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肝硬化病因治疗联合抗纤维化治疗(双抗治疗)的现状与展望

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摘要: 肝硬化是多种慢性肝病的终末阶段,持续炎症导致的肝纤维化是其发生发展的核心机制。随着疾病谱演变和对肝纤维化逆转认识的不断深入,源于乙型肝炎肝硬化治疗中抗病毒联合抗肝纤维化的“双抗治疗”,逐渐演变为肝硬化治疗中病因治疗联合抗肝纤维化和/或抗炎的广义“双抗治疗”。本文旨在系统综述肝硬化“双抗治疗”的概念演变及研究进展。

关键词: 肝纤维化; 肝硬化; 双抗治疗

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Etiological treatment combined with antifibrotic therapy (dual therapy) for liver cirrhosis: Current status and future perspectives

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Abstract: Liver cirrhosis is the end-stage of various chronic liver diseases, and hepatic fibrosis caused by persistent inflammation is the core mechanism of the development and progression of liver cirrhosis. With the evolution of disease spectrum and a deeper understanding of the reversal of hepatic fibrosis, dual antiviral-antifibrotic therapy initially applied in the treatment of hepatitis B cirrhosis has gradually evolved into a broad-sense dual therapy for liver cirrhosis, which integrates etiological treatment with antifibrotic and/or anti-inflammatory interventions. This article systematically reviews the conceptual evolution of dual therapy for liver cirrhosis and related research advances.

Key words: Hepatic Fibrosis; Liver Cirrhosis; Dual-anti Therapy

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肝硬化是多种慢性肝病终末阶段的共同结局,肝硬化及其并发症长期位居全球死亡原因前列^[1]。肝纤维化是肝硬化发生与进展的核心病理基础。已有研究证实,在病因去除或控制后,部分患者可实现不同程度的肝纤维化改善或逆转^[2-3]。病毒性肝炎作为亚洲地区、尤其是我国肝硬化的主要病因,病毒感染引起的肝脏炎症推动炎症-坏死-再生这一病理过程,最终导致肝硬化^[4]。

相比于单独抗病毒治疗,抗病毒治疗联合抗肝纤维化治疗改善肝纤维化的效果更为显著,因此,在乙型肝炎

肝硬化治疗中,衍生出了抗病毒联合抗肝纤维化的“双抗治疗”概念。随后,该理念不断拓展,演变为病因治疗联合抗肝纤维化治疗的广义“双抗治疗”。

1 “双抗治疗”理念的起源——乙型肝炎肝硬化的抗病毒治疗联合抗肝纤维化治疗

1.1 “双抗治疗”的理论基础 大量研究证实,有效的抗病毒治疗不仅能够显著降低肝功能失代偿风险,还可改善肝组织学炎症与纤维化评分^[5-6],提示其具有延缓甚至逆转肝纤维化的潜力。然而,肝纤维化的改善程度受

抗病毒疗程、基线肝纤维化严重程度等多种因素影响。数据显示,慢性乙型肝炎患者经核苷(酸)类似物治疗1年后,肝纤维化改善或逆转率约40%^[7-12],基线Ishak评分 $\geq$ F3的患者即使持续接受抗病毒治疗,仍有1/3的患者未能实现肝纤维化的改善或逆转^[13-14],提示单独抗病毒治疗对部分患者无法有效实现肝纤维化的改善或逆转,难以改善部分重度肝纤维化,尤其是肝硬化患者的预后。

乙型肝炎病毒感染作为始动因素,可引起持续的肝细胞炎症损伤,其中肝星状细胞(hepatic stellate cells, HSC)的活化是中心环节,反复的损伤和修复过程导致细胞外基质异常沉积,最终进展为肝纤维化和肝硬化,抗病毒治疗虽然能够抑制病毒复制减轻肝细胞炎症损伤,但对已激活的HSC及沉积的纤维组织无直接作用。因此,“双抗治疗”理念被提出,即在抗病毒治疗的基础上联合抗肝纤维化治疗,通过多途径阻断肝纤维化及肝硬化进展,以期进一步改善乙型肝炎肝硬化的临床预后。

