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肝移植术后胆道吻合口狭窄：现状和进展

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摘　要

肝移植已成为治疗终末期肝病的重要方法。但胆道并发症依然是肝移植术后主要并发症，尤其胆道吻合口狭窄。这严重影响患者术后的生存质量，甚至可能导致移植后患者肝功能衰竭或死亡。因此，进一步了解胆道吻合口狭窄的危险因素对改善患者的预防和治疗至关重要。本文旨在系统综合现有研究，分析肝移植术后胆道吻合口狭窄的危险因素及其机制，探讨诊断方法、治疗策略，并提出预防措施，为临床实践提供指导。

关键词

肝移植，胆道并发症，胆道吻合口狭窄，危险因素，诊治，预防

Biliary Anastomotic Strictures after Liver Transplantation: Current Status and Advances

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Abstract

Liver transplantation has become an important method for treating end-stage liver disease. However, biliary complications remain the major postoperative complications of liver transplantation,

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especially biliary anastomotic strictures. This seriously affects the postoperative quality of life of patients and may even lead to liver function failure or death in transplant recipients. Therefore, further understanding of the risk factors for biliary anastomotic stricture is crucial to improve patient prevention and treatment. This article aims to systematically synthesize existing research, analyze the risk factors and mechanisms of biliary anastomotic stricture after liver transplantation, explore diagnostic methods, and treatment strategies, and propose preventive measures to provide guidance for clinical practice.

Keywords

Liver Transplantation, Biliary Complications, Stenosis of Biliary Anastomosis, Risk Factors, Diagnosis and Treatment, Prevention

1. 前言

自 1960 年代首次进行肝移植以来，肝移植已成为终末期肝病或急性肝衰竭患者的有效治疗手段[1]。尽管手术技术、免疫治疗方案、器官保存技术和术后管理策略在不断改进，但胆道并发症仍是导致术后反复治疗、医疗费用增加甚至移植失败的重要原因[2] [3]。据报道，肝移植术后胆道并发症的发病率为 5%~32% [4]，死亡率为 8%~15% [4] [5]，其中以吻合口狭窄为主。吻合口狭窄指局限于手术吻合口 1 厘米以内的孤立性狭窄，占肝移植术后胆道并发症的 40%~60% [6]，严重影响着患者术后的生活质量。因此，进一步了解肝移植术后胆道并发症的危险因素，对于改善患者的预后和治疗策略十分重要。故本文旨在对肝移植术后吻合口狭窄的危险因素及诊疗进展进行综述，以期为临床决策提供参考。

2. 危险因素

(一) 胆道重建技术对吻合口狭窄的影响

1) Roux-en-Y 肝肠吻合、胆肠吻合和胆管端端吻合

胆道重建技术是肝移植术后胆道并发症风险的主要决定因素。目前，主要的胆道重建方式包括 Roux-en-Y 肝肠吻合、胆肠吻合和胆管端端吻合。由于 T 管的使用增加了胆道并发症的发生率，因此目前仅推荐在胆道状况较差的情况下使用 T 管[7] [8]。Roux-en-Y 肝肠吻合目前仅用于特定病例，例如原发性硬化性胆管炎、既往胆道系统手术、胆管大小明显不匹配和受体胆管长度不足的患者[9]。胆肠吻合曾因其有利于保持吻合口血液供应并实现无张力吻合而被视为标准的胆道重建方式。然而，一些回顾性研究发现胆肠吻合和胆管端端吻合术后的胆道并发症发生率相似；但前者伴有更高的细菌感染、出血和胆漏的风险[10] [11] [12]。其他研究结果却认为接受胆肠吻合术的受体更有可能患上血管并发症[13]。胆管端端吻合的优势在于能够保留 Oddi 括约肌功能、降低反流性胆管炎风险和减少吻合口数量；可以维持正常的生理结构，有利于术后内镜下的诊断和治疗，因此目前手术时更倾向于胆管端端吻合。然而，胆道重建方式的选择应综合考虑多种因素，包括潜在的肝脏病变、供体和受体胆管的大小以及既往的移植或胆道手术。

