BÖLÜM 101

KOMPANSE İLERİ KRONİK KARACİĞER HASTALIĞI

Genco GENÇDAL [1] - Hakan YILDIZ [2]

DOI: 10.37609/akya.3785.c407

GİRİŞ

Karaciğer sirozu (KS), karaciğer dokusunun geniş çapta bozulması, fibrozis ve nodüler yapıların oluşmasıyla karakterize bir tablodur. KS, genellikle uzun süreli alkol tüketimi, kronik viral hepatit enfeksiyonu, yağlı karaciğer hastalığı, otoimmün hastalıklar veya diğer karaciğer hastalıklarının sonucu olarak ortaya çıkabilir. Batıda en yaygın olarak alkole bağlı steatotik karaciğer hastalığı (ALD), ardından metabolik fonksiyon bozukluğu ile ilişkili steatotik karaciğer hastalığı (MASLD) (daha önce alkole bağlı olmayan yağlı karaciğer hastalığı (NAFLD) olarak adlandırılıyordu) gelir (Resim 1). KS prevalansı ve mortalitesi günümüzde hala artmaya devam etmektedir. Amerika Birleşik Devletleri'nden alınan verilere göre, KS'ye bağlı ölümlerin yıllık sayısı %65 artarken, KS nedeniyle hastaneye kaldırılanların sayısı on yıl içinde neredeyse iki katına çıkmıştır (1).

KS, yakın zamana kadar, kronik karaciğer hastalığının (KKH) son aşaması olarak görülüyordu. KS, tek bir klinik tablo olarak kabul görmekte, nihayetinde ölüm veya karaciğer nakli öngörülmekteydi. "Kompanse karaciğer sirozu" (KKS) terimi, asit, hepatik ensefalopati, varis kanaması (VH) ve sarılık gibi bir veya daha fazla dekompanse edici olayın olmadığı KS'yi tanımlamak için kullanılmıştır. Bir dekompansasyon olayı yaşadıktan sonra, KS hastaları her zaman dekompanse KS (DKS) olarak sınıflandırılır çünkü dekompansasyona neden olan patojenik mekanizmalar devam eder. Bir kohort çalışmasında, KS hastaları dekompanse olaylara göre iki gruba ayrıldığında, KKS hastalarında ortalama 1 yıllık sağ kalım %95 iken DKS hastalarında %61 tespit edilmiştir. Bu nedenle, KKS hastalarındaki ilk dekompansasyon, medyan sağ kalımın önemli ölçüde azalması nedeniyle prognostik bir dönüm noktası olarak kabul edilmiştir (2,3).

Son yıllarda yapılan çalışmalarda elde edilen sonuçlar ile KS'nin tek bir klinik tablo olduğu fikri değişmiş ve bu veriler KS'nin farklı aşamalarda değişen prognoza sahip heterojen bir durum olarak tanımlanmasına yol açmıştır. Wanless ve arkadaşları, KS'nin geri dönüşebilirliğini ilk tanımlayanlardır. Genellikle, KKS'li hastalar ilk birkaç yıl asemptomatik kalır ve tanı konulamaz. Asemptomatik olmalarına rağmen, KKS hastalarının üçte biri ile yarısı arasında tanı anında varisler ve "klinik olarak anlamlı portal hipertansiyon"(KAPHT) mevcuttur. Zamanla, KKS hastalarında, artan

[1] Doç. Dr., Koç Üniversitesi, Tıp Fakültesi, İç Hastalıkları AD., Gastroenteroloji BD., ggencdal@kuh.ku.edu.tr, ORCID iD: 0000-0002-5856-5384

[2] Prof. Dr., Yeniyüzyıl Üniversitesi, İç Hastalıkları AD., Gastroentroloji BD., 12yhakan@gmail.com, hakanyildiz@yeniyuzyil.edu.tr, ORCID iD: 0000-0002-3459-5669

kötüleştirebilir. Ayrıca, İKKKH'lilerde, önceden dekompansasyon episodları yaşamış hastalardan daha şiddetli bir AKKY (ACLF) yaşarlar. Dolayısıyla, böyle tetikleyici değişkenlerin kontrol edilmesi, sirozla ilişkili morbidite ve mortaliteyi önemli ölçüde azaltabilir. Antibiyotik profilaksisi ve hızlı, isabetli antibiyotik tedavisi, enfeksiyon tarafından tetiklenen AKKY'nin önlenmesine yardımcı olabilir. Profilaktik antibiyotikler, etkili gastrointestinal kanama yönetimi ile birlikte, AKKY'yi önleyebilir (87,88).

