

2023年中国肝移植临床研究年度盘点

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【摘要】 肝移植作为成熟的器官移植手术已成为终末期肝病的最佳治疗手段，提高了患者的生存质量。但目前肝移植依然面临诸多挑战，如排斥反应、感染、胆道并发症、移植物功能恢复延迟、缺血-再灌注损伤、肝细胞癌肝移植术后复发、移植后肾相关疾病、供者短缺等，亟待改善和解决。伴随着我国各位专家学者不断的尝试和经验总结，肝移植相关问题逐年突破。2023年，中国肝移植团队在临床研究领域取得了一系列重大进展，本文就2023年度肝移植临床相关的前沿以及肝移植领域的新技术进展进行综述，总结我国2023年在肝移植领域临床研究取得的成果，以期为促进我国肝移植的进一步发展提供新思路。

【关键词】 肝移植；排斥反应；缺血-再灌注损伤；感染；移植物功能恢复延迟；胆道并发症；肝细胞癌；慢性肾病

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【Abstract】 As a mature organ transplantation, liver transplantation has become the optimal treatment for end-stage liver disease, which can improve the quality of life of recipients. However, liver transplantation still faces multiple challenges, such as rejection, infection, biliary complications, delayed graft function, ischemia-reperfusion injury, recurrence of hepatocellular carcinoma after liver transplantation, kidney-related diseases after transplantation, and donor shortage, etc., which remain to be improved and urgently resolved. With persistent attempts and experience accumulated by Chinese experts and scholars, these problems related to liver transplantation have been gradually resolved year by year. In 2023, liver transplantation teams in China have achieved a series of significant progresses in the field of clinical research. In this article, clinical frontiers and novel technological progresses in the field of liver transplantation in 2023 were reviewed, and the achievements of clinical liver transplantation in China in 2023 were summarized, aiming to provide novel ideas for promoting further development of liver transplantation in China.

【Key words】 Liver transplantation; Rejection; Ischemia-reperfusion injury; Infection; Delayed graft function; Biliary complication; Hepatocellular carcinoma; Chronic kidney disease

肝移植是目前公认的唯一有效的治疗终末期肝病的方法。尽管由于近年来手术技术、麻醉管理、免疫抑制方案和重症监护室管理的进步，肝移植术后生存

率和长期预后都有了显著的改善，但受者仍旧面临多种术后并发症，影响术后生存质量^[1]。例如排斥反应、感染、移植物功能延迟恢复、缺血-再灌注损伤

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(ischemia-reperfusion injury, IRI)、肝细胞癌(肝癌)肝移植术后复发、移植后肾相关疾病等,亟待改善和解决。伴随着我国众多专家学者的不断尝试和经验总结,移植相关问题逐年突破。本文就 2023 年度肝移植临床相关的前沿以及移植领域的研究进行综述,总结我国 2023 年在移植领域取得的成果,并为移植领域的发展提供新思路 and 策略。

1 检索策略

为了解肝移植领域在 2023 年度文献发表情况,作者在 PubMed 按以下检索策略进行限定检索:选定检索词“liver transplantation[MeSH Terms] OR liver transplant*[Title/Abstract] OR hepatic transplant*[Title/Abstract]”,发表时间限定在 2023 年 1 月 1 日至 12 月 31 日;共检索出 2 774 篇文献,在此检索结果上,利用“AND China[Affiliation]”得到我国团队发表的 298 篇文献,提示全年中国发表文献占比 10.7%。同时,为更加全面,笔者也扩大了检索范围,一同解读了一些移植相关的有价值文献。

