

肝硬化门静脉高压无创评估进展

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摘 要

门静脉高压(Portal hypertension, PH)作为肝硬化失代偿的核心病理生理特征, 其特征性临床表现包括侧枝循环形成、脾功能亢进、腹水形成。尤其是临床显著性门静脉高压(clinically significant portal hypertension, CSPH), 标志着肝硬化病程进入失代偿拐点, 预后显著恶化。当前肝静脉压力梯度检测(Hepatic Venous Pressure Gradient, HVPG)是评估门脉压力的金标准, 虽能精准量化门脉压力, 但受限于侵入性操作风险、穿刺并发症及单次检测费用高等现实因素, 在临床诊疗工作中受到限制。随着无创评估技术的发展, 血清学生物标志物分析、超声肝脾硬度测定和CT影像组学等无创模型取得突破。有效的无创评估门静脉压力的方法, 能使医生更好地评估肝硬化患者病情及其并发症管理, 改善患者的预后。

关键词

门静脉高压, 肝静脉压力梯度, 无创检测, 血清学标志物, 超声检查, CT血管重建

Progress in Non-Invasive Assessment of Portal Hypertension in Cirrhosis

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Abstract

Portal hypertension (PH), as the core pathophysiological feature of decompensated cirrhosis, is characterized by clinical manifestations such as collateral circulation formation, hypersplenism, and ascites. Clinically significant portal hypertension (CSPH), in particular, marks a critical turning point in the progression of cirrhosis toward decompensation and is associated with significantly

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worsened prognosis. Currently, hepatic venous pressure gradient (HVPG) measurement remains the gold standard for assessing portal pressure. While it provides precise quantification of portal pressure, its clinical application is limited by practical challenges including invasive procedural risks, puncture-related complications, and high costs of single measurements. With advancements in non-invasive evaluation techniques, breakthroughs have been achieved in non-invasive models such as serum biomarker analysis, ultrasound-based liver and spleen stiffness measurements, and CT radiomics. Effective non-invasive methods for assessing portal pressure enable clinicians to better evaluate disease progression and complication management in cirrhosis patients, ultimately improving clinical outcomes.

Keywords

Portal Hypertension, Hepatic Venous Pressure Gradient, Non-Invasive Methods, Serological Indicators, Ultrasound Examination, CT Vascular Reconstruction

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1. 引言

肝硬化作为慢性肝病的终末阶段,分为代偿期与失代偿期两个病程,代偿期患者通常缺乏典型临床症状,而失代偿期则以肝功能受损及门静脉高压(Portal Hypertension, PH)为突出特征。门脉高压的核心病理机制为门脉系统血流动力学异常,包括血管阻力升高和/或血流量增加,继而导致门静脉及其属支血管内静力压升高并伴侧支循环形成[1],可引致致命性并发症如上消化道大出血、肝性脑病。因此精确评估门脉压力及其并发症管理具有重要临床价值。目前肝静脉压力梯度(Hepatic Venous Pressure Gradient, HVPG)仍是评估门脉压力的国际金标准[2],指通过颈静脉插管测定肝静脉楔压与游离压之差,正常范围为 3~5 mmHg,当 HVPG > 5 mmHg 即提示存在门脉高压,当 HVPG $\geq$ 10 mmHg 时称为临床显著性门静脉高压(Clinically Significant Portal Hypertension, CSPH),此时患者出现腹水、食管胃底静脉曲张破裂出血和肝性脑病等风险显著增高[3]。尽管 HVPG 检测具有诊断权威性,但其作为侵入性检查,具有创伤性、操作复杂等局限,限制了临床应用,这一现状推动了无创检测技术快速发展,包括血清标志物检测、影像学评估等无创性门脉压力评估系统。本文将系统综述近年来非侵入性检测技术在 PH 评估中的研究进展。

2. 血清学指标

在肝硬化进程中,肝细胞进行性坏死与异常修复导致纤维隔形成即再生结节增生。这些病理性结构通过机械性挤压肝窦和中央静脉,显著提升肝内血管阻力。肝星状细胞活化后转化为肌成纤维细胞,通过过量分泌细胞外基质成分,成为驱动门脉高压的关键分子机制。基于此病理生理过程,目前无创评估系统主要聚焦这几类生物标志物:肝纤维化相关指标、血管生成因子、内皮损伤因子以及肝脏炎症损伤标志物。这些指标的组合应用为动态检测门脉压力提供了新思路。

