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中性粒细胞/淋巴细胞在脓毒症中的免疫病理作用及诊断和预后价值

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摘　要

脓毒症是对感染的反应失调引起的危及生命的器官功能障碍。在脓毒症的免疫病理机制中，先天免疫系统和适应性免疫系统都起到了重要作用。中性粒细胞/淋巴细胞(NLR)作为一种新兴的炎症标志物，反应了先天(中性粒细胞)和适应性细胞免疫反应(淋巴细胞)之间的关系。同时与其他生物标志物相比，NLR具有容易获得、易于重复且低成本的特点。本文将会就中性粒细胞/淋巴细胞在脓毒症中的免疫病理以及其在诊断、预后等方面的价值研究进行综述。

关键词

脓毒症，中性粒细胞/淋巴细胞，免疫病理，诊断，预后

Immunopathology of Neutrophil to Lymphocyte Ratio in Sepsis and Its Diagnostic and Prognostic Value

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Abstract

Sepsis is a life-threatening organ dysfunction caused by the imbalance of response to infection. In the immunopathological mechanism of sepsis, both the innate immune system and the adaptive

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immune system play an important role. As a new inflammatory marker, neutrophil to lymphocyte ratio (NLR) reflects the relationship between congenital (neutrophil) and adaptive cellular immune response (lymphocyte). At the same time, compared with other biomarkers, NLR is easy to obtain, easy to repeat and low cost. This article will review the immunopathology of neutrophils/lymphocytes in sepsis and its value in diagnosis and prognosis.

Keywords

Sepsis, Neutrophil to Lymphocyte Ratio, Immunopathology, Diagnosis, Prognosis

1. 引言

脓毒症是一个全球性的公共健康问题，且具有重要的经济影响。根据一份全球疾病负担报告估计：在 2017 年全球有 4890 万脓毒症病例，其中有 1100 万死亡病例，占全球死亡人数的 19.7% [1]。在中国，五分之一的 ICU 患者患有脓毒症，其 90 天死亡率为 35.5% [2]。同时有研究显示中国 30 天脓毒症的平均死亡率 29.5%，高于欧洲和北美 24.4% [3]。据估计，中国 ICU 收治的 23 万脓毒症患者每年的医疗费用约为 46 亿美元，这是一个巨大的医疗和社会负担[4]。脓毒症的早期诊断和治疗对于提高患者生存率和降低医疗费用至关重要。为此许多生物标志物都已被用于脓毒症的研究，但大部分都受到了限制，例如中等的诊断和预后准确性、检测时间长和高成本等[5]。

中性粒细胞/淋巴细胞(NLR)是一个由中性粒细胞绝对计数除以淋巴细胞绝对计数获得的比率[6]。NLR 反映了先天性(中性粒细胞)和适应性(淋巴细胞)免疫反应之间的平衡，通常以中性粒细胞增加和淋巴细胞减少为特征[6] [7]。NLR 是一种容易获得且低成本的生物标志物，目前它已被广泛地应用于评估多种疾病的诊断或者预后，例如脑出血[8]、心血管疾病[9]、实体肿瘤[10]、新冠肺炎[11]以及脓毒症等[12]。此外，血常规中的其它参数如红细胞分布宽度(RDW) [13]、单核细胞分布宽度(MDW) [14]、平均血小板体积(NPV) [15]和血小板/淋巴细胞[16]等也都在脓毒症中得到了研究。