1.2 “双抗治疗”的用药策略与疗效 目前,西药抗肝纤维化治疗仍处于临床研究阶段,而中医药在抗肝纤维化中发挥了重要作用。我国学者结合中成药在抗肝纤维化方面的独特优势,提出了抗病毒联合中成药抗肝纤维化的“双抗治疗”方案,结果证明相比于单独抗病毒治疗,“双抗治疗”可以提高肝纤维化改善或逆转的比例、降低肝硬化并发症的发生风险,改善肝硬化患者的预后。

针对乙型肝炎肝硬化患者,已有临床研究发现,在抗病毒治疗基础上联用安络化纤丸可有效促进肝硬化逆转^[15]。相关机制研究进一步揭示,该疗法主要通过改善肝功能、抑制HSC激活、增强基质金属蛋白酶-13表达,以及抑制基质金属蛋白酶-2和组织抑制物(tissue inhibitor of metalloproteinases, TIMP)-1/2表达等多靶点途径发挥抗肝纤维化作用^[16]。一项包含25项随机对照研究、共2746例乙型肝炎肝纤维化/肝硬化患者的荟萃分析显示,扶正化瘀片/扶正化瘀胶囊联合抗病毒治疗24~48周后,患者在肝组织学改善方面显著优于单独抗病毒治疗的对照组:肝组织学活动性指数改善率达75.56%(对照组42.22%, $P<0.001$),肝纤维化Ishak分期改善率达67.90%(对照组40.91%, $P=0.005$),且治疗48周时肝脏硬度值均值较对照组下降3.43 kPa(对照组0.3 kPa)^[17]。一项纳入1000例中国慢性乙型肝炎患者的研究显示,经肝组织病理证实,复方鳖甲软肝片联合抗病毒治疗可使患者5年肝纤维化逆转率从单独抗病毒治疗的59.2%提升至76.7%^[18];亚组分析还发现,针对乙

型肝炎肝硬化患者,联合治疗组的肝纤维化改善率亦明显优于单独抗病毒治疗的对照组(41.5% vs 30.7%, $P=0.0103$)^[19]。

“双抗治疗”在降低肝硬化并发症发生风险方面也具有独特的优势^[20-21],可使食管静脉中/重度曲张患者累积出血率降低28.4%;对于有出血病史的患者,还能够降低再出血的累积发生率并推迟再出血时间;改善和提高肝硬化腹水的疗效,提升肝硬化腹水治愈和改善的比例。

现有研究表明,“双抗治疗”能够明显改善和逆转乙型肝炎肝硬化患者的肝纤维化^[17-19,22],肝纤维化逆转能够延缓和降低肝硬化的发生与发展,进一步减少肝硬化并发症、肝细胞癌(hepatocellular carcinoma, HCC)的发生,改善患者的预后。

2 “双抗治疗”的更多获益

在预防HCC发生及改善肝硬化患者长期生存方面,“双抗治疗”相比单独抗病毒治疗更具优势。一项单中心回顾性研究显示,与单独抗病毒治疗相比,联合抗肝纤维化治疗在降低慢性乙型肝炎患者HCC发生风险方面表现优异,可使5年HCC的累积发生率降低56.9%^[23]。

针对代偿期乙型肝炎肝硬化患者,多中心回顾分析进一步证实,经“双抗治疗”后,HCC的5年累积发生率明显降低(21.8% vs 9.8%, $P<0.01$)。而持续的“双抗治疗”(治疗时间 >36 个月)在降低HCC发生风险方面效果更为显著,风险比降低至0.216^[24]。这一获益在长期随访中同样得到验证:一项多中心随机对照研究显示,接受72周治疗后,抗病毒联合抗肝纤维化治疗组的患者7年HCC累积发生率和肝脏相关病死率分别为4.7%和0.2%,明显低于接受抗病毒联合安慰剂治疗组的9.3%和2.2%^[18]。

