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人工肝在重症肝衰竭中的研究进展

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摘要　肝衰竭是临床常见的严重肝病症候群，尤以急性和慢加急性肝衰竭进展迅猛，短期死亡率高。为提高患者移植等待期生存率、改善相关症状，人工肝治疗作为一种有效的桥接治疗方法被深入研究。非生物型人工肝已广泛应用于临床，依据不同模式的运行机制及靶向清除的物质，临床可实施个体化治疗方案。生物型人工肝的核心优势在于部分替代肝细胞的生理功能，目前在细胞来源及生物反应器构建方面已开展大量研究，部分成果已进入临床试验阶段。混合型人工肝整合两类人工肝技术优势，在优化疗效及推动临床转化方面展现潜力。该文系统综述了国内外非生物型、生物型及混合型人工肝技术的研究进展，对其进行总结与探讨，旨在为人工肝的临床应用及研究方向提供参考。

关键词　人工肝；肝衰竭；肝移植；生物反应器

中图分类号　R575.3　　**文献标志码**　A

Research advances of artificial liver in severe liver failure

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Abstract

Liver failure is a common clinical syndrome of severe liver disease, particularly acute and acute-on-chronic liver failure, which are characterized by rapid progression and high short-term mortality. Artificial liver support therapy has been intensively studied as an effective bridge treatment, with the objective of improving the survival rate and alleviating symptoms during transplant waiting periods. Non-biological artificial livers have been widely implemented in clinical practice, enabling individualized treatment protocols based on the operational mechanisms of different modalities and the substances targeted for removal. Biological artificial livers, with their core advantage of partially substituting hepatic physiological functions, have undergone extensive research in cell sources and bioreactor construction, with some results advancing to clinical trial stages. Hybrid artificial livers integrate the advantages of non-biological and biological systems, showing potential in optimizing

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therapeutic efficacy and promoting clinical translation. This article systematically reviews the research advancements in non-biological, biological, and hybrid artificial liver technologies worldwide, summarizes their key findings, and discusses future directions, aiming to provide references for clinical applications and research in artificial liver therapy.

Key Words Artificial Liver; Liver Failure; Liver Transplantation; Bioreactor

肝衰竭以黄疸、凝血功能障碍、肝性脑病等为主要临床表现[1],病因在中国以肝炎病毒(多为HBV)、药物和肝毒性物质为主[2]。其分为急性肝衰竭(acute liver failure, ALF),亚急性肝衰竭,慢加急性肝衰竭(acute-on-chronic liver failure, ACLF)和慢性肝衰竭,其中ALF和ACLF短期死亡率高,但定义存在差异。不同国家或地区定义ALF的肝性脑病发生时间存在差异,与病因相关[3]。ACLF的定义则因人群和发病机制不同而异:欧洲肝病研究协会-慢加急性肝衰竭联盟(EASL-CLIF)和北美终末期肝病研究联盟(NACSELD)标准定义为肝硬化患者出现多器官衰竭,合并短期高死亡率;而中国重型乙型肝炎研究组(COSSH)和亚太肝脏研究学会(APASL)标准定义为在慢性肝病基础上出现急性肝损伤/功能恶化伴有腹水、肝性脑病或器官衰竭[4]。ALF无肝移植死亡率近50%,ACLF的28 d和90 d无移植死亡率分别高达41.9%和56.1%[5-6]。此类患者体内胆红素、细胞因子和氨等毒素大量蓄积,导致疾病进展迅猛甚至多器官衰竭[7-9]。

肝移植是治疗肝衰竭最有效的方法[1]。ALF属于肝移植超紧急状态,ACLF患者的90 d死亡风险常超出终末期肝病模型-钠(model for end-stage liver disease sodium, MELD-Na)评分预期[10-11]。但器官短缺导致许多患者在等待移植期间死亡,包括近50%的ACLF患者[12-13]。人工肝作为桥接治疗手段,通过体外装置清除毒素、补充必需物质,维持内环境稳定,为肝细胞再生或移植争取时间[14]。

