

术前NLR在常见恶性肿瘤中的研究

热米拉·艾海提, 张瑞丽

新疆医科大学第一附属医院肿瘤内科, 新疆 乌鲁木齐

收稿日期: 2023年2月1日; 录用日期: 2023年2月25日; 发布日期: 2023年3月2日

摘要

近年来NLR因其易于获取及价格低廉从而广泛引起广大临床工作者的兴趣, 并取得了显著成果。近年来越来越多的研究证实, NLR的升高与恶性肿瘤患者的不良预后相关。本文就NLR在肾细胞癌、膀胱癌、前列腺癌、非小细胞肺癌、结直肠癌中的最新研究进展进行综述。

关键词

NLR, 肿瘤, 预后

Study of Preoperative NLR in Common Malignancies

Remila Aihaiti, Ruili Zhang

Department of Medical Oncology, First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

Received: Feb. 1st, 2023; accepted: Feb. 25th, 2023; published: Mar. 2nd, 2023

Abstract

In recent years, NLR has aroused the interest of clinicians because of its easy access and low price, and has achieved remarkable results. In recent years, more and more studies have confirmed that elevated NLR is associated with poor prognosis in patients with malignant tumors. This article reviews the latest research progress of NLR in renal cell carcinoma, bladder cancer, prostate cancer, non-small cell lung cancer, and colorectal cancer.

Keywords

NLR, Cancer, Prognosis

Copyright © 2023 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

从生物学上讲, 中性粒细胞与淋巴细胞比值(Netrophil to lymphocyte ratio, NLR)是全身性炎症的标志物, 并且可能反映了恶性肿瘤背景下免疫系统的平衡。已有研究表明, 炎症反应与肿瘤的发生发展密切相关, 导致肿瘤细胞增殖、促进血管生成、抑制细胞凋亡和肿瘤转移[1]。中性粒细胞计数被认为反映了炎症微环境, 进而具有促进肿瘤的活性, 包括癌细胞存活和增殖, 血管生成和转移, 以及对适应性免疫反应的颠覆[2]。而且, 中性粒细胞可能间接改变肿瘤微环境以促进癌症转移, 中性粒细胞在多种癌症类型的免疫浸润中占相当大的比例, 包括肺癌、乳腺癌和胃癌、黑色素瘤等[3]。淋巴细胞是癌症进展的有效抑制剂, 它们的存在, 尤其是在肿瘤微环境中, 被认为反映了宿主的免疫力[4]。作为全身炎症反应指标之一的 NLR 是近年来的研究热点, 随着相关研究的涌现, 诸多研究者证明了 NLR 水平升高表明着自身炎性反应增加和机体抗肿瘤能力减弱, 已被证实一些实体瘤中, NLR 升高与预后不良有关。Templeton AJ 等人[5]进行的一项 META 分析共纳入 100 项研究, 包括 40,559 例实体瘤患者, 评估 NLR 对预后的影响, 其结果显示: NLR 的临界值为 4, NLR 大于临界值与 OS 的风险比为 1.81 (95% CI = 1.67~1.97; $P < 0.001$), 在所有疾病亚组、部位和阶段中都观察到这种效应, NLR 大于 CSS、PFS 和 DFS 界值的风险比分别为 1.61、1.63 和 2.27 (均 $P < 0.001$)。NLR 是一种易于获得且廉价的生物标志物, 将其添加到已建立的预后评分中用于临床决策值得进一步研究。由于该指标易于获得且价格低廉从而广泛引起研究, 并以此来预测肿瘤患者的预后, 本文就全身炎症指标 NLR 与高发恶性肿瘤的预后研究进展作一综述。