除抗病毒治疗对乙型肝炎肝硬化患者HCC发生和生存的改善作用外,抗肝纤维化、中成药也在抑制HCC发生中发挥关键作用。现有研究提示其潜在机制包括:通过抑制HSC活化和减少肿瘤周围衰老成纤维细胞,逆转肝纤维化微环境,降低HCC发生风险^[25];通过靶向调控长链非编码RNA TUG1-微RNA-328-3p-SRSF9信使RNA轴,抑制HCC细胞增殖^[26];通过增强机体对癌前病变细胞的识别和清除能力,提升自然杀伤细胞数量和功能,重塑免疫微环境等^[27]。

基于乙型肝炎肝硬化的成功实践,“双抗治疗”策略已拓展至其他病因所致的肝硬化治疗中,由抗病毒治疗联合抗肝纤维化治疗向病因治疗联合抗肝纤维化治疗的广义“双抗治疗”概念延伸,日益受到临床关注。

3 “双抗治疗”理念的拓展——病因治疗和抗肝纤维化治疗

尽管在乙型肝炎肝硬化患者中应用的“双抗治疗”可显著改善肝纤维化逆转率,减少并发症的发生,改善临床预后,但当前我国肝硬化病因构成也在发生改变——HBV感染比例减少,代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD)、自身免疫性肝病和酒精性肝病(alcoholic liver disease, ALD)等比例逐渐增加^[28-29]。因此,我国《肝硬化临床诊治管理指南(2025版)》推荐肝硬化治疗应当积极进行病因治疗和抗肝纤维化治疗的“双抗治疗”^[30-31]。

3.1 病因治疗相关研究 广义的“双抗治疗”概念不再局限于乙型肝炎肝硬化,而是扩展为针对不同肝硬化病因的治疗策略,抗肝硬化治疗的理念也更加强调病因治疗和抗肝纤维化治疗的重要性。

以肝纤维化、肝硬化病因中占比不断上升的MAFLD为例,肥胖是MAFLD的主要危险因素之一,MAFLD治疗的基石是减重,且与肝脏脂肪变、炎症以及肝纤维化改善密切相关^[32-34]。293例经肝活组织检查确诊的MAFLD患者,接受为期52周的生活方式干预(包括低热量饮食和运动),结果显示,减重10%能够使45%的患者肝纤维化逆转^[35]。这与多国临床指南共识建议的“减重≥7%以改善肝纤维化”目标相一致^[36-38]。与此同时,药物干预手段也在不断优化,胰高血糖素样肽-1受体激动剂如司美格鲁肽可通过抑制食欲和胃轻瘫诱导体重减轻,其持续使用240周可显著降低治疗组代谢相关脂肪性肝病(metabolic associated steatohepatitis, MASH)患者的肝纤维化程度(36.8% vs 安慰剂组22.4%, $P<0.001$)^[39]。美国肝病学会2025年更新的司美格鲁肽治疗MASH指南推荐司美格鲁肽用于治疗中度至重度(F2~F3期)肝纤维化的MASH患者^[40]。

研究证实,成人的脂肪组织胰岛素抵抗和脂解作用与MASH严重程度正相关,其中的重要驱动因素可能与脂肪组织纤维化的标志物——内脂素相关^[41]。因此,改善脂肪组织胰岛素抵抗和脂解作用的药物,如过氧化物酶体增殖物激活受体激动剂也表现出良好的抗肝纤维化作用。研究显示,口服过氧化物酶体增殖物激活受体激动剂拉尼兰诺可调节全身脂质和葡萄糖代谢以及炎症,在Ⅱb期研究中,接受1 200 mg和800 mg拉尼兰诺治疗的MASH患者,肝纤维化改善比例分别达到48%和34%,明显高于安慰剂组的29%^[42]。

