

## SIROZ

Hakan Ümit ÜNAL<sup>1</sup>

### GİRİŞ

Siroz terimi ilk olarak 1826 yılında Laennec tarafından kullanılmıştır. Bu terim, sirotik karaciğerin rengi ve yüzeyinin düzensiz görünümünden dolayı Yunanca'da portakal kabuğu anlamına gelen scirrhos kelimesinden türetilmiştir. Karaciğer sirozu, karaciğer parankimindeki kronik hasara cevap olarak ortaya çıkan yaygın fibrozis ve oluşan fibröz bantların çevrelediği rejenerasyon nodüllerinin karaciğer parankimi ile yer değiştirmesi olarak tarif edilebilir. Kronik karaciğer hasarının siroz olarak tanımlanabilmesi için fibrozis ve rejenerasyon nodüllerinin bir arada gösterilmesi gereklidir. Bu nedenle, "Konjenital hepatik fibrozis" de olduğu gibi fibrozisin olduğu ancak nodül yapısının olmadığı veya "nodüler rejeneratif hiperplazi" de olduğu gibi fibrozis olmayıp nodül yapılarının olduğu hastalıklar siroz olarak tanımlanamazlar. Oluşan yaygın fibrozis ve rejenerasyon nodülleri karaciğerin yapısının ve fonksiyonlarının bozulmasına neden olur. Bu bozulma zamanla intrahepatik vasküler yapıları da içine alır (sinüzoidal kapillarizasyon ve şant oluşumu) ve bu durum portal basınç artışı (portal hipertansiyona) ile sonuçlanır. Siroz, sadece karaciğeri ilgilendiren bir hastalık değildir. Komplikasyonları ile birlikte düşünüldüğünde, vücudun neredeyse

tüm sistemlerini etkileyen sistemik bir tablo olarak değerlendirilmelidir.

Kitabın bu bölümünde karaciğer sirozunun tanımı, patogenezi, tanısı ve prognozu konu edilmiş olup klinik yaklaşım genel bir çerçevede sunulmuştur.

### EPİDEMİYOLOJİ:

Karaciğer sirozu, cinsiyet ve etnisiteye bakmaksızın tüm dünyada heterojen bir dağılım göstermektedir. Hastalık uzun süre asemptomatik bir seyire sahip olduğu için, sıklığı tam olarak bilinmemektedir. Hastalığın tanısı, ya rutin kontroller sırasında saptanan anormal laboratuvar ve muayene bulguları ile ya da asit, hepatik ensefalopati ve varis kanaması gibi hastalığın dekompanzasyon bulgularının ortaya çıkması ile konur. Kompanze siroz hastalarının yıllık dekompanzasyon hızı %5-7 arasında olup, 2017 yılında dünya genelinde on milyondan fazla hastada dekompanzasyon geliştiği rapor edilmiştir (1). Siroz hastalarında dekompanzasyon bulgularının ortaya çıkması artmış mortalite ile ilişkilidir.

2017 yılında dünyada 1320000 kişinin siroz ilişkili nedenlerden dolayı öldüğü, bu hastaların %66,7 sinin erkek olduğu bildirilmiştir (1). Siroz, dünya genelinde erişkinlerde on dördüncü

<sup>1</sup> Doç. Dr. Hakan Ümit ÜNAL, Acıbadem Mehmet Ali Aydınlar Üniversitesi Tıp Fakültesi, İç Hastalıkları AD. hakan75unal@yahoo.com

ve hasta seçiminde önceden kabul edilen kriterler değişmeye başlamıştır. Amerika Birleşik Devletleri'nde 2013 yılından beri HIV (+) hastaya, HIV (+) donörden nakil yapılabilmektedir (180). Karaciğer nakli karaciğer yetmezliği yapan hastalıklar ve siroza eşlik eden hastalıklar ile ilgili bilgi ve tecrübemiz arttıkça, tedavi seçenekleri ve endikasyonları konusunda değişime uğramaktadır. Bu nedenle tüm endikasyonlar hasta özelinde düşünülerek güncel bilgiler ile harmanlanıp uygulanacak tedavi buna göre tasarlanmalıdır.

### Sonuç

Karaciğer sirozu, karaciğerde kronik hasar oluşturan pek çok durumun zaman içerisinde oluşturduğu ortak histolojik sonuçtur. Bu sonucu ortaya çıkaran farklı etyolojilerin ortak yolağı, hepatik stallet hücre aktivasyonunun baş rolü oynadığı hepatik fibrozis sürecidir. Klinik olarak bu süreç genellikle yavaş ve sinsi bir şekilde ilerlediğinden hastalar uzun süre kompanse siroz evresinde asemptomatik olarak kalır. Bu yüzden tanı konulduğunda genellikle hastalar ileri evrededir ve siroza ait çeşitli komplikasyonlar ortaya çıkmıştır. Bu aşamada amaç karaciğer hasarının ilerlemesini durdurmak ve ortaya çıkmış olan komplikasyonlar ile mücadele etmektir.

