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中性粒细胞/淋巴细胞比值、血小板/淋巴细胞比值在慢性肾脏病中的研究进展

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摘　要

近年来中性粒细胞/淋巴细胞比值(NLR)、血小板/淋巴细胞比值(PLR)已成为研究热点，目前被认为是包括慢性肾脏病(CKD)、心血管疾病(CVD)以及恶性肿瘤的炎症状态标志物。研究表明NLR、PLR不仅参与CKD的炎症反应，更与疾病的进展和预后息息相关。同时，NLR、PLR也影响着糖尿病肾病、狼疮性肾炎等疾病的发生与发展。因此，本文就NLR、PLR在CKD中的研究进展作一综述，以期为CKD患者炎症状态、疾病进展及预后的预测提供新的证据，并为CKD的诊治提供新的思路。

关键词

中性粒细胞/淋巴细胞比值，血小板/淋巴细胞比值，慢性肾脏病

Research Progress of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Chronic Kidney Disease

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Abstract

In recent years, the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have become research hotspots. It is currently considered as a marker of inflammation including chronic kidney disease (CKD), cardiovascular disease (CVD) and malignant tumors. Studies have shown that NLR and PLR are not only involved in the inflammatory response of CKD, but are also closely related to the progression and prognosis of the disease. At the same time, NLR and PLR also affect the occurrence and development of diseases such as diabetic nephropathy and lupus nephritis. Therefore, this article reviews the research progress of NLR and PLR in CKD, hoping to provide new evidence for the prediction of inflammatory state, disease progression and prognosis of CKD patients, and provide new ideas for the diagnosis and treatment of CKD.

Keywords

Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio, Chronic Kidney Disease

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1. 引言

研究表明，慢性肾脏病(chronic kidney disease, CKD)患者的促炎因子水平较高，抗氧化剂和抗炎因子水平较低[1]。在 CKD 的病程中存在持续低水平的慢性炎症，这种持续的炎症状态与营养不良、心血管疾病(cardiovascular diseases, CVD)、疾病进展以及全因死亡率相关[2]。其原因是氧化和羰基应激、抗氧化剂摄入不足、血液中促炎细胞因子水平升高、感染、动脉粥样硬化、厌食引起的营养不良等。目前发现许多指标与 CKD 的炎症相关，如红细胞沉降、白介素-1、白介素-6 (Interleukin-6, IL-6)、白介素-8、白介素-12、肿瘤坏死因子-α (tumour necrosis factor-α, TNF-α)等，尚不清楚哪种指标是最佳指标，但 C 反应蛋白(c-reaction protein, CRP)仍然是最常用的炎症指标[1] [2] [3]。最近，中性粒细胞/淋巴细胞比率(neutrophil/lymphocyte ratio, NLR)、血小板/淋巴细胞比率(platelet/lymphocyte ratio, PLR)作为一种新的评价炎症的指标，引起了学者的兴趣。大量数据表明 NLR、PLR 可能是 CKD、CVD 以及恶性肿瘤患者炎症状态、死亡率和预后的预测因子[4] [5] [6]。

2. NLR、PLR 与炎症状态

Kuo 等[7]以 NLR 作为炎症标志物，研究了 CKD 和全身炎症之间的关系。结果显示：与年龄 < 60 岁的患者相比，年龄 ≥60 岁的患者 CKD 患病率明显更高。在年龄 <60 岁的男性中，更高的 NLR 与更高的 CKD 风险独立相关。但在年龄 ≥60 岁的男性和所有的女性患者中，没有发现这种关联。他们认为这种结果的部分原因可能是雄激素对免疫系统的影响。在各种免疫细胞中均检测到雄激素和雄激素受体，包括中性粒细胞、肥大细胞和淋巴细胞等[8]。中性粒细胞的产生和正常功能需要雄激素和雄激素受体，从而促进炎症反应[9]。Altunoren 等[10]回顾性分析了 740 例 2~4 期 CKD 患者 5 年的资料，他们认为 NLR 是 CKD 的炎症指标。但它可能不是 CKD 进展的独立预测因子，典型的危险因素如糖尿病和低肾小球滤过率(glomerular filtration rate, GFR)是更有效的进展预测因子。