近年来,瘦型MAFLD也不断受到重视,其肝纤维化风险与超重/肥胖MAFLD患者相当,且相关病死率显著增加^[43]。虽然通过适当减重减少内脏脂肪可减轻肝脏炎症和肝纤维化,使瘦型MAFLD患者临床获益,但减重是否能够实现该类患者肝纤维化逆转尚不明确。

对于其他病因如ALD引起的肝硬化,戒酒是病因治疗的核心,戒酒能够改善肝损伤组织学、降低门静脉压力、延缓纤维化进程并提高患者生存率^[44]。

综上所述,无论是MAFLD还是ALD,病因治疗联合抗肝纤维化或抗炎治疗的“双抗治疗”策略均显示出一定的适用性,能够通过病因治疗阻断炎症持续导致新的肝纤维化形成,同时利用抗肝纤维化药物的直接作用改善或逆转已有的肝纤维化。

3.2 抗肝纤维化治疗相关研究 炎症的持续刺激是肝纤维化形成的始动因素,因此,抗炎治疗的本质在于阻断持续慢性炎症引发的HSC活化及细胞外基质异常沉积,避免肝纤维化的进展。MASH是MAFLD的进展阶段,表现为肝细胞损伤、炎症和纤维化。瑞美替罗作为一种甲状腺激素受体- β 选择性激动剂,可被肝细胞特异性摄取,通过激活甲状腺激素受体- β 调控多个肝脏代谢通路,从而减少脂肪堆积,促进脂肪酸代谢和减少肝脏炎症。

在Ⅲ期临床试验中,瑞美替罗低剂量组(80 mg)和高剂量组(100 mg)患者接受52周治疗后,经肝活组织检查证实MASH缓解率分别达到25.9%与29.9%(安慰剂组9.7%, $P<0.001$);同时,两组患者的肝纤维化改善率分别为24.2%与25.9%,显著优于安慰剂组的14.2%(P 值均 <0.001)^[45],提示抗炎治疗能够改善和逆转MAFLD患者的肝纤维化。

值得注意的是,在包含成纤维细胞生长因子21类似物、脂肪酸合酶抑制剂等其他机制的MAFLD治疗药物临床试验中,已进展为肝硬化的MASH患者大多被排除在外,这可能与MASH肝硬化阶段的致病机制异于肝硬化前MASH,以及肝硬化患者的最佳用药剂量存在差异有关。然而,瑞美替罗在代偿期肝硬化患者(蔡尔德-皮尤分级A级)中开展的Ⅲ期临床研究显示,接受该药治疗2年后,MASH肝硬化患者的肝脏硬度值及临床显著性门静脉高压的Baveno风险评分等指标都有显著改善,提示具有抗炎作用的瑞美替罗也能够为MAFLD相关肝硬化患者的肝纤维化改善带来获益^[46]。

4 待解决的问题

尽管“双抗治疗”策略已取得显著成效,但在不同病因肝硬化中的应用仍需深入探索。未来亟需开展针对遗

传代谢性肝病、自身免疫性肝病、酒精性肝病等多种病因的大规模临床研究,以确立适合不同病因的具体治疗方案及最佳剂量,真正实现个体化与精准治疗。此外,虽然安络化纤丸、扶正化瘀片/扶正化瘀胶囊、复方鳖甲软肝片等中成药在乙型肝炎肝硬化患者中已获确切疗效验证,但在其他病因所致肝硬化中的抗纤维化作用仍有待进一步证实,以为临床提供更多元化的治疗选择。随着肝硬化病因谱的改变,共病因素对“双抗治疗”的影响亦不容忽视。以乙型肝炎为例,慢性乙型肝炎合并MAFLD在亚洲CHB患者中的比例高达36.5%^[47],针对此类共病患者,如何科学组合抗病毒治疗、生活方式干预、中成药及MASH靶向药物,构建新型综合治疗方案,将是未来的研究重点。

综上所述,“双抗治疗”已从最初的乙型肝炎抗病毒联合抗纤维化,演进为涵盖各类病因治疗的广义策略。这不仅体现了对疾病认知的深化,更标志着肝硬化临床管理理念的升级——既要源头阻断病因诱导的纤维化进程,又要积极逆转已有的肝纤维化。通过多途径协同干预,最终实现肝硬化逆转,减少并发症、终末期肝病及HCC的发生,改善患者的长期预后。

