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预测肝细胞癌免疫治疗的预后

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摘 要

肝细胞癌(Hepatocellular carcinoma, HCC)是世界上最常见的肝癌，也是癌症死亡相关的主要原因之一。目前临床上单免疫治疗和免疫检查点抑制剂(Immune checkpoint inhibitors, ICIs)和多靶点酪氨酸激酶抑制剂(Tyrosine kinase inhibitors, TKIs)或抗血管内皮生长因子(Vascular endothelial growth factor, VEGF)抑制剂的联合治疗已成为晚期肝细胞癌(aHCC)的新标准疗法。然而，这些治疗的临床益处仍然有限。因此，迫切需要适当的生物标志物来预测对免疫疗法的治疗反应，以最大限度提高临床益处，同时避免不必要的毒性反应。截止到目前，还没有公认的生物标志物可用于预测HCC患者对免疫治疗的预后。因此，本文综述了肝细胞癌生物标志物的预测和预后，以期为HCC生物标志物探索和临床治疗选择的研究指导方向。

关键词

肝细胞癌，免疫疗法，联合疗法，生物标志物

Biomarkers of Immunotherapy for Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common liver cancer in the world and one of the

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leading causes of cancer-related death. Currently, single immunotherapy, Immune checkpoint inhibitors (ICIs), and multi-target Tyrosine kinase inhibitors are clinically recognized. Combination therapy with TKIs or anti-vascular endothelial growth factor (VEGF) inhibitors has become the new standard of treatment for advanced hepatocellular carcinoma (aHCC). However, the clinical benefits of these treatments are still limited. Therefore, there is an urgent need for appropriate biomarkers to predict therapeutic responses to immunotherapy to maximize clinical benefit while avoiding unnecessary toxic reactions. To date, there are no recognized biomarkers that can be used to predict the prognosis of HCC patients in response to immunotherapy. Therefore, this review reviews the prediction and prognosis of biomarkers for hepatocellular carcinoma, with a view to guiding the research direction of biomarker exploration and clinical treatment selection for HCC.

Keywords

Hepatocellular Carcinoma, Immunotherapy, Combination Therapy, Biomarkers

1. 引言

肝细胞癌(HCC)是最常见的原发性肝癌，常见于慢性肝病的背景下不断发展[1]。大多数患者被诊断为中晚期，错失手术机会。此外，尽管在早期诊断中，术后 5 年内复发率仍保持在 70%左右[2]。仑伐替尼、瑞戈非尼、卡博替尼和雷莫西鲁单抗等多靶点酪氨酸激酶抑制剂(TKI)等对晚期肝细胞癌(aHCC)的全身治疗选择在一定程度上提高了 aHCC 患者的生存率，然而，远未达到临床预期。近年来，包括纳武利尤单抗和帕博利珠单抗在内的免疫检查点抑制剂(ICIs)已显示出生存益处，并已被美国食品和药物管理局(FDA)批准用于 aHCC 治疗[3] [4]，可能会进一步改善患者的预后。

2. 外周血中的循环生物标志物

2.1. 中性粒细胞与淋巴细胞比值(NLR)和血小板与淋巴细胞比值(PLR)