2) 吻合口缝合方式及缝合材料的影响

吻合口缝合主要分为间断缝合、连续缝合以及两者结合的缝合方式。Seifert 等[14]进行的一项 RCT

研究比较了连续缝合(41 例)和间断缝合(39 例)发现两者在吻合口狭窄率方面没有统计学差异，但连续缝合更快、更经济。胆道重建中缝合材料的选择尚无统一标准。一项包括 133 例患者的单中心回顾性研究发现，6-0 聚丙烯(Prolene)和 6-0 聚二氧丙烷(PDS)缝合线在胆道并发症发生率上无显著差异(P = 0.990) [15]。但 Kaldas 等[16]的多因素回归分析显示，使用不可吸收的缝合材料重建胆道是术后胆道并发症的独立危险因素(OR: 2.45, 95%CI: 1.09~5.54, P = 0.03)。这可能是因为可吸收 PDS 能减少异物肉芽肿的形成，从而预防因炎症引起的胆道狭窄。

无论如何，重建胆道时应遵循外科胆道吻合原则，包括维持最小张力的吻合口、适当的缝合间隔、准确贴合胆管黏膜、足够的血液供应，以及避免对胆管上皮造成损伤或创伤。

(二) 胆道供血系统受损

胆道树的微血管供应(即肝胆管周围血管丛)源于肝动脉分支并流入肝窦[17]。由于胆道的血液供应完全依赖于肝动脉，因此，术后早期发生肝动脉血栓的患者胆道并发症发生率较高和不良预后[16]，这可能是因为肝动脉血栓会导致胆道缺血[18]。Yuan 等[19]在动物模型中发现，肝胆管周围血管丛完全缺血时会严重损伤肝胆管上皮细胞，此时可直接观察到肝胆管上皮细胞增殖紊乱。这表明胆管供血系统损伤会造成胆管周围血管丛微循环障碍，进而引发胆管吻合口的狭窄和坏死[20]。

(三) 冷/热缺血时间

许多研究已经证实冷/热缺血时间(Cold/Warm Ischemia Time, CIT/WIT)的增加与许多并发症的发生密切相关。Pinto 等[21]认为 WIT > 35 min 会增加肝动脉血栓的风险。Blok 等[22]对 1390 名肝移植患者进行了 Cox 回归分析，发现温缺血时间 > 25 min 会增加移植物丢失率。Figiel 等[23]发现 CIT > 496 min 时移植物丢失率显著增加。Lozanovski 等[24]回顾性分析了 40288 例肝移植后发现，CIT 每增加一小时，移植物丢失的风险增加 3.4% (HR: 1.034, P < 0.001)。缺血时间(Ischemia Time, IT)对胆道吻合口的影响可能与缺血再灌注损伤(Ischemic Reperfusion Injury, IRI)有关。IRI 缺血阶段始于肝血供不足，细胞缺氧后破坏氧化呼吸链，导致三磷酸腺苷(ATP)的耗竭以及有害代谢物的积累。较长的 IT 会加重细胞水肿，从而激活蛋白酶并启动凋亡联级反应[25]。再灌注阶段使肝血流量恢复时，会促进肝细胞释放促炎细胞因子、活性氧(Reactive Oxygen Species, ROS)等代谢副产物，这加剧了缺血阶段对肝脏组织的损伤[26]。然而 Liu 等[27]在小鼠肝移植模型中发现，适当的缺血再灌注(90 min)可以激活 YAP-Hippo 通路，该通路可促进肝细胞再生和诱导抗氧化基因表达来保护肝脏免受 IR 应激从而减少 IRI 在介导的肝细胞损伤和肝纤维化中的作用，这可能为今后肝移植后 IRI 的预防提供新的思路。但在整个移植过程中，尽量减少 CIT/WIT 有助于降低术后并发症发生。

(四) 免疫因素

巨细胞病毒(Cytomegalovirus, CMV)感染可能增加肝移植术后发生胆道并发症的风险。Halme 等[28]的研究显示，既往或现有 CMV 感染的患者更容易在肝移植后出现胆道并发症，尤其是在原发性 CMV 感染的情况下。这可能与供体/受体人类白细胞抗原(Human Leukocyte Antigens, HLA)的匹配以及 CMV 诱导的 HLA 表达导致慢性排斥反应的发生有关[29]。因此对 CMV 血清检测阴性的肝移植受者实施 CMV 预防可能有助于防止胆道并发症的发生。