人工肝分为非生物型人工肝(non-bioartificial liver, NBAL)、生物型人工肝(bioartificial liver, BAL)和混合型人工肝(hybrid artificial liver, HAL),NBAL技术成熟,后两类尚处于临床试验阶段[15]。NBAL通过吸附、透析和过滤等技术清除血浆毒素,替代肝脏的解毒功能[14, 16]。中国临床常用的NBAL包括血液透析滤过(hemodiafiltration, HDF)、连续性静脉-静脉HDF(continuous venovenous hemodiafiltration, CVVHDF)、血浆置换、双重血浆分子吸附系统(double plasma molecular adsorption system, DPMAS)等[15]。美国食品药品监督管理局(FDA)已批准分子吸附剂再循环系统(molecular adsorbent recirculation system, MARS)与血浆置换,欧洲则批准了白蛋白透析相关NBAL,包括单通道白蛋白透析(single-pass albumin dialysis, SPAD)、Prometheus系统等[17]。BAL由体外培养的肝细胞与生物反应器组成,患者血液流经反应器与肝细胞进行物质交换,其兼具解毒与合成、生物转化等功能,优于NBAL[18]。但因细胞规模及培养技术导致其临床应用受限。HAL结合二者优势,使血液流经BAL前由NBAL进行预处理,提高解毒效能并减少细胞损伤。多个HAL已进行临床试验,包括HepatAssist系统、模块化体外肝脏支持(modular extracorporeal liver support, MELS)、阿姆斯特丹医学中心生物人工肝(Amsterdam Medical Center bioartificial liver, AMC-BAL)及浙江大学李兰娟院士团队研制的HAL系统。该文旨在总结和探讨人工肝国内外进展,为临床应用与研究提供参考。

1 非生物型人工肝

1.1 血液透析和血液滤过 血液透析和滤过通过对流和弥散清除中小分子水溶性毒素[19]。早期血液透析对肾衰竭有效,尝试用于肝衰竭但效果不佳[20]。随着高通量等技术发展,通过血液透析可使62%的ALF患者意识恢复[21]。1986年,研究者们[22]开发了对中分子高渗透性的大孔聚甲基丙烯酸甲酯(PMMA)膜,用于血液滤过清除引发肝性昏迷的中分子物质,成功救治1例深度昏迷的暴发性肝衰患者。后续研究[23]证实,大容量血液滤过可改善ALF患儿血压、肝性脑病分级和28 d存活率。临床上二者常联合应用:CVVHDF缓和持久,多用于肝衰竭合并急性肾损伤患者[24],可有效降低血氨、改善心血管耐受性,提升21 d无移植生存率,疗效优于间歇性治疗[25-27](图1A);其早期应用可预防极高氨血症并提高无移植生存率[28],故推荐ALF患者尽早启动CVVHDF。日本研发的在线HDF和高流量连续HDF在清除血氨和肌酐方面优于传统HDF与MARS,显

著恢复患者意识并替代肝肾功能[29-30]，但难以清除细胞因子与促进肝再生，故未能显著提高生存率。

1.2　白蛋白透析　由于肝衰竭患者血液中大部分毒素（胆红素、胆汁酸等）与白蛋白结合，常规血液透析难以清除，研究者将白蛋白嵌入透析膜用于MARS系统，有效清除毒素[31]。DELPHI共识[14]指出，白蛋白透析可显著改善ALF/ACLF患者的中毒程度、肝性脑病和短期生存率，但对长期生存率无效，可能与患者较快接受肝移植有关。MARS的治疗频次与ACLF患者存活率强相关[32]，建议对无法立即移植的患者早期多次使用。荟萃分析[33]显示，MARS是多种NBAL（BioLogic-DT、大容量血浆置换等）中降低ALF患者死亡率的最佳选择。MARS、SPAD及Prometheus清除毒素能力相当，但SPAD消耗大量白蛋白，Prometheus操作复杂，实际临床更常用MARS[34-36]（图1B）。总之，MARS在改善ALF患者的临床状态及死亡率方面最为可靠，且成本效益高。

