· 研究进展 ·

脓毒症患者预后与红细胞体积分布宽度和中性粒细胞/淋巴细胞比值的关系

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摘要：脓毒症被定义为由于宿主对感染的反应失调而导致的危及生命的器官功能障碍，其发病机制较为复杂，目前尚未完全明确，其发病率和死亡率在全球各国仍处于较高水平，但相关指标变化与脓毒症预后具有相关性。中性粒细胞与淋巴细胞比值（NLR）可能与机体炎症进展有关，红细胞体积分布宽度（RDW）升高可能与炎性生物标志物及氧化应激相关。因此，为明确 RDW 和 NLR 与脓毒症患者预后的关联性，本文围绕当前研究与进展展开综述，为评估脓毒症患者预后提供一定的参考依据。

关键词：脓毒症；中性粒细胞与淋巴细胞比值；红细胞分布宽度；预后

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Red blood cell distribution width and neutrophil-to-lymphocyte ratio in the prognosis of sepsis

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Abstract: Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and its pathogenesis is complex and has not been fully clarified at present. Its morbidity and mortality are still at a high level in countries around the world, but the changes of related indicators are related to the prognosis of sepsis. Neutrophil-to-lymphocyte ratio (NLR) may be associated with progression of inflammation, and elevated red blood cell distribution width (RDW) may be associated with inflammatory biomarkers and oxidative stress. Therefore, in order to clarify the correlation between RDW and NLR and the prognosis of patients with sepsis, this article reviews the existing research and progress, so as to provide a certain reference for evaluating the prognosis of patients with sepsis.

Keywords: Sepsis; Neutrophil-to-lymphocyte ratio; Red blood cell distribution width; Prognosis

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脓毒症是机体对各种病原体感染导致的免疫功能异常而引起的全身多器官功能障碍[1]，发病率和病死率均较高，也是全球重症监护病房（ICU）患者死亡的一大危险因素。现阶段，世界各国新发脓毒症患者约 4 890 万，因该病死亡人数约 1 110 万人[2]。研究发现，脓毒症患者早期某些指标的变化对于评估其预后具有重要意义[3-5]。现阶段脓毒症的发病机制尚未明确，且目前也未提出与预后评估相关的“金标准”。所以，为了评价脓毒症患者的预后，临床应尽量研究出简单易行且具可靠性的指标。先前研究结果显示，中性粒细胞与淋巴细胞比值（neutrophil-to-lymphocyte ratio，NLR）以及红细胞体积分布宽度（red blood cell distribution width，RDW）在评估脓毒症患者预后中具有较高的价值[6-7]。因此，本文简要回顾脓毒症定义的发展，对 RDW 和 NLR 与脓毒症患者预后的相关性进行综述。

1　脓毒症定义的发展

1991 年，美国胸科医师学会（ACCP）与重症监护医学学会（SCCM）召开第一次共识会议，会议依据临床表现和实验室指标共同制定了“脓毒症”的定义，该共识得到了众多学者的支持和广泛使用。该共识认为脓毒症为机体感染过程中的全身炎性反应综合征（SIRS），其收缩压<90 mmHg 或在无其他诱因下较基线值降低≥40 mmHg，而严重脓毒症则同时伴有器官

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功能障碍、低灌注或低血压[包括乳酸酸中毒、少尿和急性精神障碍][8]。

2001 年,欧洲危重病医学会(European Society of Intensive Care Medicine, ESICM)和 SCCM 召开了第二次共识会议对脓毒症定义进行修改,该定义增加了相关临床症状、体征以及临床经验。该共识成为未来多年脓毒症临床诊疗和研究的基础[9]。

2014 年,ESICM 和 SCCM 邀请 19 位专家更新脓毒症的定义,从而消除以往定义特异性有限和敏感性不足的缺点。因此于 2016 年发布了脓毒症和脓毒症休克的第三次国际共识(Sepsis-3),将脓毒症界定为对各类感染因素免疫反应紊乱引发的、对患者生命安全存在威胁的多器官功能障碍性疾病,在该定义中对早期脓毒症的诊断进行更新,将序贯器官衰竭评分(SOFA)≥2 分纳入诊断指标,即脓毒症的诊断标准为,感染的同时 SOFA 评分为 2 分及以上。但此界定中,去掉了先前定义中的 SIRS 部分,说明目前对该病着重强调患者对各种病原体感染所导致的危及生命的多器官功能障碍性疾病[1]。