(五) 供体和受体的自身因素

1) 供体

a) 中重度肝脂肪变性(>30%)增加了吻合口狭窄的发生风险[30]。肝脂肪变性可诱导肝脏线粒体、库普弗细胞和窦细胞水平的改变，加重冷缺血期间的细胞损伤，并加剧缺血再灌注损伤[31]。

b) 供体的年龄(>40 岁)可能影响胆道吻合的效果[32]。这是因为随着年龄的增加，肝脏的合成、排泄

和代谢功能逐渐下降[33]，这些因素降低了肝脏对 IRI 的耐受性，从而影响了吻合口的愈合过程。

c) 供体吸烟史：相较于不吸烟人群，供体吸烟史与术后早期血栓形成独立相关(OR: 2.42, 95%CI: 1.29~4.52)，且肝移植后血栓形成的风险增加两倍以上[34]。

2) 受体

a) MELD 评分：终末期肝病模型(Model for End-stage Liver Disease, MELD)已广泛应用于评估终末期肝病的严重程度，不仅可以预测患者短期死亡率，还作为供肝分配的参考[35]。多项研究表明，高 MELD 评分与胆道吻合口并发症存在相关性[16] [36]。这可能是因为高 MELD 评分的患者通常患有更严重的肝病，因此术后康复困难，从而影响了手术后吻合口的愈合。

b) 感染：受体术前感染可导致术后早期并发症的发生率更高，生存期更短，感染部位的类型和数量也会影响肝移植受体的预后[37]。

(六) 器官保存液对移植肝脏胆道并发症的影响

肝脏在离体后经历的冷热缺血、再灌注损伤以及胆管毛细血管的灌注程度，均与术后胆道并发症的风险密切相关。保存液的成分对其性能和保存效果发挥着关键作用。肝脏离体后应立即使用肝素化液充分冲洗，以消除管腔内血栓和肝内微血栓的形成。Shadike 等[38]研究发现，相较于康斯特液(HTK 组)，威斯康星大学保存液(UW)组胆道并发症和缺血相关的胆道损伤发生率更高。然而其他研究比较发现，UW 组在术后 90 天移植物存活率高于 HTK 组(97.38% vs 94.39%, $P < 0.001$) [39]。这些结果表明 UW 液和 HTK 对胆道的保护效果可能存在相似或相反的影响。理论上，由于康斯特液(HTK)具有低黏滞和低钾的特性，这有利于对供肝组织细胞、细微胆管和毛细血管进行完全的冲洗和灌注，因此灌注不彻底等原因引起的并发症应该相对少见。

(七) 其他

1) 胆漏：胆漏多发生于吻合口部位，与多种因素相关，如胆道重建技术、吻合口缝合方式及线材、肝动脉血栓和术后感染等。胆漏增加吻合口狭窄的机制可能是渗漏的胆汁诱导吻合部位产生炎症反应和纤维增生[40]。

2) 活体肝移植(Living Donor Liver Transplantation, LDLT)：LDLT 的胆道并发症发生率是尸体肝移植的 2~3 倍[41]。这主要是由于供受体胆管直径不匹配或存在多个吻合口，导致更易发生吻合口狭窄[9]。

3. 临床症状和诊断

(一) 临床症状

胆道吻合口狭窄临床症状多样。患者早期临床症状多不明显，主要表现为血清胆红素水平升高或转氨酶异常，也可能表现为黄疸、发热、腹痛。随着病情进展可能出现胆汁淤积、感染甚至移植肝衰竭。

(二) 诊断

对怀疑吻合口狭窄的患者，腹部超声是首选检查方法。该检查可以初步发现并评估胆道扩张程度，从而判断吻合口是否存在狭窄[42]。一项回顾性研究对比了腹部超声和金标准胆道造影在诊断胆漏或吻合口狭窄方面的表现，发现超声的敏感度为 77%，特异度为 67%，阳性预测值为 26%，阴性预测值为 95% [43]。这表明超声在诊断吻合口狭窄时具有较高的参考价值。

对于超声无法确诊的吻合狭窄，磁共振胰胆管成像(Magnetic Resonance Cholangiopancreatography, MRCP)可作为进一步检查方案。一些研究发现，MRCP 可以有效识别缺血型胆道病变、吻合口和非吻合口狭窄以及结石等疾病，其检出率与内镜逆行胰胆管造影(Endoscopic Retrograde Cholangiopancreatography, ERCP)、经皮穿刺肝胆管造影术(Percutaneous Transhepatic Cholangiography, PTC)以及经 T 管胆道造影相当[44] [45]。对于上述无创检查均无法确诊、但临床上又怀疑狭窄存在的患者，最佳选择是进行直接