1.3　血浆置换　血浆置换通过用新鲜冰冻血浆替换患者血浆去除毒素并补充白蛋白、凝血因子等必需物质[37]。高容量血浆置换可减轻肝性脑病[38]、减弱先天免疫活化，提高ALF患者3个月无移植生存率[39]。高容量虽可彻底替代患者血浆，但也可能引发输血相关并发症和脑水肿。标准体积血浆置换同样能清除血浆毒素、改善炎症和提高肝衰竭患者21、30、90 d生存率[40-43]。荟萃分析[44]表明血浆置换在总生存期结局和3个月无移植生存期方面优于其他人工肝，但真实世界研究并未完全证实其生存获益[45]，可能与研究人群异质性、研究的观察性质有关。但血浆置换全面的毒素清除和独特的物质补充能力，使其仍具有广阔的研究前景（图1C）。

1.4　血液灌流/血浆灌流　血液/血浆灌流通过吸附剂清除代谢产物、毒素和药物[24]。活性炭灌流用于治疗急性中毒、肝/肾功能衰竭已久，在去除胆红素和氨方面与血浆置换相当[46]。但活性炭、树脂等传统吸附剂效率有限[47]，本团队前期已全面综述了可用于清除肝肾衰竭常见毒素的血液灌流吸附剂，详细阐述了各结构设计、吸附性能机理、血液相容性等关键特性，不在此赘述[7]。欧洲的CytoSorb®柱内含生物相容性新型材料，可有效清除细胞因子、胆红素等[48]，比MARS更快且显著但可能导致白蛋白丢失[49]（图1D）。中国专利DPMAS由胆红素吸附器和灌流器组成[50]，在提高HBV-ACLF患者12周生存率方面与血浆置换相当[51]，二者联合可进一

