

新型炎症标志物与急性心肌梗死的研究进展

宋笑然^{1,2}, 魏庆民^{1*}

¹邢台市人民医院心血管内科, 河北 邢台

²承德医学院研究生院, 河北 承德

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摘要

急性心肌梗死(AMI)作为常见心血管疾病,具有起病急、病情重的特点,可引发心律失常、心力衰竭甚至猝死,严重威胁人类健康。近年研究已证实,炎症反应与AMI的发生、发展及预后密切相关,各类炎症细胞作为免疫系统的重要组成部分,参与了AMI的病理进程。本文综述了近年来炎症生物标志物在AMI中的作用,旨在为AMI的诊疗发展提供新依据。

关键词

急性心肌梗死, 炎症, 动脉粥样硬化

Research Progress on Novel Inflammatory Markers and Acute Myocardial Infarction

Xiaoran Song^{1,2}, Qingmin Wei^{1*}

¹Department of Cardiovascular Medicine, Xingtai People's Hospital, Xingtai Hebei

²Graduate School of Chengde Medical University, Chengde Hebei

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Abstract

Acute myocardial infarction (AMI) is a common cardiovascular disease with acute onset and severe conditions, which can lead to arrhythmia, heart failure and even sudden death, posing a serious threat to human health. Recent studies have confirmed that inflammatory response is closely related to the occurrence, development and prognosis of AMI. Various inflammatory cells, as an important part of the immune system, are involved in the pathological process of AMI. This article reviews the role of inflammatory biomarkers in AMI in recent years, aiming to provide a new basis for the diagnosis and treatment of AMI.

*通讯作者。

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Keywords

Acute Myocardial Infarction, Inflammation, Atherosclerosis

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1. 引言

急性心肌梗死的发病机制主要是由于动脉粥样硬化斑块出现破裂或者糜烂的情况, 这一病理变化会进一步引发冠状动脉内血栓的形成, 从而致使冠状动脉发生急性完全闭塞或者不完全闭塞的现象, 这种闭塞状况最终会导致心肌细胞处于缺血缺氧的状态, 进而引发心肌细胞坏死。在动脉粥样硬化斑块的发生、不稳定以及破裂的过程当中, 炎症反应起着极为关键的作用[1]。一旦急性心肌梗死(AMI)发生, 机体就会产生非常强烈的炎症反应, 比如说在 ST 段抬高型心肌梗死(STEMI)发作之后, 会出现免疫调节异常的情况, 并且伴随着中性粒细胞计数、C 反应蛋白(CRP)、淋巴细胞计数等能够反映全身免疫炎症状态的指标发生相应的变化, 而这些指标同样可以被用于对疾病的预后进行评估[2]-[5]。不过, 传统的炎症指标在反映炎症状态的时候存在一定的局限性, 与之相比, 新型的炎症指标能够更为敏感、更加精准地体现机体的炎症状态。

2. PLR 与 NLR

当机体遭受炎症刺激的时候, 中性粒细胞是外周血里一种最主要的白细胞类型, 在整个炎症反应过程中起着极为关键的作用。中性粒细胞能够借助趋化因子以及黏附分子的力量, 聚集在内皮发生损伤的部位, 并且与血小板产生相互作用, 这种相互作用会加强单核细胞向着受损内皮处的浸润进程。并且, 中性粒细胞还能够通过释放出细胞因子以及活性氧等物质, 促使动脉粥样硬化斑块发生破裂[6]。一项针对 815 例接受初级经皮冠状动脉介入治疗(PCI)的急性心肌梗死(AMI)患者的回顾性研究结果表明, 中性粒细胞计数或许可以成为高血栓负荷以及全冠状动脉闭塞情况下的一个独立预测因子[7]。而对于急性心肌梗死(AMI)患者而言, 其体内淋巴细胞数量减少的情况, 可能和应激反应引发淋巴细胞出现凋亡现象、对其增殖分化过程产生抑制作用存在关联[8]。中性粒细胞 - 淋巴细胞比值(NLR)是指外周血当中中性粒细胞数量与淋巴细胞绝对数量之间的比值, 血小板 - 淋巴细胞比值(PLR)是指外周血当中血小板数量与淋巴细胞绝对数量之间的比值, 这两个比值能够有效地反映出全身的炎症状态。已经有多项研究证实了 NLR 在对心血管患者不良结局事件进行预测方面具有非常重要的价值: 一项以 2618 名住院的中国急性心肌梗死(AMI)患者为对象的队列研究表明, 当中性粒细胞与淋巴细胞比值(NLR)高于 5.509 时, 和急性心肌梗死(AMI)患者住院期间死亡风险之间存在着正相关关系。此外, 还有一项规模相对较小的研究也对上述发现给予了证实, 该研究表明 NLR 是急性心肌梗死(AMI)患者主要不良心血管事件(MACE)的一个重要预测指标[9] [10]; 还有另外一项回顾性分析纳入了 806 例伴有左主干和/或三支血管疾病的急性心肌梗死(AMI)患者, 结果发现 NLR 是患者 2 年全因死亡的有效预测因子[11]。在接受经皮冠状动脉介入治疗(pPCI)的急性心肌梗死(AMI)患者群体中, 有一项多中心回顾性队列研究发现, 高血小板淋巴细胞比值(PLR)与严重心力衰竭、院内主要不良心血管事件(MACEs)以及心肌再灌注不足等情况有关联, 并且是一个独立的危险因素。除此之外, 高 PLR 组患者植入支架的平均直径明显更小, 血栓抽吸量更大, 血小板计数更高。另外, 经皮冠状动脉介入治疗(PCI)之后, 这些患者的心肌梗死溶栓治疗(TIMI)分级和心肌灌注分级

