·综述·

终末期肝病合并心房颤动的流行病学及发病机制

任洁雅 龙敏聪 刘辉 唐努尔 郑嵘灵 鲁晓擘
新疆医科大学第一附属医院感染·肝病中心,乌鲁木齐 830000
通信作者:鲁晓擘,Email:xjykdluxiaobo@126.com

【摘要】 肝脏疾病与心血管疾病会相互作用和影响,是彼此病情加重的危险因素。心房颤动是终末期肝病患者肝功能恶化及预后不良的预测因素。本文综述终末期肝病患者合并心房颤动的流行病学现状及其潜在的发病机制,阐明其与长期预后的关系。

【关键词】终末期肝病;房颤;流行病学; 危险因素;发病机制
基金项目:国家自然科学基金(82060115)
DOI: 10.3760/cma.j.cn331340-20211105-00216

Advances in the epidemiology of patients with end-stage liver disease combined with atrial fibrillation and its pathogenesis

Ren Jieya, Long Mincong, Liu Hui, Tang Nuer, Zheng Rongjiong, Lu Xiaobo
Center for Infection-Liver Diseases, the First Affiliated Hospital of Xinjiang Medical University, Urumqi 830000, China
Corresponding author: Lu Xiaobo, Email: xjykdluxiaobo@126.com

【**Abstract**】 Liver diseases and cardiovascular diseases interact and influence each other. Incidence of atrial fibrillation is the predictor for deterioration of liver function and poor prognosis in patients with end-stage liver disease. In this review, the current epidemiology of patients with end-stage liver disease combined with atrial fibrillation and its potential pathogenesis, as well as its relationship with long-term prognosis are summarized.

【**Key words**】End stage liver disease; Atrial fibrillation; Epidemiology; Risk factors;Pathogenesis
Fund program: National Natural Science Foudation of China(82060115)
DOI: 10.3760/cma.j.cn331340-20211105-00216

终末期肝病(ESLD)是指各种慢性肝病终末期阶段,主要表现为肝细胞功能严重受损,包括急性肝衰竭、肝硬化急性失代偿、慢性肝衰竭和晚期肝细胞癌[1],其主要特征是反复出现食管胃静脉曲张破裂出血、顽固性腹水、低钠血症和肝肾综合征[2-3]。研究显示,ESLD 发病率和致死率均较高,其患者症状负担与癌症晚期相当[4-5]。我国每年约有 65 万人死于HBV 感染所致的相关并发症及 ESLD[6]。心血管疾病和肝脏疾病间的相互作用和影响,是患者病情加重的危险因素[7]。早在 1950 年, 有研究报道约 50%的 ESLD 患者发展为肝硬化心肌病,包括心肌收缩、舒张功能障碍[8]。2019 年肝硬化诊疗指南中提到 40%~60%的肝硬化患者存在明显心脏电生理异常, 其表现主要是 QT 间期延长和发生心房纤颤[9-12]。因此,关于 ESLD 合并心房颤动(房颤)患者的流行病学研究、发病机制、诊断治疗等问题值得深入研究。

一、肝病合并房颤患者的流行病学

房颤是临床最常见的心律失常之一,截至 2019 年,全球房颤患者估测约 5 970 万例[13],进行性心力衰竭、心脏骤停及脑卒中是房颤患者主要的死因,房颤导致女性全因死亡率增加 2 倍、男性增加 1.5 倍[14]。在 ESLD 患者中,由于肝硬化心肌病、心脏离子通道重构、电解质失衡、自主神经功能受损、肝肾综合征、代谢异常、高龄、炎症综合征等危险因素的存在,常导致心脏电生理异常,已有报道出现的心律失常包括房颤、心房扑动(房扑)、房性早搏和室性早搏[15]。即使没有潜在的心脏病,ESLD 患者发生房颤的风险也会增加。一项平均

