒中溶栓治疗患者预后及其并发症的发生，为指导急性缺血性脑卒中的预防、溶栓治疗不良预后高危人群的筛选及干预等临床工作做出贡献。

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