

外周血指标与卵巢癌诊治及预后相关性研究进展

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收稿日期: 2023年10月8日; 录用日期: 2023年11月3日; 发布日期: 2023年11月8日

摘要

卵巢癌是全球女性癌症相关死亡的第八大原因, 严重威胁着全球女性的生命和健康。目前, 卵巢癌的早期筛查、治疗及预后监测方面仍有较大的研究空间。肿瘤微环境中与肿瘤相关的各种炎症指标可能是癌症发生和进展的关键因素。基于全血细胞计数的复合炎症标志物, 即SII、PLR、NLR、LMR等, 不仅在多种癌症中得到广泛研究, 而且与OC的发生、发展具有相关性。本文综述SII、PLR、NLR及LMR在卵巢癌的诊断及预后评估中的研究进展, 以期对未临床实践提供帮助。

关键词

卵巢癌, 外周血指标, 诊治, 预后

Research Progress of the Relationship between Peripheral Blood Indexes and the Diagnosis, Treatment and Prognosis of Ovarian Cancer

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Received: Oct. 8th, 2023; accepted: Nov. 3rd, 2023; published: Nov. 8th, 2023

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文章引用: 严洁, 宋小苏, 唐惠华, 王蓓. 外周血指标与卵巢癌诊治及预后相关性研究进展[J]. 临床医学进展, 2023, 13(11): 17362-17373. DOI: 10.12677/acm.2023.13112432

Abstract

Ovarian cancer (OC) is the eighth leading cause of female cancer-related deaths in worldwide, which seriously threatens the life and health of women all over the world. At present, there is still a large research space in the early screening, treatment and prognosis monitoring of ovarian cancer. Various markers of inflammation associated with tumors in the tumor micro environment may be key factors in the development and progression of cancer. Complex inflammatory markers based on complete blood count, namely SII, PLR, NLR, LMR, etc., which not only been widely studied in a variety of cancers, but also have a correlation with the occurrence and development of OC. This article reviews the research progress of SII, PLR, NLR and LMR in the diagnosis and prognosis estimation of ovarian cancer, in order to provide help for future clinical practice.

Keywords

Ovarian Cancer, Peripheral Blood Indexes, Diagnosis and Treatment, Prognosis

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1. 引言

卵巢癌(Ovarian Cancer, OC)是妇科恶性肿瘤中致死率最高的。据统计, 卵巢癌的发病率为 3.4%, 死亡率为 4.7%, 每年有 30 多万名妇女患病, 约有 152,000 名妇女死于卵巢癌, 这些数据足以表明这种疾病对妇女的健康和生存构成严重威胁[1]。目前卵巢癌的主要治疗方案: 手术 + 铂类药物化疗[2]。然而, 卵巢癌患者预后差, 生存率仅为 30% [3]。由于 OC 发病隐匿, 加之疾病进展快, 所以超过 70% 的患者一经诊断已是晚期[4]。其次, OC 的复发率高, 据统计超过一半的患者会在两年内复发, 导致生存率几乎没有改善[5] [6]。有研究报道, 早期疾病的 5 年总生存率约为 92%, 而晚期疾病的 5 年总生存率为 29% [7]。因此, 早期发现和诊断对改善预后具有重要意义。

尽管对卵巢癌进行了多年的研究, 致力于寻找可靠的肿瘤标志物, 但仍然缺乏可靠的筛查及诊断方法[8] [9] [10]。越来越多的研究证实了肿瘤诱发炎症、炎症进一步促进肿瘤进程。而近年研究发现系统免疫炎症指数(Systemic immune-inflammation index, SII)、血小板与淋巴细胞比值(Platelet to Lymphocyte Ratio, PLR)、中性粒细胞与淋巴细胞比值(Neutrophil to Lymphocyte Ratio, NLR)、单核细胞与淋巴细胞比值(Monocyte-to-lymphocyte ratio, LMR)是反映全身炎症反应较好的指标, 而且它们在恶性肿瘤的诊断和预后评估中具有一定价值。本文旨在通过概述外周血指标与 OC 发生、发展的关系, 以期为 OC 的诊疗及预后提供一种新思路。