而在透析患者中，也发现 NLR、PLR 与炎症状态相关。Pineault 等[11]研究发现随着 NLR 的增加，CRP 升高，白蛋白降低。An 等[12]研究表明腹膜透析(peritoneal dialysis, PD)患者的 NLR 高于健康对照组，并发现 NLR 和 CRP 水平较高的 PD 患者的 CVD 和全因死亡率较高。Okyay 等[13]研究表明 PD、血液透析(hemodialysis, HD)和透析前 CKD 患者的 NLR 高于健康对照组。NLR 与 CRP ($r = 0.264$, $p = 0.002$) 和 IL-6 ($r = 0.393$, $p < 0.001$)水平呈正相关，与血清白蛋白水平呈负相关($r = -0.400$, $p < 0.001$)。另一项研究显示，高 NLR 值的终末期肾病(end stage renal disease, ESRD)患者的 TNF-α 水平较高[14]。Turkmen 等[15]研究发现 PLR 与 NLR、IL-6 和 TNF-α 呈正相关。比较 PLR 和 NLR 与 IL-6 和 TNF-α 的相关性时，发现 PLR 在 ESRD 患者的炎症方面的预测作用优于 NLR。

由此可见，由于 NLR 和 PLR 可以常规计算，而不需要从全血细胞计数中增加成本，是一种很好的炎性生物标志物，NLR、PLR 有能力提高对潜在的亚临床疾病的检测率。

3. NLR、PLR 与蛋白尿

微量白蛋白尿定义为尿中白蛋白为 30~300 mg/d 之间。糖尿病患者和高血压患者微量白蛋白尿的患病率分别高达 28.8%和 16%。微量白蛋白尿的存在是血管损伤和内皮功能障碍的标志，因此在许多疾病中是肾脏损伤的早期征象[16]。同时，微量白蛋白尿也是 CVD 和肾功能恶化的预测因子[17] [18]。研究发现，正常范围内蛋白尿的增加与 CVD 的风险增加相关[16]。

少数研究调查糖尿病患者中蛋白尿与 NLR 或 PLR 的关系，他们发现尤其在有蛋白尿的糖尿病患者中 NLR 水平更高，NLR 与蛋白尿呈正相关[19] [20] [21] [22]。Akbas 等[19]在一项研究中调查了 200 名糖尿病患者的 NLR 和 PLR 值，他们发现蛋白尿与 NLR 或 PLR 呈正相关。有研究表明，早期糖尿病肾病(diabetic nephropathy, DN)患者的 NLR 水平高于非 DN 患者[21] [22]。同时，NLR 被发现是糖尿病患者肾功能进展的预测因子[20]。有学者探讨了 NLR、PLR 与蛋白尿的关系，研究中有 174 例 GFR ≥ 60 ml/min/1.73m^2 的患者，根据尿白蛋白情况将患者分为微量白蛋白组和正常白蛋白组，结果显示：在 GFR 正常的微量白蛋白尿患者中 NLR 水平较高，蛋白尿和 NLR 之间也存在显著的正相关[23]。在一项包括 3~4 期 CKD 患者和健康对照的研究中，NLR 在有蛋白尿的 CKD 患者中最高，并且在 CKD 患者中检测到蛋白尿和 NLR 显著相关[24]。因此，NLR、PLR 有助于发现有微量白蛋白尿的患者，并可能是早期肾损害的有用生物标志物。

4. NLR、PLR 与肾功能进展

CKD 是一种以渐进性和不可逆的肾功能丧失为特征的疾病，最终进入尿毒症状态，需要透析或肾移植。这一重大公共卫生问题影响了 14.3%的成年人口[25]。因此，重要的是要确定导致肾功能恶化的风险。

最近有越来越多的数据表明 NLR、PLR 不仅是炎症的指标，而且是 CKD 疾病进展的预测因子。Altunoren 等[10]回顾性分析显示：NLR 随着 CKD 分期的增加而增加，随访时 NLR 显著升高。高 NLR 患者的平均生存期明显低于低 NLR 患者。他们认为 NLR 可能是处于晚期的 CKD 患者的疾病进展的预测因子，并反映了相关的炎症。Kocyigit 等[26]对 105 例 4 期 CKD 患者的研究表明，高 NLR 患者的基线 CRP 水平更高，GFR 下降更快，更早进展到 ESRD。然而，高 NLR 和快速进展到 ESRD 的患者的基线 GFR 水平较低。Tatar 等[27]研究发现随着时间的增加，NLR 值更高的患者死亡率和 RRT 启动率更高。此外，他们发现 GFR < 29 ml/min/1.73m^2 的患者除了有较高的死亡率和 RRT 启动率外，还有较高的 NLR 值。Kim 等[28]研究表明 CKD 患者的相对淋巴细胞计数与 ESRD 进展相关。Tonyali 等[29]研究发现在接受部分或根治性肾切除术的患者中，NLR 随着 GFR 降低和疾病进展而增加。因此，NLR 可能是除肌酐外 CKD 病程进展的一个实用预测因子。Yılmaz 等[30]的研究也显示，在 CKD 患者中随着 GFR 降低和蛋