胆管造影(ERCP、PTC 或经 T 管胆道造影)。然而，这三种检查均存在潜在的不良反应风险，因此在进行选择时需要谨慎考虑。

4. 治疗

治疗吻合口狭窄的目标是确保胆汁能够正常通过吻合口排出。微创治疗目前是首选方法，其中包括 ERCP 内镜治疗、PTC 和磁吸引吻合术(Magnetic Compression Anastomosis, MCA)。

(一) ERCP 内镜治疗

随着内镜技术的不断进步，ERCP 已被广泛应用于治疗吻合口狭窄。虽然不同研究结果存在较大差异，但研究表明超过 75%的患者在接受 ERCP 治疗后效果良好[46] [47]。目前 ERCP 支架植入治疗主要包括单次塑料支架、多次塑料支架(Multiple Plastic Stent, MPS)以及全覆盖自膨胀金属支架(Fully Covered Self-Expandable Metal Stents, FC-SEMS)。研究表明，与单次塑料支架相比，MPS 和 FC-SEMS 治疗后的狭窄消退率更高(分别为 61%和 88%) [48]。与 MPS 相比，FC-SEMS 的优点是无需重复 ERCP 放置支架。

(二) 经皮穿刺肝胆管造影术(PTC)

对于行胆肠吻合术致解剖结构改变或内镜治疗狭窄失败的患者，PTC 被视为重要的补充手段。PTC 通常采用单纯球囊扩张术，因其术后复发率较高(47%)，患者常需反复手术扩张吻合口[49]。多项研究已证实，球囊扩张联合支架置入相较于单独使用球囊扩张或支架置入，在手术成功率和狭窄复发率方面更为有效[50] [51]。2018 年，Dhondt 等[52]提出了一种名为经皮三重球囊扩张(percutaneous threefold balloon dilatation protocol)的方法用于治疗胆道吻合口狭窄。该技术在 PTC 辅助下，留置导管及球囊在患者胆道内，从而可以在短期内多次对狭窄部位进行扩张而无需重新穿刺。据报道，其手术成功率和有效率分为 99%和 87%，为吻合口狭窄治疗提供了新思路。

(三) 磁吸引吻合术(MCA)

对于导丝难以通过的重度胆道吻合口狭窄，MCA 可能是一种可行的替代手术方法。该方法通过联合运用内镜和 PTC，将磁铁分别放在吻合口狭窄部位的近端和远端，磁铁吸引所产生的压迫会导致它们之间的组织坏死，从而产生可供导丝穿过的瘘管[53]。研究表明，MCA 的成功率较传统方法更高，并且术后瘘管复发率低，显示了 MCA 的安全性、可行性和有效性[54] [55]。尽管如此，目前 MCA 的临床应用报道较少，因此仍需要进一步的研究来验证该方法的可靠性。

(四) 手术重建胆道

当上述方法均难以奏效时，通过手术切除狭窄部位重建胆道应作为最后的治疗手段。重建方式主要包括 Roux-en-Y 肝肠吻合、胆肠吻合和胆管端端吻合。重建方式取决于术中具体情况，但为保持吻合口最小张力，一般多选择 Roux-en-Y 肝肠吻合、胆肠吻合。

5. 预防

(一) 手术技术

胆道重建技术在预防肝移植术后的胆道并发症中起着重要作用。首先，供肝体积应与受体体重相匹配。若为 LDLT，移植肝与受体体重比(Graft and Recipient Weight Ratio, GRWR) > 0.8%有助于降低术后胆道并发症的发生[56]；其次，术中应确保胆道吻合正确和无张力，并具有良好的血供。目前胆管端端吻合被认为是原位肝移植胆道重建的首选方法，其优势在于可以保证患者胆道口括约肌功能正常，更符合人体的自然生理状态，能有效减少肠道内容物反流对胆道的刺激。理论上，胆道端对端吻合术可以降低术后胆道并发症的发生率[57]，但重建方式的选择应取决于术中具体情况。对于右后叶的 LDLT，Lin 等[58]提出 Glissonian 鞘－胆管吻合术(Glissoniansheath-to-Duct, GD)用于处理多根胆管吻合的情况。在 60.8 个

月的平均随访期中，GD 组的胆道狭窄率明显低于端端吻合组(13.5%, 27/200 vs 26.7%, 32/120, P = 0.003)，这表明 GD 吻合可作为 LDLT 胆道重建的替代方法。此外，Ma 等[59]在 2023 年报道中采用吲哚菁绿荧光技术完成一例患者的胆肠吻合术。该技术可实时监测吻合口灌注和机械稳定性，有望减少吻合口狭窄的发生。