Başka bir önemli önleme stratejisi, viral hepatit için aşılama yapılmasıdır. Tüm İKK hastaları için hepatit B aşısı önerilir. Ancak, normal bireylere kıyasla, sirozlu hastalar HBV aşısı sonrası daha düşük seroproteksiyon oranlarına ulaşırlar (ortalama yanıt oranı %47). Hepatit E virüsü (HEV) ve hepatit A virüsü (HAV) süper enfeksiyonu, endemik bölgelerde ACLF'nin iyi bilinen bir nedenidir. Birçok ülke, Kronik karaciğer hastaları için HAV aşılama önerir. Rekombinant HEV aşıları da geliştirilmiştir ancak dünya çapında yaygın olarak bulunmamaktadır veya onaylanmamaktadır. Aşılama bir seçenek olmadığında, hijyenik koşulların iyileştirilmesi ve temiz su temininin sağlanması gibi genel önleyici önlemler, HEV/HAV kaynaklı AKKY insidansını azaltabilir(89-91).

SONUÇ

İKKH'lilerin yaşam beklentisi genellikle yüksektir. Dolayısıyla, İKKH'nin erken tespitini kolaylaştırmak için invaziv olmayan teknikler daha sık kullanılmalıdır. İKKH'nin erken teşhisi, altta yatan nedenleri tedavi etme ve karaciğer hastalığının ilerlemesini önleme veya durdurma fırsatı sunar. Viral İKKH için ve daha az ölçüde non-viral İKKH için, altta yatan neden ilerlemeden önce tedavi edildiğinde fibrozis regresyonu, sirozun geri dönüşü sağlanabilir. İKKKH'den İDKKH'ye geçiş çoğunlukla PHT derecesine bağlıdır. Bu geçiş, ortalama sağ kalım oranlarında dramatik bir düşüşle birlikte gelir. NSBB'ler şu anda PHT'nin tedavisinin temelini oluştururken, gelecekte özelleştirilmiş çoklu stratejilere yol açabilecek bir dizi yeni tedavi yaklaşımı olabilir. Bazı daha yeni ilaçlar, PHT'yi azaltmada umut vadetmiştir ancak KS hastalarındaki güvenlik ve etkinliklerini belirlemek için daha güvenilir ve tutarlı verilere ihtiyaç vardır. Ayrıca, İKKH'nin dekompansasyonu için bilinen birkaç risk faktörü ve tetikleyici olay bulunmaktadır. İKKKH'nin etiyolojisinden bağımsız olarak, hastalığın değişen klinik tablosunu etkileyebilecek ve İKKH ile ilişkilendirilen yük, morbidite ve mortalitede azalmaya yol açabilecek yeni tedavi yaklaşımları olabilir.

KAYNAKLAR

1. Allen AM, Kim WR, Moriarty JP, et al. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology.* 2016;64:2165-2172.
2 D'Amico G, Pasta L, Morabito A, et al. Vizzini G, Politi F, Luca A, Virdone R, Licata A, Pagliaro L. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther.* 2014;39:1180-1193.
3 D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol.* 2006;44:217-231.
4 Ripoll C, Groszmann R, Garcia-Tsao G,et al.; Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology.* 2007;133:481-488.
5 Barr RG, Wilson SR, Rubens D, et al. *Update of the Society of Radiologists in Ultrasound (SRU) Consensus* 2019 Radiology 2020; 296:263–274https://doi.org/10.1148/radiol.2020192437
6 De Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63:743-752. DOI:10.10.1016/J.JHEP.2015.05.022
7 Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. *Arch Pathol Lab Med.* 2000;124:1599-1607.
8 Roccarina D, Rosselli M, Genesca J, et al. Elastography methods for the non-invasive assessment of portal hypertension. *Expert Rev Gastroenterol Hepatol.* 2018;12:155-164.
9 Lee YA, Wallace MC, Friedman SL. Pathobiology of liver fibrosis: a translational success story. *Gut.* 2015;64:830-841.
10 Samonakis DN, Koulentaki M, Coucoutsi C, et al. Clinical outcomes of compensated and decompensated cirrhosis: A long term study. *World J Hepatol.* 2014;6:504-512.