9 年的前瞻性临床研究发现，肝硬化患者发生房颤的风险比非肝硬化患者高 46%，以男性患者更为常见，该研究认为肝硬化是发生房颤的独立危险因素[16]。Gundling 等[17]分析了 293 例 ESLD 患者，其中 16%的患者合并心律失常，以房颤(68.8%)和房扑(6.7%)常见，ESLD 患者的房颤发病率明显高于无肝硬化患者。然而，也有研究认为 ESLD 患者发生房颤的风险较低，一项前瞻性研究纳入了 335 例肝硬化患者，在随访 24 个月后，发现合并房颤的发生率仅为 6.2%[18]。目前 ESLD 患者房颤的患病率研究仍较少，同时存在结论矛盾的情况，仍需大规模前瞻性研究进一步论证。

二、ESLD 患者发生房颤的危险因素

房颤的发生率随肝硬化严重程度的加重而升高，此或与 ESLD 患者血浆中有毒代谢物质如氨、一氧化氮、胆红素、细菌内毒素和继发于肾功能衰竭的代谢废物水平升高严重损害心肌功能，使其收缩功能及心电活动明显恶化相关[19-20]。明确 ESLD 患者发生房颤的相关危险因素，及早识别此类患者并指导下一步治疗非常重要。Gundling 等[17]发现，与无心律失常患者相比，肝硬化合并房颤患者发生感染、电解质紊乱、腹水、动脉硬化性疾病的比例更高，且多为高龄、肝硬化失代偿期患者。在一项对 57 177 例 ESLD 患者的回顾性研究中发现共有 15%的患者曾出现过心律失常，以房颤最常见，高龄、男性以及合并肝肾综合征和心血管疾病是导致房颤发生的危险因素[19]。在一项纳入 1 727 例等待肝移植的 ESLD 患者队列研究中，房颤患病率约为 11.2%，且随着 ESLD 模型(MELD)评分的增加，新发房颤的风险显著增高，危险因素包括年龄、睡眠呼吸暂停、感染、腹水、血流动力学不稳定和左心室射血分数降低等[21]。

三、ESLD 合并房颤患者的预后

在 ESLD 患者中，房颤与较差的远期预后相关。近期的一项研究显示，在 ESLD 住院患者中，合并房颤患者死亡率为非心律失常患者的 2 倍，同时住院时间明显延长，休克、呼吸和肾功能衰竭的风险更大[22]。此外一项基于全国住院样本的研究显示，在 309 959 例 ESLD 患者中，10.6%(32 858 例)伴有房颤，此类患者的院内死亡率明显高于未合并房颤的 ESLD 患者。多变量分析结果显示，房颤是 ESLD 患者死亡的独立预测因子[23]。另一项对接受肝移植 ESLD 患者的研究中也显示，伴有房颤的 ESLD 患者肝移植术后死亡风险显著增加 [24]。

四、ESLD 合并房颤的潜在发病机制

已知自主神经系统在房颤发生中起重要作用[25-26]。心房尤其是靠近肺静脉口区域分布有丰富的自主神经丛，房颤时常出现自主神经传递异常，副交感神经和交感神经激活增加[27]等现象，在非酒精性脂肪肝及 ESLD 中普遍存在自主神经功能障碍，常表现为继发于副交感神经活性相对降低和交感神经张力增加其自主神经失衡[28-31]。ESLD 导致自主神经功能障碍的危险因素包括：酒精引起的直接神经损伤、脂质代谢改变、维生素 E 缺乏、免疫机制及高毒性代谢物蓄积[32]。同时，ESLD 患者心电图常提示 QT 间期延长，这与肝硬化性心肌病相关，是电生理异常和自主神经功能障碍的一种表现[12]。ESLD 患者可因交感神经的过度激活、QT 间期延长从而提高了心肌细胞自律性和触发活动，导致心肌细胞的电重塑，同时患者的高动力循环、心输出量增加等病理生理改变可能诱导心肌重塑和心室肥大，这些均为发生房颤的重要基础。此外，ESLD 也可导致机体神经肽水平升高，肝硬化时血管活性肠肽也有所增加[33]，这些与房颤的发生有关[34-35]。