2 中国肝移植临床研究进展

2.1 排斥反应

免疫检查点抑制剂(immun checkpoint inhibitor, ICI)可以阻止 T 细胞表面的受体与程序性细胞死亡蛋白 1(programmed cell death protein 1, PD-1)结合,从而激活先天免疫系统来杀死肿瘤细胞^[2]。ICI 作为移植后复发或新发肿瘤患者的最后选择,近年来已逐渐应用于器官移植受者^[3]。然而,ICI 可能导致器官移植受者发生排斥反应^[4]。中山大学附属第一医院器官移植中心的研究发现,肝移植术前使用 PD-1 抑制剂可能增加术后排斥反应的发生率,但与免疫相关的移植物丢失和受者死亡无关^[5]。提出 PD-1 抑制剂与肝移植之间的短间隔可能会增加移植物排斥反应的发生率,建议患者应尽早开始免疫抑制治疗,并适当增加剂量及延长最后 1 次 PD-1 抑制剂治疗与肝移植的时间间隔^[5]。

2.2 感染

术前营养不良、免疫功能低下,手术复杂、冗长、创伤严重,术中大量输血和输液,深静脉插管、留置导尿管、气管插管之类的侵入性手术,加上广谱抗生素、糖皮质激素(激素)和免疫抑制药的使用等均会增加肝移植受者感染的风险^[6-7]。其对肝移植受

者的生活质量产生严重影响,甚至可导致死亡。中南大学湘雅三医院研究团队通过分析肝移植术后细菌感染的致病性分布、药物敏感性和危险因素,确定了肝移植术后细菌感染的独立危险因素包括受者为女性、手术时间>400 min、术中失血量>3 000 mL 等,通过实施优化手术策略和减少失血策略等,可减少肝移植术后细菌感染的发生率^[8]。脓毒症是肝移植术后死亡的主要原因之一。中山大学附属第三医院麻醉科建立了肝移植术后脓毒症预测模型,该模型纳入术中和术中变量,为预测肝移植术后脓毒症的临床应用提供了重要参考^[9]。

2.3 胆道并发症

肝移植相关技术进展迅速,但胆道并发症的发生率仍然很高,两种最常见的胆道并发症是胆漏和吻合口狭窄^[10]。原位肝移植术后胆漏的发生率为 20%,27% 的患者会有晚期吻合口狭窄。虽然影响原位肝移植术后吻合口狭窄和胆漏的因素很多,如冷缺血时间、慢性排斥反应、肝动脉血栓形成等,但吻合口技术引起的吻合口狭窄和胆漏被认为是主要原因^[11]。笔者团队利用胆管成形术重建胆总管,具有很好的安全性和实用性,特别是对于胆总管直径较小或供受者胆管直径差异较大的患者,可以明显降低术后胆道并发症的总体发生率^[12]。肝移植术后胆管吻合口狭窄原因与缝合技术、胆漏、局部缺血、感染等因素有关。内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)或经皮经肝胆道引流术(percutaneous transhepatic cholangial drainage, PTCD)已在很大程度上取代了手术,成为胆道吻合口狭窄的首选治疗方法,成功率为 60%~100%^[13-14]。西安交通大学第一附属医院肝胆外科提出胆管镜下导丝穿刺技术用于完全梗阻的吻合口再通,对胆道吻合术完全狭窄安全可行且成功率较高^[15]。

2.4 缺血-再灌注损伤

传统供器官是在用器官保存液冷冲洗后获得的,储存在冰上然后紧急植入,以缩短缺血时间,由此产生的 IRI 被认为是器官移植不可避免的^[16-18]。然而,中山大学附属第一医院器官移植中心开创了一种无缺血肝移植技术,与常规方法相比,无缺血肝移植能减少终末期肝病患者 IRI 相关并发症的发生^[19]。

2.5 肿瘤复发

肿瘤复发是肝癌肝移植受者术后最常见的死亡原因之一,严重影响了受者的预后^[20]。目前,肝癌肝移

植受者的选择标准,如米兰标准、加州大学旧金山分校标准,仅包括肿瘤负荷、远处转移和大血管侵犯,即使符合米兰的标准,仍有15%~20%的受者术后会发生肿瘤复发^[21-22]。因此,还需要一些额外的指标来评估受者的预后。天津市第一中心医院团队基于 γ -谷氨酰转肽酶与淋巴细胞比值(γ -glutamyl transpeptidase-to-lymphocyte ratio, GLR)和全身免疫炎症指数(systemic immune-inflammation index, SII)建立的新模型可以有效预测肝癌肝移植术后肿瘤复发,有望指导术前受者的选择和术后随访^[23]。此外,复旦大学附属中山医院团队建立的深度病理组学评分(deep pathomics score, DPS)有助于肝癌特异性结构的组织学诊断,并可预测肝移植术后肿瘤复发^[24]。