2　脓毒症流行病学

在世界范围内,脓毒症是 ICU 患者的主要并发症之一。值得注意的是,脓毒症发病率在过去几十年持续增加[10-12],给世界各国医疗保健系统造成了巨大的经济负担[12-13]。在全球范围内,2012 年 29.5%的 ICU 住院患者中发生脓毒症,而其中死亡率为29.8%,住院患者死亡率为 35.3%[14]。Li 等[15]对亚洲 22 个国家 386 个 ICU 病房调查发现脓毒症发病率为 22.4%,而发病率与国家收入相关,低收入国家和中收入国家发病率分别为 20.9%和 24.5%,亚洲地区脓毒症患者 90 d 内死亡率超过 1/3。Liu 等[16]分析发现我国脓毒症发病率约为 33.6%,死亡率约为 29.0%。在 2015 年,中国脓毒症标准化死亡率为66.7/10 万人,估计每年 100 万患者死于脓毒症。上述研究说明在亚洲地区我国脓毒症发病率较高。

3　NLR 与脓毒症

3.1　*NLR 在脓毒症中的意义*　NLR 可体现机体对炎症的反应,但关于 NLR 参考值范围目前尚未形成统一标准。在不同国家和地区分别对健康成年人群 NLR 正常范围进行的相关研究显示,东南亚地区健康成年人群 NLR 均值为 1.95(95%*CI*:1.20~2.30),欧洲国家比利时健康成年人群 NLR 均值为1.65(95%*CI*:0.78~3.53),北非部分国家健康成年人群 NLR 均值为1.20(95%*CI*:0.75~3.19),东北亚地区健康成年人群 NLR 均值为 1.65(95%*CI*:0.10~3.19)[17-19]。此外,也有大样本量研究 NLR 的正常范围,如 Azab 等[20]对纽约州 9 427 例公民进行调查显示,NLR 均值为 2.15(95%*CI*:2.11~2.19)。根据上述研究可推测 NLR 最佳正常范围,可依据临床试验和流行病学调查结果进行优化。NLR 反映机体炎症强度也非常直观,其值越高表明机体炎症反应越高,即 NLR 值 2.3~3.0 时可视为潜在、亚临床或低级别炎症状态,NLR 值>3.0~7.0 时为轻中度炎症状态,NLR 值>7.0~11.0 时为中重度炎症、全身感染、脓毒症,NLR 值>11.0~17.0时为重度炎症状态、重度脓毒症,NLR 值>17.0~<23.0 时是重度免疫炎性反应,如感染性休克,而若 NLR 值≥23.0 时属于重度全身性炎症状态。

上述所获得的 NLR 值及 95%*CI* 均是基于成年人群研究获取,而目前关于儿童 NLR 值尚未明确。因此,为明确 NLR 在全人群中的意义,还需要进行大量的临床研究。

3.2　*NLR 评估脓毒症预后的价值*　NLR 是通过计算中性粒细胞计数与淋巴细胞计数的比值获得。在炎症反应患者血清中中性粒细胞计数增多,而淋巴细胞计数则减少,因此 NLR 在炎症患者外周血中会处于升高状态。目前已明确单一指标预测脓毒症预后价值较低,但 NLR 代表两种炎性指标,对炎症患者的病情严重程度及预后具有一定的预测价值。有研究发现,NLR 与感染性并发症(如发热、SIRS、脓毒症等)和恶性肿瘤具有相关性[21],NLR 升高的患者血清中 IL-6、IL-8 及 IL-12 等明显升高[22-23]。上述炎性因子在机体组织微环境中大量蓄积,从而引起侵袭性炎症或肿瘤转移。此外,在 NLR 升高的恶性肿瘤患者病灶中也观察到巨噬细胞的浸润。也有假说认为,机体炎症可促进花生四烯酸代谢物和血小板活化因子等物质的合成释放,从而引起机体中性粒细胞大量增多,皮质醇诱导的应激可导致相对淋巴细胞计数减少。由上述研究说明,NLR 可能对反映潜在的炎症过程具有较高的准确性。NLR 可很方便地由全血细胞计数中获得[24],其反映机体特异性免疫能力[25]。许多研究表明,NLR 是脓毒症的炎症指标之一,也是脓毒症预后的独立危险因素[25-28]。此外,有研究发现,NLR 是评估急诊住院患者脓毒症预后的一个指标[29],被证实与脓毒症的严重程度和预后相关[30]。超过一半的中度至重度 NLR 升高的脓毒症患者在住院期间有较高的死亡率[31]。Gameiro 等[32]研究发现,NLR 与腹部大手术后急性肾损伤(AKI)的发生率具有相关性,且 NLR 水平是治疗期间脓毒症合并 AKI 患者死亡的危险因素。有研究表明,脓毒症患者 NLR、降钙素原(PCT)、急性生理学及慢性健康状况(APACHE)Ⅱ评分及 SOFA 评分均显著高于脓毒症以外的感染者(P<0.05),将 NLR=7.97 作为最佳截断值时,NLR 评估脓毒症的灵敏度和特异度分别为64.26%和80.16%[26];另一研究将 NLR=16.935 作为最佳截断值时,NLR 评估患者死亡预后的灵敏度和特异度分别为 82.00%和69.00%[33]。上述研究提示 NLR 评估可能为预测脓毒症患者休克或死亡的重要指标。此外,也有前瞻性研究评价 NLR 作为炎性标志物对脓毒症患者预后的预测价值,发现脓毒症死亡患者 NLR 值显著高于存活患者,NLR 预测患者死亡的 AUC=0.695,相关性分析得出 NLR 值升高与脓毒症患者疾病严重程度呈正相关关系[34]。

