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肝细胞癌微血管浸润术前预测研究进展

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摘　要

目的：探讨肝细胞癌(HCC)微血管侵犯(MVI)的发生机制、术前预测新策略及其对临床精准诊疗的指导价值。方法：系统回顾相关文献，重点分析“炎症－癌症”轴及上皮－间质转化(EMT)在MVI形成中的病理作用，评估血清标志物、液体活检及人工智能影像组学的预测效能，并探讨MVI状态对治疗决策的影响。结果：MVI的发生植根于慢性炎症微环境，涉及中性粒细胞胞外诱捕网(NETs)释放及巨噬细胞极化等机制。在术前预测方面，异常凝血酶原(PIVKA-II)及系统免疫炎症指数(SII)显示出优于甲胎蛋白(AFP)的诊断价值；循环肿瘤细胞(CTC)和ctDNA等液体活检技术揭示了早期微转移的分子特征。特别是基于深度学习的多模态影像模型(如DL-TriFusion)，通过整合影像与临床特征，显著提升了预测的灵敏度与特异性。结论：MVI是HCC术后复发的核心危险因素。构建高精度的多模态术前预测体系，对于制定个体化治疗方案至关重要。它不仅指导外科手术方式的选择(如解剖性肝切除)，还为筛选围手术期辅助治疗(如HAIC)及靶向免疫治疗的获益人群提供了科学依据。未来需开展多中心前瞻性研究以推动其临床转化。

关键词

肝细胞癌，微血管浸润，术前预测

Research Progress on Preoperative Prediction of Microvascular Invasion in Hepatocellular Carcinoma

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Abstract

Objective: To explore the pathogenesis of microvascular invasion (MVI) in hepatocellular carcinoma

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(HCC), novel preoperative prediction strategies, and their guiding value for precision clinical diagnosis and treatment. Methods: A systematic review of relevant literature was conducted, focusing on the pathological roles of the inflammation-cancer axis and epithelial-mesenchymal transition (EMT) in MVI formation. The predictive efficacy of serum biomarkers, liquid biopsy, and artificial intelligence-based radiomics was evaluated, and the impact of MVI status on treatment decisions was investigated. Results: The occurrence of MVI is rooted in a chronic inflammatory microenvironment, involving mechanisms such as neutrophil extracellular traps (NETs) release and macrophage polarization. In terms of preoperative prediction, abnormal prothrombin-II (PIVKA-II) and systemic immune inflammatory index (SII) showed superior diagnostic value compared to alpha-fetoprotein (AFP). Liquid biopsy techniques such as circulating tumor cells (CTC) and ctDNA revealed the molecular characteristics of early micrometastases. In particular, deep learning-based multimodal imaging models (such as DL-TriFusion) significantly improved the sensitivity and specificity of prediction by integrating imaging and clinical features. Conclusion: MVI is a core risk factor for HCC recurrence after surgery. Constructing a high-precision, multimodal preoperative prediction system is crucial for developing individualized treatment plans. It not only guides the selection of surgical procedures (such as anatomical hepatectomy) but also provides a scientific basis for screening patients who will benefit from perioperative adjuvant therapy (such as HAIC) and targeted immunotherapy. Future multicenter prospective studies are needed to promote its clinical translation.

Keywords

Hepatocellular Carcinoma, Microvascular Invasion, Preoperative Prediction

1. 引言

全球范围内，肝细胞癌(HCC)作为高致死率的恶性肿瘤(发病率居第六，死亡率居第三)，其健康危害不容忽视[1]。我国面临的防控形势尤为严峻，新发病例与死亡病例分别占据了国内癌症统计数据的 7.6%和 41.7% [2]。目前手术切除仍是主要根治手段，但即便达到根治标准，患者术后 5 年复发率仍可高达 70%，成为制约长期生存的关键瓶颈[3]。微血管侵犯(MVI)是肝癌侵袭性强的重要病理标志，被视为术后复发与死亡的独立危险因素[4]。MVI 的存在意味着癌细胞已进入微循环系统，转移风险显著增加。因此，术前能否准确识别 MVI 状态，对个体化治疗策略的优化至关重要：例如，MVI 阳性提示早期患者不宜单纯接受容易导致治疗不彻底的射频消融(RFA)；在手术规划中，这类患者往往需要更广泛的切缘(>1 cm)或进行解剖性切除；同时，MVI 状态也是决定是否启动围手术期靶向或免疫辅助治疗的关键依据[5]。综上所述，探索一种经济、高效且精准的术前 MVI 预测方法，对于改善肝癌患者预后具有重要的临床应用价值。

