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·综述·

血清炎症指数评估甲状腺癌预后的研究进展

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摘 要:血清炎症指数是一类基于外周血炎症相关细胞计数计算得到的新型标志物,能够反映机体的全身炎症状态。炎症在大多数恶性肿瘤的病理生理学中发挥着关键作用,长期慢性炎症最终会诱发肿瘤并促进其生长。大量研究发现,炎症指数与多种恶性肿瘤的预后及临床结局相关,并可作为预后评估的潜在血清标志物。近年来,甲状腺癌在全球范围内呈现出明显的上升趋势,不同病理类型的甲状腺癌预后差别显著,有关血清炎症指数与甲状腺癌预后的研究成为热点。本文综述了血清炎症指数对不同类型甲状腺癌患者生存情况、复发/转移和疗效的预测价值,以期为临床决策提供证据支持。

关 键 词:甲状腺癌;血清炎症指数;生存期;复发;预后

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Research advances in serum inflammation indexes for evaluating the prognosis of thyroid cancer

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Abstract: Serum inflammation indexes are novel biomarkers derived from the counting of inflammation-related cells in peripheral blood, which reflects the systemic inflammatory status of the body. Inflammation plays a pivotal role in the pathophysiology of most malignant tumors. Chronic persistent inflammation ultimately induces tumorigenesis and promotes its progression. Numerous studies have demonstrated that inflammation indexes are associated with the prognosis and clinical outcomes of various malignant tumors. The inflammation indexes can serve as potential serum biomarkers for prognostic assessment. In recent years, the global incidence of thyroid cancer has shown a significant increasing. There are significant differences in prognosis among different pathological subtypes. Consequently, it has become a hotspot of investigation on the relationship between serum inflammation indexes and thyroid cancer prognosis. This review summarizes the predictive value of serum inflammation indexes for survival outcomes, recurrence/metastasis, and treatment efficacy in different types of thyroid cancer. It will provide evidence for clinical treatment.

Keywords: Thyroid cancer; Serum inflammation indexes; Survival; Recurrence; Prognosis

炎症在肿瘤生物学中发挥着重要作用,肿瘤微环境和慢性炎症与恶性肿瘤的发生、发展及预后相关。炎症细胞可通过改变肿瘤微环境从而影响肿瘤发展,外周血中的淋巴细胞、单核细胞及中性粒细胞在一定刺激下可聚集到肿瘤部位,进而分化为肿瘤浸润淋巴细胞、肿瘤相关巨噬细胞(tumor-associated macrophages,TAMs)和肿瘤相关中性粒细胞,这些细胞均与恶性肿瘤的预后密切相关。基于外周血细胞计数计算所得的血清炎症指数包括中性粒细胞与淋巴细胞计数比值(neutrophil to lymphocyte ratio, NLR)、血小板与淋巴细胞计数比值(platelet to lymphocyte ratio, PLR)、淋巴细胞与单核细胞计数比值(lymphocyte to monocyte ratio, LMR)、血小板计数与NLR的乘积即系统性炎症免疫指数(systemic

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immune-inflammation index, SII)和预后营养指数(prognostic nutritional index, PNI)等。这些指数可以反映肿瘤患者的全身炎症状态,并可预测包括甲状腺癌在内的多种癌症患者的预后。

甲状腺癌是内分泌系统常见的恶性肿瘤,分为甲状腺乳头状癌(papillary thyroid cancer, PTC)、甲状腺滤泡状癌(follicular thyroid cancer, FTC)、甲状腺髓样癌(medullary thyroid cancer, MTC)、甲状腺低分化癌(poorly differentiated thyroid cancer, PDTC)和甲状腺未分化癌(anaplastic thyroid cancer, ATC),前两者合称为分化型甲状腺癌(differentiated thyroid cancer, DTC)。由于血清炎症指数获取方便、易于计算,其在甲状腺癌诊治及预后评估中的应用前景备受关注。本文就血清炎症指数与不同类型甲状腺癌预后的研究进展进行综述,以期为临床决策提供一定的证据支持。

