

肝切除术后肝功能衰竭预测的研究进展

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摘 要

吲哚菁绿15 min滞留率(ICG-R15)、肝脏体积测定是目前临床上常用的术前肝功能评估方法,但在临床应用过程中只作为单一的肝功能评估指标,存在一定的局限性,而两者相联合可以更加精确地评估肝脏的各段功能,从而极大地提高了手术的安全性和有效性。通过查阅相关文献资料并结合文献要点对在肝切除术后肝功能衰竭(PHLF)预测的相关研究进展进行综述。

关键词

肝切除术, 肝功能衰竭, 癌, 肝细胞, 预测

Advances in the Prediction of Post Hepatectomy Liver Failure

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Abstract

Indocyanine green 15 min retention rate (ICG-R15) and liver volume measurement are currently commonly used in preoperative liver function evaluation methods, but in clinical application, they are only used as a single liver function evaluation index, which has certain limitations. However, the combination of the two can more accurately evaluate the function of each segment of the liver. Thus, the safety and effectiveness of the operation are greatly improved. This paper reviews the

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research progress on the prediction of PHLF by referring to the relevant literature and combining the key points of the literature.

Keywords

Hepatectomy, Liver Failure, Cancer, Liver Cell, Prediction

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1. 引言

肝细胞癌(Hepatocellular Carcinoma, HCC)是全球第六大常见的恶性肿瘤,是癌症相关死亡的第四大原因[1]。肝切除术是早期、可选择性的中期及晚期伴有可切除肿瘤、肝功能中度的 HCC 患者最有效的治疗方式[2] [3]。在过去的几十年里,手术技术和围术期管理的进步极大地提高了术中安全性及术后效果[4],然而国际肝外科研究组(ISGLS, the International Study Group for Liver Surgery)定义的 B 级或 C 级肝切除术后肝功能衰竭(PHLF)仍然是一个严重的并发症,是术后死亡的主要原因[5] [6],故术前及术后预测 PHLF 对指导临床治疗有着重要的意义。本文总结近年来的肝功能评分系统、实验室及影像学检查对 PHLF 预测的相关研究进展并进行综述。

2. PHLF 定义及诊断标准

PHLF 的定义在不同国家及同一国家的医院之间均存在差异,大部分定义因复杂的计算或仅含有实验室检查结果而使其效用存在局限性,如肝促凝血活酶实验或透明质酸水平等[7]。终末期肝病模型(MELD 评分)用血清肌酐值、INR 和胆红素值定义 PHLF,需要一个复杂的数学公式进行计算[8]。“50-50 标准”即 $PT < 50\%$ 和胆红素 $> 50 \mu\text{mL/L}$ [9]作为 PHLF 的一个简单的定义,然而此定义不考虑任何临床参数,仅依赖于两个实验室值。以上两个定义只考虑了实验室检查结果,未考虑全身情况、未来残肝的体积(FLRV)及其功能。2011 年,国际肝外科研究组(ISGLS, the International Study Group for Liver Surgery)提出了 PHLF 的标准化定义和严重程度分级,在评估超过 50 个 PHLF 的研究后,将 PHLF 定义为肝切除术后肝脏维持其合成、代谢和解毒的功能下降,特点是术后第 5 天或之后的 INR 上升合并高胆红素血症[10]。虽然有其他中心利用生化实验室检查指标或临床参数对 PHLF 进行定义,但 ISGLS 定义(表 1)更易于计算和比较,进而成为标准化的诊断与分级标准,根据该标准确定的 A、B、C 级 PHLF 患者的围手术期的死亡率分别为 0%、12%和 54%。

3. PHLF 的危险因素

由于病因、肝病特征和外科手术方式的差异,相关文献报道的 PHLF 发病率范围为 1.2%至 32% [6] [11]。PHLF 的独立危险因素分为三类[5] [12]: 1) 患者因素包括:年龄、性别、营养不良、糖尿病、心肺、肾或脑功能障碍等; 2) 肝脏疾病相关因素包括:乙型或丙型病毒性肝炎、脂肪变性、胆管炎、酒精性肝病和肝硬化; 3) 手术相关因素包括:未来残肝体积(FLRV)、术中失血过度、手术时间过长、Pringle 法操作导致肝的缺血-再灌注损伤。在亚太地区地区 70%至 90%的 HCC 病例与慢性乙型肝炎相关[13],是促使肝硬化进展为肝功能失代偿期的主要原因。