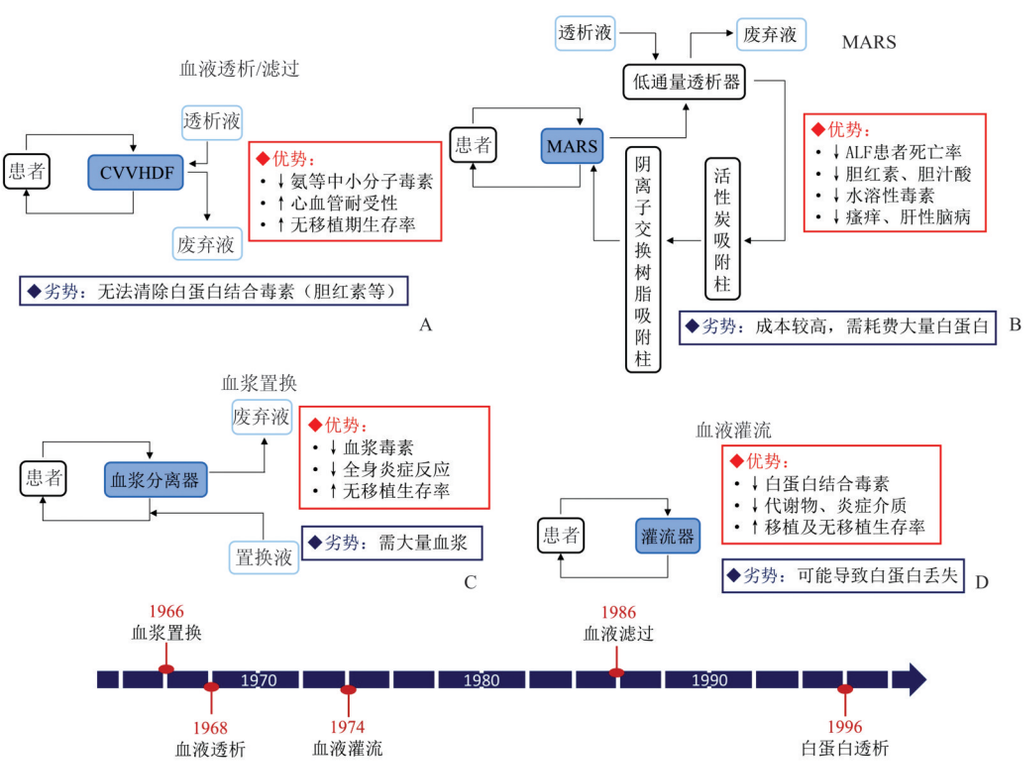


图1　非生物型人工肝效果对比及发展时间轴

注：上方A～D均为模式图，即血液透析/滤过模式图及优劣势（A）、MARS模式图及优劣势（B）、血浆置换模式图及优劣势（C）、血液灌流模式图及优劣势（D）。下方时间轴展示了各类非生物型人工肝首次应用于重症肝衰竭患者的报道年份。

步提高28、90 d生存率,并降低不良反应和治疗成本[52-55]。本团队[56]研发了甲壳素/碳纳米管复合纳米纤维微球(CCNC-NMBBA)胆红素吸附剂,其中甲壳素有良好的生物相容性,碳纳米管较大的比表面积及高度结合胆红素的赖氨酸等使之具备高吸附能力。该吸附剂还可支持BAL肝细胞。临床小样本(40例)试验证实,CCNC-NMBBA可改善MELD评分>30患者的生存率,将3个月等待期死亡率由80%降至50%,将移植1年存活率由50%~65%提升至87%~92%。通过对CCNC-NMBBA材料的不断更新与深入研究,将CCNC-NMBBA应用于血液灌流,可成为临床支持肝衰竭患者治疗的有前景的候选方案。

1.5 组合模式 为克服单一NBAL模式的局限性[57-58](图1),多组合形式的人工肝应运而生,如血浆透析滤过(plasma diafiltration,PDF)、配对血浆滤过吸附(coupled plasma filtration adsorption,CPFA)等。PDF结合血浆分离与透析滤过,可清除白蛋白结合毒素及中小分子毒素,但需补充白蛋白[59-60]。CPFA通过吸附和透析滤过两步清除毒素,对生存期有积极影响[61-62]。李氏人工肝系统结合低容量血浆置换、高通量滤过和血液灌流,可提高HBV-ACLF患者的21、28、90 d生存率[63-64]。DI-ALIVE系统专为ACLF设计,可超滤白蛋白和细胞因子[65],能改善酒精性ACLF患者的炎症和内毒素水平,但对28 d死亡率的影响仍需验证[66]。序贯联合疗法(如血浆置换联合CVVHDF、血浆灌注联合置换)可显著改善ALF患者循环状况、逆转器官衰竭、提高生存率[67-68]。组合模式可用于危重症及个性化治疗,但其长期疗效证据不足等问题仍需深入研究。

2 生物型人工肝

2.1 肝细胞 猪肝细胞易得且功能与人类相近,早期BAL多以其作为种子细胞,虽能改善ALF患者生理指标[69],但存在病毒传播风险,欧洲部分国家已禁用[70-71]。

原代人肝细胞是BAL的最佳选择,但供体短缺且离体培养技术有限,要获得大量高质的原代肝细胞相当困难[72]。肝癌细胞系C3A用于体外肝脏辅助装置(extracorporeal liver assist device,ELAD)系统进行临床试验,在年轻(<46.9岁)且MELD<28组中显示生存率提高的趋势,但对老年和重症组效果较差,需确定其适应证[73]。基因工程改造的肝癌细胞系(HepG2-GS、cBAL119)虽增强氨代谢能力等[74-75],但仍存在致瘤风险。近期研发的可逆性永生化NKNT-3细胞,在动物实验中表现良好,可提高90%肝切除术诱导的ALF大鼠的生存率,但其在大动物模型、临床前研究中的获益仍待进一步跟进[76]。