(二) 血供保护

作为术后移植肝的主要血液来源，肝动脉任何的异常都可能引起胆道的并发症。肝动脉变异率约为 20%~50% [60]，这增加了手术难度，因此修整供肝时应特别注意。此外多项研究表明，接受过显微外科培训的整形外科医生在手术中应用显微外科技术进行动脉吻合，可降低肝动脉血栓(Hepatic Artery Thrombosis, HAT)的发生[61] [62] [63]。目前国际上尚未发布预防 HAT 的指南，且术后是否使用阿司匹林预防 HAT 仍存在争议。Wolf 等[64]发现阿司匹林组与非阿司匹林组在 HAT 发生率(3.7% vs 4.0%)上并无差异。Oberkofler [65]则认为低剂量阿司匹林可有效降低 HAT，且不会增加阿司匹林相关的出血性并发症。总之，在预防 HAT 时，在有特定风险因素的患者中，阿司匹林可能带来出血风险，这需要仔细考量和个体化治疗。

(三) 机械灌注

众多研究已经展示了机械灌注技术在减少供肝缺血再灌注损伤方面的显著效果[66]。这些技术包括常温区域灌注[67]、低温携氧灌注[68]和常温机械灌注[60]。它们已被证明能有效减少胆管损害，并因此显著降低肝移植后胆道狭窄的发生率。例如，Amelia 等[67]的研究表明，与冷贮液快速保存组相比，常温区域灌注组在整体胆道并发症(OR: 0.14, 95%CI: 0.06~0.35, P < 0.001)和缺血性胆道损伤(OR: 0.11, 95%CI: 0.02~0.57, P = 0.008)等方面均有显著改善。2018 年，Nasralla 等[69]发表的一项随机对照试验研究，将 222 例供肝随机分为常温机械灌注组和冷贮液快速保存组。研究结果显示，常温机械灌注组受体术后血清谷丙转氨酶峰值降低，供肝保存时间延长近 54%，器官弃用率降低近 50%。这些研究结果一致表明，机械灌注相对于静态冷冻保存具有明显的优势，可有效减少缺血再灌注损伤对肝细胞的损害，从而降低吻合口狭窄的发生率。然而，目前尚无研究比较不同机械灌注方法在胆道保护方面的效果。此外骨髓来源间充质细胞联合常温机械灌注已被证明有助于保护肝细胞和胆管上皮细胞功能，其作用优于静态冷保存组和单纯常温机械灌注组，但其临床疗效仍存在争议[70] [71] [72] [73]。机械灌注可能是通过维持细胞的代谢活动和提供必要的氧合来减轻缺血再灌注损伤[74]，减少异常胆汁盐生成[75]，促进胆管上皮细胞的修复和再生[76]，从而改善胆管损伤。

(四) 无缺血肝移植

冷/热缺血引起的缺血再灌注损伤是肝移植术后的一个重要并发症危险因素，而无缺血肝移植(ischemia-free liver transplant, IFLT)则几乎可以完全消除冷/热缺血时间。IFLT 是指在肝脏的获取、保存和植入的整个过程中保持常温含氧血液供应。2023 年的一项多中心临床随机对照实验首次比较了 IFLT 和常规肝移植，其中 2 名受试者(6%, 2/32)随机接受 IFLT 治疗，8 名受试者(24%, 8/35)随机接受(Conventional Liver Transplantation, CLT)治疗[77]。结果显示，在移植后的第一年，IFLT 组的综合并发症指数为 30.48 (95%CI: 23.25~37.71)，而 CLT 组为 42.14 (95%CI: 35.01~49.26)。这些结果表明相较传统方法，IFLT 显著减少了与缺血再灌注损伤相关的并发症，尽管这需要更多的研究来进行验证。

6. 小结

综上所述，肝移植术后吻合口狭窄的危险因素涉及供体/受体因素(如脂肪变性、年龄 > 40 岁、吸烟史、感染、CMV、终末期肝病)和医疗因素(如外科吻合技术缺陷、供血系统受损、延长的冷/热缺血时间、不当的器官保存液)。尽管其病因和机制仍不完全清楚，但及早进行诊治极为重要。临床上需要对围手术

期进行合理评估，制定系统的手术方案，并对患者术后进行定期检查，以便早期发现并管理吻合口狭窄，从而降低其进展的风险。

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