炎症与感染也是 ESLD 患者发生房颤的重要因素。肺部感染、脓毒血症、脓毒性休克患者中，房颤的发病率明显升高[36-38]。在 ESLD 患者中，由于肠道细菌以及免疫功能异常，常导致各类感染和全身慢性炎症反应，肝硬化失代偿期患者中，更易发生自发性腹炎、肺部感染、脓毒血症及感染性休克[39-41]，而在房颤及 ESLD 患者中，均能发现促炎细胞因子的失调，IL-6、IL-8、IL-10、TNF-α 和单核细胞趋化蛋白，明显变化，引起房颤及肝硬化病情加重[42-43]。

五、结语

肝脏疾病与心血管疾病相互作用及影响，大量临床研究表明 ESLD 患者中房颤的发病率较高，同时肝病的严重程度常常会增加房颤发生的风险，男性及高龄、血流动力学紊乱及肝肾综合征的发生常为新发房颤的危险因素，而两者共同的危险因素及自主神经功能紊乱及炎症、感染的发生可能为其潜在的发病机制。临床工作中，心血管及肝病科医师应通过询问心律失常症状，并考虑定期使用心电图和动态监测仪进行评估。

利益冲突　所有作者均声明不存在利益冲突

参　考　文　献

[1] 陈韬, 宁琴. 终末期肝病合并感染诊治的热点与难点[J].中华临床感染病杂志,2017,10(5):389-393. DOI: 10.3760/cma.j.issn.1674-2397.2017.05.014.

[2] Peng JK, Hepgul N, Higginson IJ, et al. Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis[J]. Palliat Med, 2019,33(1):24-36. DOI: 10.1177/0269216318807051.

[3] Righi E. Management of bacterial and fungal infections in end stage liver disease and liver transplantation: current options and future directions[J]. World J Gastroenterol, 2018,24(38):4311-4329. DOI: 10.3748/wjg.v24.i38.4311.

[4] Jordan RI, Tandon P. Emerging role of palliative care in patients

with advanced liver disease; proceedings of the seminars in liver disease[C]. Thieme Medical Publishers, 2020.

[5] Woodland H, Hudson B, Forbes K, et al. Palliative care in liver disease: what does good look like?[J]. Frontline Gastroenterol, 2020,11(3):218-227. DOI: 10.1136/flgastro-2019-101180.

[6] 白萧萧, 东冰, 徐光华. 慢性 HBV 感染免疫控制期与免疫逃逸期研究进展[J].肝脏,2018,23(4):344-347. DOI: 10.3969/j.issn.1008-1704.2018.04.024.

[7] Jansen C, Al-Kassou B, Lehmann J, et al. Severe abnormal heart rate turbulence onset is associated with deterioration of liver cirrhosis[J]. PLoS One, 2018,13(4):e0195631. DOI: 10.1371/journal.pone.0195631.

[8] Zardi EM, Abbate A, Zardi DM, et al. Cirrhotic cardiomyopathy[J]. J Am Coll Cardiol, 2010,56(7):539-549. DOI: 10.1016/j.jacc.2009.12.075.

[9] Kwon HM, Hwang GS. Cardiovascular dysfunction and liver transplantation[J]. Korean J Anesthesiol, 2018,71(2):85-91. DOI: 10.4097/kjae.2018.71.2.85.

[10] Zhao J, Qi X, Hou F, et al. Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis[J]. Am J Med Sci, 2016,352(3):285-295. DOI: 10.1016/j.amjms.2016.06.012.

[11] Vannucci A, Rathor R, Vachharajani N, et al. Atrial fibrillation in patients undergoing liver transplantation-a single-center experience [J]. Transplant Proc, 2014,46(5):1432-1437. DOI: 10.1016/j.transproceed.2014.02.020.

[12] 中华医学会肝病学分会. 肝硬化诊治指南[J].临床肝胆病杂志, 2019,35(11):2408-2425. DOI: 10.3969/j.issn.1001-5256.2019.11.006.