(MBG)显著更低[12]。在 ST 段抬高型心肌梗死(STEMI)患者当中, 冠状动脉无复流现象的发生和临床预后不佳存在关联。在 200 例接受 pPCI 的 ST 段抬高型心肌梗死(STEMI)患者当中, 无复流组的 PLR 明显高于正常复流组[13]。PLR-NLR 联合指标对于急性心肌梗死(AMI)患者的预后评估有着重要意义, 这个联合指标数值越高, 主要不良心血管和脑血管事件(MACCE)发生率就越高, GRACE 评分风险等级越高, 生存率越低, 预后也就越差[14]; 而且这两个指标联合起来可以有效预测急性心肌梗死(AMI)患者院内死亡风险[15]。最新的一项研究结果显示, 术前中性粒细胞淋巴细胞比值(NLR)和血小板淋巴细胞比值(PLR)是急性冠脉综合征(ACS)患者经皮冠状动脉介入治疗(PCI)后发生对比剂肾病(CIN)风险的有效预测标志物。特别是在非 ST 段抬高型心肌梗死(NSTEMI)患者当中, NLR 的预测表现更为突出。对于慢性肾脏病(CKD)合并急性心肌梗死(AMI)的患者来说, 炎症标志物升高会提高主要不良心血管和脑血管事件(MACCE)的发生风险, 其中, NLR 是一个独立并且更具优势的预后预测指标[16] [17]。血小板淋巴细胞比值(PLR)和中性粒细胞 - 淋巴细胞比值(NLR)作为简单、廉价的生物标志物, 能够有效预测非 ST 段抬高型心肌梗死(NSTEMI)和不稳定型心绞痛(UA)患者的高风险 HEART 评分, 尤其适用于资源有限的地区, 在临床风险分层和及时干预方面起到辅助作用[18]。上述所有的结果都支持血小板淋巴细胞比值(PLR)、中性粒细胞 - 淋巴细胞比值(NLR)能够有效预测冠状动脉不良结局及严重状况, 作为简便易获取的炎症指标, 更加适合基层医院用来评估急性心肌梗死(AMI)患者预后。