他克莫司已被证明在体外促进肿瘤生长。南京中医药大学鼓楼临床医学院的一项研究证明,利用他克莫司治疗目标范围内的时间百分比可用于预测肝癌肝移植术后肿瘤复发,且中国指南推荐的范围比国际共识推荐的范围更适合中国肝癌肝移植受者,能在随访中更好区分高危患者^[25]。全身炎症反应指数(systemic inflammatory response index, SIRI)是根据淋巴细胞、中性粒细胞和单核细胞计数计算出来的,其对恶性肿瘤预后的预测价值已被证实,然而SIRI在肝癌中的研究较少。笔者团队研究显示,高SIRI与肝癌肝移植受者术后不良的长期预后有明显的相关性^[26]。浙江大学团队研究表明,对于多发肿瘤的肝癌患者,肝移植是较好的根治性治疗方法。对于现有的米兰标准等,部分多发肝癌患者不符合肝移植指征,其建立的改良甲胎蛋白(α -fetoprotein, AFP)模型可以有效地识别出多发性肿瘤的低复发风险肝癌患者,使其获得肝移植手术机会^[27]。除此以外,浙江大学医学院附属第一医院肝胆胰外科研究发现,术前存在生物学行为[非术前经导管动脉化疗栓塞(transarterial arterial chemoembolization, TACE)等抗肿瘤治疗]引起的肿瘤细胞微坏死会使患者预后更差^[28]。肝癌肝移植术后复发的主要治疗方法包括手术切除和TACE,福建医科大学团队证实TACE联合索拉非尼治疗原位肝移植术后复发性肝癌有明显疗效,其轻度毒性患者可承受^[29]。乙型病毒性肝炎是肝癌手术后复发的危险因素之一,中山大学附属第三医院团队研究证实,与恩替卡韦相比,替诺福韦可明显降低肝移植术后乙型病毒性肝炎相关肝癌复发的

风险^[30]。

2.6 移植后肾相关疾病

肝移植术后急性肾损伤(acute kidney injury, AKI)与重症监护室入住时间、病死率、排斥反应和慢性肾病发展相关^[31-33]。早期识别和预防,避免使用肾毒性药物,必要时早期干预,如肾脏替代治疗,可改善肝移植术后AKI患者的预后,因此,早期发现评估AKI风险至关重要。北京佑安医院基于临床参数和术后胱抑素C水平组合建立的列线图模型有助于早期发现AKI,改善肝移植受者的预后^[34]。中山大学孙逸仙纪念医院团队提出并验证包括术前和术中预测因素的列线图模型来预测肝移植受者AKI的发生,能较好地鉴别和校准手术结束时高危AKI患者,避免不必要的术后肾损伤^[35]。慢性肾病是肝移植术后的长期并发症,会显著降低受者的生存率^[36]。浙江大学医学院附属第一医院肝胆胰外科团队建立的列线图模型对肝移植术后慢性肾病的诊断效果较好,并提出在术后早期及时处理血脂异常和肾功能不全可能有助于预防慢性肾病的发生^[37]。