11 Reiberger T, Hofer BS. The Baveno VII concept of cirrhosis recompensation. *Dig Liver Dis.* 2023;55:431-441.
12 Wang Q, Zhao H, Deng Y, et al. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. *J Hepatol.* 2022;77:1564-1572.
13 Lee YA, Wallace MC, Friedman SL. Pathobiology of liver fibrosis: a translational success story. *Gut*. 2015;64:830-841.
14. Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2019; 393: 1597-1608.
15. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis-a histological classification of the severity of cirrhosis. *J Hepatol* 2006; 44: 111-117.
16. Jain D, Sreenivasan P, Inayat I, et al. Thick Fibrous Septa on Liver Biopsy Specimens Predict the Development of Decompensation in Patients With Compensated Cirrhosis. *Am J Clin Pathol* 2021; 156: 802-809.
17. Manne V, Akhtar E, Saab S. Cirrhosis regression in patients with viral hepatitis B and C: a systematic review. *J Clin Gastroenterol* 2014; 48:e76-e84.
18. Cárdenas A, Arroyo V. Mechanisms of water and sodium retention in cirrhosis and the pathogenesis of ascites. *Best Pract Res Clin Endocrinol Metab* 2003; 17: 607-622.
19. Kumar R, Anand U, Priyadarshi RN. Lymphatic dysfunction in advanced cirrhosis: Contextual perspective and clinical implications. *World J Hepatol* 2021; 13: 300-314.
20. Liu TL, Trogdon J, Weinberger M,et al. Diabetes Is Associated with Clinical Decompensation Events in Patients with Cirrhosis. *Dig Dis Sci* 2016; 61: 3335-3345.
21. Berzigotti A, Garcia-Tsao G, Bosch J, et al. Portal Hypertension Collaborative Group. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* 2011; 54: 555-561 .
22. Cespiati A, Meroni M, Lombardi R, et al. Impact of Sarcopenia and Myosteatosis in Non-Cirrhotic Stages of Liver Diseases: Similarities and Differences across Aetiologies and Possible Therapeutic Strategies. *Biomedicines* 2022; 10.
23. Nahon P, Lescat M, Layese R, Bourcier V,et al. ANRS CO12 CirVir and Microcir Groups. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). *Gut* 2017; 66: 330-341.
24. Trebicka J, Fernandez J, Papp M, et al. PREDICT STUDY group of the EASL-CLIF CONSORTIUM. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. *J Hepatol* 2021; 74: 1097-1108.
25. Klein LM, Chang J, Gu W, et al. The Development and Outcome of Acute-on-Chronic Liver Failure After Surgical Interventions. *Liver Transpl* 2020; 26: 227-237.
26. Hytiroglou P, Theise ND. Regression of human cirrhosis: an update, 18 years after the pioneering article by Wanless et al. *Virchows Arch* 2018; 473: 15-22.
27. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003; 124: 105-117.
28. 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. *Gastroenterology* 2006; 131: 1743-1751.
29. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; 122: 1303-1313.
30. Mauro E, Crespo G, Montironi C, et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after sustained virological response in recurrent hepatitis C. *Hepatology* 2018; 67: 1683-1694.
31. Sanyal AJ, Anstee QM, Trauner M, et al. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology* 2022; 75: 1235-1246.
32. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. *Gastroenterology* 2020; 159: 1290-1301.e5.
33. Garcia-Tsao G, Bosch J, Kayali Z,et al. Randomized placebo-controlled trial of emricasan for non-alcoholic steatohepatitis-related cirrhosis with severe portal hypertension. *J Hepatol* 2020; 72: 885-895.
34. Chalasani N, Abdelmalek MF, Garcia-Tsao G, et al. Belapectin (GR-MD-02) Study Investigators. Effects of Belapectin, an Inhibitor of Galectin-3, in Patients With Nonalcoholic Steatohepatitis With Cirrhosis and Portal Hypertension. *Gastroenterology* 2020; 158: 1334-1345.e5.
35. Harrison SA, Bedossa P, Guy CD, et al. MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med.* 2024 Feb 8;390(6):497-509. doi: 10.1056/NEJMoa2309000. PMID: 38324483.
36. Hofer BS, Simbrunner B, Hartl L, et al. Alcohol Abstinence Improves Prognosis Across All Stages of Portal Hypertension in Alcohol-Related Cirrhosis. *Clin Gastroenterol Hepatol* 2022.
37. Czaja AJ, Carpenter HA. Decreased fibrosis during corticosteroid therapy of autoimmune hepatitis. *J Hepatol* 2004; 40: 646-652.
38. de Veer RC, van Hooff MC, Corpechot C, et al. Ursodeoxycholic acid treatment-induced GLOBE score changes are associated with liver transplantation-free survival in patients with primary biliary cholangitis. *Am J Gastroenterol* 2022.
39. Bardou-Jacquet E, Morandeau E, Anderson GJ, et al. Regression of Fibrosis Stage With Treatment Reduces Long-Term Risk of Liver Cancer in Patients With Hemochromatosis Caused by Mutation in HFE. *Clin Gastroenterol Hepatol* 2020; 18: 1851-1857.
40. Villanueva C, Albillos A, Genescà J, et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension.*Hepatology* 2016; 63: 197-206 .
41. Rabiee A, Garcia-Tsao G, Tapper EB. Nonselective Beta-Blockers in Portal Hypertension: Why, When, and How? *Clin Liver Dis (Hoboken)* 2022; 19: 118-123.
42. Gluud LL, Krag A. Banding ligation versus beta-blockers *for primary prevention in oesophageal varices in adults.*