1 DTC

有关研究支持血清炎症指数在DTC预后评估中的作用,主要是基于其对复发风险及生存情况的预测。NLR是恶性肿瘤(包括甲状腺癌)中研究最广泛的炎症预后指标,其升高通常提示预后较差。研究证实,中性粒细胞可直接与循环肿瘤细胞相互作用,驱动其在血流中的细胞周期进程并加速转移定植[1],而淋巴细胞可被趋化至肿瘤部位,并转化为肿瘤浸润淋巴细胞发挥抗肿瘤效应。因此,NLR反映出机体促癌炎症反应与抗癌免疫防御能力之间的平衡状态,而这种平衡状态可影响肿瘤患者的临床结局。Yildiz等[2]报道NLR与PTC预后分级系统之间存在显著统计学差异,高复发风险PTC患者的NLR高于低复发风险患者,且与美国甲状腺协会指南中的复发风险相关。Zhao等[3]研究发现NLR<2.51是甲状腺乳头状微小癌低复发风险的独立预测因子。有研究显示,DTC患者术后6个月疗效反应不佳者的NLR明显高于疗效确切者[4]。Lee等[5]认为NLR升高是疗效反应不佳的独立危险因素,因此NLR可反映DTC术后残留或复发。NLR在晚期PTC/DTC患者中更高[6-7],且与较短的无病生存期相关[8-9]。一项长期随访的回顾性研究显示,高NLR(>2.704)PTC患者的无病生存期显著缩短[10];远处转移性DTC患者NLR>3时,5年和10年的疾病特异性生存率较低(分别为50.4%和23.9%)[11]。这些研究表明NLR与DTC术后复发及不良预后有重要的预测价值。Feng等[12]的荟萃分析发现,高NLR与甲状腺癌患者的无病生存期、肿瘤大小及转移状态相关,但该研究中缺乏对DTC和MTC患者的亚组分析。另一项荟萃分析的结果未显示NLR、PLR、LMR与DTC患者无病生存期存在显著相关性[13],原因可能与各研究的临界值设定不一(NLR:1.6~3.15;LMR:3.62~10.42;PLR:124.3~180.0)、纳入标准不同(分期、放射性碘治疗)等有关,这也导致研究间存在显著异质性,因此对其结果的解读需持谨慎态度。

NLR与局部晚期或转移性甲状腺癌靶向治疗的反应性相关,进而影响患者的总体预后。在接受乐伐替尼治疗的放射性碘难治性DTC(radioiodine-refractory differentiated thyroid cancer, RAIR-DTC)患者中,疗效满意者NLR显著下降,疾病进展后NLR再次升高,且高NLR与较短的总生存期(overall survival, OS)相关[14],Ito等[15]的类似研究也支持NLR作为RAIR-DTC患者使用乐伐替尼治疗时评估和监测的指标。韩国一项多中心研究结果显示,NLR<2.2、PLR<140.1和LMR≥3.4与RAIR-DTC患者乐伐替尼治疗后OS显著延长相关[16],其后续研究发现NLR≥2是乐伐替尼治疗RAIR-DTC OS较短的独立预测因素[17]。Treistman等[18]研究认为NLR>3是局部晚期或转移性RAIR-DTC预后较差的独立预测因子。一项国际注册的多中心随机对照临床试验(NCT01321554)的研究结果显示,基线NLR≤3的患者无进展生存期和OS明显优于NLR>3的患者,由此认为NLR≤3可能是乐伐替尼治疗RAIR-DTC疗效较好的预测因子[19]。这些研究结果证实了NLR可有效预测晚期或RAIR-DTC患者的生存情况以及对小分子酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKI)治疗的疗效反应。

