Hans 汉斯

中性粒细胞与淋巴细胞比值与病毒感染性疾病的研究进展

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摘 要

传统上认为中性粒细胞作为固有免疫的主力军在抵抗细菌和真菌方面起作用，越来越多的研究发现中性粒细胞在遏制和消除病毒感染方面也发挥重要作用。在很多病毒感染性疾病中，中性粒细胞增多可能标志着疾病进展。近年来与中性粒细胞相关的一种新的免疫激活标志物——中性粒细胞与淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)备受人们关注。它结合了固有免疫和适应性免疫两方面，具有良好预测病情严重程度和评估临床预后的价值，并且被认为比单独中性粒细胞绝对计数或淋巴细胞绝对计数更加稳定可靠。NLR已经在很多感染性疾病中被报道，本文将重点综述COVID-19、病毒性脓毒症、SFTS、CCHF、AIDS等病毒感染中NLR的研究进展。

关键词

中性粒细胞与淋巴细胞比值(NLR)，感染性疾病，病毒感染，预测

Research Progress of Neutrophil to Lymphocyte Ratio and Viral Infectious Diseases

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Abstract

Traditionally, neutrophils have been considered a major force in innate immunity, playing a role in resistance to bacteria and fungi. A growing body of research has found that neutrophils also play an influential role in containing and eliminating viral infections. In many viral infectious diseases, neutropenia may signal disease progression. In recent years, neutrophil to lymphocyte ratio (NLR), a new immune activation marker associated with neutrophils, has attracted much attention. It combines both innate and adaptive immunity, is of good value in predicting disease severity and assessing clinical prognosis, and is considered more stable and reliable than absolute neutrophil counts or absolute lymphocyte counts alone. NLR has been reported in many infectious diseases. This paper will focus on the progress of NLR in COVID-19, viral sepsis, SFTS, CCHF, AIDS and other viral infections.

Keywords

Neutrophil to Lymphocyte Ratio (NLR), Infectious Diseases, Viral Infection, Forecasting

1. 引言

中性粒细胞是循环中最丰富的白细胞，约占外周血白细胞的 50%~70%，是抵御感染和维持组织稳态的第一道防线[1]。传统上认为淋巴细胞参与适应性免疫在抗病毒方面发挥重要作用，中性粒细胞作为固有免疫的主力军在细菌、真菌感染中起重要作用。近些年，研究发现中性粒细胞在识别和消除病毒感染中也发挥重要作用[2] [3] [4] [5]。在病毒感染期间，中性粒细胞主要参与早期抗病毒防御，中性粒细胞由粒细胞集落刺激因子、白细胞介素-6、白细胞介素-8 等介导增殖和迁移到感染部位[6]。除了吞噬病毒外，中性粒细胞还可以产生细胞因子限制病毒的复制和释放 NETs 捕获并杀灭病毒[7]。有研究发现，中性粒细胞表达广谱的病原体识别受体(pathogen recognition receptors, PRRs)，用于识别病毒中的病原体相关分子模式(pathogen-associated molecular patterns)以诱导免疫反应[3]。此外，中性粒细胞在抗病毒反应期间可以充当抗原呈递细胞，促进与 T 细胞的双向串扰来增强或抑制适应性免疫反应过程[7] [8]。中性粒细胞与适应性细胞之间通过 Toll 样受体(Toll-like receptors, TLRs)和 I 型干扰素进行复杂的串扰[3]。同时，中性粒细胞还有促炎功能，在病毒感染期间，适当的宿主免疫对于维持和恢复稳态至关重要，但是中性粒细胞过度增加可能会导致持续的免疫激活和组织损伤[4]。

研究发现，中性粒细胞功能障碍是一种重要的反映病情严重的标志物，它参与某些病毒感染的病理过程[9]。在很多病毒感染性疾病中，中性粒细胞增多可能标志着疾病进展。近些年与中性粒细胞相关的一种新的生物标志物——中性粒细胞与淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)，它结合了固有免疫和适应性免疫两方面，被认为比单独中性粒细胞绝对计数或淋巴细胞绝对计数更加稳定可靠[10] [11]。