[13] 中华医学会心电生理和起搏分会, 中国医师协会心律学专业委员会, 中国房颤中心联盟心房颤动防治专家工作委员会. 心房颤动:目前的认识和治疗建议(2021)[J].中华心律失常学杂志, 2022,26(1):15-88. DOI: 10.3760/cma.j.cn113859-20211224-00264.

[14] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS[J]. Kardiol Pol, 2016,74(12):1359-1469. DOI: 10.5603/KP.2016.0172.

[15] Boyer T, Manns M, Sanyal A. Zakim and Boyer's hepatology: a textbook of liver disease[Z]. Philadelphia, PA: Saunders. Elsevier, 2012.

[16] Lee H, Choi EK, Rhee TM, et al. Cirrhosis is a risk factor for atrial fibrillation: a nationwide, population-based study [J]. Liver Int, 2017,37(11):1660-1667. DOI: 10.1111/liv.13459.

[17] Gundling F, Schmidtler F, Zelihic E, et al.Frequency of cardiac arrhythmia in patients with liver cirrhoses and evaluation of associated factors[J]. Z Gastroenterol, 2012,50(11):1149-1155. DOI: 10.1055/s-0032-1313182.

[18] Mwalitsa JP, Maimone S, Filomia R, et al. Atrial fibrillation in patients with cirrhosis[J]. Liver Int, 2016,36(3):395-400. DOI: 10.1111/liv.12928.

[19] Møller S, Bendtsen F. Cirrhotic multiorgan syndrome[J]. Dig Dis Sci, 2015,60(11):3209-3225. DOI: 10.1007/s10620-015-3752-3.

[20] Chayanupatkul M, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment[J]. Hepatol Int, 2014,8(3):308-315. DOI: 10.1007/s12072-014-9531-y.

[21] Huang WA, Dunipace EA, Sorg JM, et al. Liver disease as a predictor of new-onset atrial fibrillation[J]. J Am Heart Assoc, 2018,7(15):e008703. DOI: 10.1161/JAHA.118.008703.

[22] Adejumo AC, Adejumo KL, Akanbi O, et al. Predictors, burden and impact of cardiac arrhythmias among patients hospitalized with end-stage liver disease[J]. Heart Lung, 2020,49(1):73-79. DOI: 10.1016/j.hrtlng.2019.07.002.

[23] Muhammad ZK, Muhammad UK, Safi UK, et al. Atrial fibrillation is a risk factor for worse outcomes in patients with end stage liver disease[J]. J Atr Fibrillation, 2020,12(5):2248. DOI: 10.4022/jafib.2248.

[24] Moon YJ, Kwon HM, Park YS, et al. Brief episodes of newly developed intraoperative atrial fibrillation predicts worse outcomes in adult liver transplantation[J]. Transplant Proc, 2018,50(4):1142-1146. DOI: 10.1016/j.transproceed.2018.01.039.

[25] Chen PS, Chen LS, Fishbein MC, et al. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy [J]. Circ Res, 2014,114(9):1500-1515. DOI: 10.1161/CIRCRESAHA.114.303772.

[26] Qin M, Zeng C, Liu X. The cardiac autonomic nervous system: a target for modulation of atrial fibrillation[J]. Clin Cardiol, 2019,42(6):644-652. DOI: 10.1002/clc.23190.

[27] Linz D, Elliott AD, Hohl M, et al. Role of autonomic nervous system in atrial fibrillation[J]. Int J Cardiol, 2019,287:181-188. DOI: 10.1016/j.ijcard.2018.11.091.

[28] Kumar MS, Singh A, Jaryal AK, et al. Cardiovascular autonomic dysfunction in patients of nonalcoholic fatty liver disease[J]. Int J Hepatol, 2016,2016:5160754. DOI: 10.1155/2016/5160754.