2. 脓毒症的免疫病理机制

脓毒症是由宿主对感染的反应失调引起的危及生命的器官功能障碍，以过度炎症和免疫抑制为特征[17]。就其失调的免疫反应而言，先天性免疫系统和适应性免疫系统都受到了影响。感染后，先天免疫细胞如巨噬细胞、树突状细胞和中性粒细胞等通过模式识别受体(pattern recognition receptors, PRRs)识别病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)启动了不同的信号通路，进而多种转录因子如 NF-KB 和干扰素调节因子被激活[18]。最后这些转录因子通过转录相关靶基因如促炎细胞因子诱导炎症反应。免疫反应的程度取决于宿主(如年龄、遗传、合并症和药物等和病原体(如微生物载量和毒力等) [19]。脓毒症与先天免疫系统过度激活导致的“细胞因子风暴”或者过度炎症相关，最终这可导致多器官功能障碍[20] [21]。此外，补体系统、凝血系统和内皮系统的激活也参与了脓毒症的炎症反应[17]。同时树突状细胞和其他免疫细胞通过向 T 淋巴和 B 淋巴细胞呈递抗原触发适应性免疫系统，进而导致病原体特异性的抗体和免疫记忆的产生[19]。脓毒症诱导的免疫抑制以 T 细胞、B 细胞和树突状细胞的凋亡、T 细胞的衰竭、调节性 T 细胞和髓

源性抑制细胞的扩增以及抗原呈递细胞(如单核细胞和巨噬细胞)的重编程导致的 HLA-DR 表达降低和产生促炎细胞因子的能力降低为特征，这表明免疫抑制同样也影响了先天免疫系统和适应性免疫系统[17]。免疫抑制与脓毒症患者对由机会性病原体和病毒在活化引起的继发感染的易感性增加相关[19]。总之，脓毒症的免疫病理机制是非常复杂的，过度炎症和免疫抑制以及先天性和适应性免疫系统都是同样重要的，并代表了改善脓毒症结局的潜在免疫治疗靶点[22]。

3. 中性粒细胞/淋巴细胞在脓毒症中的免疫病理作用

3.1. 中性粒细胞在脓毒症中的免疫病理作用

在脓毒症中，中性粒细胞起着矛盾的作用。中性粒细胞是重要的先天免疫细胞，通过其快速迁移到感染部位的能力，提供宿主防御脓毒症的第一道防线[23]。中性粒细胞在体内的迁移包括四个不同的阶段：从骨髓中动员和释放、边缘和滚动、粘附和游出，这些阶段在脓毒症时都受到损害[24]。另外中性粒细胞还可以从炎症部位迁移回血液循环中，这一现象称为中性粒细胞逆向迁移(PMN rM) [25]。PMN rM 既可以通过促进先天免疫反应的有效解决起到保护作用，也可能通过炎症的播散造成组织损伤[26]。在到达感染部位后，中性粒细胞除了通过吞噬、脱粒和释放 ROS 外并能产生中性粒细胞外陷阱(NETs)消灭病原微生物[26]。NETs 是由 DNA-组蛋白复合物和活化的中性粒细胞释放的蛋白质组成的网状结构[27]。NETs 可以杀死细菌、真菌、病毒和寄生虫等病原体来保护宿主免受感染[28]。除了杀死病原微生物外，越来越多的证据表明，NETs 对脓毒症诱导的多器官损伤的发病机制有显著影响，包括动脉低血压、低氧血症、凝血病以及肾、神经和肝功能障碍[29]。中性粒细胞一种寿命比较短的免疫细胞，在人类中其循环半衰期为 6~8 小时[30]。在正常情况下，中性粒细胞通过凋亡死亡，这是一种程序性死亡[31]。但在脓毒症期间，中性粒细胞的自发凋亡受到抑制，并可能出现了一些其他类型的细胞死亡，包括坏死、坏死性凋亡、细胞焦亡和自噬等，同时这些细胞死亡类型并非都对宿主起到积极的保护作用，它们也有可能会加重炎症[31]。此外由于循环中未成熟中性粒细胞细胞的释放和循环中中性粒细胞凋亡的延迟，脓毒症患者通常具有不同程度的循环中性粒细胞数量显著增加[32]。