NLR 是一种新兴的生物标志物，是中性粒细胞绝对计数除以淋巴细胞绝对计数得到的值，它反映了固有免疫(中性粒细胞)和适应性免疫(淋巴细胞)之间的平衡[12]。NLR 这个综合指标认为比单独的中性粒细胞绝对计数或淋巴细胞绝对计数更加稳定可靠[10] [11]，它还具有相对便宜、简单、快速、容易获得的优势。NLR 受多种因素的影响，包括性别、年龄、种族、药物和慢性疾病等[13]，比如，女性 NLR 普遍

高于男性(男性和女性的所有年龄段的平均 NLR 分别为 1.63 和 1.66)，亚洲人的 NLR 普遍低于其他种族[14]。全世界不同种族健康成年人 NLR 正常值的中位数为 1.65 (范围为 1.2~2.15)，成人高于 3 或者低于 0.7 为病理状态，而且 NLR 的动态变化通常早于临床状态数小时，是一个很好的应激和全身炎症的有效标志物[13]。本文将重点综述 COVID-19、病毒性脓毒症、SFTS、CCHF、AIDS 等病毒感染中 NLR 的研究进展。

2. NLR 与 COVID-19

新型冠状病毒感染(corona virus disease 2019, COVID-19)是由严重急性呼吸综合征冠状病毒 2 型 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)感染引起的一种严重急性呼吸道传染病[15]。COVID-19 患者病情严重程度与肺中性粒细胞浸润增加和外周血中性粒细胞水平升高有关[9] [16]。而且，淋巴细胞减少也是危重患者的显著特征，淋巴细胞的明显减少可以预测 COVID-19 病情严重程度[16]。淋巴细胞的减少可能与病毒直接感染淋巴细胞或抗病毒反应抑制骨髓造血有关[17]。除此之外，细胞因子风暴也会导致淋巴细胞凋亡[9]。中性粒细胞的升高和淋巴细胞的减少都可以导致 COVID-19 患者中 NLR 的升高，很多研究也发现 NLR 升高是 COVID-19 严重感染的一个指标，它可以预测 NLR 的疾病进展和病死率[9] [18]。

Liu J.等[19]分析了 115 例 COVID-19 患者的临床数据发现，NLR 是 COVID-19 患者病情危重症的独立预后因素。根据 NLR 和年龄分层，年龄 ≥50 岁且 NLR < 3.13 的 COVID-19 患者病情危重症发生率为 9.1%，年龄 ≥50 岁且 NLR ≥ 3.13 的 COVID-19 患者病情危重症发生率为 50%。Bastug A. [16]等研究发现 COVID-19 严重程度的曲线下面积(area under the curve，AUC)为 0.861，敏感度是 84.4，特异度是 62.8。入院时 NLR 越高，病情越严重，特别是，NLR > 4 是入住 ICU 的预测因素[20]，而 NLR < 3 可能有更好的临床结果[21]。

入院 NLR 水平的升高不仅与 COVID-19 病情严重程度有关，还与 COVID-19 患者的死亡结局有关[17]。NLR > 9 时 COVID-19 患者的病死率比 NLR < 9 的患者高 25 倍，且 NLR > 9 的患者平均 ICU 住院时间较长[22]。在 70 岁的 COVID-19 患者中，NLR > 6.5 与疾病严重程度相关的几率是其他患者的两倍，NLR > 6.5 与死亡相关的几率为 1.44，并且与患者的性别没有显著影响[21]。