中性粒细胞和血小板已经被发现与肿瘤生长和进展密切相关的细胞因子和生长因子[5] [6]。根据临床研究报道，NLR 和 PLR 也是多种癌症类型的预测因素[7] [8] [9] [10] [11]。NLR 和 PLR 升高也与肝细胞癌患者经动脉化疗栓塞(Transhepatic arterial chemoembolization, TACE)和索拉非尼治疗预后不良有关[12]。然而，在肝细胞癌的免疫治疗中，也有相同的预测作用。在 CheckMate 040 试验的 242 例患者的队列研究中，低 NLR 患者比高 NLR 患者表现出更好的 OS (p = 0.015) [13]。在 PLR 中也观察到了类似的结果，完全缓解或部分缓解(CR/PR)患者的 PLR 低于进展性疾病(PD)患者(p = 0.05)。在另一项研究中接受纳武利尤单抗治疗的 aHCC 患者中，基线 NLR 为≥3 的患者的无进展生存期(PFS)较差[11.0 vs 7.1; HR = 1.52 (95% CI 1.11~2.07), p = 0.01]和 OS [61.3 vs 21.0; HR = 2.72 (95% CI 1.86~3.99), p < 0.001]。此外，4 周时 NLR 值升高与死亡风险增加有关[HR = 1.79, 95% CI (1.19~2.68)]。有趣的是，在这项研究中，NLR 在 4 周时升高在预测超进展性疾病(HPD)方面也起作用，这可能有助于指导早期的治疗计划[14]。在一项接受单药或联合免疫治疗肝癌患者研究中，基线 NLR 和 PLR 较高的患者门静脉血栓形成(PVT)发生率更高，NLR ≥ 5 患者的 OS 和 PFS 明显缩短(OS：7.7 个月 vs 17.6 个月，p < 0.0001；PFS：2.1 vs 3.8 个月，

p = 0.03)和 PLR ≥ 300 (OS：6.7 vs 16.5 个月，p < 0.0001；PFS：1.8 vs 3.7 个月，p = 0.0006) [15]。

总之，在上述不同的研究分析表明，NLR 和 PLR 在 HCC 免疫治疗中具有很强的生存预测能力及对预后的预测趋势。至于潜在的预测机制，根据一些报道说，肿瘤分泌的 IL-8 和其他肿瘤生长因子可能会促进中性粒细胞募集[16]。增加的循环和肿瘤内中性粒细胞可以进一步分泌血管内皮生长因子(VEGF) [17]，从而引起肿瘤中更高水平的 VEGF 并促进血管生成有关。

2.2. 甲胎蛋白(AFP)和 C-反应蛋白(CRP)

甲胎蛋白(AFP)最常见于肝细胞癌的监测、诊断及预后。近年来，多项研究以探索其作用，并定义为 HCC 治疗预后相关的生物标志物[18]-[22]。在接受纳武利尤单抗或帕博利珠单抗治疗的研究中，ICI 治疗开始时 AFP < 400 μg/L 的患者比 AFP ≥ 400 μg/L 的患者具有更高的 CR 或 PR 率(24% vs 13%)，且基线血清 AFP < 400 μg/L 的患者出现更长的 PFS (5.4 个月 vs 2.6 个月，p < 0.05)和 OS (21.8 vs 8.7 个月，p < 0.0001) [23]。此外，最近报道了一种简单且易于应用的评分，由 CRP 和 AFP 组成的 CRAFITY 评分，该评分是通过对接受基于 CRP 和 AFP 的单药或联合免疫疗法的 aHCC 患者的分析构建的[24]。在这个分数中，AFP ≥ 100 ng/ml 和 CRP ≥ 1 mg/dl 都被分配了 1 分。患者可以达到 0、1 或 2 分，具体取决于这两个变量的水平。结果显示，基线血清 AFP ≥ 100 ng/ml 和 CRP ≥ 1 mg/dl 与 ICI 治疗的肝癌患者 OS 恶化独立相关。0 分(CRAFITY 低，n = 53)、1 分(CRAFITY 中度，n = 75)和 2 分(CRAFITY 高，n = 62)患者的中位 OS 分别为 27.6 对 11.3 个月和 6.4 个月(p < 0.001)。此外，高 CRAFITY 评分也表现出疾病控制率(Disease control rate, DCR)较差，分别为 80%和 64%和 39%，得分分别为 0、1 和 2 (p < 0.001)。Yang 等人进一步验证了 TKI 加免疫治疗和仑伐替尼单药治疗队列中的 CRAFITY 评分，研究结果示高分预测了较差的客观缓解率(Objective response rate, ORR)和 DCR [25]。这种简单的预后评分有助于免疫治疗的早期生存评估，并有望在应用于临床中。然而，CRP 是一种急性期蛋白，在受伤或感染后可能会增加，因此在应用评分之前，应考虑导致增加 CRP 水平的疾病。