2. 炎症与恶性肿瘤

肿瘤微环境在癌细胞生长的过程中起着至关重要的作用, 是肿瘤发生、发展的“土壤”。而肿瘤微环境的概念, 得益于英国学者首次提出的“种子 - 土壤”理论。它是一个极其复杂的细胞网络, 其中, 肿瘤细胞和基质细胞(如成纤维细胞)会诱导多种炎症因子分泌, 从而构建一个炎症微环境。这种炎症微环境调节肿瘤发生及发展的生物过程, 从而影响肿瘤的恶性特征[11] [12]。因此, 可以说癌症的主要特征之

一是炎症，它影响肿瘤恶性特征的表达、肿瘤血管生成以及改变基因组的稳定性[13] [14] [15]。关于炎症和癌症的临床联系可以追溯到 19 世纪末，当时 Virchow 在注意到癌组织中存在白细胞浸润后，首次把炎症与肿瘤联系起来[16]。

众所周知，炎症是对感染或损伤的一种反应，就其本质上而言对机体是有益的，通常会随着正常组织结构和功能的恢复而消退，但是当炎症持续时，一方面，会导致组织损伤和功能丧失，另一方面，可能会促进肿瘤的发生和发展[17]。随着对炎症和肿瘤的不断研究，Rodriguez 等学者首次确立了炎症与癌症之间的联系。此后，越来越多的研究均表明了炎症与肿瘤之间相互影响、相互作用，炎症和肿瘤之间的联系得到了很好的证实[16]。一方面，在肿瘤的形成过程中，会诱导炎症的发生。炎症细胞在多种趋化因子的作用下聚集、浸润，并诱导炎症相关细胞因子的转录和表达，从而诱发肿瘤周围局部的炎症，甚至是全身性的炎症。另一方面，炎症环境有利于肿瘤的发生发展。在炎症环境中，炎症细胞及炎症介质的聚集，促进细胞因子的分泌，诱导大量的活性氧和炎性因子的释放，进一步导致 DNA 损伤、加剧肿瘤基因突变，激活原癌基因、抑制抑癌基因，并促进肿瘤相关的血管及淋巴管的生成，进而促进肿瘤的发生和发展[18] [19] [20]。比如说，促炎细胞因子，特别是肿瘤坏死因子 α (TNF- α)和白细胞介素 6 (IL-6)，会促进肿瘤细胞的增殖，在癌变中起作用。由此可见，炎症与肿瘤密切相关，在肿瘤的发生及发展过程中相互作用、相互影响。

3. 炎症与卵巢癌

目前，卵巢癌的发病机制尚不明确。随着医学研究的不断发展，就此提出了一些假说及理论：基于高雌激素水平的促性腺激素假说、炎症假说、月经逆行理论和持续性排卵理论等[21]。在排卵过程中，卵巢皮质破裂及自然愈合涉及炎症反应。其次，在一项前瞻性研究中，发现卵巢癌患者在定期服用阿司匹林或非阿司匹林的甾体抗炎药之后，可以提高卵巢癌患者的特异性生存率。另外，有研究表明，子宫内膜异位症、盆腔炎的患者会增加患卵巢癌的风险[22]。由此可见，炎症环境有利于肿瘤的发生。在卵巢癌发生之前，肿瘤细胞就会诱导机体产生适合肿瘤发生发展的环境，其中包括炎症微环境。所以，炎症可能是卵巢癌发生发展的病理生理因素。

4. 炎症相关细胞在肿瘤中的作用

经研究证实，外周血中的中性粒细胞、血小板、淋巴细胞也会导致肿瘤细胞侵袭并扩散至远处器官，与多种肿瘤的进展密切相关[23]。了解中性粒细胞、血小板和淋巴细胞及单核细胞在癌症中的作用，将有助于阐明癌症、免疫和炎症之间的关系。