4　RDW 与脓毒症

4.1　*RDW 生物学功能*　RDW 为外周血循环中易于获得的反映红细胞体积、大小变异程度的一项重要指标,其参考值范围为 11%~15%。既往研究表明 RDW 在多种血液系统疾病的临床诊断、治疗效果评估及患者预后预测等方面具有重要意义,特别是在贫血相关疾病的诊断中效能更高[35]。目前,研究证

实 RDW 与恶性肿瘤、心脑血管疾病、泌尿系统疾病等具有相关性[34-40]。

4.2 RDW 评估脓毒症预后的价值　目前大量研究发现 RDW 值的变化与感染性疾病具有相关性,可用于评估相关疾病的预后情况。RDW 升高可准确预测冠状动脉搭桥术术后脓毒症和肺炎发生风险[41],同时其也与社区获得性肺炎、严重脓毒症或脓毒症休克患者的死亡等相关[42-44]。RDW 在评估 ICU 严重脓毒症患者临床预后方面具有重要价值。Han 等[45]对 ICU 收治的4 264例脓毒症患者进行为期 4 年的随访研究发现,RDW 值较高(≥15.6%)的患者全因死亡风险明显增加。Sadaka 等[46]收集外科 ICU 279 例住院患者进行多中心回顾性队列研究,结果表明与 RDW<13.5%患者相比,RDW 13.5%~15.5%、RDW 15.6%~17.5%、RDW 17.6%~19.4%及 RDW>19.4%患者死亡率显著增高,RDW 预测脓毒症休克患者住院期间死亡的 AUC=0.74。上述研究说明 RDW 在评估脓毒症患者预后方面具有较好的效果。Lorente 等[47]进行多中心的前瞻性观察研究,通过对 ICU 重度脓毒症患者进行住院 1 d、4 d 及 8 d 的 RDW 值连续监测发现,死亡组患者 RDW 值显著高于存活组。Wang 等[48]对急诊 ICU 收治的 117 例老年脓毒症患者进行回顾性队列研究表明,RDW 预测老年脓毒症患者院内死亡的 AUC=0.63(95% *CI*=0.52~0.74),多变量 Cox 比例风险模型分析显示,RDW 值增加 1%,患者死亡率增加 18%。由上述研究结论可推测 RDW 对预测老年脓毒症患者院内死亡具有重要价值。

Chen 等[49]纳入 6 973 例脓毒症患者作为研究对象,根据 RDW 值四分位数将患者分为 4 组,RDW 四分位值最高组(RDW>15.6%)患者住院期间死亡风险显著高于 RDW 四分位值第二高组(15.6%<RDW>14%)患者(16.7% *vs* 7.3%),而 RDW 四分位值最低组(RDW<13.1%)患者死亡率仅为 1.6%。该研究还将脓毒症患者进一步分为严重脓毒症组和非严重脓毒症组,结果表明严重脓毒症组患者死亡风险显著高于非严重脓毒症组患者。龚艳等[50]纳入 196 例脓毒症患者作为研究对象,依据纳入患者入院时与出院时 RDW 值的变化分为升高组和非升高组,结果显示 RDW 值升高组患者28 d和 90 d 累积生存率均较 RDW 非升高组明显降低,研究认为 RDW 升高可作为脓毒症患者病情进展及更差临床结局的重要预测指标。

5 结　语

脓毒症具有较高的发病率和死亡率,其发病机制较为复杂,目前尚未明确,患者病情多较为严重、预后较差,因此选择一类易于获得、评估效能高的指标对早期评估患者预后具有重要意义。且在不同年龄脓毒症患者的临床诊断及预后评估中同一指标可能效果不同,说明脓毒症的临床预后评估现阶段仍面临较大的挑战。大量研究结果表明,在脓毒症患者病情判断、预后评估方面,NLR、RDW 起着重要作用,但单一评估存在不足,而二者联合应用可能提高其预测价值。未来仍需要开展 NLR 联合 RDW 在脓毒症患者预后评估效能上的多中心、大样本量、前瞻性的临床研究进一步探讨。

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