2.1. 血管性血友病因子抗原与 VITRO 评分

血管性血友病因子(von Willbrand Factor, vWF)作为内皮细胞活化的重要标记物,其生物合成受血管损伤信号(如 $\text{TNF-}\alpha$ 、 $\text{IL-1}\beta$)调控。当血管内皮细胞受到炎症因子刺激后激活,通过 Willbrand 因子多聚酶介导,分泌具有多聚体结构的 vWF。该蛋白通过桥接血小板表面糖蛋白 1b 与内皮下胶原,不仅启动血小

板黏附级联反映,更通过促进肝窦微血栓形成加剧门脉系统血流阻力。临床采用血管性血友病因子抗原(vWF-Ag)定量检测(ELISA法)评估其血浆浓度。研究显示肝硬化门脉高压患者vWF-Ag水平显著升高,较高的vWF-Ag水平与肝硬化食管胃底静脉曲张、腹水、死亡率均高度相关[4]-[7]。当临界值设定为241%时,其诊断CSPH的AUC为0.85[8]。Simbrunner团队[9]对229名肝硬化门静脉高压患者的前瞻性队列研究证实VWF-Ag水平及其前肽VWF-N诊断CSPH的AUC分别为0.748、0.728,提示其在门脉高压分层管理中的应用潜力。

VITRO评分即vWF-Ag与血小板计数比值,其创新性在于整合了门脉高压的两种关键病理要素:内皮损伤(vWF-Ag)与脾功能亢进(血小板减少)。血小板计数作为肝硬化进展的经典预后指标,与门脉高压成负相关,在一定程度上可以反映肝脏疾病的严重程度[10][11]。多项研究证实,VITRO评分对CSPH具有较好的诊断效能[12]。Baveno-VII标准[3]中建议 $LSM < 15 \text{ kPa}$ 和血小板 $> 150 \times 10^9/L$ 排除CSPH, $LSM \geq 25 \text{ kPa}$ 确诊CSPH,但仍有部分患者处于“诊断灰区”。Jachs等人[13]证实VITRO评分对这类“灰区”患者CSPH具有补充诊断价值(AUC为0.909)。Semmler团队[14]再次验证了VITRO评分对CSPH的诊断性能(AUC为0.889),并提出诊断阈值(≥ 2.5)。值得注意的是,VITRO评分 ≥ 5.65 的乙肝肝硬化患者发生肝移植、肝硬化相关性死亡不良预后的风险是VITRO评分 < 5.65 患者的5.58倍[15]。且最新的研究[16]显示VITRO评分预测代偿期肝硬化患者1~2年内发生失代偿风险(包括腹水、静脉曲张破裂出血、肝性脑病、肝癌、肝移植和死亡)的能力与HVPg的预测能力相当(AUC分别为0.811、0.739),标志着无创评估技术已接近侵入性检测的临床价值。

2.2. 增强的肝纤维化评分(Enhanced Liver Fibrosis Score, ELF)