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参考文献:

- [1] THAM EKJ, TAN DJH, DANPANICHKUL P, et al. The global burden of cirrhosis and other chronic liver diseases in 2021[J]. *Liver Int*, 2025, 45(3): e70001. DOI: 10.1111/liv.70001.
- [2] TAN Z, SUN HB, XUE TX, et al. Liver fibrosis: Therapeutic targets and advances in drug therapy[J]. *Front Cell Dev Biol*, 2021, 9: 730176. DOI: 10.3389/fcell.2021.730176.
- [3] Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Gastroenterology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Consensus on the diagnosis and therapy of hepatic fibrosis (2019)[J]. *J Clin Hepatol*, 2019, 35(10): 2163-2172. DOI: 10.3969/j.issn.1001-5256.2019.10.007. 中华医学会肝病学会, 中华医学会消化病学分会, 中华医学会感染病学分会. 肝纤维化诊断及治疗共识(2019年)[J]. *临床肝胆病杂志*, 2019, 35(10): 2163-2172. DOI: 10.3969/j.issn.1001-5256.2019.10.007.
- [4] LIN J. Virus-related liver cirrhosis: Molecular basis and therapeutic options[J]. *World J Gastroenterol*, 2014, 20(21): 6457. DOI: 10.3748/wjg.v20.i21.6457.
- [5] de ZAWADZKI A, LEEMING DJ, SANYAL AJ, et al. Hot and cold fibrosis: The role of serum biomarkers to assess immune mechanisms and ECM-cell interactions in human fibrosis[J]. *J Hepatol*, 2025, 83(1): 239-257. DOI: 10.1016/j.jhep.2025.02.039.
- [6] LIAW YF, SUNG JJY, CHOW WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease[J]. *N Engl J Med*, 2004, 351(15): 1521-1531. DOI: 10.1056/nejmoa033364.
- [7] LAI CL, CHIEN RN, LEUNG NWY, et al. A one-year trial of lamivudine for chronic hepatitis B[J]. *N Engl J Med*, 1998, 339(2): 61-68. DOI: 10.1056/nejm199807093390201.
- [8] MARCELLIN P, CHANG TT, LIM SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B[J]. *N Engl J Med*, 2003, 348(9): 808-816. DOI: 10.1056/nejmoa020681.
- [9] HADZIYANNIS SJ, TASSOPOULOS NC, HEATHCOTE EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years[J]. *Gastroenterology*, 2006, 131(6): 1743-1751. DOI: 10.1053/j.gastro.2006.09.020.
- [10] LAI CL, SHOUVAL D, LOK AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B[J]. *N Engl J Med*, 2006, 354(10): 1011-1020. DOI: 10.1056/NEJMoa051287.
- [11] LAI CL, GANE E, LIAW YF, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B[J]. *N Engl J Med*, 2007, 357(25): 2576-2588. DOI: 10.1056/nejmoa066422.
- [12] MARCELLIN P, HEATHCOTE EJ, BUTI M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B[J]. *N Engl J Med*, 2008, 359(23): 2442-2455. DOI: 10.1056/NEJMoa0802878.
- [13] MARCELLIN P, GANE E, BUTI M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study[J]. *Lancet*, 2013, 381(9865): 468-475. DOI: 10.1016/S0140-6736(12)61425-1.