Parthasarathi A.等[23]对 64 项(共 16205 例)关于 COVID-19 患者的 NLR 荟萃分析显示，NLR 在预测 COVID-19 病情严重程度的 AUC 为 0.833，敏感性为 80.2%，特异性为 75.8%；NLR 在预测 COVID-19 病死率的 AUC 为 0.820，敏感性为 78.8%，特异性为 73.0%。并且研究发现，在预测病死率时，NLR > 6.5 患者的病死率明显增加，比 NLR < 6.5 患者的病死率高出两倍以上。值得注意的是，Parthasarathi A.人[23]结果显示 NLR 值在预测病情严重程度和病死率时均不受年龄、性别、糖尿病、高血压、心血管疾病的影响，但这似乎与其他文献报告的不一致，Wang S. [17]等发现在年龄较小、不合并其他基础疾病等临床危险因素的情况下，NLR 在预测 COVID-19 的患者的病情严重程度和死亡预后方面的价值更大。

此外，研究发现，NLR 在预测 COVID-19 死亡预后价值比血小板比淋巴细胞比值(platelet to lymphocyte ratio, PLR)和淋巴细胞比单核细胞比值(lymphocyte to monocyte ratio, LMR)都高[24]。而且 Sun 等[25]研究发现，只有 NLR 与 COVID-19 患者 ICU 入院风险相关，而 PLR 和 LMR 都与 COVID-19 患者 ICU 入院风险不相关。

3. NLR 与 SFTS

发热伴血小板减少综合征(severe fever with thrombocytopenia syndrome, SFTS)是一种新发现的传染病，由 SFTS 病毒引起。临床表现为发热、白细胞减少、血小板减少、胃肠道症状、出血、弥漫性血管内凝

血甚至多器官功能障碍[26] [27]，病死率高达 11.2%~30% [26]。

SFTS 的发病机制尚未完全阐明，在 SFTS 病毒感染早期，白细胞介素-1 受体拮抗剂(IL-1RA)、白细胞介素-6、白细胞介素-10、粒细胞集落刺激因子(Granulocyte colony-stimulating factor, G-CSF)和单核细胞趋化蛋白-1 (Monocyte chemoattractant protein-1, MCP-1) [27]等促炎细胞因子释放，中性粒细胞被大量招募和激活到达感染部位。在疾病的进展阶段，SFTS 病毒直接或者炎症反应间接损害宿主免疫系统，导致淋巴细胞减少[28]。

Wang X.等[26]研究了 415 例来自中国五个医院的 SFTS 患者发现，死亡组 SFTS 患者入院的 NLR 明显高于存活组，急性期 SFTS 患者的 NLR 高于恢复期患者的 NLR，且 NLR 与死亡风险模型呈正相关。NLR 大于 5.4 可增加 SFTS 患者死亡风险。Wei Y.等[29]分析了两家医院共 228 例病人发现，NLR 是 SFTS 患者入院 28 天内死亡结局的预测因素，它的 AUC 为 0.738，仅次于 SFTS 病毒载量(AUC = 0.919)，Kaplan-Meier 生存曲线显示，SFTSV 病毒载量高于 50 万或 NLR 高于 2.0 的患者病死率明显增加。类似地，Liu Y.等[28]分析了急诊科 182 例 SFTS 患者也发现 NLR 是 SFTS 患者 28 天病死率的独立预测因子，NLR 预测 28 天内病死率的 AUC 为 0.743，最佳临界值为 4.19 (敏感性为 54.2，特异性为 89.2%)。NLR ≥ 4.19 患者的 28 天病死率明显高于 NLR < 4.19 的患者。研究结果还显示，死亡组 SFTS 患者的中性粒细胞计数高于存活组，而死亡组 SFTS 患者的淋巴细胞低于生存组。

4. NLR 与 CCHF

克里米亚–刚果出血热(Crimean-Congo hemorrhagic fever, CCHF)是由布尼亚病毒目内罗病毒科的病毒引起的一种严重形式的出血热，在非洲、东南欧、亚洲(特别是中东)流行[30]。人类通过蜱虫叮咬或接触动物血液而感染。CCHF 是医学上仅次于登革热的重要的虫媒传播病毒[31]，病死率高达 30% [31] [32]。

单核细胞和淋巴细胞计数的减少和中性粒细胞计数的增加与 CCHF 患者预后不良相关[33]。淋巴细胞和单核细胞减少导致免疫衰竭，中性粒细胞增加导致细胞因子过量释放，过量的细胞因子产生的细胞毒性作用会造成内皮细胞的激活和血管通透性的增加[34]。