2. NLR 与肿瘤的预后

2.1. NLR 与肾细胞癌的预后

肾细胞癌是常见的泌尿系统肿瘤之一, 也是全球最常见的十大肿瘤之一。近年来其发病率和死亡率呈上升趋势[6]。若通过影像学检查早期发现肾细胞癌, 长期生存率一般都很好, 而当肾细胞癌出现症状时, 预后较差[7]。然而, 目前仍未发现可靠的适合临床应用的生物标志物, 目前除影像学检查外, 尚无有效的方法对肾细胞癌进行早期诊断及预后判断。因此, 为了改善肾细胞癌患者的预后, 有必要寻找有效的预处理生物标志物来监测、诊断和治疗该疾病。越来越多的证据表明, 免疫反应和全身炎症是人类癌症发生发展的关键组成部分[8]。De Martin [9]等人的研究表明, NLR 是患者手术后无进展生存率的独立预后因子, 它显著提高了判断预后因素的准确性, 每增加 1.0 倍, 复发风险增加 15% (HR 1.15, $P < 0.028$), 多因素分析显示 TNM 组(HR 2.84, $P < 0.025$)、Fuhrman 分级(HR 3.40, $P < 0.001$)和中性粒细胞与淋巴细胞比值(HR 1.17, $P < 0.022$)与无病生存率独立相关。增加中性粒细胞与淋巴细胞的比率, 使预测无病生存率的基础模型的准确性从 78.8%提高到 80.8%, NLR 可为患者术后辅助治疗和临床试验设计提供有意义参考。W Yong 等[10]进行的 META 分析显示, NLR 升高预示着更差的预后。亚组分析显示, 肾细胞癌 NLR 高的患者 OS 低, 且肾细胞癌、膀胱癌和尿路上皮癌中 RFS/CSS 差。Tollefson 等研究人员发现, 术前 NLR 升高也与肿瘤复发风险(HR = 1.04)、肿瘤特异性死亡率(HR = 1.04)和全因死亡率(HR = 1.03)显著增加相关, NLR 增加 1 个单位, 则复发风险、肿瘤特异性死亡率和全因死亡率分别增加 4%、4%和 3%。而在 RCC 领域中, Ohno 等人发表了第一个有关 NLR 可作为评估 RCC 预后指标的报告。迄今为止, 在已发表的研究中, 包括 RCC [11]或其亚型 ccRCC [12]的研究发现在多因素分析中, 治疗前后 NLR 的变化具

有统计学意义。Pichler 等[13]证实术前 NLR 是非转移性 ccRCC 患者的独立预后因素。郭晓波[14]的研究结果显示, NLR 是影响肾癌患者预后的独立危险因素。

2.2. NLR 与膀胱癌的预后

膀胱癌是一种高度流行的疾病, 在全球范围内, 估计每年有超过 40 万例新发病例和 16.5 万人死亡[15]。在西方国家, 约 75% 诊断为膀胱癌的患者为非肌肉侵袭性膀胱癌(Nonmuscle invasive bladder cancer, NMIBC) [16], 经尿道膀胱肿瘤切除术(Transurethral resection of bladder tumor, TURBT)加膀胱辅助灌注治疗是非肌肉侵袭性膀胱癌的治疗标准[17]。为了改善个性化护理, 预后模型已被开发, 以帮助在日常临床决策。这些模型基于标准的临床病理特征, 如 T 分期、分级、多灶性、性别、肿瘤直径、复发率和伴随的原位癌[18]。但模型的预测准确性在护理提供方面仍未达到最佳水平[19]。炎症在癌症中的作用被越来越多的研究, 以帮助揭示癌的发生、抵抗和进展/转移的机制。在预后炎症标志物中, 中性粒细胞与淋巴细胞比值(NLR)是研究最广泛的。一项荟萃分析[20]显示, 在膀胱癌中, 术前 NLR 被发现与无疾病复发(RFS) (风险比, HR = 1.58)和无进展生存(PFS) (HR = 1.33)相关。有研究发现术前 NLR 高与 TURBT 后疾病复发独立相关, 在多变量分析中, 较高的术前 NLR 预测更差的 RFS [21]。