- [14] XU B, XU GG, GUO Q, et al. Long term treatment of lamivudine in chronic hepatitis B patients with severe liver fibrosis: Ten-year follow-up outcomes of NUCB 4006 trial[J]. *Chin J Infect Dis*, 2010, 28(11): 656-661. DOI: 10.3760/cma.j.issn.1000-6680.2010.11.004. 许蓓, 徐国光, 郭清, 等. 拉米夫定对慢性乙型肝炎伴重度肝纤维化患者的长期应用疗效: NUCB 4006十年随访研究[J]. *中华传染病杂志*, 2010, 28(11): 656-661. DOI: 10.3760/cma.j.issn.1000-6680.2010.11.004.
- [15] TIAN FX, XIA HZ, DING WC. Observation on therapeutic effect of adefovir dipivoxil tablets combined with Anluohuaxian pills on early cirrhosis after hepatitis B[J]. *Chin J Exp Clin Virol*, 2008, 22(4): 315. DOI: 10.3760/cma.j.issn.1003-9279.2008.04.026. 田发勋, 夏和中, 丁伟村. 阿德福韦酯片联合安络化纤丸治疗乙肝早期肝硬化疗效观察[J]. *中华实验和临床病毒学杂志*, 2008, 22(4): 315. DOI: 10.3760/cma.j.issn.1003-9279.2008.04.026.
- [16] WANG L, LU W, GAO YH, et al. Effect of Anluohuaxianwan on the expression of matrix metalloproteinases and their inhibitors in rat liver with fibrosis[J]. *Chin J Hepatol*, 2019, 27(4): 267-273. 王林, 卢玮, 高玉华, 等. 安络化纤丸对肝纤维化大鼠肝组织基质金属蛋白酶及其抑制物表达的影响[J]. *中华肝病杂志*, 2019, 27(4): 267-273.
- [17] FAN Y, HAO KY, LI P, et al. Meta-analysis of the efficacy of the Fuzheng Huayu formula in the treatment of hepatitis B-associated liver fibrosis or cirrhosis[J]. *Chin J Hepatol*, 2024, 32(12): 1141-1152. DOI: 10.3760/cma.j.cn501113-20240612-00293. 范晔, 郝坤艳, 李平, 等. 扶正化瘀组方治疗乙型肝炎肝纤维化或肝硬化疗效的荟萃分析[J]. *中华肝病杂志*, 2024, 32(12): 1141-1152. DOI: 10.3760/cma.j.cn501113-20240612-00293.
- [18] JI D, CHEN Y, BI JF, et al. Entecavir plus Biejia-Ruangan compound reduces the risk of hepatocellular carcinoma in Chinese patients with chronic hepatitis B[J]. *J Hepatol*, 2022, 77(6): 1515-1524. DOI: 10.1016/j.jhep.2022.07.018.
- [19] RONG GH, CHEN YP, YU ZJ, et al. Synergistic effect of Biejia-Ruangan on fibrosis regression in patients with chronic hepatitis B treated with entecavir: A multicenter, randomized, double-blind, placebo-controlled trial[J]. *J Infect Dis*, 2022, 225(6): 1091-1099. DOI: 10.1093/infdis/jiaa266.
- [20] Chinese Society of Hepatology, Chinese Society of Gastroenterology, and Chinese Society of Digestive Endoscopy of Chinese Medical Association. Guidelines on the management of esophagogastric variceal bleeding in cirrhotic portal hypertension[J]. *J Clin Hepatol*, 2023, 39(3): 527-538. DOI: 10.3969/j.issn.1001-5256.2023.03.znygf. 中华医学会肝病学会, 中华医学会消化病学分会, 中华医学会消化内镜学分会. 肝硬化门静脉高压食管胃静脉曲张出血的防治指南[J]. *临床肝胆病杂志*, 2023, 39(3): 527-538. DOI: 10.3969/j.issn.1001-