3. SII 与 SIRI

系统免疫炎症指数(Systemic immune-inflammation index, SII)这一概念最早是由 Hu 等人[19]提出。它的计算方法是将(中性粒细胞计数 $\times$ 血小板计数)/淋巴细胞计数, 而全身免疫炎症反应指数(SIRI)的计算公式为(中性粒细胞计数 $\times$ 单核细胞计数)/淋巴细胞计数。这两个指标综合了外周血中的中性粒细胞、淋巴细胞、单核细胞以及血小板的计数情况, 能够有效地反映出全身炎症反应与免疫反应之间的平衡状态。臧建波等人[20]在他们的研究当中有了重要发现, 即 SII 的升高与急性心肌梗死(AMI)患者在接受经皮冠状动脉介入治疗(PCI)术后的死亡风险增加有关, 并且还主要不良心血管事件(MACE)的发生率增加相关, 当把 SII 与全球急性冠状动脉事件注册(GRACE)评分联合起来使用时, 可以提高 GRACE 评分对 AMI 患者 MACE 的预测价值。对于合并有高血压的 AMI 患者而言, SII 与患者 30 天、365 天的全因死亡率存在联系, 同时也与充血性心力衰竭、心源性休克的发生相关, 并且随着 SII 数值的升高, 患者的死亡率也会相应地增加[21]。另有一项研究针对来自 MIMIC-IV 数据库中的 2784 名急性心肌梗死(AMI)患者开展了回顾性分析。研究结果表明, SII 和 SIRI 是 AMI 患者住院期间以及短期死亡率的独立风险因子。如果能够对这些标志物进行监测, 就可以优化对患者的风险评估工作以及临床管理工作[22]。另外, SII 和 SIRI 还是 AMI 患者冠状动脉病变程度的独立危险因素, 并且与冠状动脉病变程度(Gensini 评分)呈正相关关系[23]。SII 和 SIRI 还与 AMI 患者术后 MACE 的发生有着显著的相关性, 并且对 MACE 具有预测价值, 同时它们还与 GRACE、Gensini、QTc 等风险因素存在关联[24]。Jin 等人开展了一项针对 85154 人的前瞻性大型队列研究, 该研究的中位随访时间为 10 年。研究结果显示, 系统免疫炎症指数(SII)和全身免疫炎症反应指数(SIRI)的数值越高, 则患上卒中和心血管疾病(CVD)的风险也就越高[25]。还有一项大型前瞻性研究着重分析了 SII 和 SIRI 的动态状态与 CVD 风险之间的关系, 将二者分为了“低稳定型”“中等稳定型”“增加型”“减少型”这 4 种轨迹模式。研究结果显示, 与“低稳定型”相比, “中等稳定型”和“上升型”会显著增加 CVD 风险, 然而“下降型”则没有显著差异, 这一结果提示我们 SII 和 SIRI 的动态状态与 CVD 风险有着非常密切的联系[26]。随着研究的不断深入, SII 和 SIRI 在 AMI 风险分层以及个体化治疗方面的应用前景将会变得越来越广阔。不过, 在未来还需要更多的前瞻性、多中心的临床研究来进一步验证它们的最佳临界值以及与其他生物标志物联合应用的价值。

4. C 反应蛋白与白蛋白比值(CAR)与 CALLY 指数

炎症反应在动脉粥样硬化病变的发生、发展以及演变过程中扮演着极为关键的角色。C 反应蛋白(CRP)作为一种由肝脏合成的急性时相反应蛋白,它不仅仅是冠心病的一项重要危险因素,还有可能直接参与急性心肌梗死(AMI)的病理生理过程之中。具体而言,CRP 通过诱导黏附分子的表达、降低内皮型一氧化氮合酶的表达水平与活性、增加纤溶酶原激活物抑制剂-1 的活性等方式,进一步加剧冠状动脉粥样硬化的进程以及血栓的形成,从而促进急性心肌梗死的发生和发展[27]-[30]。血清白蛋白这一指标,是用于评估机体营养状况或者炎症反应的常规指标,现已证实是急性心肌梗死(AMI)患者不良结局的一个显著预测指标。并且,这一指标不受急性心肌梗死临床严重程度及其亚型(ST 段抬高型心肌梗死/非 ST 段抬高型心肌梗死)的影响,在远期预后的评估方面具有相当重要的价值[31]。临床研究已经证实,心肌梗死后 C 反应蛋白(CRP)水平升高与复发性冠状动脉事件(例如非致死性心梗、致死性冠脉事件)风险增加存在相关性,处于最高五分位数的患者的相应风险相比于最低五分位数的患者高出 75% [32]。在非 ST 段抬高急性冠脉综合征(NSTACS)患者群体中,C 反应蛋白(CRP)大于 10 mg/L 的患者其 4 年生存率(78%)明显低于 C 反应蛋白(CRP)小于 3 mg/L 的患者(92%),而且 C 反应蛋白(CRP)是长期死亡率的一个独立预测因子[33]。对于经皮冠状动脉成形术(PTCA)来说,术前 C 反应蛋白(CRP)大于 0.3 mg/dL 的患者,其早期并发症(如急性闭塞、缺血复发)的发生率高达 22%,1 年的临床再狭窄率更是达到 63%,这显著高于正常组的相关数据[34]。C 反应蛋白与白蛋白比值(CAR)是急性冠脉综合征(ACS)患者高 SYNTAX 评分(SS)和高 SYNTAX 评分 II 的独立预测因子,并且其预测效能要优于单独使用 C 反应蛋白(CRP)或者白蛋白的情况[35]。同时,它也是 ST 段抬高型心肌梗死(STEMI)患者住院及长期全因死亡率的独立预测因子,与血栓负荷、急性肾损伤等存在关联[36]。在非 ST 段抬高型心肌梗死(NSTEMI)病例中,C 反应蛋白与白蛋白比值(CAR)对冠状动脉疾病(CAD)严重程度的预测效能优于中性粒细胞与淋巴细胞比值(NLR) [37]。CALLY 指数是一种整合了 C 反应蛋白(CRP)、白蛋白和淋巴细胞计数的综合性生物标志物,能够全面地反映出患者的炎症反应、营养状况以及免疫状态等情况。Iida 等人[38]首次提出了这个指数,并且发现低 CALLY 指数与肝细胞癌患者肝切除术后生存率差存在相关性。尽管 CALLY 指数在不同癌症中的预测价值已经被证实[39]-[43],但是在心血管事件中的相关研究却比较少。Ying Pan 等人在 2024 年的研究发现,CALLY 指数与冠心病(CAD)患者经皮冠状动脉介入治疗(PCI)术后不良临床结局存在相关性[44];并且对 ST 段抬高型心肌梗死(STEMI)患者短期及长期的主要不良心血管事件(MACE)均具有保护作用[45]。目前国内,对于 CALLY 指数的研究正处于发展阶段,其在心血管领域的临床应用价值仍然需要进一步深入探索。