2.3. NLR 与前列腺癌的预后

前列腺癌是世界范围内最常见的恶性肿瘤之一, 也是男性癌症死亡的原因之一[22]。中性粒细胞与淋巴细胞比值(NLR)是一些实体恶性肿瘤的独立预后因素, 包括前列腺癌[23]。之前的研究也表明, 在接受醋酸阿比特龙治疗的去势抵抗性前列腺癌(CRPC)患者中, NLR 较高的组与 NLR 较低的组相比, 无复发和总生存期较差[24]。Kumano [25]进行的一项 MATE 分析, 将患者分为两组: NLR 较高组(≥ 2.14 ; $n = 71$)和低 NLR 组(< 2.14 ; $n = 35$), 其结果显示: CRPC 患者中 NLR 较高与死亡风险增加相关(HR: 2.27, 2.809, p : 0.015, 0.033)。有研究[26]显示, 具有强烈或高度提示性的证据表明, NLR 升高预示前列腺癌的 OS、PFS 和 RFS 更差。

2.4. NLR 与非小细胞肺癌的预后

肺癌已成为癌症相关死亡的主要原因。根据全球癌症观察组织(globcan)的数据, 2020 年, 全世界约有 220 万新病例和 180 万人死于肺癌[27]。最常见的肺癌类型是非小细胞肺癌(NSCLC), 包括腺癌、鳞状细胞癌和大细胞癌, 占肺癌的 85% [28]。在所有的肺癌患者中, 40% 的新诊断患者处于 IV 期[29]。尽管有报道称免疫治疗比化疗更有益, 但并非所有的 NSCLC 病例都得到了有效治疗[30]。因此, 需要预后标志物来评估非小细胞肺癌患者的免疫治疗结果[31]。许多研究显示 NSCLC 免疫治疗后 NLR 与标准预后值显著相关[32]。NLR 可作为免疫治疗 NSCLC 患者的潜在预后因素[33]。一项荟萃分析共纳入 1719 例患者, 其结果显示 NLR 患者的无进展生存期(PFS)和总生存期(OS)的危险比(HR)结果显示了显著的结果, 支持 NLR 作为预后指标(NLR: HR PFS 2.21 [95% CI: 1.50~3.24; $p < 0.0001$] 和 HR OS 2.68 [95% CI: 2.24~3.6; $P < 0.0001$]; 亚组分析显示 NLR 的临界值为 5, 也显示了显著的结果。NLR 水平升高与预后不良相关[34]。

2.5. NLR 与结直肠癌的预后

结直肠癌是最常见的胃肠道恶性肿瘤之一, 是全球癌症相关死亡的第四大常见原因[35]。然而, 近年来, 由于医疗治疗和外科手术技术的改进, 加上在专门的专科中心引入多学科团队管理, 以及通过有针对性的筛查方案及早诊断, 总体死亡率已显著下降[36]。近几十年来, 炎症和癌症发展之间的联系得到了更好的描述[37]。越来越多的证据表明, 癌症引发的炎症在结直肠癌的发生中起着至关重要的作用。此外,

一些研究表明全身炎症(生物)标记物是预测复发时间和长期生存的潜在替代标记物[38]。有研究表明[39], NLR 可用于术前和术后准确预测 II/III 期结直肠癌手术切除患者的长期生存; 前 NLR > 5 与局限性结直肠癌患者和肝转移患者的长期生存率较低相关。有趣的是, 有研究发现, 定期服用消炎药的患者患 CRC 的风险显著降低。尽管心血管事件和胃肠道副作用的发生率增加, 但常规使用环氧合酶-2 抑制剂和其他非甾体抗炎药已被发现不仅能降低 CRC 的发生率, 而且还能降低转移进展和总死亡率[40]。NLR 是一个有用的生物标志物, 可用于区分预后较差的患者和可能受益于辅助治疗的患者。