- 5256.2023.03.znygf.
- [21] DENG X, LIANG J, LIU ZW, et al. Treatment of posthepatic cirrhosis by Fuzheng Huayu Tablet for reinforcing qi and resolving stasis[J]. *Chin J Integr Med*, 2013, 19(4): 289-296. DOI: 10.1007/s11655-013-1433-7.
- [22] ZHAO ZM, ZHU CW, HUANG JQ, et al. Efficacy and safety of Fuzheng Huayu tablet on persistent advanced liver fibrosis following 2 years entecavir treatment: A single arm clinical objective performance criteria trial[J]. *J Ethnopharmacol*, 2022, 298: 115599. DOI: 10.1016/j.jep.2022.115599.
- [23] SHI K, LIU Y, WANG XJ, et al. Adjuvant fuzheng Huayu capsule reduces the incidence of hepatocellular carcinoma in patients with hepatitis B-caused cirrhosis[J]. *Evid Based Complement Alternat Med*, 2020, 2020: 8826091. DOI: 10.1155/2020/8826091.
- [24] FAN HN, LEI SJ, ZHAO ZM, et al. Beneficial effects of traditional Chinese medicine fuzheng Huayu on the occurrence of hepatocellular carcinoma in patients with compensated chronic hepatitis B cirrhosis receiving entecavir: A multicenter retrospective cohort study[J]. *J Clin Transl Hepatol*, 2024, 12(5): 505-515. DOI: 10.14218/jcth.2023.00521.
- [25] FAN HN, HUANG K, DAI YK, et al. Effect and mechanism of Fuzheng Huayu Decoction on carcinogenesis in mice with liver fibrosis[J]. *Chin J Integr Tradit West Med Dig*, 2023, 31(2): 110-117. 范海纳, 黄恺, 代云凯, 等. 扶正化瘀方对肝纤维化小鼠肝癌发生的影响与机制[J]. *中国中西医结合消化杂志*, 2023, 31(2): 110-117.
- [26] LIU YD, MAO X, MA ZC, et al. Aberrant regulation of LncRNA TUG1-microRNA-328-3p-SRSF9 mRNA Axis in hepatocellular carcinoma: A promising target for prognosis and therapy[J]. *Mol Cancer*, 2022, 21(1): 36. DOI: 10.1186/s12943-021-01493-6.
- [27] CHENG Q, LI N, CHEN MQ, et al. Fuzheng Huayu inhibits carbon tetrachloride-induced liver fibrosis in mice through activating hepatic NK cells[J]. *J Ethnopharmacol*, 2013, 145(1): 175-181. DOI: 10.1016/j.jep.2012.10.047.
- [28] LU KQ, SUI JJ, YU WH, et al. An analysis of the burden of liver cirrhosis: Differences between the global, China, the United States and India[J]. *Liver Int*, 2024, 44(12): 3183-3203. DOI: 10.1111/liv.16087.
- [29] HUANG DQ, TERRAULT NA, TACKE F, et al. Global epidemiology of cirrhosis: Aetiology, trends and predictions[J]. *Nat Rev Gastroenterol Hepatol*, 2023, 20(6): 388-398. DOI: 10.1038/s41575-023-00759-2.
- [30] Chinese Society of Hepatology, Chinese Medical Association. Chinese guidelines for clinical diagnosis, treatment, and management of cirrhosis(2025) [J]. *Chin J Hepatol*, 2025, 33(10): 958-976. DOI: 10.3760/cma.j.cn501113-20250728-00298. 中华医学会肝病学分会. 肝硬化临床诊治管理指南(2025版)[J]. *中华肝脏病杂志*, 2025, 33(10): 958-976. DOI: 10.3760/cma.j.cn501113-20250728-00298.
- [31] XU XY, DING HG, YOU H, et al. Chinese guidelines for clinical diagnosis, treatment, and management of cirrhosis (2025) [J]. *J Clin Transl Hepatol*, 2026, 14(1): 96-115. DOI: 10.14218/JCTH.2025.00517.
- [32] Chinese Society of Hepatology, Chinese Medical Association. Guidelines for the prevention and treatment of metabolic dysfunction-associated (non-alcoholic) fatty liver disease (Version 2024) [J]. *J Prac Hepatol*, 2024, 27(4): 494-510. DOI: 10.3760/cma.j.cn501113-20240327-00163. 中华医学会肝病学分会. 代谢相关(非酒精性)脂肪性肝病防治指南(2024年版)[J]. *实用肝脏病杂志*, 2024, 27(4): 494-510. DOI: 10.3760/cma.j.cn501113-20240327-00163.