4.1. 中性粒细胞

研究表明，中性粒细胞可以提升癌细胞增殖、侵袭及远处转移的能力[24] [25]。在一项研究中发现肿瘤诱导的中性粒细胞能抑制细胞毒性 CD8+ T 淋巴细胞的激活，进而促进转移，而中性粒细胞的缺失则减少了癌细胞向肺部和淋巴结转移[26]。Lee 等人报道了卵巢肿瘤来源的中性粒细胞通过形成中性粒细胞外陷阱(NET)，从而刺激定植在大网膜中的卵巢癌细胞，最终实现大网膜转移。而另一项研究发现，当中性粒细胞特异性缺乏时，癌细胞向大网膜定植并转移显著减少[27]。此外，中性粒细胞具有促进活性氧、活性氮或蛋白酶等的释放能力，从而促进肿瘤的发生；可诱导血管内皮生长因子 A (VEGFA)、MMP9 的分泌，从而促进肿瘤血管的生成；可促进精氨酸酶-1 的分泌，从而阻碍 T 淋巴细胞活化，进而影响 T 淋巴细胞诱导的抗肿瘤作用；此外，可以抑制自然杀伤(NK)细胞功能，从而促进肿瘤细胞外渗、扩散[28]。

4.2. 血小板

癌细胞与肿瘤微环境的相互作用是肿瘤从进展到转移的重要决定因素。血小板与肿瘤细胞之间通过不同的作用机制,从而促进肿瘤细胞的增殖和转移[29][30]。比如说,血小板与肿瘤细胞可以直接相互作用,从而激活肿瘤中细胞因子的 TGF- β 和 NF- κ B 信号通路,促进肿瘤细胞转移[29]。在 Yao 等人的研究中,将乳腺癌患者与健康人对照,发现血小板表达明显升高之后,从而增强了癌细胞的迁移能力[31]。在小鼠模型中,血小板通过高表达转化生长因子 β 1 (tgf- β 1)促进卵巢癌的生长。因此,当小鼠缺乏血小板特异性 tgf- β 1 时,会抑制肿瘤生长、血管生成和血小板外渗[32]。血小板与肿瘤细胞之间的相互作用,除了以血液为基础,还可以在腹水和肿瘤微环境中发挥作用。血小板可以外渗到肿瘤微环境中,在一定程度上取决于血小板表达的局灶黏附激酶(FAK) [33]。有研究将血小板与卵巢癌细胞系共同孵育,结果表明血小板通过激活上皮-间质转化,从而促进癌细胞转移[34][35]。此外,血小板作为循环血管生成的重要来源,可以调解肿瘤血管的生成及完整性[36]。由此可见,血小板不是肿瘤发生发展的“旁观者”,而是肿瘤生长和转移过程中的功能性的“参与者”。

4.3. 淋巴细胞

众所周知,淋巴细胞是机体特有的免疫细胞,可以阻止癌细胞的增殖及扩散,从而发挥抗感染、抗肿瘤的作用。淋巴细胞释放 IFN- γ 和 TNF- α 细胞因子,抑制肿瘤细胞的生长和转移;因此,淋巴细胞减少常表明机体的免疫监测功能受损,与许多癌症患者的不良预后有关[37]。

4.4. 单核细胞

炎症可激发单核细胞从骨髓向外周血动员,在募集到肿瘤细胞后,单核细胞分化为肿瘤相关巨噬细胞[38]。肿瘤相关巨噬细胞可以通过肿瘤来源的趋化因子募集到肿瘤组织,诱导氧自由基、氮自由基等的产生,刺激肿瘤相关的血管生成、从而促进癌细胞扩散及转移。也就意味着,外周血中的单核细胞能反映肿瘤相关巨噬细胞的形成或存在[39]。而淋巴细胞在肿瘤细胞浸润时建立了一种防御屏障,可诱导细胞死亡、抑制肿瘤细胞的增殖和迁移,从而防止癌症扩散[24]。据报道,在血液和肿瘤基质中,淋巴细胞计数减少导致机体对肿瘤的免疫反应下调[40]。因此,血液中淋巴细胞计数的减少是各种癌症 OS 的独立预后因素[41]。