NLR 与 CCHF 的住院时间呈负相关，并且 NLR 可以预测 CCHF 患者的病死率[35]。入院 NLR 升高也与病死率有关，尽管存活组和死亡组 CCHF 患者入院时的 NLR 的中位值都在正常范围内，但死亡组患者 NLR 的中位值大约是存活组的两倍[31]。NLR 预测病死率方面比 CRP 好，但是不如基于血小板参数的血小板比淋巴细胞比值(platelet to lymphocyte ratio, PLR)和全身免疫炎症指数(systemic immune-inflammation index, SII) [35]。Kazancioglu S.等[36]发现与存活组患者相比，死亡组患者的中性粒细胞和 NLR 均较高。同时，他们比较了入院第一天和入院第三天的 NLR 的预测死亡价值，发现第三天 NLR 的 AUC 比第一天的 NLR 高。

5. NLR 与 AIDS

获得性免疫缺陷综合征(acquired immune deficiency syndrome, AIDS)，又称艾滋病，是由人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染引起的慢性传染病。HIV 主要破坏 CD4+ T 淋巴细胞介导的免疫能力丧失。中性粒细胞在 HIV 感染阶段，它通过产生 ROS、精氨酸酶 1 (arginase-1, Arg1)等多种方式抑制 T 细胞功能，在 HIV 感染过程中发挥重要作用。

Raffetti E.等[12]首次表明 NLR 这个简单可靠的炎症标志物的升高与 HIV 感染者的全因病死率相关，独立于 CD4 水平和其他公认的艾滋病毒死亡风险因素。Hanberg J.S.等[37]也发现 NLR 与 HIV 感染者病死率密切相关。

Merriman R.C.等[38]发现 NLR 升高不但发生在患者在接受抗逆转录病毒治疗的阶段(病毒载量检测

不到)，也发生在感染控制不佳的新诊断为 HIV 感染的患者中。当其他血液结果(如 CRP)没有异常时候，临床医生可能会使用 NLR 来怀疑 HIV 阳性患者的感染。此外有研究发现，NLR 升高是 HIV 感染患者发生心血管疾病风险的预测因子[39]，独立与吸烟、年龄、糖尿病、高血压等传统的心血管疾病危险因素。NLR 升高能预测 HIV 感染者发生结核病的风险，NLR 结合结核病症状可以提高 HIV 感染患者中结核病筛查的准确性[40]。

6. NLR 与病毒性脓毒症

病毒性脓毒症是一种致命性的严重综合症，定义为宿主对病毒感染反应失调导致的危及生命的器官功能障碍[41] [42]。中国脓毒症和感染性休克的发生率和病死率极高，远高于北美和欧洲国家[43]。脓毒症是宿主促炎和抗炎过程的复杂相互作用，它通过多种机制损害固有免疫和适应性免疫[44]，其中，持续激活中性粒细胞延迟凋亡会导致脓毒症患者的非特异性组织损伤，持续性脓毒症诱导细胞凋亡导致淋巴丢失[45]。中性粒细胞绝对计数、淋巴细胞绝对计数和 NLR 是脓毒症的预测因子[46]，但是 NLR 的预测效能比单独的淋巴细胞和中性粒细胞预测效能好[10] [11]。

虽然脓毒症大多数是细菌引起的，但是高达 42%的脓毒症细菌培养阴性。虽然病毒性脓毒症的患病率尚不清楚，但是几乎任何病毒都可以引起脓毒症，比如流感病毒、登革热病毒、汉坦病毒、单纯疱疹疱疹病毒、肠道病毒等[41]。研究发现无论是何种来源的脓毒症——包括病毒性脓毒症，NLR 对其都有比较好的预测能力[47]。在很多研究中脓毒症的来源是细菌还是病毒未给予说明，我们在此一并综述。