Cochrane Database Syst Rev 2012; CD004544.
43. Poynard T, Calès P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. *N Engl J Med* 1991; 324: 1532-1538.
44. Turco L, Reiberger T, Vitale G, et al. Carvedilol as the new non-selective beta-blocker of choice in patients with cirrhosis and portal hypertension. *Liver Int* 2023; 43: 1183-1194 .
45. Sinagra E, Perricone G, D'Amico M, et al. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther* 2014; 39: 557-568.
46. Bhardwaj A, Kedarisetty CK, Vashishtha C, et al. Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. *Gut* 2017; 66: 1838-1843.
47. Villanueva C, Torres F, Sarin SK, et al. Carvedilol-IPD-MA-group and the Baveno Cooperation: an EASL Consortium. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. *J Hepatol* 2022; 77: 1014-1025.
48. Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. *Gut* 2020; 69: 953-962.
49. Zafra C, Abraldes JG, Turnes J, et al. Simvastatin enhances hepatic nitric oxideproduction and decreases the hepatic vascular tone in patients with cirrhosis. *Gastroenterology* 2004; 126: 749-755
50. Abraldes JG, Albillos A, Bañares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009; 136: 1651-1658.
51. Huang YW, Lee CL, Yang SS, et al. Statins Reduce the Risk of Cirrhosis and Its Decompensation in Chronic Hepatitis B Patients: A Nationwide Cohort Study. *Am J Gastroenterol* 2016; 111: 976-985.
52. Kim RG, Loomba R, Prokop LJ, et al. Statin Use and Risk of Cirrhosis and Related Complications in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2017; 15: 1521-1530.e8.
53. Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, Rodriguez M, Castellote J, García-Pagán JC, Torres F,Calleja JL, Albillos A, Bosch J; BLEPS Study Group. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. *Gastroenterology* 2016; 150: 1160-1170.e3.
54. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; 388: 2532-2561.
55. Vilaseca M, García-Calderó H, Lafoz E, et al. The anticoagulant rivaroxaban lowers portal hypertension in cirrhotic rats mainly by deactivating hepatic stellate cells. *Hepatology* 2017; 65: 2031-2044 .
56. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012; 143: 1253-1260.e4.
57. Iqbal U, Dennis BB, Li AA, et al. Use of anti-platelet agents in the prevention of hepatic fibrosis in patients at risk for chronic liver disease: a systematic review and meta-analysis. *Hepatol Int* 2019; 13: 84-90.
58. Ahn JC, Sundaram V. Obesity and Liver Decompensation. *Clin Liver Dis (Hoboken)* 2019; 14: 12-15 .
59. Sundaram V, Jalan R, Ahn JC, Charlton MR, Goldberg DS, Karvellas CJ, Noureddin M, et al. Class III obesity is a risk factor for the development of acute-on-chronic liver failure in patients with decompensated cirrhosis. *J Hepatol* 2018; 69: 617-625.
60. Miñambres I, Rubio MA, de Hollanda A, et al. Outcomes of Bariatric Surgery in Patients with Cirrhosis. *Obes Surg* 2019; 29: 585-592.
61. Kumar R. Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis. *Indian J Endocrinol Metab* 2018; 22: 552-559.
62. Wong F, Logan A, Blendis L. Hyperinsulinemia in preascitic cirrhosis: effects on systemic and renal hemodynamics, sodium homeostasis, forearm blood flow, and sympathetic nervous activity. Hepatology 1996; 23: 414-422.
63. Kumar R, García-Compeán D, Maji T. Hepatogenous diabetes: Knowledge, evidence, and skepticism. *World J Hepatol* 2022; 14: 1291-1306.
64. Verrill C, Markham H, Templeton A,et al. Alcohol-related cirrhosis--early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction* 2009; 104: 768-774.
65. Xie YD, Feng B, Gao Y, et al. Effect of abstinence from alcohol on survival of patients with alcoholic cirrhosis: A systematic review and meta-analysis. Hepatol Res 2014; 44: 436-449.
66. Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: Clinical nutrition in liver disease. *Clin Nutr* 2020; 39: 3533-3562.
67. Liu F, Wang X, Wu G, et al. Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A MetaAnalysis. *PLoS One* 2015; 10: e014245.
68. Wong F, Liu P, Blendis L. Sodium homeostasis with chronic sodium loading in preascitic cirrhosis. *Gut* 2001; 49: 847-851.
69. Jalan R, Hayes PC. Sodium handling in patients with well compensated cirrhosis is dependent on the severity of liver disease and portal pressure. *Gut* 2000; 46: 527-533.
70. Konstantakis C, Tselekouni P, Kalafateli M, et al. Vitamin D deficiency in patients with liver cirrhosis. *Ann Gastroenterol* 2016; 29: 297-306.
71. Udomsinprasert W, Jittikoon J. Vitamin D and liver fibrosis: Molecular mechanisms and clinical studies. *Biomed Pharmacother* 2019; 109:1351-1360.
72. Abramovitch S, Sharvit E, Weisman Y, et al. Vitamin D inhibits development of liver fibrosis in an animal model but cannot ameliorate established cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2015; 308: G112-G120.
73. Gregson CL, Armstrong DJ, Bowden J, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2022;17:58.
74. Roskilly A, Rowe IA. Surveillance for hepatocellular can-