5. 泛免疫炎症值(PIV)

泛免疫炎症值(pan-immune-inflammation value, PIV)这一概念是在 2020 年被首次提出,它是一种全新的生物标志物。这一标志物通过将中性粒细胞、单核细胞、淋巴细胞以及血小板计数进行整合,从而能够以一种非常直观的方式反映出促炎过程与抗炎过程之间所存在的动态平衡状态[46]。具体来说,其计算公式为: $PIV = \text{中性粒细胞计数} \times \text{单核细胞计数} \times \text{血小板计数} / \text{淋巴细胞计数}$ 。大量的研究表明,在患者群体当中,那些具有较高 PIV 值的患者,其主要不良心血管事件(MACE)的发生率明显要比低 PIV 组的患者高得多。并且,PIV 还是 ST 段抬高型心肌梗死(STEMI)患者在接受经皮冠状动脉介入治疗(PCI)术后发生 MACE 的一个独立预测因子[47]。在对 ST 段抬高型心肌梗死患者进行 PCI 治疗之后的住院预后情况以及严重冠状动脉狭窄状况的预测方面,PIV 的表现要优于系统免疫炎症指数(SII)、血小板与淋巴细胞比值(PLR)和中性粒细胞与淋巴细胞比值(NLR) [48] [49]。此外,当涉及到对 1 年全因死亡率和 1 个月全因死亡率的预测时,PIV 同样展现出比中性粒细胞与淋巴细胞比值(NLR)、血小板与淋巴细胞比值(PLR)和系统免疫炎症指数(SII)更优越的性能,它是 ST 段抬高型心肌梗死患者死亡率的一个独立预后因素[50]。

这些研究成果都表明, PIV 可以作为一种有效的工具, 用于预测 ST 段抬高型心肌梗死高危患者的情况。如果能够在临床实践中监测 PIV 的水平, 那么就有助于指导临床医生进行早期干预, 进而改善患者的预后情况。然而, 就目前的状况而言, 有关 PIV 与心血管疾病(CVD)之间关联的研究还处于刚刚起步的阶段。现有的研究大多采用的是单中心、回顾性的研究设计, 所以 PIV 与心血管疾病之间的相关性仍然需要通过大规模多中心的前瞻性研究来进一步验证。

6. 总结与展望

总之, 新型炎症标志物为 AMI 的精准诊疗开辟了新路径, 未来通过多学科、多维度的研究, 有望进一步挖掘其临床价值, 推动 AMI 从“经验性治疗”向“个体化风险分层指导下的精准治疗”转变, 最终降低 AMI 的死亡率与不良心血管事件发生率, 改善患者长期生存质量。

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