干细胞技术[如诱导多能干细胞(iPSC)、间充质干细胞等]诱导分化的肝样细胞因安全性和增殖能力成为研究热点[77],含iPSC的BAL能使ALF猪的肝功能恢复正常[78]。含人成纤维细胞转分化的肝细胞的BAL在肝切除术后肝衰竭猪模型中有显著的生存获益、促进肝脏再生,为改善极限肝切除术患者的预后奠定了基础[79]。受制于成本,目前仍处在研究阶段。

2.2 生物反应器 生物反应器为肝细胞提供生长和物质交换环境。中空纤维生物反应器最为基础,患者血浆流经纤维管,肝细胞位于管外间隙[80]。此种分布虽降低剪切力,但同时限制了物质传输效率与细胞的三维结构形成[81]。

流化床生物反应器使肝细胞球状体悬浮,提高了药物过量和肝切除术后ALF同种异体模型的生存率,有神经保护作用[82-83]。李兰娟院士团队[84]也研发了基于流化床的BAL,呈现良好的肝功能且显著延长了肝衰竭动物的生存时间。

径向流生物反应器模拟肝脏血流以优化物质交换。基于半乳糖基化壳聚糖纳米纤维支架的多层径向流生物反应器可诱导肝细胞球体形成,纳米纤维使细胞紧密黏附于支架[85]。为堆叠平板设计微加工凹槽可改善剪切应力并提高氧供,使肝细胞在灌注5 d内仍保持稳定的白蛋白和尿素合成速率[86]。

3D支架的纳米纤维结构(如聚己内酯-壳聚糖-明胶静电纺丝纳米纤维)可模拟细胞外基质,促进细胞增殖和功能维持[87-88]。微载体3D细胞培养有高表面体积比,可提高细胞密度,均质悬浮利于环境调控和采集代表样本[89]。生物聚合物为材料的微载体有卓越的生物相容性和降解性,如基于几丁质的纳米纤维微球等可良好支持细胞扩增和迁移[90-91]。相较于微球,微凝胶中包封细胞可避免剪切损伤,含甲基丙烯酸明胶的微凝胶能够监测细胞互作[92]。

微流控器件使用聚二甲基硅氧烷制造,生物相容性和透气性良好,但微通道结构致其流速难以满

足临床需求[93]。

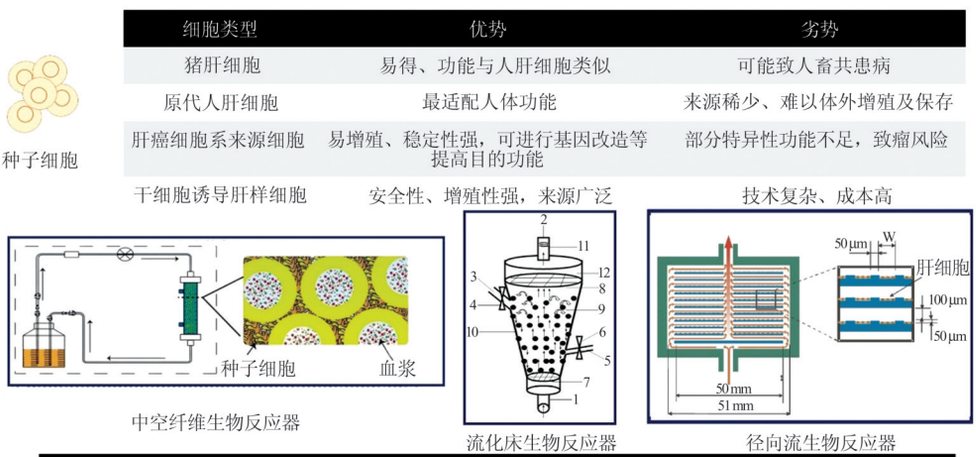
目前仅猪肝细胞、C3A 细胞系、中空纤维生物反应器和径向流生物反应器开展了临床试验，多数仍处于临床前研究阶段[94]。根据各自特点，可通过不同组合及临床试验明确未来研究方向（图 2）。