肝脏慢性修复的过程中,肝星状细胞异常活化引发细胞外基质(ECM)代谢失衡,表现为I/III型胶原、层粘连蛋白等成分病理性沉积,这种“纤维化-硬化”级联反映可通过血清ECM成分定量监测。增强的肝纤维化评分(ELF)通过整合三类关键ECM代谢标志物:透明质酸(HA)、基质金属蛋白酶组织抑制因子-1(TIMP-1)和氨基末端III型胶原前肽(PIIINP)在非酒精性脂肪性肝病患者的纤维化筛查、评估及管理展现独特价值[17]。在一项纳入162例非酒精性脂肪性肝炎代偿期肝硬化和门脉高压受试者的研究中显示ELF评分与肝脏不良结局(包括新发腹水、静脉曲张出血和肝性脑病)的短期风险密切相关。当ELF评分 > 9.8 时,预测52周肝脏相关不良预后的敏感性、特异性、阳性预测值和阴性预测值分别为87.9%、26.6%、23.6%和89.5%;当ELF评分 ≥ 11.3 时,预测52周肝脏相关不良预后的敏感性、特异性、阳性预测值和阴性预测值分别为51.5%、72.7%、32.7%和85.3%[18]。ELF评分的诊断价值已不再局限于非酒精脂肪性肝病,最新证据显示其在多元肝病谱系中具有普适性。Simbrunner B团队的多病因队列研究(201例含病毒性/酒精性/其他病因的晚期慢性肝病患者)提示ELF评分诊断CSPH的AUC为0.833($P < 0.001$),特别在酒精性肝病患者表现出极高的诊断效能(AUC为0.978, $P < 0.001$);并且提出高特异性截断值,当阈值设为 ≥ 11.1 时阳性预测值达98%,虽敏感性61%存在局限,但阴性预测值24%提示需联合其他指标补充[19]。sCD163是巨噬细胞激活标志物,sCD163水平与肝脏炎症和免疫激活有关,研究证实将sCD163联合ELF评分可提高对CSPH的诊断性能(ELF评分单独和联合sCD163的AUC分别为0.80、0.91)[20]。

2.3. 天冬氨酸转氨酶/血小板比率指数(APRI)

APRI(天冬氨酸氨基转移酶(AST)-血小板比值指数),是基于AST生物标志物和血小板计数的计算模型,其公式表述为 $AST \text{ 实测值}/\text{正常值上限} \times 100/\text{血小板}(10^9/L)$ 。作为肝细胞炎症损伤的敏感指标,AST的动态变化与血小板减少现象共同构成了该模型的病理生理学基础。现有研究提示该指标与HVPg存在相关性,但诊断效能存在局限。Verma团队[21]通过临床验证发现,当APRI阈值设为1.09时,对

HVPG > 12 mmHg 的识别敏感度为 66%, 特异度 73%, 总体诊断准确率不足 70%。值得注意的是, 近期一例纳入 9 项研究 2492 名患者的荟萃分析[22]显示, 该指标对临床显著性门脉高压(CSPH)的检测灵敏度仅为 56%, 特异度 68%。在慢性乙型肝炎肝硬化人群中的研究[23]进一步证实, 当 APRI > 2 时, 对 CSPH 的阳性预测值仅为 32.1%。该模型局限性可能源于以下因素: AST 指标的生物特异性不足, 多种病理状态下(急性重型肝炎、药物性肝损害、横纹肌溶解症等)均可导致 AST 异常升高; 抗炎保肝药物使用可能造成 AST 水平人为降低, 进而影响评分系统的准确性; 血小板计数的临床意义具有多向性, 除肝纤维化程度外, 还受骨髓抑制、脾功能亢进等多因素调控。目前认为, APRI 对门脉高压的评估存在一定的辅助诊断价值, 但临床应用仍存在病因特异性差异明显, 药物干扰因素复杂等争议。这提示该模型需通过多中心、大样本研究进行标准化验证, 同时临床解读时需结合其他无创诊断工具进行综合判断。

除传统血清学标志物外, 近年来涌现出多个具有门脉高压诊断潜力的新型生物标志物。上皮钙黏蛋白(ECAD)作为细胞间连接的关键调控因子, 其表达水平的下调已被证实会破坏细胞间连接结构的完整性, 门脉高压患者血浆 ECAD 浓度较正常 HVPG 组呈现显著升高趋势[24]。丝氨酸蛋白酶抑制剂 Kazal I 型(SPINK1)被发现与乙型病毒性肝炎进展存在密切关系, 其在 PH 患者中的异常高表达提示可能参与肝纤维化调控通路[24]。胎盘生长因子(PIGF)作为血管内皮生长因子家族成员, 通过激活 VEGFR-1 信号通路促进病理性血管新生, 临床研究[25]显示该因子在临床显著性门脉高压患者外周血中的浓度较对照组显著升高(分别为 28.20 pg/ml、17.20 pg/ml, $P = 0.006$)。轴突生长抑制因子 A (Nogo-A)作为网状蛋白 4 家族新进的血管生成调节介质, 其血浆水平与 HVPG 呈负相关($r = -0.267, P = 0.007$), 且 CSPH 患者组检测值较非 CSPH 组明显降低(分别为 1.96 ± 1.39 ng/mL、 2.77 ± 1.53 ng/mL, $P = 0.011$) [25]。尽管这些新型标志物展现出独特的病理生理学价值, 但其临床应用仍面临多重挑战。首先, 现有研究多局限单中心、小样本队列; 其次, 生物标志物的检测标准化方案尚未建立; 再者, 不同病因门脉高压的特异性反映谱仍需系统解析。后续研究应建立多病因大样本验证平台, 开发配套检验试剂标准化流程, 探索多指标联合诊断模型。