3.2. 淋巴细胞在脓毒症中的免疫病理作用

淋巴细胞是适应性免疫系统的重要细胞。在脓毒症中，淋巴细胞的数量和功能都受到了影响，同时正如前面所言，淋巴细胞参与了脓毒症诱导的免疫抑制。就淋巴细胞的数量而言，不仅在脓毒症患者的尸检研究中发现脾、肠等组织器官的淋巴细胞存在丢失，而且在脓毒症期间，循环淋巴细胞绝对计数也出现了减少[33]。脓毒症患者的严重或者持续的淋巴细胞减少与死亡率增加相关[34]。脓毒症患者的淋巴细胞减少通常是由细胞凋亡诱导的[35]，这种细胞凋亡可能与多种触发因素激活的死亡受体和线粒体途径相关[36]。脓毒症中细胞凋亡增加的病理生理学的重要性已在某些动物模型中得到体现，即通过抑制细胞凋亡的干预措施可以提高生存率[37]。值得注意的是，外渗和募集到炎症部位也可能是脓毒症中持续淋巴细胞减少的原因之一[37]。然而在脓毒症患者中，循环调节性 T 细胞的百分比显著增加，这在脓毒症诱导的免疫抑制中也起到重要作用[38]。另外就淋巴细胞的功能而言，T 细胞衰竭是 T 细胞功能障碍的一种状态[39]。衰竭的 T 细胞具有受损的效应功能、增加的抑制性免疫检查点分子的表达和独特的转录状态[40]。其中临床前和临床研究表明，特异性细胞表面抑制性免疫检查点受体和配体，包括 PD-1、PD-L1、CTLA4、BTLA、TIM3、OX40 和 2B4，通过介导宿主免疫能力和免疫抑制之间的良好平衡，在脓毒症的病理生理学中发挥重要作用[41]。同时针对免疫检查点的疗法在脓毒症患者的治疗中具有潜在的临床应用潜力[41]。

4. 中性粒细胞/淋巴细胞在脓毒症诊断和预后中价值

4.1. 中性粒细胞/淋巴细胞在脓毒症诊断中的价值

在急诊科，脓毒症的患病率约为 1.2% [42]。Ljungström 等研究纳入 425 名急诊脓毒症患者，结果发现：NLR 和 PCT 诊断菌血症的敏感性分别为 80%、66%，诊断严重败血症伴菌血症的敏感性分别为 85%、70%，诊断严重败血症但无菌血症的敏感性分别为 71%、61 [43]。Hou 等人纳入了在急诊科就诊的脓毒血症患者 296 例和非脓毒血症患者 1184 例，结果显示：当 NLR 的截断值大于 9 时，其诊断脓毒症的 AUC 为 0.707，敏感性为 69.6，特异性为 71.9。同时该研究构建了一个由 NLR > 9 时评分为 2 和 qSOFA > 1、PLR > 210 以及 MDW > 20 时评分为 1 组成的评分系统模型，且该模型显示出中度至高度的诊断准确性(AUC: 0.755, 95% CI: 0.726~0.784) [44]。另外由于手术和侵入性操作，ICU 患者也是脓毒症的高危人群[42]。Tian 等共纳入 ICU 脓毒症患者 194 例对 PCT、CRP、NLR、CRP*PCT 等在脓毒症中诊断价值进行了研究，结果表明：NLR 诊断脓毒症的价值属于中等水平(ROC：0.78 敏感性：1.87%，特异性：72.84%)，并同时发现 CRP*PCT 诊断价值最好(AUC：0.915 敏感性：90.62%，特异性：81.48%) [45]。然而 Kim 等人纳入了 276 例 ICU 脓毒症患者和 388 例 ICU 非脓毒症患者，研究发现：与 CRP 和 PCT 相比，NLR 对于 ICU 患者脓毒症的诊断准确性较低(AUC：0.66，敏感性：65.7%，特异性：53.0%)，但明显高于白细胞计数和中性粒细胞计数[46]。此外，在一项前瞻性观察性研究中发现第一天的 NLR 可作为脓毒症的一个有用的诊断标志物(敏感性：87.5%，特异性：90%) [47]。同样在一项回顾性研究中也发现 NLR 具有良好的脓毒症诊断准确性，该研究结果显示：当 NLR 的最佳截断值为 7.97 时，其 AUC、敏感性、特异性、PPV 和 NPV 分别为 0.74%、64.26%、80.16%、86.49%和 53.18%，并且当其与其他生物标志物联合时能获得更好的诊断价值[48]。