2. MVI 定义及形成机制

微血管侵犯(microvascular invasion, MVI)主要指仅能在显微镜下观察到、在覆衬有内皮细胞的微小血管腔内存在的癌细胞巢团，多见于肿瘤包膜内和癌旁肝组织内的门静脉微小分支，MVI 的发生是肿瘤生物学行为与宿主微环境多维互作的结果，临床上依据病灶数量及分布范围进行分级，其中：M0 级，未发现；M1 级，≤5 个 MVI，且发生于近癌旁肝组织区域(≤1 cm)；M2 级，>5 个 MVI，或 MVI 发生于远癌旁肝组织区域(>1 cm) [4]。

2.1. 肿瘤血管生成与侵袭

肿瘤血管生成是实体瘤生长的基础。血管内皮生长因子(VEGF)及其通路的异常激活，致使新生血管结构紊乱且基底膜缺损，为癌细胞透壁侵袭开辟了物理通道[6]。此外，缺氧环境诱导 HIF-1α 表达上调，在促进 VEGF 分泌的同时激活基质金属蛋白酶(MMPs)，通过降解细胞外基质进一步加速 MVI 进程[7]。

2.2. 上皮－间质转化(EMT)的驱动作用

EMT 是上皮细胞获取运动与侵袭表型的关键环节。受 TGF-β、Wnt/β-catenin 等信号通路驱动，HCC 细胞下调 E-cadherin 并上调 N-cadherin 及 Vimentin 表达，从而获得“干性”特征。发生表型转化的肿瘤细胞具备更强的血管壁穿透力，这也佐证了为何血清循环肿瘤细胞(CTC)多呈现间质型特征[8]。

2.3. 慢性炎症背景与免疫微环境

肝癌多植根于慢乙肝或肝硬化病理背景，伴随微环境内 IL-6、TNF-α 等炎性因子持续高表达。中性粒细胞通过释放胞外诱捕网(NETs)捕获循环癌细胞并协助其定植栓塞[9]。同时，M2 型极化的肿瘤相关巨噬细胞(TAMs)在抑制免疫应答的同时重塑血管基质，为 MVI 演进创造有利条件[10]。这种“炎症－癌症”轴的相互作用，这种“炎症－癌症”轴的互作机制，确立了外周血炎症指标预测 MVI 的理论前提。

3. MVI 相关危险因素及术前预测

研究表明，MVI 是 HCC 患者术后出现早期复发的重要诱因，其发生率约在 11%~60%，高危患者的复发风险更是高达 90% [11] [12]。因此，通过分析 MVI 的危险因素来评估复发风险，对于指导临床制定个性化的治疗方案具有核心价值。当前，实现 MVI 术前无创预测的手段主要聚焦于四大领域：血清学指标筛查、影像学特征分析、液体活检技术应用以及多维预测模型的构建。

3.1. 血清学与炎症指标

3.1.1. 甲胎蛋白(AFP)

AFP 是诊断 HCC 的经典标志物。高水平 AFP 往往与肿瘤低分化、高肿瘤负荷及不良预后相关[13]。尽管多项回顾性队列证实 AFP 水平与 MVI 风险呈正相关[14] [15]。但其预测效能存在局限：一方面，约 30%~40%的 HCC 患者 AFP 呈阴性；另一方面，活动性肝炎或生殖系肿瘤亦可引起 AFP 假阳性升高[16]。因此，单一 AFP 指标在 MVI 精准预测上存在特异性不足的短板。

3.1.2. 异常凝血酶原(PIVKA-II/DCP)

PIVKA-II 是维生素 K 缺乏或拮抗剂-II 诱导的蛋白质。在 HCC 细胞中，由于凝血酶原前体羧化酶系统的缺陷，导致 PIVKA-II 大量产生。近年高水平证据一致显示，PIVKA-II 对 MVI 的预测效能优于 AFP [17] [18]。就预后而言，PIVKA-II 的过度表达与较差的 OS 和 DFS 有关[19]，机制上，PIVKA-II 不仅反映肿瘤负荷，更具备生物学活性：它可作为配体结合血管内皮细胞 Met 受体，激活 JAK/STAT 及 MAPK 通路，直接驱动血管新生与肿瘤迁移[20]。临床上，其高表达与晚期分期、MVI 高发及靶向免疫治疗耐药显著相关[21]。此外，整合了 PIVKA-II、AFP 及肿瘤体积的 ADV 评分，在结合代谢活性指标(如 PET-CT 代谢参数)后，能进一步优化患者的风险分层[22]。