[29] Houghton D, Zalewski P, Hallsworth K, et al. The degree of hepatic steatosis associates with impaired cardiac and autonomic function [J]. J Hepatol, 2019,70(6):1203-1213. DOI: 10.1016/j.jhep.2019.01.035.

[30] Targher G, Mantovani A, Grander C, et al. Association between non-alcoholic fatty liver disease and impaired cardiac sympathetic/parasympathetic balance in subjects with and without type 2 diabetes-The Cooperative Health Research in South Tyrol (CHRIS)-NAFLD sub-study[J]. Nutr Metab Cardiovasc Dis, 2021,31(12):3464-3473. DOI: 10.1016/j.numecd.2021.08.037.

[31] Tsiompanidis E, Siakavellas SI, Tentolouris A, et al. Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity [J]. World J Gastrointest Pathophysiol, 2018,9(1):28-36. DOI: 10.4291/wjgp.v9.i1.28.

[32] Pimentel C, Salvadori R, Feldner A, et al. Autonomic dysfunction is common in liver cirrhosis and is associated with cardiac dysfunction and mortality: prospective observational study[J]. Sao Paulo Med J, 2022,140(1):71–80. DOI: 10.1590/1516-3180.2021.

0111.R1.18052021.

[33] Long MT, Ko D, Arnold LM, et al. Gastrointestinal and liver diseases and atrial fibrillation: a review of the literature[J]. Therap Adv Gastroenterol, 2019,12:1756284819832237. DOI: 10.1177/1756284819832237.

[34] Liu Y, Scherlag BJ, Fan Y, et al. Inducibility of atrial fibrillation after GP ablations and "autonomic blockade": evidence for the pathophysiological role of the nonadrenergic and noncholinergic neurotransmitters [J]. J Cardiovasc Electrophysiol, 2013,24(2):188-195. DOI: 10.1111/j.1540–8167.2012.02449.x.

[35] Xi Y, James Chao ZY, Yan W, et al. Neuronally released vasoactive intestinal polypeptide alters atrial electrophysiological properties and may promote atrial fibrillation[J]. Heart Rhythm, 2015,12(6):1352-1361. DOI: 10.1016/j.hrthm.2015.03.003.

[36] Kuipers S, Klein Klouwenberg PM, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review[J]. Crit Care, 2014,18(6):688. DOI: 10.1186/s13054-014-0688-5.

[37] Ungprasert P, Srivali N, Kittanamongkolchai W. Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis[J]. Int J Rheum Dis, 2017,20(4):434-441. DOI: 10.1111/1756-185X.12820.

[38] Walkey AJ, Hogarth DK, Lip G. Optimizing atrial fibrillation management: from ICU and beyond[J]. Chest, 2015,148(4):859-864. DOI: 10.1378/chest.15-0358.

[39] Cannon MD, Martin P, Carrion AF. Bacterial infection in patients with cirrhosis: don't get bugged to death [J]. Dig Dis Sci, 2020,65(1):31-37. DOI: 10.1007/s10620-019-05943-6.

[40] Arvaniti V, D&#x27, Amico G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis[J]. Gastroenterology, 2010,139(4):1246-1256, 1256.e1-5. DOI: 10.1053/j.gastro.2010.06.019.

[41] 施烨敏, 盛吉芳. 肝硬化合并严重肝损伤并发感染的临床特点及危险因素分析[J].中国微生态学杂志,2018,30(5):570-575. DOI: 10.13381/j.cnki.cjm.201805018.

[42] Zhou X, Dudley SC Jr. Evidence for inflammation as a driver of atrial fibrillation[J]. Front Cardiovasc Med, 2020,7:62. DOI: 10.3389/fcvm.2020.00062.

[43] Dirchwolf M, Podhorzer A, Marino M, et al. Immune dysfunction in cirrhosis: Distinct cytokines phenotypes according to cirrhosis severity[J]. Cytokine, 2016,77:14-25. DOI: 10.1016/j.cyto.2015.10.006.

（收稿日期：2021-11-05）