3. 影像学检查

3.1. 瞬态弹性成像(TE)

相较于血清生物标志物, 影像学生物力学评估在临床显著性门脉高压的无创诊断中展现出更优的临床价值。瞬态弹性成像(TE)作为当前临床应用最广泛的肝纤维化评估技术, 其核心参数肝脏硬度测量(LSM)联合血小板计数已被纳入国际主流指南的 CSPH 诊断流程: Baveno VII 共识[3]提出 $LSM < 15$ kPa 和血小板 $> 150 \times 10^9/L$ 可作为排除 CSPH 的可靠标准。2022 年 AASLD 指南[26]和 2021 年 EASL 指南[27]共同建议将 $LSM \geq 20 \sim 25$ kPa 作为 CSPH 的诊断阈值。Berzigotti 团队[28]的多中心研究验证, LSM 对 CSPH 的鉴别效能显著优于其他单一指标($AUC = 0.883, P < 0.0001$)。最新荟萃分析[22]纳入 2492 例多病因患者数据显示, $LSM > 25$ kPa 诊断 CSPH 敏感性为 57%~85%, 特异性为 82%~93%。然而该项技术存在体质特异性误差、病因依赖性阈值差异等局限。肥胖患者($BMI \geq 30$ kg/m²)皮下脂肪层可衰减剪切波信号, 从而降低检测的准确性和成功率。研究[29]显示非肥胖非酒精性脂肪性肝病(NAFLD)人群中应用 25 kPa 阈值时, CSPH 的阳性预测值 > 90%, 而肥胖非酒精性脂肪性肝炎(NASH)患者阳性预测值骤降至 62.8%。Lemoine [30]等人对比研究揭示, 酒精性肝病患者诊断 CSPH 最佳诊断阈值为 34.9 kPa ($AUC = 0.94, P = 0.03$), 显著高于丙型肝炎肝硬化患者的 20.5 kPa ($AUC = 0.76, P = 0.07$)。为突破 TE 技术瓶颈, 新型复合参数不断涌现。肝-脾联合参数(LSPS)是指肝脏硬度 $\times$ 脾脏大小/血小板计数。Abraldes JG 等人[31]建立的风险预测模型显示, $LSPS > 2.65$ 时 CSPH 的发生概率超过 80%。脾脏硬度测量(SSM)对 CSPH 的诊断

效能也被证实, 2021 年纳入 3952 例患者荟萃分析[32]证实 SSM 诊断 CSPH 的敏感度/特异度达 85%/86% (AUC = 0.92)。其病理生理优势在于当门脉压力 > 10 mmHg 时, 脾脏被动充血引发的组织重构使 SSM 与 HVPG 的相关性强于 LSM [33]-[35], 且不受肝脏炎症活动、胆汁淤积等干扰[36]。