3.1.3. 中性粒细胞与淋巴细胞比值(NLR)

NLR 是反映促肿瘤炎症反应(中性粒细胞)与抗肿瘤免疫反应(淋巴细胞)平衡状态的指标。高 NLR 提

示机体处于促肿瘤微环境：中性粒细胞分泌 MMP-9、VEGF 及弹性蛋白酶协助破坏血管基底膜，而淋巴细胞匮乏则意味着免疫监视失效。2024 年的一项涉及 35 个队列的 Meta 分析确证，术前高 NLR 与 MVI 显著相关[23]。最新研究已成功将 NLR 纳入多维预测模型，不仅验证了其独立预测价值，更显示出其作为炎症标志物在辅助临床决策中的潜力[24]。

3.1.4. γ-谷氨酰转肽酶(GGT)

在临床上，GGT 常被视为胆道梗阻或酒精性肝损的指标。然而，GGT 在肿瘤氧化应激中扮演关键角色。肿瘤细胞通过上调 GGT 代谢谷胱甘肽以对抗氧化应激，从而获得更具侵袭性的生存优势[25] [26]。多项证据表明，GGT 水平异常升高不仅与肿瘤大直径相关，更是 MVI 发生的独立危险预测因子[4] [27]。

3.1.5. 系统免疫炎症指数(SII)

SII 通过公式(血小板 × 中性粒细胞/淋巴细胞)整合了三类血细胞信息[28]。相较于 NLR，SII 引入了血小板这一关键变量。在 MVI 形成中，活化的血小板充当“保护伞”：它们聚集于癌细胞周围形成物理屏障，既能抵御血流剪切力与 NK 细胞杀伤，又能辅助癌细胞在内皮特定位点停靠[29]。Li 等人的研究指出，SII 在预测 MVI 的敏感度与特异度上均优于 NLR 及 PLR，是构建高精度列线图模型的重要参数[30] [31]。

3.2. 液体活检

3.2.1. 循环肿瘤细胞(CTC)

CTCs 指脱离原发灶并进入脉管系统的肿瘤细胞，其出现往往标志着微血管侵犯(MVI)早期生物学事件的启动。研究证实 CTCs 具有高度异质性，并非所有亚群均具备转移潜能；唯有经历上皮–间质转化(EMT)并获取间质表型(Mesenchymal phenotype)的细胞才表现出强侵袭力。临床改进型 CellSearch 系统结合波形蛋白(Vimentin)标记显示，术前外周血中高负荷的间质型 CTC 与病理确诊的 MVI 风险呈显著正相关[32]。此外，CTC 团簇(CTC clusters)凭借细胞间连接有效抵抗失巢凋亡(Anoikis)，其转移效能较单个 CTC 高出 23 至 50 倍，已成为当前解析肿瘤转移机制及预后评估的核心焦点[33] [34]。

3.2.2. 循环肿瘤 DNA(ctDNA)

ctDNA 作为承载肿瘤特有遗传信息的游离 DNA 片段，其定性与定量分析对肿瘤早期筛查及动态监测具有重要价值[35]。利用高通量测序(NGS)探究 ctDNA 突变负荷(TMB)及特定基因变异(如 TP53、CTNNB1)与 MVI 的关联已获初步成效。Wang 等研究指出，术前 ctDNA 阳性且伴随 TP53 突变的患者，其 MVI 发生率显著攀升[36]。另有 Zhou 等通过全外显子组测序，对比了 MVI 阳性与阴性 HCC 患者的基因组图谱。结果发现，在 MVI 阳性组中，原发灶、门静脉癌栓(PVTT)及 ctDNA 展现出高度一致的克隆起源与基因组景观。这一发现从基因组学维度证实，驱动转移的关键变异早在原发阶段即已形成，并遗传至循环系统，确立了 ctDNA 与 MVI 之间内在的分子关联[37]。

3.2.3. 外泌体(Exosomes)及非编码 RNA

作为细胞间通讯的关键载体，肿瘤细胞分泌的外泌体富含 miRNA 及 lncRNA 等生物活性分子。研究表明，血清外泌体中 miR-122、miR-21 等非编码 RNA 的表达丰度与 MVI 密切相关[38]。这些非编码 RNA 通过调节受体细胞(如血管内皮细胞)的通透性，为肿瘤细胞的血管浸润与定植铺平道路[39]。