Table 1. PHLF definition, diagnosis and grading criteria for ISGLS [10]**表 1.** ISGLS 的 PHLF 定义、诊断和分级标准[10]

分级	临床描述	特殊治疗	诊断	临床症状	护理地点
A	肝功能恶化	不需要	尿排出量 > 0.5 mL/Kg/h 肌酐 < 150 mg/dL 血氧饱和度 > 90% INR < 1.5	无	外科病房
B	偏离预期的术后病程, 但无需侵入性治疗。	需要非侵入性治疗: 输注新鲜冷冻血浆、白蛋白、利尿剂。	尿排出量 ≤ 0.5 mL/Kg/h 肌酐 < 150 mg/dL 吸氧后血氧饱和度 < 90% 1.5 ≤ INR < 2.0	腹水 体重增加 轻度呼吸功能不全 意识模糊 肝性脑病	中级护理病房或重症监护病房
C	多系统功能衰竭, 需要侵入性治疗。	需要侵入性治疗: 机械通气、血液透析、插管、体外肝支持。	尿排出量 > 0.5 mL/Kg/h 肌酐 ≥ 150 mg/dL 高流量吸氧后血氧饱和度 ≤ 85% INR ≥ 2.0	肾功能衰竭 血流动力学不稳 呼吸功能衰竭 大量腹水 肝性脑病	重症监护病房

4. PHLF 的预测

4.1. 术前预测

4.1.1. 术前评分系统对 PHLF 的预测

判断 HCC 肝切除术可行性应该首先评估 PHLF 发生的可能性[5] [12]。Child-Pugh 分级[14]、终末期肝病模型(MELD 评分) [15]、血清白蛋白 - 胆红素(ALBI)评分[16] [17]、血小板 - 血清白蛋白 - 胆红素(PALBI)评分和天冬氨酸转氨酶 - 血小板比率指数(APRI) [18]是常用的评估 PHLF 评分, 但由于这些评分标准的局限性导致其预测性能仍存在争议。

Child-pugh 分级是使用最广泛的肝功能评分系统, 已纳入临床常规的外科诊疗过程中[15], 但存在一定的局限性: 1) 在血清胆红素水平 > 55 $\mu\text{mol/L}$ 时对 Child-pugh 分级的评分影响与 >550 $\mu\text{mol/L}$ 相同, 但两者对患者疾病进展的实际影响却不同; 2) 没有明确的区分轻、中度腹水的指南, 所以无法确定利尿剂治疗对腹水分级的确切影响; 3) 给予患者镇静剂治疗时常误导肝性脑病的诊断[19]。

MELD 评分用于评估急性肝衰竭死亡风险并对移植候选者进行排名[20] [21], 术后第 5 天评分 > 8 时患者的 PHLF 发病率与死亡风险明显上升[5], 但 MELD 评分在术前预测 PHLF 的可靠性较差[5] [6] [15]。

ALBI 评分排除了主观因素, 有研究显示术前[22] Child-pugh 分级、MELD 评分和 ICG-R15 预测 PHLF 的准确性比 ALBI 评分高[17] [22]。但有时 ALBI 评分 3 级的梗阻性黄疸比肝功能失代偿引起的黄疸患者肝功能和预后更好, 进而影响了 ALBI 的分级在术前预测 PHLF 的准确性[23] [24]。

PALBI 评分在各种治疗方式上预测 HCC 患者的生存率的准确性均优于 ALBI 评分和 MELD 评分, 但由于 PALBI 预测 PHLF 的相关研究较少, 需进一步深入地评估其准确性和可靠性。

APRI 评分是评估肝纤维化和肝硬化患者肝功能的一种无创、可靠的方法[25] [26], 研究显示术前 APRI 评分 > 0.55 的 HCC 患者发生 PHLF 的风险显著高于术前 APRI 评分 < 0.55 的患者, 预测 PHLF 的敏感性为 72.2%、特异性为 68.0% [27]。然而血清 AST 和 PLT 水平并不是监测肝功能理想的、直接的指标, 在预测 PHLF 时还须考虑肝功能储备和肝硬化的严重程度的影响, 故需进一步研究 APRI 联合 ICG-R15、LS 值对 PHLF 的预测来提高预测的准确性。