5. SII、NLR、PLR、LMR 在肿瘤中的作用

5.1. SII

SII 对肿瘤复发和转移等临床结局有一定预测价值。而 SII 升高,通常意味着血小板增多或中性粒细胞增多及淋巴细胞减少,这可能反映了机体的高炎症水平及较弱免疫反应。虽然确切的机制尚不清楚,但中性粒细胞和血小板的促肿瘤功能以及淋巴细胞的肿瘤抑制作用,能说明高 SII 在癌症中的预后价值。在 2014 年, Hu 等学者证实了 SII 在预测肝癌患者预后的可行性及临床价值,与其他血液复合炎症指标相比,它更客观地反映机体炎症和免疫之间的平衡,并且预测价值更高[37]。并且 SII 的高预测价值,在肝癌、宫颈癌、食管癌和肺癌等肿瘤中得到证实[42]。

5.2. NLR

机体的炎症水平和免疫状况可以通过外周血的中性粒细胞、淋巴细胞水平体现。鉴于中性粒细胞在肿瘤中有异质性和多样性的特点,淋巴细胞是重要的免疫细胞,进一步研究了中性粒细胞与淋巴细胞两种细胞的绝对值之比,即 NLR,能反映炎症的严重程度。相关研究报道,通过监测 NLR 的值可以判断

恶性肿瘤的进展情况。在许多实体肿瘤中，无论是早期还是晚期，NLR 升高提示预后不良。而 NLR 升高也就意味着中性粒细胞升高、淋巴细胞减少。近年来，NLR 被用于预测各种癌症的临床结局和预后，比如胃肠道间质肿瘤[43]、胶质母细胞瘤[44]、前列腺癌[45]、乳腺癌[46]。

5.3. PLR

PLR 系血小板与淋巴细胞的比值，PLR 升高是对癌症相关炎症的非特异性反应，一定程度上反应了机体血栓形成，炎症水平及免疫状态。而 PLR 升高意味着血小板计数增多而淋巴细胞减少。一个多世纪前，Leopold Riess 首次发现血小板计数增多与肿瘤有关。相关研究表明血小板计数的增加被认为是隐匿性恶性肿瘤发生的预测因子[47]。在卵巢癌中，肿瘤源性白细胞介素 6 (IL-6)刺激肝脏产生血小板生成素 (TPO)，诱导巨核生成和血小板增多，导致与卵巢癌[48]、结直肠癌[49]的不良预后相关。在一项实验中，将卵巢癌细胞注入雌性裸鼠腹腔中，注入血小板后增加了肿瘤重量，减弱了多西他赛的抗肿瘤作用，并经体外实验证实了血小板的抗肿瘤作用[50]。由此可见血小板增多与肿瘤的发生、发展有关。已有研究表明，PLR 升高是结直肠癌[51]、胰腺癌[52]等多种癌症的预后因素，并预测临床结局和预后。

5.4. LMP

LMP 是单核细胞与淋巴细胞的比值，可以反映患者淋巴细胞水平和单核细胞水平之间的平衡。据报道，LMP 在多种癌症中具有重要的诊断和预后价值。LMP 与恶性淋巴瘤[53] [54] [55]，实体肿瘤，比如头颈部肿瘤[56]、乳腺癌[57]、肺癌[39] [58]、食管癌[59]、胃癌[60]、结直肠癌[61] [62]、胰腺癌[63] [64]和宫颈癌[40]患者的生存期有关。在上述的报道中，低 LMR 与各种肿瘤的不良预后相关，是各种癌症的潜在生物标志物。虽然低 LMR 与癌症不良预后之间的机制尚未完全明确，但 LMR 可能反映了淋巴细胞在癌症进展中的有利作用以及单核细胞的不利作用之间的一种平衡状态[56]。

6. SII、NLR、PLR、LMR 在卵巢癌中的作用

6.1. SII 在卵巢癌中的作用

近年来，关于 SII 与卵巢癌的研究也逐渐开展。在 2018 年，Nie D 等人探讨 SII 在上皮性卵巢癌(epithelial ovarian cancer, EOC)患者中的预后价值，发现高水平的 SII 与患者的 FIGO 分期、淋巴结转移和肿瘤复发相关，缩减无进展生存期(PFS)和降低总生存期(OS)，并证实了 SII 是 EOC 患者的独立预后因素[65]。有学者探究 SII 对 III 期卵巢癌患者新辅助化疗疗效和预后的预测价值，结果显示，高 SII 与卵巢癌患者新辅助化疗无效、缩短无进展生存期和降低总生存期有关，并与不良预后有关，与上述研究结果相一致[66]。通过上述研究可以发现，高水平的中性粒细胞、血小板和低水平的淋巴细胞导致 SII 升高，最终可能导致卵巢癌的发生发展，并与患者预后不良有关。另外，有研究表明 SII 可以作为评估贝伐珠单抗治疗 EOC 的预测因子[67]。这些发现表明，SII 可以作为 OC 生存和进展的预后指标，可能是有价值的预测因子。