- [33] ARMANDI A, BUGIANESI E. Dietary and pharmacological treatment in patients with metabolic-dysfunction associated steatotic liver disease[J]. *Eur J Intern Med*, 2024, 122: 20-27. DOI: 10.1016/j.ejim.2024.01.005.
- [34] RINELLA ME, NEUSCHWANDER-TETRI BA, SIDDQUI MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease[J]. *Hepatology*, 2023, 77(5): 1797-1835. DOI: 10.1097/hep.0000000000000323.
- [35] VILAR-GOMEZ E, MARTINEZ-PEREZ Y, CALZADILLA-BERTOT L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis[J]. *Gastroenterology*, 2015, 149(2): 367-378.e5. DOI: 10.1053/j.gastro.2015.04.005.
- [36] FRANCQUE SM, MARCHESINI G, KAUTZ A, et al. Non-alcoholic fatty liver disease: A patient guideline[J]. *JHEP Rep*, 2021, 3(5): 100322. DOI: 10.1016/j.jhepr.2021.100322.
- [37] CUSI K, ISAACS S, BARB D, et al. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings[J]. *Endocr Pract*, 2022, 28(5): 528-562. DOI: 10.1016/j.eprac.2022.03.010.
- [38] YOUNOSSI ZM, COREY KE, LIM JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: Expert review[J]. *Gastroenterology*, 2021, 160(3): 912-918. DOI: 10.1053/j.gastro.2020.11.051.
- [39] SANYAL AJ, NEWSOME PN, KLIERS I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis[J]. *N Engl J Med*, 2025, 392(21): 2089-2099. DOI: 10.1056/nejmoa2413258.
- [40] BANSAL MB, PATTON H, MORGAN TR, et al. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance[J]. *Hepatology*, 2026, 83(5): 1326-1340. DOI: 10.1097/HEP.0000000000001608.
- [41] SUN K, PARK J, GUPTA OT, et al. Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction[J]. *Nat Commun*, 2014, 5: 3485. DOI: 10.1038/ncomms4485.
- [42] FRANCQUE SM, BEDOSSA P, RATZIU V, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH[J]. *N Engl J Med*, 2021, 385(17): 1547-1558. DOI: 10.1056/nejmoa2036205.
- [43] CHEAH MCC, CRANE H, GEORGE J. Global prevalence, metabolic characteristics, and outcomes of lean-MAFLD: A systematic review and meta-analysis[J]. *Hepatol Int*, 2025, 19(3): 607-618. DOI: 10.1007/s12072-025-10801-x.
- [44] Fatty Liver Expert Committee, Chinese Medical Doctor Association, National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association. Guidelines of prevention and treatment for alcoholic liver disease: A 2018 update[J]. *J Clin Hepatol*, 2018, 34(5): 939-946. DOI: 10.3969/j.issn.1001-5256.2018.05.006. 中华医学会肝病学分会脂肪肝和酒精性肝病学组, 中国医师协会脂肪性肝病专家委员会. 酒精性肝病防治指南(2018年更新版)[J]. *临床肝胆病杂志*, 2018, 34(5): 939-946. DOI: 10.3969/j.issn.1001-5256.2018.05.006.
- [45] HARRISON SA, BEDOSSA P, GUY CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis[J]. *N Engl J Med*, 2024, 390(6): 497-509. DOI: 10.1056/nejmoa2309000.
- [46] Two-Year Time Course of Biomarker and Imaging Responses in Patients With Well-Compensated MASH Cirrhosis Treated With Resmetirom[J]. *Gastroenterol Hepatol (N Y)*, 2025, 21(12 Suppl 11): 6-7.
- [47] ZHOU R, YANG LP, ZHANG BB, et al. Clinical impact of hepatic steatosis on chronic hepatitis B patients in Asia: A systematic review and meta-analysis[J]. *J Viral Hepat*, 2023, 30(10): 793-802. DOI: 10.1111/jvh.13872.

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