白尿的增加，NLR 的增加。

5. NLR、PLR 与死亡率和预后

国内的一项研究探讨了 1~4 期 CKD 患者 NLR 与 ESRD、CVD 和全因死亡率进展的关系，结果表明 NLR 与中国 CKD 4 期患者发生 ESRD 的风险相关。NLR 可用于 4 期 CKD 患者发生 ESRD 的风险评估[31]。Tatar 等[29]探讨 3~5 期 CKD 老年患者 NLR 和 PLR 与临床结局的关系。研究显示基础 NLR 是死亡的独立预测因子，基础 GFR 是需要肾替代治疗的独立预测因子。然而，PLR 与死亡和肾替代治疗需求无关，只有 NLR 老年 CKD 患者全因死亡的预测因子。Yoshitomi 等[32]研究的目的是确定 NLR 是否与 CKD 患者的肾脏预后相关。研究表明高 NLR 与较差的肾脏预后相关，这提示 NLR 可能是 CKD 患者预后有用的预测指标。由此可见，NLR 除了可用于 4 期 CKD 患者 ESRD 风险评估，也可作为老年 CKD 患者全因死亡的预测因子，更是 CKD 患者的有用预后指标。

HD 患者中常用的死亡率预测指标包括血清白蛋白水平、BMI、CRP 和血红蛋白水平。多项研究表明 NLR、PLR 与 HD 患者炎症增加有关，并可以预测 HD 患者的死亡率[33]。Yaprak 等[34]调查 NLR、PLR 和 HD 患者全因死亡率之间的关系，结果显示：虽然 NLR 和 PLR 均与 HD 患者的全因死亡率相关，但只有 PLR 能独立预测 HD 患者的全因死亡率。但另外一项研究发现，高 NLR 可以预测短期内 HD 患者的死亡率。他们认为 NLR 与血清白蛋白一起纳入预测模型，在临床和流行病学研究环境中可以作为营养和炎症状态的有效生物标志物[35]。

NLR、PLR 很容易获得，这为成熟的临床和生化生物标志物增加了有价值的预后信息。NLR 或许可用于改善 4 期 CKD 患者的风险分层。

6. NLR、PLR 与 CVD

CVD 是全世界死亡率增加的主要原因之一。2015 年约有 1770 万人死于 CVD，占全球死亡总人数的 31%，每年造成的损失约为 3161 亿美元[36]。既往研究表明 NLR、PLR 作为新的炎症标志物对一般人群的 CVD 有预测价值。研究发现，在高血压患者中 NLR 升高，并与高同型半胱氨酸血症呈正相关[37]。在高血压患者升主动脉动脉瘤的发病机制中，NLR 作为炎症标志物可能发挥重要作用[38]。在缺血性脑卒中患者中，NLR 的动态变化已被证明可以预测溶栓后的出血性风险[39]。ST 段抬高型心肌梗死患者 NLR 与自发性再灌注的心电图征象相关[40]。在非紧急经皮冠状动脉介入治疗的患者中，较高的 NLR 增加了术中心肌梗死的风险[41]。在无症状普通人群中，NLR 也与微血管疾病显著相关[42]。在有周围动脉闭塞性疾病的患者中，NLR 升高与较高的死亡率相关[43]。在晚期心力衰竭患者中，NLR 升高与死亡率增加或心脏移植风险升高相关[44]。同时，Durmus 等[45]发现在心力衰竭的患者中 NLR 较高，截断值为 5.1 时可预测心力衰竭患者的死亡风险。Cho 等[46]证明了 NLR 在严重主动脉狭窄患者的风险分层方面的潜在效用。Erturk 等[25]的研究也发现在外周动脉闭塞性疾病患者中，NLR 增加与更高的 CVD 死亡率相关。