4.1.2. 术前动态肝功能测定对 PHLF 的预测

ICG 清除试验是一种在东方国家使用较为广泛的肝功能试验[28], ICG 清除率为先采集患者清晨空腹的静脉血,并以 0.5 mg/kg 的剂量静脉注射 ICG,15 分钟后观察血液中滞留的 ICG 百分比(ICG-R15) [29],或 ICG 血浆清除率(ICG-PDR) [30], ICG-R15 > 15%或 ICG-PDR < 18%/min 时发生 PHLF 的风险较高[31]。研究表明,在肝硬化、HCC 以及肝门周围胆管癌患者中 ICG 预测 PHLF 的准确性较高[28]。有研究显示,ICG 血浆清除率的值联合 FLR 百分比(ICGK-FLR)比 FLR 百分比预测门静脉栓塞(PVE)后 PHFL 的准确性更高[32],其中正常和病变肝脏 ICGK-FLR 最佳截断值分别为 0.04 和 0.05 对应的肝切除体积极限的百分比分别为 70%和 65% [33]。但 ICGK-FLR 取决于肝血流量及胆汁分泌情况,故肝门静脉血栓(PVT)、肝动脉门静脉分流(APS)、肝门静脉高压(PHT)和胆道梗阻会影响试验结果的准确性 [34]。

用 ^{99m}Tc 标记的二亚乙基三胺五乙酸和半乳糖人血清白蛋白(GSA)肝胆闪烁显像(HBS)是一种临床核医学技术。GSA 是一种只在肝脏吸收的唾液糖蛋白类似物,与肝细胞上的特定受体结合且并滞留至少 30 min [35],这些受体在慢性肝病中生成不足[36]。由于 GSA 的吸收不受血清胆红素水平的影响,所以胆汁淤积的患者可用 ^{99m}Tc -GSA-HBS 测定其肝功能[40]。静脉注射 ^{99m}Tc -GSA 后用伽玛相机照射肝脏并生成需要测定的肝脏区域,通过平面动态闪烁成像计算 ^{99m}Tc -GSA 在肝脏的摄取率、血浆清除率和最大清除率与 PHLF 相关性[37]。因 ^{99m}Tc -GSA-HBS 未提供有关节段性肝功能的的信息,故在 ^{99m}Tc -GSA 摄取正常的患者中也出现了 PHLF [40]。所以 ^{99m}Tc -GSA-HBS 联合 FLR 百分比后得到的 FLR 摄取 ^{99m}Tc -GSA 的百分比来评估 FLR 的功能[38]是更准确的 PHLF 预测因子[39]。

用 ^{99m}Tc 标记的亚胺二乙酸(IDA)衍生物- ^{99m}Tc -甲溴菲宁是另一种 HBS 的标记物。 ^{99m}Tc -IDA 为利多卡因类似物,在肝细胞吸收后不进行生物转化而直接排泄到胆道系统[41]。 ^{99m}Tc -甲溴菲宁是与 ICG 性质相似的具有肝脏吸收率高、尿排泄率低和胆红素置换率低特性的 ^{99m}Tc -IDA 衍生物,故用 ^{99m}Tc -甲溴菲宁-HBS 获取肝脏功能成像评估多种胆道疾病的肝功能[36] [41]。静脉注射 ^{99m}Tc -甲溴菲宁后通过 HBS 技术测量肝脏的摄取率并绘制所测定区域的时间-活动曲线。因个体代谢率的差异, ^{99m}Tc -甲溴菲宁摄取率需根据体表面积($\%/ \text{min}/\text{m}^2$)进行校正,随后进行三维 SPECT-CT 扫描进行评估和区分功能性和非功能性肝段[43]。DeGraaf 等人研究显示,FLRV 的 ^{99m}Tc -甲溴菲宁摄取 $< 2.69\%/ \text{min}/\text{m}^2$ 是 PHLF 的预测因子[42]。有其它研究表明, $2.3\%/ \text{min}/\text{m}^2$ 可作为识别 PHLF 高危患者的临界值[44]。亦有研究表明用 ^{99m}Tc -甲溴菲宁-HBS 的 FLRV 功能评估与联合肝脏离断和门静脉结扎的分阶段肝切除术(ALPPS)第二阶段后 PHLF 风险和死亡率相关,故目前术前肝体积联合肝功能的评估是预测 PHLF 的最准确和可靠的方法之一,在肝切除术的术前评估过程中至关重要,且 ^{99m}Tc -甲溴菲宁-HBS 具有操作方便、无创及低成本的优势[45]。