### KAYNAKLAR

1. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. [Comparative Study Research Support, Non-U.S. Gov't]. 2020 Mar;5(3):245-66.
2. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030. *J Clin Oncol*. 2016 May 20;34(15):1787-94.
3. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. *Gastroenterology*. [Research Support, U.S. Gov't, Non-P.H.S. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2017 Mar;152(4):812-20 e5.
4. Byass P. The global burden of liver disease: a challenge for methods and for public health. *BMC Med*. 2014 Sep 18;12:159.
5. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. [Comment]. 2015 Mar;148(3):547-55.
6. Fauerholdt L, Schlichting P, Christensen E, Poulsen H, Tygstrup N, Juhl E. Conversion of micronodular cirrhosis into macronodular cirrhosis. *Hepatology*. [Comparative Study]. 1983 Nov-Dec;3(6):928-31.
7. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol*. [Review]. 2011;6:425-56.
8. Benyon RC, Arthur MJ. Extracellular matrix degradation and the role of hepatic stellate cells. *Semin Liver Dis*. [Research Support, Non-U.S. Gov't Review]. 2001 Aug;21(3):373-84.
9. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2008 Mar 8;371(9615):838-51.
10. Wake K. "Starnzellen" in the liver: perisinusoidal cells with special reference to storage of vitamin A. *Am J Anat*. 1971 Dec;132(4):429-62.
11. Friedman SL, Roll FJ. Isolation and culture of hepatic lipocytes, Kupffer cells, and sinusoidal endothelial cells by density gradient centrifugation with Stractan. *Anal Biochem*. [Research Support, U.S. Gov't, P.H.S.]. 1987 Feb 15;161(1):207-18.
12. Puche JE, Saiman Y, Friedman SL. Hepatic stellate cells and liver fibrosis. *Compr Physiol*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2013 Oct;3(4):1473-92.
13. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol*. [Review]. 2017 Jul;14(7):397-411.
14. Friedman SL. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. *J Biol Chem*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. 2000 Jan 28;275(4):2247-50.
15. Bachem MG, Melchior R, Gressner AM. The role of thrombocytes in liver fibrogenesis: effects of platelet lysate and thrombocyte-derived growth factors on the mitogenic activity and glycosaminoglycan synthesis of cultured rat liver fat storing cells. *J Clin Chem Clin Biochem*. [Research Support, Non-U.S. Gov't]. 1989 Sep;27(9):555-65.
16. Tacke F. Targeting hepatic macrophages to treat liver diseases. *J Hepatol*. [Review Research Support, Non-U.S. Gov't]. 2017 Jun;66(6):1300-12.
17. Canbay A, Higuchi H, Bronk SF, Taniai M, Sebo TJ, Gores GJ. Fas enhances fibrogenesis in the bile duct ligated mouse: a link between apoptosis and fibrosis. *Gastroenterology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2002 Oct;123(4):1323-30.
18. Mehal W, Imaeda A. Cell death and fibrogenesis. *Semin Liver Dis*. [Research Support, N.I.H., Extramural Review]. 2010 Aug;30(3):226-31.
19. Canbay A, Taimr P, Torok N, Higuchi H, Friedman S, Gores GJ. Apoptotic body engulfment by a human stellate cell line is profibrogenic. *Lab Invest*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2003 May;83(5):655-63.
20. Nieto N, Friedman SL, Cederbaum AI. Cytochrome P450 2E1-derived reactive oxygen species mediate paracrine stimulation of collagen I protein synthesis by hepatic stellate cells. *J Biol Chem*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2002 Mar 22;277(12):9853-64.
21. Nieto N, Friedman SL, Cederbaum AI. Stimulation and