3. 结论

尽管 NLR 构成了包括膀胱癌、前列腺癌、非小细胞肺癌、乳腺癌[41]、结直肠癌[42]和食管癌[43]在内的不同癌症的预后指标, 但它不仅与癌症预后相关, 它也与许多其他疾病的预后有关, 如心血管疾病[44], 败血症[45], 甚至在创伤学[46]和精神疾病[47]。确切的病理生理学解释至今仍不清楚, 也不能很好地理解和解释。此外, 与非转移性疾病相比, 转移性疾病的高 NLR 与较差 OS 的相关性有一个趋势, 这可能反映了更大的肿瘤负荷或更长的慢性炎症过程[48]。高 NLR 和癌症患者预后差的相关机制尚不清楚。NLR 预后影响的一个潜在机制可能是高 NLR 与炎症的关联。近年来, 人们在生物标记物的开发上投入了大量的精力和资源, 这有助于为癌症患者量身定制治疗方法。针对癌症患者的相关研究表明, 化疗可以在治疗开始后早期使 NLR 升高恢复正常, NLR 恢复正常的患者可能有良好的预后[49]。早期停止无效的治疗, 引入有效的治疗, 可避免不必要的毒性, 并可提高癌症患者的生活质量。血液 NLR 的变化可能有助于对缺乏可靠生物标志物的晚期癌症患者进行针对性治疗。尽管 NLR 在早期癌症中的预后作用不如晚期癌症, 但它的作用仍可能与评估系统治疗的早期疗效有关。NLR 是一种容易获得且廉价的生物标志物, 它作为临床决策的预后评分的补充值得进一步研究。

参考文献

- [1] Gregory, A.D. and Houghton, A.M. (2011) Tumor-Associated Neutrophils: New Targets for Cancer Therapy. *Cancer Research*, **71**, 2411-2416. <https://doi.org/10.1158/0008-5472.CAN-10-2583>
- [2] Mantovani, A., Allavena, P., Sica, A. and Balkwill, F. (2008) Cancer-Related Inflammation. *Nature*, **454**, 436-444. <https://doi.org/10.1038/nature07205>
- [3] Shaul, M.E. and Fridlender, Z.G. (2019) Tumour-Associated Neutrophils in Patients with Cancer. *Nature Reviews Clinical Oncology*, **16**, 601-620. <https://doi.org/10.1038/s41571-019-0222-4>
- [4] Gooden, M.J., de Bock, G.H., Leffers, N., et al. (2011) The Prognostic Influence of Tumour-Infiltrating Lymphocytes in Cancer: A Systematic Review with Meta-Analysis. *British Journal of Cancer*, **105**, 93-103. <https://doi.org/10.1038/bjc.2011.189>
- [5] Templeton, A.J., McNamara, M.G., Seruga, B., et al. (2014) Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. *JNCI: Journal of the National Cancer Institute*, **106**, dju124. <https://doi.org/10.1093/jnci/dju124>
- [6] Siegel, R.L., Miller, K.D. and Jemal, A. (2019) Cancer Statistics, 2019. *CA: A Cancer Journal for Clinicians*, **69**, 7-34. <https://doi.org/10.3322/caac.21551>
- [7] Shao, Y., Wu, B., Jia, W., et al. (2020) Prognostic Value of Pretreatment Neutrophil-to-Lymphocyte Ratio in Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. *BMC Urology*, **20**, 90. <https://doi.org/10.1186/s12894-020-00665-8>
- [8] Greten, F.R. and Grivnickov, S.I. (2019) Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity*, **51**, 27-41. <https://doi.org/10.1016/j.immuni.2019.06.025>
- [9] de Martino, M., Pantuck, A.J., Hofbauer, S., et al. (2013) Prognostic Impact of Preoperative Neutrophil-to-Lymphocyte Ratio in Localized Nonclear Cell Renal Cell Carcinoma. *Journal of Urology*, **190**, 1999-2004. <https://doi.org/10.1016/j.juro.2013.06.082>
- [10] Wei, Y., Jiang, Y.Z. and Qian, W.H. (2014) Prognostic Role of NLR in Urinary Cancers: A Meta-Analysis. *PLOS ONE*, **9**, e92079. <https://doi.org/10.1371/journal.pone.0092079>