3　混合人工肝

HepatAssist 系统结合血浆分离、吸附及含猪肝细胞的中空纤维生物反应器[96]，是唯一完成Ⅱ/Ⅲ期临床试验的 HAL，可提高 ALF 患者生存率且有良好安全性[97]。MELS 系统的模块化设计可根据患者需要添加组合使用，包含原代人肝细胞、白蛋白透析和 CVVHDF 模块，Ⅰ期临床试验中改善了 8 例患者的神经系统症状和凝血功能，6 例桥接至移植[98]。AMC-BAL 结合了血浆吸附与含猪肝细胞的螺旋缠绕三维无纺聚酯基质，血浆与猪肝细胞直接接触以模拟肝窦结构[99]，改善了 7 例伴Ⅲ/Ⅳ期肝性脑病 ALF 患者的神经系统症状和血流动力学，成功过渡至肝移植或肝脏再生[100]。李兰娟院士团队[101]开发的 HAL 综合血浆置换和含猪肝细胞的中空纤维生物反应器，改善了 15 例慢性重度肝炎患者的胆红素、内毒素水平及凝血功能，存活率达 73.3%。

4　总结与展望

肝衰竭致死率高且耗费大量医疗成本，肝移植虽有效但供体短缺。人工肝有重要桥接价值。NBAL 已广泛应用于临床，中国指南推荐对 ALF/早期 ACLF 患者使用李氏人工肝 3.0，其集成血浆分离、吸附、滤过和置换为一体，全面清除毒素且节省血浆，流程简便[1]。在实际的临床工作中应注重个性化治疗，如合并肝性脑病或急性肾损伤时推荐尽早启动 CVVHDF，HBV-ACLF 应首选血浆置换，高炎症状态可采用血液吸附，通过准确掌握患者病情及生理指标，可侧重性使用相应 NBAL 或序贯/组合模式。目前检索到的国外指南推荐人工肝治疗较少，因临床试验常无生存获益，这与研究对象的病情异质性关系密切，需更细化患者分层研究。晚期 ALF/ACLF 患者则被指出需谨慎使用人工肝，故早期诊断和支持是关键。BAL 对重症肝衰竭可能更具潜力。ELAD、新型生物人工肝支持系统、径向流生物反应器 BAL 等系统已开展临床试验，显示良好的安全性和症状改善；球状体储藏 BAL、流化床 BAL、UCLBAL、人诱导肝细胞 BAL 在临床前试验中效果显著。HAL 综合优势明显，HepatAssist、MELS、AMC-BAL、李氏人工肝及本



细胞类型	优势	劣势
猪肝细胞	易得、功能与人肝细胞类似	可能致人畜共患病
原代人肝细胞	最适配人体功能	来源稀少、难以体外增殖及保存
肝癌细胞系来源细胞	易增殖、稳定性强，可进行基因改造等提高目的功能	部分特异性功能不足，致瘤风险
干细胞诱导肝样细胞	安全性、增殖性强，来源广泛	技术复杂、成本高

生物反应器类型	效果
中空纤维生物反应器	适合物质交换，低剪切应力；但物质传输效率低、限制肝细胞结构形成
流化床生物反应器	悬浮肝细胞微球，提高物质传输效率
径向流生物反应器	血液沿径向流动，提高物质传输效率
3D支架	模拟胞外基质，促进细胞增殖、迁移和分化
微载体	提高细胞数量，易监测、控制环境参数，促进细胞增殖、迁移和分化
微流控器件	良好的生物相容性、高透气性，但流速低

图 2　生物型人工肝效果对比

注：中空纤维生物反应器模式图改编引用自文献[77]，流化床生物反应器模式图引用自文献[95]，径向流生物反应器模式图改编引用自文献[86]。

团队经10余载研发的基于CCNC-NMBBA的天然高分子生物人工肝均已进行临床试验,效果良好。未来需解决BAL/HAL的临床转化挑战,如细胞来源安全性、规模化培养、干细胞诱导分化维持技术的发展;生物反应器设计可针对材料改造以降低成本,尝试细胞共培养、代谢情况实时调控等,提升BAL效能。随着多学科交叉融合,人工肝有望为肝衰竭提供更高效、个体化的生命支持。

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