2.7 代谢组学

无缺血肝移植技术在不断更新,以避免在器官获取、保存和植入过程中的移植物缺血^[38]。然而,供肝在原位和非原位常温机器灌注,以及标准供者和扩大标准供者之间的代谢差异仍未知。中山大学附属第一医院器官移植中心在原位获取及非原位常温机器灌注期间采集供肝门静脉和肝静脉血浆样本,采用超高效液相色谱-质谱法研究肝叶内代谢物交换,在原位和非原位条件下都发现了丰富的半胱氨酸和蛋氨酸代谢,以及氨基酰基-转运RNA(transfer RNA, tRNA)的生物合成,而D-精氨酸、D-鸟氨酸、精氨酸和脯氨酸代谢仅在原位条件下发现,在RNA表达水平上证实了在非原位条件下尿素循环途径的活性抑制^[39]。此外,与扩大标准供者相比,标准供者在代谢组学水平上有更活跃的肝内代谢物交换^[39]。该研究展示了无缺血肝移植过程中代谢活动的特点,为设计常温机器灌注装置,改善灌注液成分,并重新定义移植物活力的标准提供了参考。

2.8 儿童肝移植

儿童肝移植是儿童急性肝衰竭及自身免疫性、胆汁淤积性、代谢性或遗传性肝病的主要治疗方法^[40]。尽管儿童肝移植术后1年和5年生存率分别超过90%和85%^[41],但目前仍缺乏分析同种异体移植物

结果相关危险因素的全面研究以及评估移植物存活率的准确预测模型。上海交通大学医学院附属仁济医院肝脏外科团队根据肝移植术后生存危险因素建立了儿童肝移植术后移植物存活率评分模型,该模型具有良好的预测效果^[42]。移植术后免疫抑制药的使用可对儿童造成风险,上海交通大学医学院附属仁济医院肝脏外科团队还建立了一个列线图模型,预测以他克莫司为基础的免疫抑制方案导致儿童肝移植不良结果的风险,并帮助临床医师快速以环孢素作为替代方案^[43]。供者年龄也可能影响儿童肝移植术后生存质量,天津市第一中心医院的一项研究发现,供者年龄<10岁与供者年龄为10~45岁行劈离式肝移植的结果相似,移植物存活率均为92.3%,而对于45~55岁的供者年龄组,虽然受者生存率有所降低,但受者和移植物的1年存活率均超过了80%^[44]。

2.9 供者短缺

肝移植作为目前终末期肝病的标准治疗方法,其需求逐年增加,供肝数量无法满足需求。器官供需不平衡导致扩大标准供者的产生,包括循环死亡后器官捐献供者、老年供者、肝脏脂肪变性供者等,但其并发症风险较高,如早期移植物功能障碍、原发性移植物无功能和非吻合口狭窄等^[45-47]。中山大学附属第一医院器官移植中心证实充分的抗病毒预防和治疗下,使用乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)阳性供肝不会增加早期并发症的发生率,但受者的无进展生存期和总生存期较差^[48]。使用ABO血型不相容供肝可在一定程度上扩大肝移植供者库,从而减少移植等待时间。山东大学齐鲁医院器官移植科研究表明,对于终末期肝病模型(model for end-stage liver disease, MELD)评分 ≤ 30 分的患者,ABO血型不相容肝移植的预后与ABO血型相容肝移植相当,认为是一种可行的选择;对于MELD评分 ≥ 40 分的患者,在紧急情况下应慎用ABO血型不相容肝移植;对于MELD评分为31~39分的患者,ABO血型不相容肝移植的预后较差,并且应保证冷缺血时间 < 8 h^[49]。劈离式肝移植也是解决供者短缺的重要手段^[50]。青岛大学附属医院器官移植中心采用供者髂血管桥接已切断的部分IV段门静脉分支,从而保住IV段肝脏的门静脉供血,保证肝功能容量,提高劈离式肝移植的成功率,并且IV段门静脉重建技术有利于术后早期肝功能恢复^[51]。

3 小结与展望

2023年,中国肝移植领域研究取得了一系列重大发展,这离不开国内各位专家学者的不断刻苦钻研。过去一年,研究者们做了大量工作,努力寻找预测患者肝移植预后的标准,研究改善术后并发症的方法以及围手术期预后的影响因素等,对于现今各个热点问题,也提出了解决方案。这些进展为无数终末期肝病患者带来了福音,也为中国移植领域研究在国际的地位奠定了一个新的高度。

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