cer. *Clin Med (Lond)* 2018;18:s66–9.
75. NICE. Cirrhosis in over 16S: assessment and management: *NICE guideline.* NG50; 2016
76. UKHSA. 2013. Available: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-greenbook.
77. Tandon P, Raman M, Mourtzakis M, et al. A practical approach to nutritional screening and assessment in cirrhosis. *Hepatology* 2017;65:1044–57.
78. Merli M, Berzigotti A, Zelber-Sagi S. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;70:172–93.
79. Berzigotti A, Garcia-Tsao G, Bosch J, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* 2011;54:555–61
80. Jang YO, Kim MY, Cho MY, et al. Effect of bone marrow-derived mesenchymal stem cells on hepatic fibrosis in a thioacetamide-induced cirrhotic rat model. *BMC Gastroenterol* 2014; 14: 198.
81. Moore JK, Stutchfield BM, Forbes SJ. Systematic review: the effects of autologous stem cell therapy for patients with liver disease. *Aliment Pharmacol Ther* 2014; 39: 673-685.
82. Shasthry SM, Sharma MK, Shasthry V, et al. Efficacy of Granulocyte Colony-stimulating Factor in the Management of SteroidNonresponsive Severe Alcoholic Hepatitis: A Double-Blind Randomized Controlled Trial. *Hepatology* 2019; 70: 802-811.
83. Newsome PN, Fox R, King AL, et al. Granulocyte colony-stimulating factor and autologous CD133-positive stem-cell therapy in liver cirrhosis (REALISTIC): an open-label, randomised, controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2018; 3: 25-36.
84. Schwarzer R, Kivaranovic D, Mandorfer M, et al. Randomised clinical study: the effects of oral taurine 6g/day vs placebo on portal hypertension. *Aliment Pharmacol Ther* 2018; 47: 86-94.
85. Zipprich A, Gittinger F, Winkler M, et al. Effect of ET-A blockade on portal pressure and hepatic arterial perfusion in patients with cirrhosis: A proof of concept study. *Liver Int* 2021; 41: 554-561.
86. Younossi ZM, Ratziu V, Loomba R, et al. REGENERATE Study Investigators. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2019; 394: 2184-2196.
87. Piano S, Tonon M, Vettore E, et al. Incidence predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *J Hepatol* 2017; 67: 1177-1184.
88. Cullaro G, Sharma R, Trebicka J, et al. Precipitants of Acute-on-Chronic Liver Failure: An Opportunity for Preventative Measures to Improve Outcomes. *Liver Transpl* 2020; 26: 283-293.
89. Aggeletopoulou I, Davoulou P, Konstantakis C, et al. Response to hepatitis B vaccination in patients with liver cirrhosis. *Rev Med* Virol 2017; 27.
90. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virüs superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; 338: 286-290.
91. Wu T, Huang SJ, Zhu FC,et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. *Hum Vaccin Immunother* 2013; 9:2474-2479.