6.2. NLR 在卵巢癌中的作用

然而，卵巢癌并不是一种单一的疾病，它是一组基于不同形态和分子遗传特征的异质性肿瘤。随着医学的进步，也开始探索 NLR 与卵巢癌的关系，发现 NLR 可以预测卵巢癌的预后。在卵巢癌中，NLR 被证明与较差的病理特征相关，如肿瘤晚期[68]，NLR 升高预示着不良结局[69]。有研究称，在卵巢癌恶性病例中，NLR 的值显著升高，是预测恶性肿瘤的第二大敏感指标，仅次于糖类抗原 19-9 (CA19-9) [70]。Cho 等学者对照了 EOC 患者与良性卵巢肿瘤患者、良性卵巢肿瘤患者及健康人的 NLR 水平，他们发现 NLR 的值可以帮助鉴别卵巢肿瘤的良恶性并预测 OS；高水平的 NLR 预示卵巢癌的不良结局，为 NLR

与 EOC 之间的关联提供了证据[71]。此后, 在一项研究中分析了 519 例卵巢癌患者的临床资料, 其结果表明较高的 NLR 水平与较高的肿瘤分期和分级、腹水量及预后不良相关[69]。Zhang 等人也得出了类似的结论, 高 NLR 水平与 FIGO 分期、CA125 水平和腹水量具有相关性, 与上述研究结果相一致; 此外, 有研究发现卵巢癌患者的 NLR 水平越高, 其化疗完全缓解率越低, 预示着 NLR 在预测化疗敏感性方面有潜在作用, 并且在一定程度上可以反映肿瘤负荷[72]。在一项接受新辅助化疗的卵巢癌患者的研究中, 表明了 NLR 是卵巢癌患者新辅助化疗的预后指标, 已被确定为铂耐药和疾病预后的潜在生物标志物, 且可以作为 OS 的有效预测因子[73]。卵巢癌患者 FIGO 分期、淋巴结转移及腹水量等指标与患者的预后相关, 体现病情的活动性, 故证实了 NLR 在一定程度上可成为 OC 患者评估病情及推测预后的重要参考指标。

6.3. PLR 在卵巢癌中的应用

有多篇研究证实 PLR 是卵巢癌患者独立的预后因素, 且 PLR 升高与卵巢癌患者的不良预后密切相关[74] [75]。此外, 有研究报道, 高 PLR 是 EOC、输卵管癌和原发性腹膜癌患者接受铂类药物化疗后生存预后差的潜在独立预测因素[76]。随后, 有研究称当 PLR 值 ≥ 205.4 时, 预测 OC 患者的不完全缓解(CR, 准确率为 71.6%) [77]。这对临床工作有一定的指导作用。

6.4. LMR 在卵巢癌中的作用

有研究发现 LMR 升高与更长的生存期密切相关, 并且通过风险模型确定了 LMR 升高是 EOC 患者生存的独立预后因素[75]。一项研究中, 报道了 NLR、PLR 和 LMR 可以帮助我们更好地鉴别肿瘤的良好恶性[78], 并指导后续的治疗方案[79]。然而, 绝大多数研究是依据术前 LMR 进行的, 有学者研究术后 LMR, 发现其可作为 EOC 患者手术后的独立预后因素[80]。此外, 有研究联合血清 CA125 及 LMR, 探究其与卵巢癌分期之间的关系[81]。这为卵巢癌的预测预后打开了新思路, 提供了新可能。联合运用相关指标有利于 OC 的早期诊断及治疗, 如何将外周血指标与传统检测指标结合起来提高诊断 OC 的敏感性和特异性是未来研究的重点。