3.3. 影像学特征与人工智能辅助诊断

基于多模态影像的 MVI 预测已从单纯的形态学观察迈向功能成像与数据挖掘的新阶段。

3.3.1. 多模态影像学特征

多期动态增强 MRI 通过清晰呈现肿瘤血供动力学及癌旁组织微环境改变，成为评估 MVI 的重要工具。CT 影像同样蕴含丰富的表型信息：一项影像基因组学研究基于对比增强 CT 特征，构建了源自 91 个基因表达谱的“静脉侵袭”替代标志物。该标志物不仅能高精度预测组织学 MVI，还与患者的不良总生存期(OS)及高复发风险显著相关[40]。此外，CT 图像中肿瘤内部动脉特征被证实是预测患者能否从术后辅助 TACE 治疗获益的关键影像依据[41]。在超声领域，造影超声(CEUS)正逐步与 MRI 及临床生物学信息融合，构建多模态评估体系以量化肿瘤侵袭性，从而精准指导热消融等介入治疗策略的制定[42]。

3.3.2. 影像基因组学：微观病理与宏观影像的桥接

影像基因组学(Radiogenomics)深刻解码了宏观表型背后的分子活动。例如，肿瘤缺氧微环境会刺激血管内皮生长因子等通路异常活跃，催生大量高通透性的无序毛细血管网；同时，基质重塑加剧纤维化并提高局部组织硬度。这些微观病变直接干扰了病灶局部血流动力学与水分子游走机制：紊乱的微血管床在造影时表现为动脉期不规则高强化和快速廓清；而致密基质则限制组织间隙液流动，在表观弥散系数(ADC)图上映射为信号的明显滑落。通过这种“基因–病理–像素”的级联对应，无创成像得以精准反推微血管浸润的高危分子指纹[43]。

3.3.3. 人工智能与深度学习应用

人工智能(AI)，尤其是深度学习技术，在挖掘海量影像数据与自动提取高维特征方面展现出传统手段无法比拟的优势。AI 算法能够捕捉人眼难以辨识的微观像素模式，建立其与肿瘤生物学行为的深层联系。典型的如 DL-TriFusion 模型，该深度学习框架整合了多期 MRI 影像特征与临床变量，在多中心外部验证中表现出卓越的鲁棒性。值得注意的是，该模型在预测术后复发风险的分层能力上，甚至优于基于术后病理确诊的 MVI 状态，提示其不仅是诊断工具，更是强有力的预后评估系统[44]。AI 的应用疆界正进一步从“诊断预测”向“治疗指导”延展。针对 MVI 阳性患者的异质性，一项多中心研究开发了基于影像学的生物标志物，通过整合动脉期瘤周强化、肿瘤边界特征及坏死区域分层等参数，成功识别出能真正从辅助性肝动脉灌注化疗(HAIC)中获益的亚群[45]。然而，尽管前景广阔，现阶段计算机辅助诊断在向真实临床场景转化的过程中仍面临诸多挑战。首先，各家医疗机构扫描设备的参数设定差异导致了数据标准化的严重缺失；其次，大量既往研究高度依赖回顾性单中心样本，需要开展大规模、前瞻性的多中心联合验证以确保预判模型的真实泛化能力。此外，许多高精度深度网络本质上属于“黑盒”模型，其推理决策过程的不可解释性(Explainability)极大制约了临床医师的接受度与信任度。因此，开发兼顾高预测精度与逻辑透明度的可解释性人工智能(Explainable AI, XAI)体系，或将成为未来该领域研究的核心方向[46]。

3.4. 综合预测模型的构建与评价

为突破单一指标在预测精度上的瓶颈，整合血清学与影像学数据的多模态融合模型已成为当前研究的主流范式。这种策略利用不同维度信息的互补优势，旨在绘制更全面的肿瘤生物学画像。在方法学上，研究者广泛采用逻辑回归、Cox 比例风险模型及随机生存森林等统计学或机器学习算法，深度整合影像组学特征、血清标志物(如 AFP、PIVKA-II 及炎症因子)与临床病理参数(如肿瘤径线、数目及硬化背景)，构建了多种高精度的列线图(Nomogram)及风险评分系统[41] [47] [48]。此类综合模型高度契合临床实际需求。医生可在术前依据血液检验与影像报告的量化评分，快速预判 MVI 风险，进而制定个体化治疗路径——例如识别出需接受新辅助治疗的高危患者，或规划更广泛的手术切除边界。但目前大多数模型属于单中心回顾性研究，缺乏外部验证。一个优秀的预测模型不仅要有高的区分度(C-index)，还要有良好的