众所周知，CVD 是导致 CKD 患者死亡的主要原因之一，尤其是 HD 患者和 ESRD 患者。HD 患者的 CVD 死亡率远高于普通人群，传统危险因素尚不能完全解释 CVD 的发病诱因[47]。微炎症是 CKD 及 HD 患者 CVD 发病的重要因素之一，可进一步加速动脉粥样硬化的进展[48]。

Solak 等[5]认为 NLR 与内皮功能障碍独立相关，在中重度 CKD 患者中，NLR 可以独立于传统的危险因素预测 CVD 的终点事件。Sevenca 等[49]的研究纳入 271 例 eGFR ≥ 30 ml/min/1.73m^2 的原发性高血压患者，结果显示与蛋白尿和尿酸类似，NLR 被发现是 CKD 3 期患者的一个特殊标志物。然而，NLR 和 PLR 并不是影响 eGFR 的独立危险因素。Chen 等[50]对 148 例晚期 CKD 伴外周动脉疾病的患者进行

评估，发现在接受经皮腔内血管成形术治疗的患者中，NLR 是临床结局的重要预测因子。Ozcicek 等[51]的研究纳入 43 例 HD 患者和 30 名健康对照者，结果表明 HD 患者的 NLR 明显高于健康对照组，NLR 是 HD 患者心外膜脂肪组织增厚的独立预测因素。他们认为这种关系可能归因于尿毒症患者的炎症增加。Li 等[52]研究了 NLR 和心血管危险标志物之间的关系。结果表明，较高的 NLR 是脉压、左心室质量指数和内膜－中膜厚度的独立预测因子。有趣的是，他们进一步发现 NLR ≥ 3.5 是 HD 患者全因死亡率和 CVD 的预测因子。

对于 CVD，PLR 也可作为预测 CVD 事件的标志物[53]。同时，PLR 被发现是临界肢体缺血的一个新的生物学标记，高水平的 PLR 表明血小板过度激活和血栓前状态[54]。Chen 等[55]研究的目的是探讨 PD 患者 PLR 与 CVD 之间的关系，结果表明 PLR 与 CVD 事件独立相关。高 PLR 可用于预测 PD 患者发生 CVD 的风险。PLR 检测方法简便，可作为临床常规检测手段。

因此，NLR、PLR 可能是用于评估 CKD 患者和 HD 患者中 CVD 高风险的新型生物标志物。但是，仍有许多问题需要进一步研究，例如 NLR 及 PLR 对 CKD 患者和 HD 患者 CVD 的影响机制等。

7. NLR、PLR 与其他疾病

糖尿病是CKD患者发展到ESRD最常见的原因之一，其患病率在1988年到2008年间增加了34% [56]。重要的是，糖尿病合并 DN 患者的死亡率高于高血压肾病和原发性肾脏疾病患者。这主要是由于与 DN 相关的严重并发症，包括 CVD 和感染。Sato 等[57]的研究证明 NLR 水平对 ESRD 合并 DN 的患者全因死亡率的具有预测作用，NLR ≥ 3.5 的患者死亡率显著高于 NLR < 3.5 的患者。NLR 的 1 年生存曲线下面积明显大于其他常用的营养和炎症指标。因此，NLR 或许是一个比其他已知标志物更准确的预测因子。另一项研究分析 HD 患者 NLR 与营养指标和健康结果的关系。结果发现基线 NLR 与营养指标(白蛋白、BMI)相关，基线时低 NLR 是 HD 合并糖尿病患者住院风险较低的预测因子[58]。

系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种病因不明的慢性全身性炎症性自身免疫性疾病，具有影响不同组织的多种临床表现。其特征是由于对自身抗原免疫耐受的广泛丧失而导致免疫复合物的沉积，以及过度的促炎细胞因子产生，导致多器官系统的损伤。SLE 患者的肾脏活检提示，几乎100%的患者存在肾脏受累。研究发现 SLE 患者的 NLR 和 PLR 明显高于健康对照组。此外，狼疮性肾炎患者的 NLR 水平高于非肾炎患者(P = 0.027)。因此，NLR 和 PLR 可能是评估 SLE 患者疾病活动性有效的炎症标志物[59]。Wu 等[60]对 154 名 SLE 患者和 151 名健康对照者进行了回顾性研究。结果显示在 SLE 患者中观察到 NLR、PLR 增加，NLR、PLR 与 SLE 疾病活动指数(SLEDAI)评分呈正相关。此外，NLR 为 2.065 被确定为 SLE 的预测临界值(敏感性 74.7%，特异性 77.5%，AUC = 0.828)。多元回归分析表明，NLR 与 SLE 活动度独立相关。NLR 和 PLR 能反映 SLE 患者的炎症反应和疾病活动。