- [11] Ohno, Y., Nakashima, J., Ohori, M., *et al.* (2012) Follow-Up of Neutrophil-to-Lymphocyte Ratio and Recurrence of Clear Cell Renal Cell Carcinoma. *Journal of Urology*, **187**, 411-417. <https://doi.org/10.1016/j.juro.2011.10.026>
- [12] Jagdev, S.P., Gregory, W., Vasudev, N.S., *et al.* (2010) Improving the Accuracy of Pre-Operative Survival Prediction in Renal Cell Carcinoma with C-Reactive Protein. *British Journal of Cancer*, **103**, 1649-1656. <https://doi.org/10.1038/sj.bjc.6605973>
- [13] Pichler, M., Hutterer, G.C., Stoeckigt, C., Chromecki, T.F., Stojakovic, T., Golbeck, S., Eberhard, K., Gerger, A., Mannweiler, S., Pummer, K. and Zigeuner, R. (2013) Validation of the Pre-Treatment Neutrophil-Lymphocyte Ratio as a Prognostic Factor in a Large European Cohort of Renal Cell Carcinoma Patients. *British Journal of Cancer*, **108**, 901-907. <https://doi.org/10.1038/bjc.2013.28>
- [14] 郭晓波. 肾癌患者外周血中性粒细胞淋巴细胞比值与其预后的关系分析[J]. 长治医学院学报, 2016, 30(2): 121-124.
- [15] Antoni, S., Ferlay, J., Soerjomataram, I., *et al.* (2017) Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *European Urology*, **71**, 96-108. <https://doi.org/10.1016/j.eururo.2016.06.010>
- [16] Burger, M., Catto, J.W., Dalbagni, G., *et al.* (2013) Epidemiology and Risk Factors of Urothelial Bladder Cancer. *European Urology*, **63**, 234-241. <https://doi.org/10.1016/j.eururo.2012.07.033>
- [17] Babjuk, M., Böhle, A., Burger, M., *et al.* (2017) EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder: Update 2016. *European Urology*, **71**, 447-461. <https://doi.org/10.1016/j.eururo.2016.05.041>
- [18] Xylinas, E., Kent, M., Kluth, L., *et al.* (2013) Accuracy of the EORTC Risk Tables and of the CUETO Scoring Model to Predict Outcomes in Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. *British Journal of Cancer*, **109**, 1460-1466. <https://doi.org/10.1038/bjc.2013.372>
- [19] Vartolomei, M.D., Porav-Hodade, D., Ferro, M., Mathieu, R., *et al.* (2018) Prognostic Role of Pretreatment Neutrophil-to-Lymphocyte Ratio (NLR) in Patients with Non-Muscle-Invasive Bladder Cancer (NMIBC): A Systematic Review and Meta-Analysis. *Urologic Oncology*, **36**, 389-399. <https://doi.org/10.1016/j.urolonc.2018.05.014>
- [20] Tang, X., Du, P. and Yang, Y. (2017) The Clinical Use of Neutrophil-to-Lymphocyte Ratio in Bladder Cancer Patients: A Systematic Review and Meta-Analysis. *International Journal of Clinical Oncology*, **22**, 817-825. <https://doi.org/10.1007/s10147-017-1171-5>