血小板及其衍生物通过与肿瘤微环境中的炎症细胞相互作用,影响恶性肿瘤的进展及预后。PLR与肿瘤细胞生物学行为相关的具体机制尚不明确,可能与血小板介导的白细胞介素(interleukin, IL)(如IL-1、IL-2和IL-6)释放有关[20]。PLR已在多种恶性肿瘤的预后中显示出潜在的预测价值,高PLR可能与预后不良相关。相对于早期DTC患者,PLR在晚期患者中显著升高,并与其无复发生存期相关[21]。Lee等[9]的研究也发现在45岁以下的PTC患者中,PLR升高与无病生存期缩短相关,且PLR>164.24是预测复发的独立危险因素。Riguetto等[22]报道PLR>124.34与DTC患者远处转移、疾病

进展和死亡相关,而无病生存状态的患者PLR则较低,Huang等[10]的研究得出了与之相似的结论。日本的一项多中心回顾性真实世界数据也表明,较高的NLR和PLR与局部晚期或RAIR-DTC患者的预后较差相关,索拉非尼作为一线治疗可使患者无病生存期明显获益[23]。少数研究显示PLR与PTC复发之间无相关性[3,24],原因可能与研究的患者纳入标准或PLR临界值的不同有关。

低LMR与多种恶性肿瘤的不良预后相关,可反映机体抗肿瘤免疫功能减弱,并提示有利于肿瘤生长的微环境[25]。低LMR与PTC患者(尤其是晚期患者)的高复发风险显著相关,因此可预测晚期或中高危PTC患者的无复发生存期及复发情况[24,26]。Katoh等[27]证实术前低LMR是晚期PTC复发的独立预测因素,并发现复发性PTC微环境中的TAMs增加。因此,LMR影响PTC预后的潜在机制可能为循环单核细胞聚集在肿瘤部位后分化为TAMs,促进肿瘤生长。Song等[28]研究发现高LMR可显著改善高危PTC患者的OS及无病生存期,且患者发生RAIR-DTC与术前低LMR相关。对于接受索拉非尼治疗的RAIR-DTC患者,LMR<4可预测其无进展生存期和死亡风险[29]。另一项类似的研究也发现LMR<3.4是无病生存期缩短的独立预测因素,高LMR则与患者OS显著延长相关[16]。尽管有报道称LMR与低危DTC患者的肿瘤复发无关[30],但LMR可能是预测高危、晚期或难治性DTC患者复发及生存情况的一个有前景的指标。

PNI可由人血白蛋白值(g/L)+5×外周血淋巴细胞计数($\times10^9$/L)计算所得,被广泛用于癌症患者生活质量及预后的评估。一项回顾性多中心临床研究结果显示,低PNI与PTC较晚的T分期有关,PNI≤53.1和NLR≤1.6是预测复发的独立危险因素[31]。Zhang等[32]发现术前低PNI与PTC患者TNM分期显著相关,且PNI≤55.79是无复发生存期的独立预测因素,也有研究报道PNI与低风险DTC患者的复发无关[30],可能与研究的患者人群不同有关。

2 MTC

Figueiredo等[33]认为术前NLR、PLR及SII与MTC的侵袭性临床病理特征相关,亦有研究发现上述炎症指数与MTC侵袭性病理特征及转移无关[34]。贾辰乐等[35]报道称NLR是MTC发生淋巴结转移的独立预测因素,Xu等[36]也观察到术前NLR与淋巴结/远处转移之间的关联,并且当NLR>1.784时可预测转移发生。虽然NLR可能是MTC转移筛查和强化管理的评估指标,但研究结论来自单中心、小样本的回顾性研究,因此需要深入研究NLR作为MTC预后标志物的价值。

研究报道较高的PLR与MTC淋巴结转移、术后复发率增加以及无病生存期缩短相关。PLR预测复发和无病生存期的临界值分别为129.8[37]和128.9[38]。另一项研究认为,PLR>138.3虽可预测MTC包膜侵犯,但并非淋巴结转移、降钙素升高和复发的预测因素,而LMR≤4.7是MTC术后降钙素升高的独立预测因素[39]。这些研究表明,血清炎症指数在识别高危MTC患者及指导随访和(或)治疗策略方面可能有一定的辅助作用。