肾细胞癌(renal cell carcinoma, RCC)是最常见的肾癌类型，约占成人恶性肿瘤的 3%。在 RCC 中，肾透明细胞癌(clear cell renal cell carcinoma, ccRCC)最常见，占所有病例的 80%~90% [61]。越来越多的证据表明，全身炎症的存在影响包括 RCC 在内的各种恶性肿瘤的预后[62]。Chang 等[63]探讨 ccRCC 射频消融术后，NLR 作为预后指标的作用。结果发现术前、术后较高的 NLR 与局部复发和远处转移的风险增加显著相关。结合 NLR 等预后指标，可用于评价 ccRCC 射频消融术后复发风险。Elghiaty 等[64]研究了术前 NLR 对非转移性肾透明细胞癌(non-metastatic clear cell renal cell carcinoma, nmccRCC) (≤7 cm)预后的预测能力，他们认为术前 NLR 是 nmccRCC 术后无复发和癌症特异性生存率的独立预后指标。

转移性肾细胞癌(metastatic renal cell carcinoma, mRCC)往往是不可预测的，患者生存率低(5 年生存率 8%)。Kim 等[65]对 190 例 mRCC 患者的研究表明，NLR 是影响 mRCC 患者生存率的重要预后因素。在 Heng 模型中加入 NLR 可显著提高 mRCC 风险预测的判别能力。Tanaka 等[66]和 Motzer 等[67]的研究显

示对于接受靶向治疗的 mRCC 患者，用 NLR 替换中性粒细胞可以提高预测预后的准确性。

集合管癌(collecting duct carcinoma, CDC)又称为 Bellini 管癌，是一种罕见的恶性肿瘤，起源于远端肾单位，占肾脏恶性肿瘤的 1%。Taguchi 等[68]分析显示 NLR ≥ 4 与肿瘤特异性生存率差有关。值得注意的是，唯一存活的患者在最初诊断和发生远处转移时，NLR 均维持在较低水平(<4)。提示 NLR 可作为 CDC 及其他恶性肿瘤的一个有用的生物标志物。因此，NLR 是一种具有成本效益的预后生物标记物，它可以为评估癌症治疗后患者的生存率提供有意义的辅助证据。NLR 的动态变化可以作为传统因素的一个重要辅助指标，对生存率提供更好、更全面的预后评价。

天然动静脉瘘(arteriovenous fistula, AVF)是 HD 患者的血管通路，已被广泛应用 50 多年。AVF 作为 HD 通路的第一选择，因为它在持久性和发病率较低方面优于其它模式的通路。此外，早期 AVF 的失败主要是由静脉狭窄引起的，据报道高达 20%~60% [69] [70] [71]。早期 AVF 的失败的后果包括需要临时放置静脉导管和进一步的外科干预，这会增加发病率和死亡率的风险以及护理费用。因此，早期 AVF 失败风险的识别将是有利的。最近的数据表明炎症和早期 AVF 的失败之间存在联系。Wongmahisorn [72] 探讨了术后 NLR 对 AVF 失败的影响，并研究了 396 例患者的完整数据。结果显示早期 AVF 失败的发生率为30.6%，预测早期AVF失败的术前和术后NLR的最佳临界值分别为2.7(敏感性82.6%和特异性52.0%)和 2.9 (敏感性 78.5%和特异性 73.1%)。通过单变量和多变量分析发现，术前和术后高 NLR 与早期 AVF 失败显著相关。

8. 总结与展望

综上，廉价且容易获得的 NLR、PLR 可能是 CKD 患者及 HD 患者的炎症状态、疾病进展及预后的有效生物标志物。然而，还需要进一步的研究来确定 NLR、PLR 的临床显著阈值及其临床相关性，并验证 NLR 和 PLR 是否可以作为预后模型设计中的有效生物标志物进行预测。此外，未来的研究需要确定 NLR、PLR 水平升高的 CKD 患者及 HD 患者是否会从抗炎治疗和干预中获益，从而改善患者的生活质量以及预后。

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