作为门脉高压无创评估的常用技术, 瞬态弹性成像(TE)虽可通过肝脾硬度测量实现临床诊断, 但其缺乏可视化功能、对肥胖(BMI $\geq 30\text{kg/m}^2$)及腹腔积液患者检测失败率高、单点采样易受肝脏异质性影响的技术局限性不容忽视。基于声辐射力脉冲成像(ARFI)的二维剪切波弹性成像(2D-SWE)技术采用矩阵式超声探头发射多组剪切波束, 结合超高速成像系统, 在实现弹性模量分布图可视化分析的同时支持多个感兴趣区同步量化评估, 显著提升检测可靠性。该技术的自适应聚焦脉冲算法使超声波穿透力比传统 TE 显著升高, 可穿透皮下脂肪和腹腔积液, 实现对肥胖和腹腔积液患者的测量。研究证实其诊断 CSPH 的 AUC 达 0.818 [37], 与 CSPH 相关性为 0.646 ($P < 0.001$) [38]。一项纳入 9 项研究 746 例肝硬化患者的荟萃分析[39]显示, 2D-SWE 通过测量肝脏硬度诊断 CSPH 的敏感性/特异性达到 85%/85% (AUC = 0.88)。除此之外, 磁共振弹性成像(Magnetic Resonance Elastography, MRE)在 HVPG 评估中的应用日益受到关注, MRE 通过机械波在组织中的传播特性生成弹性图, 量化肝脾硬度, 反映肝脏纤维化程度, 通过 MRE 测量脾脏硬度可评估肝硬化食管胃底静脉曲张程度及门静脉压力[40]-[42]。其中 3D-MRE 可支持多方向波传播分析, 减少因解剖结构或波传播方向偏差导致的测量误差, 实现全器官覆盖, 避免单平面采样导致的局部信息丢失。研究揭示[43]通过 3D MRE 测量脾脏硬度与 HVPG 有较强相关性($r = 0.686, P < 0.001$), 且较 2D MRE、SWE 在诊断 CSPH 方面表现出更佳性能(AUC 0.911 vs 0.845 vs 0.583)。但因 3D-MRE 存在扫描时间较长、数据处理复杂、临床标准化不足的局限, 限制了临床应用。

3.2. 计算机体层成像(CT)

CT 技术凭借其经济性优势及亚毫米级空间分辨率, 已成为门脉高压放射学评估的首选成像模态。其核心价值体现在多平面建模技术可精准量化门静脉直径及侧枝循环解剖特征, 且不受患者腹水、肥胖等体质因素干扰, 具有客观性强、可重复性佳的技术优势。目前, 基于 CT 影像组学的预测模型开发取得突破性进展。Sartoris 团队[44]通过深度学习法提取肝包膜形态特征, 建立肝脏表面结节(liver surface nodularity, LSN)评分系统, 其最佳阈值为 2.8, 对 CSPH 的阳性预测值为 86% (AUC = 0.87)。我国一项多中心研究[45]创新性整合增强 CT 血管三维重建与计算流体动力学(CFD)技术, 实现虚拟肝静脉压力梯度(vHVPG)无创测量, 验证组 AUC 达 0.89(Kappa 值: 操作者间 0.88, 操作者内 0.96), 与有创 HVPG 显著相关($r = 0.61, P < 0.001$)。此外, 肝脾体积(VI)指数模型在 175 名肝硬化肝细胞癌人群中验证显示, VI 指数(脾体积 $\times$ 肝段 I~III/IV~VIII 体积比)诊断 CSPH 的 AUC 为 0.83 [46]。当前影像组学模型虽展现临床巨大转化潜力, 但面临不同 CT 机型影像组学特征的可比性差异、病因异质性等问题影响模型泛化能力, 需进一步开展多中心验证及临床工作整合研究。

4. 总结与展望

门静脉压力无创评估系统呈现多模态协同发展态势, 血清学生物标志物通过整合肝纤维化指数、血管生成因子及内皮损伤标记物构建的多维度模型, 在临床显著性门静脉高压诊断中展现出高度的敏感性与特异性, 但受限于个体生物变异度及检测成本差异等技术经济学瓶颈; 弹性成像技术中, 瞬态弹性成像与二维剪切波弹性成像分别通过单点瞬时测量和动态矩阵扫描实现肝脾硬度量化, 对门脉高压具有较高的诊断效能, 但受到肥胖、腹水患者诊断准确性低及不同病因最佳截断值差异大等限制; CT 影像组学创新性融合肝表面结节量化、虚拟血流动力学及肝脾体积指数, 实现多参数诊断, 但其累积辐射计量及影像医师操作依赖性制约了临床普及。当前技术均未突破 HVPG 金标准地位, 未来研究需聚焦于开发

不同病因特异性诊断阈值, 构建多中心标准验证平台, 推进辐射零剂量 MRI 弹性成像(如 3D-MRE 联合 4D 血流分析)技术创新, 通过血清 - 影像-AI 三元融合策略, 最终实现门脉高压评估从“替代指标”向“个体化诊疗决策系统”的转变。

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