4.2. 中性粒细胞/淋巴细胞在脓毒症预后价值

NLR 与脓毒症患者的相关死亡率有关，其中相对较少的研究发现 NLR 可预测住院死亡率[49] [50]，但是 Chebl 等人的一项前瞻性研究发现 NLR 的最佳临界值与脓毒症患者的住院死亡率无关[51]。此外较多的研究探讨了 NLR 与脓毒症患者 28 天死亡率的关系。Ye 等人共纳入 3043 例脓毒症患者，根据 NLR 的四分位数分成 4 组，在多变量 COX 回归分析中发现第四个四分位数(NLR (>20.25)与成人脓毒症患者 28 天全因死亡率增加相关(HR 1.22, 95% Cl: 1.01~1.49, P = 0.046) [52]。Li 等人首次将 NLR 与 SOFA 评分结合来确定脓毒症患者的危险因素，结果发现 SOFA 评分 + NLR 是脓毒症患者 28 天死亡率的危险因素(OR 1.455, 95%CI: 1.318~1.605, P < 0.001) [53]。其他几项研究也都发现 NLR 是脓毒症患者 28 天死亡率的独立预测因子[54] [55] [56]。一项回顾性研究还探讨了 NLR 的动态变化(第 1、3、5、7 天)对腹腔感染所致脓毒症患者 28 天死亡率的的预测价值，在调整混杂因素后多变量 COX 回归显示：第 7 天的 NLR 是脓毒症患者 28 天死亡率的独立预测因子(HR: 0.773, 95%CI: 0.659~0.905, P = 0.001) [57]。此外，一项前瞻性研究发现 NLR 与通过 SOFA 评分评估的脓毒症严重程度(R = 0.65)以及广泛研究的脓毒症预后标记物 press sin (R = 0.56)显著相关，因此该研究认为 NLR 可能成为 ICU 脓毒症患者预后的有用工具[58]。更重要地是 Huang 等人进行的一项包括 14 项研究共有 11,564 名脓毒症患者的荟萃分析显示非存活者的 NLR 显著高于存活者的 NLR (SMD: 1.18, 95% CI: 0.42~1.94, P = 0.002)，而且较高的 NLR 与脓毒症患者的预后不良相关(HR: 1.75, 95% CI: 1.56~1.97) [59]。

4.3. 中性粒细胞/淋巴细胞在脓毒症其他方面的研究

在并发症方面，已经研究表明 NLR 是脓毒症患者急性肾损伤的独立预测因子[60] [61] [62]。在治疗

方面，有研究发现 NLR 可以预测脓毒症患者的抗生素反应性，且该研究建议使用前 3 天的 NLR 来评估抗生素治疗[63]。此外激素在脓毒症的治疗中常常起到了重要作用。那么有没有一种简单且快速的指标来判断什么情况下需要使用激素呢？在一项包括 12,862 名住院新冠肺炎患者的大样本回顾性分析中发现，入院 NLR 值 > 6.11 的患者，皮质类固醇治疗与降低 60 天全因死亡率的风险相关，而在 NLR ≤ 6.1 的患者中，皮质类固醇治疗与死亡率降低无关[64]。这项研究说明 NLR 决定了皮质类固醇治疗新冠肺炎患者的临床疗效，该指标可能有助于做出开始皮质类固醇治疗的临床决策[64]。皮质类固醇在各种炎症性疾病中的使用是基于能够抑制系统性炎症和细胞因子风暴[64]。由此看来，NLR 也可能成为脓毒症患者应用类固醇激素治疗的一个重要参考指标，但这就需要我们进一步通过研究来证实。

5. 结论

脓毒症具有较高的发病率和死亡率，且具有重要的经济负担，因此促进它的诊断和识别预后不良的患者对于改善脓毒症的管理和降低医疗成本是非常重要的。脓毒症的免疫病理机制涉及多种先天和适应性免疫细胞。NLR 是一种容易获得且低成本的生物标志物，其本身或者联合其他指标在脓毒症的诊断和预后中具有重要的价值，但是还需要大样本量的前瞻性研究来进一步明确其临床意义。

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