6.5. NLR 和 PLR 联合检测在卵巢癌中的作用

NLR 和 PLR 也可用于预测妇科恶性肿瘤的远处转移情况[82], 而且 NLR 和 PLR 的值会随着 OC 期别的增加而呈上升趋势[83]。有相关研究探讨了 NLR 和 PLR 在卵巢癌中的预后价值, 结果表明 NLR 及 PLR 的高水平状态会降低卵巢癌患者的 PFS 和 OS, 二者是卵巢癌的有效预后预测因子[84]。在 Prodromidou 等学者的研究中, 探究 PLR、NLR 联合检测对于诊断卵巢癌的价值, 发现这两者都可能是 EOC 的筛查有效预测指标[85]。此外, 在 EOC 患者在接受铂类化疗后, 有学者探讨了 NLR 和 PLR 预测化疗反应和生存结局的价值, 结果提示 NLR 和 PLR 有助于鉴别预后不良的患者, 并且在预测 EOC 患者铂耐药方面具有潜在的临床价值[86]。

而与单一血液参数作为炎症标志物相比, SII、PLR、NLR、LMR 等血液炎症复合标志物的敏感性和稳定性较好。它们已被证实不同卵巢癌患者的诊断和预测预后的价值, 包括上皮性卵巢癌(EOC)、高级别浆液性卵巢癌(HGSOC)和卵巢透明细胞癌(OCCC)。通过一系列的临床研究证实, 观察上述这些血液学指标与疾病预后的关系是合理的, 其较高的比例可能是肿瘤发生转移的一个早期征兆, 也是一个有价值的预后指标[87]。然而, 对这些指标的应用价值仍存在一些争议, 有研究表明 PLR 在监测 OC 患者术后状态方面没有价值[88], 并且对于预测 OC 患者的 OS 无显著意义[89] [90] [91]。另外, Raunkaewmanee 等人也发现 NLR 与 OC 患者 PFS 或 OS 无相关性[92]。除此之外, Topcu 等学者研究表明 NLR 并不是预

测盆腔肿块恶性特征的有效指标[93]。虽然这些血液炎症复合标志物已经研究多年,但与血清 CA125、HE4 等生物标志物相比,在临床实践中仍未得到广泛应用。目前,很少有指南或共识声明强调这些标志物的预测价值,对这些标志物的研究也没有很好的总结,今后需要大量的研究进一步证实。此外,SII、PLR、NLR、LMR 属于炎症指标,易受到其他炎症疾病、药物等的影响,在使用该类指标进行临床分析时应该对患者的基本情况进行分析。

糖类抗原 125 (CA125)、人附睾蛋白 4 (HE4)是临床诊断和监测 OC 复发常用的肿瘤标志物,但早期诊断的敏感性和特异性不高,因此临床应用价值有限。此外,据统计大约 1%的健康人群,5%的女性在月经期阶段、子宫内膜异位症的患者,其血清 CA125 水平也会有不同程度的升高,因此 CA125 作为筛查指标的作用有限[94]。这种高假阳性率可能给未患卵巢癌的妇女带来重大的不必要的心理和治疗负担。而外周血指标的检测简单易行,且在各种肿瘤的诊断及预测方面有一定的临床价值,因此,可与 CA125 及 HE4 联合检测,从而对卵巢肿瘤的性质及预后进行预测,以提高卵巢癌的早期诊断,改善预后,但相关报道尚少。

7. 结论与展望

综上所述,考虑到外周血指标是常规血液工作分析的一部分,具有易于测定、费用低廉、易于重复及动态观察等优势。独立的 SII、PLR、NLR 和 LMR 可以作为日常筛查的生物标志物用于早期 OC 的检测。然而,SII、PLR、NLR 和 LMR 联合在一起可能具有更好的诊断预测效果,可能是 OC 筛查的潜在组合,有望在未来的临床实践中用于 OC 的早期筛查、病情判断及预后的预测因子。当然,这些指标用于 OC 的诊断及预测预后各有利弊,因而,必要时与多种诊断指标联合检测对 OC 的早期筛查、临床诊断、降低发病率和病死率并改善预后以及监测治疗及复发可能更有价值。

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