校准度(Calibration plot)。近年来，基于机器学习(如随机森林、支持向量机)的算法被引入 MVI 预测，进一步提高了模型的非线性拟合能力，显著提升了预测效能，但其内生的“黑箱(Black Box)”属性导致决策逻辑难以追溯，这种可解释性的缺失仍是其临床广泛应用的主要障碍[49]。

4. MVI 术前预测对临床决策的指导价值

MVI 的术前预测与术后确诊，其核心价值在于能够深刻影响 HCC 治疗策略的各个环节，从手术方式的抉择、围手术期方案的制定，到术后辅助治疗的筛选及系统治疗的调整，MVI 均为实现患者个体化预后管理的关键路标。

4.1. 外科手术策略的优化

在根治性手术规划中，MVI 状态直接决定了切除范围的界定。鉴于 MVI 阳性提示肿瘤具备高侵袭性及肝内微转移潜能，“解剖性肝切除(Anatomical Resection, AR)”被视为首选策略。相较于非解剖性切除，AR 旨在完整移除荷瘤门静脉流域，从而从理论上彻底清除潜伏于该区域内的微小病灶。荟萃分析数据显示，尽管存在研究异质性，AR 在提升患者 1 年、3 年及 5 年总生存率(OS)与无病生存率(DFS)方面均展现出显著优势[50]。此外，对于热消融治疗，若多模态模型提示高侵袭风险，临床需扩大最小消融边缘(Safety Margin)以降低局部进展率。在肝移植领域，MVI 则是评估移植后复发风险的强独立因子；诸如 R3-AFP 等评分系统已将 MVI 纳入核心变量，用以动态评估复发风险并指导术后免疫抑制与监测方案的调整[51]。

4.2. 围手术期及辅助治疗的选择

在围手术期及辅助治疗领域，MVI 状态是筛选治疗获益人群的关键生物标志物。大量循证医学证据表明，对于携带 MVI、大肿瘤或多发结节等高危复发因素的患者，术后辅助治疗能显著改善预后。一项多中心真实世界研究证实，针对高危亚群，肝切除术后联合辅助治疗组的 OS 及 DFS 均显著优于单纯手术组[52]。基于 FOLFOX 方案的术后辅助性肝动脉灌注化疗(HAIC)已被证实能使 MVI 阳性患者获益[45]。对于孤立性巨块型 HCC，采用“HAIC + 仑伐替尼 + PD-1 抑制剂”的三联合方案，其 DFS 获益显著优于单纯靶向治疗[53]。在晚期不可切除 HCC 的治疗中，MVI 状态甚至能指导二线方案的切换。例如，对于接受“T + A”方案(阿替利珠单抗 + 贝伐珠单抗)后出现影像学进展的患者，若无 MVI 证据，继续原方案可能仍有生存获益；反之，若存在 MVI，则提示需及时转换为后续化疗方案[54]。

4.3. 精准预后评估体系

MVI 已超越传统 TNM 分期，成为新一代预后评分系统的核心组件。以 MSE 评分系统为例，该模型整合了 MVI、卫星灶及 Edmondson-Steiner 分级，在预测 BCLC 0-A 期早期 HCC 患者的术后复发风险方面，其判别效能显著优于传统的 mVI/S 评分及 AFP 指标[55]。这些整合了 MVI 权重的复合评分工具，能够实现患者风险等级的精准分层，从而指导临床医生制定个体化的术后随访频率与影像学监测路径，以实现医疗资源的优化配置与复发灶的早期捕捉。

5. 结论

MVI 作为决定 HCC 患者术后复发与长期生存的关键病理指标，目前仍缺乏公认的术前无创诊断“金标准”。未来研究应致力于构建多模态融合体系，依托人工智能与深度学习技术，深度整合血清炎症指标、液体活检及影像组学特征，以突破单一模态的预测局限。同时，需进一步揭示 MVI 形成的分子机制(如炎症微环境与 EMT)，挖掘更具特异性的干预靶点。亟需开展大规模、多中心的前瞻性临床试验，验

证预测模型的泛化能力与临床净获益，从而推动基于 MVI 风险分层的个体化精准诊疗，优化手术规划与辅助治疗策略，切实改善患者的预后及生活质量。

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