- [21] Ogihara, K., Kikuchi, E., Yuge, K., *et al.* (2016) The Preoperative Neutrophil-to-Lymphocyte Ratio Is a Novel Biomarker for Predicting Worse Clinical Outcomes in Non-Muscle Invasive Bladder Cancer Patients with a Previous History of Smoking. *Annals of Surgical Oncology*, **23**, 1039-1047. <https://doi.org/10.1245/s10434-016-5578-4>
- [22] Kimura, T. and Egawa, S. (2018) Epidemiology of Prostate Cancer in Asian Countries. *International Journal of Urology*, **25**, 524-531. <https://doi.org/10.1111/iju.13593>
- [23] Kawahara, T., Yokomizo, Y., Ito, Y., *et al.* (2016) Pretreatment Neutrophil-to-Lymphocyte Ratio Predicts the Prognosis in Patients with Metastatic Prostate Cancer. *BMC Cancer*, **16**, 111. <https://doi.org/10.1186/s12885-016-2134-3>
- [24] Murata, H., Koyama, K., Takezawa, Y. and Nishigaki, Y. (2018) Baseline Neutrophil-to-Lymphocyte Ratio Predicts the Prognosis of Castration-Resistant Prostate Cancer Treated with Abiraterone Acetate. *Molecular and Clinical Oncology*, **8**, 587-591.
- [25] Kumano, Y., Hasegawa, Y., Kawahara, T., *et al.* (2019) Pretreatment Neutrophil to Lymphocyte Ratio (NLR) Predicts Prognosis for Castration Resistant Prostate Cancer Patients Underwent Enzalutamide. *BioMed Research International*, **2019**, Article ID: 9450838. <https://doi.org/10.1155/2019/9450838>
- [26] Mjaess, G., Chebel, R., Karam, A., *et al.* (2021) Prognostic Role of Neutrophil-to-Lymphocyte Ratio (NLR) in Urological Tumors: An Umbrella Review of Evidence from Systematic Reviews and Meta-Analyses. *Acta Oncologica*, **60**, 704-713. <https://doi.org/10.1080/0284186X.2021.1886323>
- [27] Sung, H., Ferlay, J., Siegel, R.L., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **71**, 209-249. <https://doi.org/10.3322/caac.21660>
- [28] Nicholson, A.G., Tsao, M.S., Beasley, M.B., *et al.* (2022) The 2021 WHO Classification of Lung Tumors: Impact of Advances since 2015. *Journal of Thoracic Oncology*, **17**, 362-387. <https://doi.org/10.1016/j.jtho.2021.11.003>
- [29] Zhu, X., Song, H., Chen, Y., *et al.* (2020) Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Blood to Distinguish Lung Cancer Patients from Healthy Subjects. *Disease Markers*, **2020**, Article ID: 8844698. <https://doi.org/10.1155/2020/8844698>
- [30] Liu, J., Li, S., Zhang, S., *et al.* (2019) Systemic Immune-Inflammation Index, Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio Can Predict Clinical Outcomes in Patients with Metastatic Non-Small-Cell Lung Cancer Treated with Nivolumab. *Journal of Clinical Laboratory Analysis*, **33**, e22964. <https://doi.org/10.1002/jcla.22964>
- [31] Raedler, L.A. (2015) Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable

- or Metastatic Melanoma. *American Health & Drug Benefits*, **8**, 96-100.
- [32] Katayama, Y., Yamada, T., Chihara, Y., *et al.* (2020) Significance of Inflammatory Indexes in Atezolizumab Monotherapy Outcomes in Previously Treated Non-Small-Cell Lung Cancer Patients. *Scientific Reports*, **10**, Article No. 17495. <https://doi.org/10.1038/s41598-020-74573-0>
- [33] Lababede, O. and Meziane, M.A. (2018) The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. *Oncologist*, **23**, 844-848. <https://doi.org/10.1634/theoncologist.2017-0659>
- [34] Platini, H., Ferdinand, E., Kohar, K., *et al.* (2022) Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Markers for Advanced Non-Small-Cell Lung Cancer Treated with Immunotherapy: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)*, **58**, 1069. <https://doi.org/10.3390/medicina58081069>
- [35] Haggar, F.A. and Boushey, R.P. (2009) Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. *Clinics in Colon and Rectal Surgery*, **22**, 191-197. <https://doi.org/10.1055/s-0029-1242458>
- [36] Ait Ouakrim, D., Pizot, C., Boniol, M., *et al.* (2015) Trends in Colorectal Cancer Mortality in Europe: Retrospective Analysis of the WHO Mortality Database. *BMJ*, **351**, h4970. <https://doi.org/10.1136/bmj.h4970>
- [37] Moore, M.M., Chua, W., Charles, K.A. and Clarke, S.J. (2010) Inflammation and Cancer: Causes and Consequences. *Clinical Pharmacology & Therapeutics*, **87**, 504-508. <https://doi.org/10.1038/clpt.2009.254>
- [38] Haram, A., Boland, M.R., Kelly, M.E., *et al.* (2017) The Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Colorectal Cancer: A Systematic Review. *Journal of Surgical Oncology*, **115**, 470-479. <https://doi.org/10.1002/jso.24523>
- [39] Kubo, T., Ono, S., Ueno, H., *et al.* (2014) Impact of the Perioperative Neutrophil-to-Lymphocyte Ratio on the Long-Term Survival Following an Elective Resection of Colorectal Carcinoma. *International Journal of Colorectal Disease*, **29**, 1091-1099. <https://doi.org/10.1007/s00384-014-1964-1>
- [40] Grivennikov, S.I., Greten, F.R., Karin, M. *et al.* (2010) Immunity, Inflammation, and Cancer. *Cell*, **140**, 883-899. <https://doi.org/10.1016/j.cell.2010.01.025>
- [41] Ethier, J.L., Desautels, D., Templeton, A., *et al.* (2017) Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Breast Cancer: A Systematic Review and Meta-Analysis. *Breast Cancer Research*, **19**, Article No. 2. <https://doi.org/10.1186/s13058-016-0794-1>
- [42] Mazaki, J., Katsumata, K., Kasahara, K., *et al.* (2020) Neutrophil-to-Lymphocyte Ratio Is a Prognostic Factor for Colon Cancer: A Propensity Score Analysis. *BMC Cancer*, **20**, Article No. 922. <https://doi.org/10.1186/s12885-020-07429-5>
- [43] Arigami, T., Okumura, H., Matsumoto, M., *et al.* (2015) Analysis of the Fibrinogen and Neutrophil-Lymphocyte Ratio in Esophageal Squamous Cell Carcinoma: A Promising Blood Marker of Tumor Progression and Prognosis. *Medicine (Baltimore)*, **94**, e1702. <https://doi.org/10.1097/MD.0000000000001702>
- [44] Bhat, T., Teli, S., Rijal, J., *et al.* (2013) Neutrophil to Lymphocyte Ratio and Cardiovascular Diseases: A Review. *Expert Review of Cardiovascular Therapy*, **11**, 55-59. <https://doi.org/10.1586/erc.12.159>
- [45] Huang, Z., Fu, Z., Huang, W. and Huang, K. (2020) Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Sepsis: A Meta-Analysis. *The American Journal of Emergency Medicine*, **38**, 641-647. <https://doi.org/10.1016/j.ajem.2019.10.023>
- [46] Park, J.M. (2017) Neutrophil-to-Lymphocyte Ratio in Trauma Patients. *Journal of Trauma and Acute Care Surgery*, **82**, 225-226. <https://doi.org/10.1097/TA.0000000000001266>
- [47] Mazza, M.G., Lucchi, S., Tringali, A.G.M., *et al.* (2018) Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Mood Disorders: A Meta-Analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **84**, 229-236. <https://doi.org/10.1016/j.pnpbp.2018.03.012>
- [48] Aggarwal, B.B., Vijayalekshmi, R.V. and Sung, B. (2009) Targeting Inflammatory Pathways for Prevention and Therapy of Cancer: Short-Term Friend, Long-Term Foe. *Clinical Cancer Research*, **15**, 425-430. <https://doi.org/10.1158/1078-0432.CCR-08-0149>
- [49] Kao, S.C., Pavlakis, N., Harvie, R., Vardy, J.L., *et al.* (2010) High Blood Neutrophil-to-Lymphocyte Ratio Is an Indicator of Poor Prognosis in Malignant Mesothelioma Patients Undergoing Systemic Therapy. *Clinical Cancer Research*, **16**, 5805-5813. <https://doi.org/10.1158/1078-0432.CCR-10-2245>