3. 细胞因子

3.1. 转化生长因子 *β*

转化生长因子 *β* (TGF-*β*)被称为免疫抑制和纤维化细胞因子。大约 38%的 HCC 患者在 TGF-*β* 通路中存在体细胞突变[26]。多项研究证明，高 TGF-*β* 水平表现为肿瘤的侵袭性更强，并且还可能通过上调 HCC 中的 PD-1 信号传导导致 T 细胞衰竭，结果表明 TGF-*β* 在介导免疫治疗耐药性方面具有特异性免疫抑制作用[27] [28] [29] [30]。Feun 等人在 aHCC 患者中对帕博利珠单抗进行了 2 期研究，在生物标志物分析中，有反应者(CR、PR、SD)中的血浆 TGF-*β* 水平低于无反应者(141.9 vs 1071.8 pg/ml, p = 0.004)。生存分析显示血浆 TGF-*β* ≥ 200 pg/ml 患者的 PFS (2 个月以上，p = 0.008)和 OS (7 个月与 25 个月以上，p = 0.005)明显较短，结果表明较高的 TGF-*β* 水平与不良的治疗结果相关[31]。说明血浆中高 TGF-*β* 可能是治疗反应和免疫治疗预后不良的潜在生物标志物，这可能与 TGF-*β* 形成的肿瘤中 T 细胞浸润减少的肿瘤微环境有关[32]。然而，TGF-*β* 在肝细胞癌中的作用仍处于探索阶段，其预测价值需前瞻性大规模临床研究进一步证实。

3.2. CD137

CD137 又称 4-1BB 或 TNF 受体超家族成员 9 (TNFRSF9)，是肿瘤坏死因子家族的成员，也是 T 细胞活化过程中起重要作用，也具有增强 T 细胞的抗肿瘤作用[33]。CD137 主要由活化的 CD4 和 CD8 T 细胞表达[34]，它广泛存在于 NK 细胞，中性粒细胞，树突状细胞和单核细胞表面[35]。CD137 在 HCC 中的

表达高于其他类型的癌症，并且发现主要在 PD-1 上和 CD8 T 细胞[36]，以及外周活化的 T 细胞高表达[37] [38]。临床研究发现 PD-1 及程序性死亡配体 1 (PD-L1)抑制剂与 CD137 信号通路的激活之间存在协同抗肿瘤活性[39]。外周血中 CD137CD8 T 细胞数量的增加与接受单克隆抗体加纳武利尤单抗治疗的黑色素瘤患者的无病生存期(Disease-free survival, DFS)更长相关[40]。一项研究中对接受信迪利单抗的 aHCC 患者进行中发现了血清 CD137 的具有潜在预测作用。在检测到血清 CD137 的患者中，发现 CD137 升高的患者预后较好($p = 0.034$)，并且在高 CD137 浓度的患者中观察到明显更长的 PFS (14.2 个月 vs 4.1 个月，$p < 0.001$)和 OS (15.6 个月，$p = 0.023$) [41]。然而，目前研究样本量较小，可能存在差异，其预测作用仍有欠缺，需进一步大量研究证明后应用于临床。

4. 讨论

我们综述了关于预测 HCC 免疫治疗的预后。NLR、PLR 和 CRAFITY 评分作为外周血生物标志物，不仅易于采集，而且具有较高的预后价值，对未来预测模型的构建具有重要意义。CD137 也是具有潜在预测因子，但上述指标预测预后仍有不足。首先，上述研究是回顾性的。其次，它们是在单中心进行的，一些研究的病例数很少，可能导致潜在的预后偏倚，需要在多中心的大规模前瞻性研究中进行验证。结合各种指标构建模型预测 HCC，是有助于改善患者的预后，并且提高临床疗效，有待进一步探索。

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