Nii-Trebi N.I.等[11]对 14 项(包括 11,564 例脓毒症患者)脓毒症研究进行荟萃分析发现，死亡组脓毒症患者的 NLR 明显高于存活组，较高的 NLR 可能表明脓毒症患者预后不良。此外，矫正混杂因素后，发现 NLR 可以作为脓毒症患者的独立预测指标，并且是一种可靠的预测指标。但是遗憾的是，这项研究没有找到理想的 NLR 截断值。

NLR 在评估脓毒症严重方面具有潜在价值，尤其是当 NLR > 10 时[48]。而且 Dragoescu A.N.等[48]将 NLR 与脓毒症严重程度标志物做相关性分析发现 NLR 与可溶性 CD14 亚型(soluble CD14 subtype, sCD14-ST or presepsin)和 SOFA (sequential organ failure assessment)评分显著相关($P < 0.001$)，这证实了 NLR 预测脓毒症不良预后的潜在能力，NLR 预测脓毒症预后的价值可能与 presepsin 和 SOFA 评分相似。值得注意的是，NLR 的诊断能力与 C 反应蛋白相比具有相当或者更好的预测价值，然而在脓毒症或感染性休克方面预测价值不如降钙素原(procalcitonin, PCT)。也有研究动态观察重症监护病房(intensive care unit, ICU)脓毒症患者的 NLR 发现，第 1、3、5 天的 NLR 都与住院病死率相关，尤其是五天的 NLR 与住院病死率独立相关。第 5 天 NLP 联合年龄和 SOFA 评分可能有助于预测 ICU 脓毒症住院患者的病死率[49]。Chebl R.B. [50]预测脓毒症病死率的 NLR 的最佳截断值为 14.2 (AUC = 0.552)，敏感性为 44.8%，特异性为 65.3%。Liu Y.等[51]研究发现 NLR 预测脓毒症 28 天病死率的最佳值为 14.08，与文献 Chebl R.B.等研究结果的截断值近乎一致，但是 Liu Y 等发现其敏感性和特异性分别为 78.3%和 50% [50] [51]。Gharebaghi N.等[52]研究发现入院前三天 NLR 的增加表明脓毒症严重程度和病死率的增加，在死亡患者中 NLR 大于 10，而出院患者中 NLR 小于 NLR。

据报道，严重的小儿脓毒症的病死率远远高于成人脓毒症[45]，NLR 在小儿脓毒症的研究比较多。NLR 可以用于新生儿脓毒症的早期诊断[53]，Li T.等[46]研究发现 NLR 是诊断新生儿的独立预测因子，NLR > 1.62 (AUC = 063)，可预测新生儿脓毒症的存在。同样地，NLR 是预测小儿脓毒症病情的严重标志物，而且 Zhong X.等[45]发现 NLR (AUC = 0.715)预测病情进展的能力高于儿童死亡风险评分(AUC = 0.647)。Zhong X.等[45]还提出 NLR 和降钙素原(PCT)联合应用有利于小儿脓毒症的早期诊断。NLR 与其他指标联合预测小儿脓毒症的早期诊断在其他研究中也有提出，比如，像 Sumitro K.R. [54]和 Alkan

Ozdemir S.等[55]研究提出 NLR 与 CRP 联合能更好的诊断脓毒症的存在。

此外，在肾综合征出血热[56]、慢性乙型肝炎[57]、慢性丙型肝炎[58]、新型禽流感病毒 H7N9 亚型[59]等病毒感染性疾病中都有关于 NLR 预测预后的报道。

7. 结论

NLR 是一种新型的生物标志物，具有简单有效、相对便宜、容易获得的优点，被认为是预测病情严重程度和预后的敏感指标，在 COVID-19、病毒性脓毒症、SFTS、CCHF、AIDS 等病毒感染性疾病中已有大量报道，NLR 有潜力成为病毒感染性疾病的重要生物标志物，未来进一步研究 NLR 的动态变化和临床相关的临界值可能有助于临床应用，提高病毒感染重症预警能力，及早干预，改善治疗结果，降低院内病死率。

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