4.1.3. 术前肝剪切波弹性成像(SWE)对 PHLF 的预测

有文献显示[46],依据 ISGLS 标准,在行肝剪切波弹性成像(SWE)检查的 77 名患者中有 35.1% (27 例)发生了 PHLF,其中 A、B 级患者分别为 2 例与 25 例。多变量分析表明,升高的 SWE 测量的肝硬度值(LSM) ($P = 0.002$)和组织学肝硬化($P = 0.003$)是 PHLF 的独立预测因子,当患者的 LSM ≥ 6.9 kPa 发生 PHLF 风险较高,故 LSM 预测 HCC 患者的 A、B 级 PHLF 是有效、可靠的且性价比较高,可作为肝切除术前评估的常规检查。

有研究发现[47],在患有慢性乙型肝炎且 HBsAg 阳性 >6 个月的 247 名患者中,76 名(30.8%)患有肝硬化,37 名(14.98%)患者发生 PHLF,术前 LSM 为 PHLF 的独立危险因素,预测 PHLF 的最佳截断值为 14 kPa,可用于与 HBV 肝炎相关 HCC 患者的诊疗过程中。

4.2. 术后预测 PHLF

4.2.1. 术后相关实验室检查对 PHLF 的预测

Squires 等人在 719 名接受肝切除术患者的研究中分析了肝切除术后血磷值下降与 PHLF 的相关性。单因素及多因素分析表明, 患者术后第 2 天血磷水平持续 >2.4 mg/dL 和术后第 3 天后血磷水平达到最低点的 PHLF 发生率显著上升, 术后 30 天和 90 天死亡率是术后第 2 天血磷水平 <2.4 mg/dL 患者的 2 倍以上[48]。Salem 和 Tray 的一项研究显示[49], 肝切除术后尿磷酸盐的排泄量在最初几个小时内显著增加, 亦有研究表明[50]是因人体内存在一种磷酸盐蛋白导致了该现象。最近, 一项动物模型中研究[51]显示肝脏手术后的低磷血症与烟酰胺磷酸核糖转移酶(nicotinamide phosphoribosyltransferase, Nampt)在肾小管近端细胞激活引起的肾细胞中烟酰胺(nicotinamide, NAM)代谢异常有关, 但术后磷酸盐减低与 PHLF 的关系仍需进一步研究以得到更加准确、可靠的结论。

有研究显示, 术后即刻 $PLT < 100 \times 10^9/L$ 的患者: 1) PHLF 发生率、死亡率比 $PLT \geq 100 \times 10^9/L$ 的患者更高; 2) 术后第 3 天和第 5 天的 ALT 水平以及术后第 1 天、第 3 天和第 5 天的 TBil 水平较高。多变量分析显示[52], 术后即刻 $PLT < 100 \times 10^9/L$ 是 PHLF 的独立危险因素。Ohkohchi 等人给予患者输注 PLT 后肝功能得到改善证实了 PLT 减低的临床影响[52] [53], 故术后应及时补充 PLT 以预防 PHLF。

4.2.2. 术后肝功能测定对 PHLF 的预测

一项国内研究显示, 119 例接受肝切除术的患者中共有 33 例(27.7%)发生 PHLF [54], 术后第 3 天 ICG-R15 预测 PHLF 发生的 ROC 曲线下面积较术前 ICG-R15 大, 前者的临界值为 7.75%, 后者为 3.35%, 表明术后第 3 天 ICG-R15 能预测 PHLF 的发生, 且可能优于术前 ICG-R15, 但该研究为单中心研究且样本量不足, 仍需要进一步进行多中心、大量样本的研究。

5. 总结与展望

目前实验室检查、肝脏体积评估、ICG 清除试验已经成为肝切除术患者术前、术后 PHLF 预测的常规检查, 而现代核医学成像技术对动态肝功能的测定则更为精准, 但以上检查反应的均是全肝功能, 无法评估区分功能性肝段与非功能性肝段的功能。而三维 SPECT-CT 扫描只能评估肝脏体积, 区分功能性肝段与非功能性肝段来计算肝脏极限切除体积, 但无法评估肝脏功能。以上研究表明用单独一项检查无法准确地预测 PHLF, 而动态肝功能测定联合肝体积进而分析肝各段功能可获得更完整的肝功能评估结果, 极大地提高了对 PHLF 预测的准确性。术前肝功能评估方法对 PHLF 预测的效用仍需进一步前瞻性研究来比较, 从而提高对 PHLF 预测的准确性与可靠性, 避免非必要的手术。

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