3 PDTC

仅有少数研究评估了血清炎症指数在PDTC中的作用。Cho等[40]报道NLR高低与甲状腺癌的分化程度有关,NLR>3.8时可区分PDTC和ATC,进而帮助判断预后。Oba等[41]研究发现高NLR(>2.88)是PDTC患者OS较差的独立预测因素,其后续研究进一步发现NLR在PDTC(低分化成分≥50%)患者中显著高于单纯PTC和低分化成分<50%的PTC患者[42],表明NLR能够反映甲状腺癌低分化比例并可作为PDTC辅助诊断的生物标志物。Ahn等[43]比较了索拉非尼治疗的40例RAIR-DTC患者的LMR水平,发现LMR在PDTC、PTC、FTC之间无显著差异。

4 ATC

研究发现与晚期DTC相比,ATC患者的NLR和PLR更高,LMR更低,且LMR≤4.38是ATC生存期较短的危险因素[21]。亦有研究报道,LMR<4的ATC患者更容易发生颈部淋巴结转移,且总生存率显著降低[43]。此外,Park等[44]发现高NLR(≥3.47)是影响ATC手术患者生存的危险因素,放疗前后NLR均较高与ATC不良预后显著相关。Tomoda等[45]发现NLR≥4的ATC患者生存期更短,NLR >31.67时应考虑临终关怀(生存期<6周)。即便是发生远处转移的ATC患者,NLR较低的患者生存获益也明显[46]。法国的一项多中心

研究结果表明 NLR≥5.05 是 ATC 预后不良的独立预测因素,并且与患者 OS 缩短显著相关[47],进一步印证了 NLR 升高是 ATC 预后较差的危险因素。

Yamazaki 等[48]发现接受乐伐替尼治疗的 ATC 患者 NLR 增加同样与较短的中位生存期相关。Fukuda 等[49]的研究也反映出低 NLR(<8)ATC 患者在乐伐替尼治疗后疾病控制率较高,且无进展生存期和 OS 更长。另一项临床研究报道 TKI 治疗 ATC 的效果与 NLR 变化有关,TKI 治疗后 NLR 下降,治疗失败时 NLR 再次升高,NLR 升高可预测 TKI 疗效及耐药[50]。因此,NLR 可以作为 ATC 预后评估的血清标志物,同时也是乐伐替尼治疗 ATC 有效的早期评价指标。

5 总结和展望

机体免疫系统通过影响肿瘤微环境在癌症发生和进展中发挥重要作用,了解肿瘤局部炎症状态及其相关标志物可为研究甲状腺癌的发生机制提供思路。而且,血清炎症标志物有助于优化患者风险分层和指导术前治疗决策,也可作为术后评估指标,辅助制订术后治疗方案并预测患者治疗结局。因此,血清炎症相关指标的研究有望成为甲状腺癌研究的新兴领域,通过证实其在预后评估和 TKI 治疗中的疗效预测价值,进而为甲状腺癌尤其是高危或晚期患者的治疗决策提供重要依据。

血清炎症指数作为一类新型的复合型肿瘤预后标志物,具有无创获取、应用方便和价格低廉等优势。已有众多研究表明,血清炎症指数(NLR、PLR 和 LMR)与甲状腺癌的侵袭性生物学行为相关,在预测甲状腺癌复发及生存结局方面表现出良好的应用前景。然而,其临床应用仍面临挑战,比如不同研究确定血清炎症指数临界值的方法存在显著差异(包括中位数、三分位数和受试者工作特征曲线等),导致临界值的界定标准不一。血清炎症指数临界值标准化体系的缺失,是制约其向临床应用转化的一大障碍。因此需要积极开展多中心的前瞻性研究甚至是随机对照临床试验,将这些预后相关标志物纳入其中并进行严格、专业的算法处理,获得更加明确、可靠的数据,以详细、准确地确定外周血炎症指数在甲状腺癌预后评估中的应用价值。总之,血清炎症指数有助于预测甲状腺癌的侵袭性、复发和预后,前景广阔,值得进一步深入研究。

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