- proliferation of primary rat hepatic stellate cells by cytochrome P450 2E1-derived reactive oxygen species. *Hepatology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2002 Jan;35(1):62-73.
22. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. *J Hepatol*. [Research Support, Non-U.S. Gov't Review]. 2001 Aug;35(2):297-306.
  23. Jaeschke H. Mechanisms of Liver Injury. II. Mechanisms of neutrophil-induced liver cell injury during hepatic ischemia-reperfusion and other acute inflammatory conditions. *Am J Physiol Gastrointest Liver Physiol*. [Research Support, N.I.H., Extramural Review]. 2006 Jun;290(6):G1083-8.
  24. Nussler AK, Di Silvio M, Billiar TR, Hoffman RA, Geller DA, Selby R, et al. Stimulation of the nitric oxide synthase pathway in human hepatocytes by cytokines and endotoxin. *J Exp Med*. [Research Support, U.S. Gov't, P.H.S.]. 1992 Jul 1;176(1):261-4.
  25. Venkatraman A, Shiva S, Wigley A, Ulasova E, Chhieng D, Bailey SM, et al. The role of iNOS in alcohol-dependent hepatotoxicity and mitochondrial dysfunction in mice. *Hepatology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2004 Sep;40(3):565-73.
  26. Rosmorduc O, Housset C. Hypoxia: a link between fibrogenesis, angiogenesis, and carcinogenesis in liver disease. *Semin Liver Dis*. [Research Support, Non-U.S. Gov't Review]. 2010 Aug;30(3):258-70.
  27. Clement S, Pascarella S, Conzelmann S, Gonelle-Gispert C, Guilloux K, Negro F. The hepatitis C virus core protein indirectly induces alpha-smooth muscle actin expression in hepatic stellate cells via interleukin-8. *J Hepatol*. [Research Support, Non-U.S. Gov't]. 2010 May;52(5):635-43.
  28. Bataller R, Paik YH, Lindquist JN, Lemasters JJ, Brenner DA. Hepatitis C virus core and nonstructural proteins induce fibrogenic effects in hepatic stellate cells. *Gastroenterology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2004 Feb;126(2):529-40.
  29. Schulze-Krebs A, Preimel D, Popov Y, Bartenschlager R, Lohmann V, Pinzani M, et al. Hepatitis C virus-replicating hepatocytes induce fibrogenic activation of hepatic stellate cells. *Gastroenterology*. [Research Support, Non-U.S. Gov't]. 2005 Jul;129(1):246-58.
  30. Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. *Best Pract Res Clin Gastroenterol*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2011 Apr;25(2):195-206.
  31. Schuppan D, Ruehl M, Somasundaram R, Hahn EG. Matrix as a modulator of hepatic fibrogenesis. *Semin Liver Dis*. [Research Support, Non-U.S. Gov't Review]. 2001 Aug;21(3):351-72.
  32. Jarnagin WR, Rockey DC, Koteliansky VE, Wang SS, Bissell DM. Expression of variant fibronectins in wound healing: cellular source and biological activity of the EIIIA segment in rat hepatic fibrogenesis. *J Cell Biol*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1994 Dec;127(6 Pt 2):2037-48.
  33. Yaqoob U, Cao S, Shergill U, Jagavelu K, Geng Z, Yin M, et al. Neuropilin-1 stimulates tumor growth by increasing fibronectin fibril assembly in the tumor microenvironment. *Cancer Res*. [Research Support, N.I.H., Extramural]. 2012 Aug 15;72(16):4047-59.
  34. Rojkind M, Giambone MA, Biempica L. Collagen types in normal and cirrhotic liver. *Gastroenterology*. [Research Support, U.S. Gov't, P.H.S.]. 1979 Apr;76(4):710-9.
  35. Gressner AM. The cell biology of liver fibrogenesis - an imbalance of proliferation, growth arrest and apoptosis of myofibroblasts. *Cell Tissue Res*. [Review]. 1998 Jun;292(3):447-52.
  36. McGuire RF, Bissell DM, Boyles J, Roll FJ. Role of extracellular matrix in regulating fenestrations of sinusoidal endothelial cells isolated from normal rat liver. *Hepatology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1992 Jun;15(6):989-97.
  37. Hammoutene A, Rautou PE. Role of liver sinusoidal endothelial cells in non-alcoholic fatty liver disease. *J Hepatol*. [Review Research Support, Non-U.S. Gov't]. 2019 Jun;70(6):1278-91.
  38. Perepelyuk M, Terajima M, Wang AY, Georges PC, Janney PA, Yamauchi M, et al. Hepatic stellate cells and portal fibroblasts are the major cellular sources of collagens and lysyl oxidases in normal liver and early after injury. *Am J Physiol Gastrointest Liver Physiol*. [Research Support, American Recovery and Reinvestment Act Research Support, N.I.H., Extramural]. 2013 Mar 15;304(6):G605-14.
  39. Muiznieks LD, Keeley FW. Molecular assembly and mechanical properties of the extracellular matrix: A fibrous protein perspective. *Biochim Biophys Acta*. [Review]. 2013 Jul;1832(7):866-75.
  40. Miao M, Sitarz E, Bellingham CM, Won E, Muiznieks LD, Keeley FW. Sequence and domain arrangements influence mechanical properties of elastin-like polymeric elastomers. *Biopolymers*. [Research Support, Non-U.S. Gov't]. 2013 Jun;99(6):392-407.
  41. Pellicoro A, Ramachandran P, Iredale JP. Reversibility of liver fibrosis. *Fibrogenesis Tissue Repair*. 2012;5(Suppl 1):S26.
  42. Pellicoro A, Aucott RL, Ramachandran P, Robson AJ, Fallowfield JA, Snowdon VK, et al. Elastin accumulation is regulated at the level of degradation by macrophage metalloelastase (MMP-12) during experimental liver fibrosis. *Hepatology*. 2012 Jun;55(6):1965-75.
  43. Kinnman N, Housset C. Peribiliary myofibroblasts in biliary type liver fibrosis. *Front Biosci*. [Research Support, Non-U.S. Gov't Review]. 2002 Feb 1;7:d496-503.
  44. Martinez-Noguera A, Montserrat E, Torrubia S, Villalba J. Doppler in hepatic cirrhosis and chronic hepatitis. *Semin Ultrasound CT MR*. [Review]. 2002 Feb;23(1):19-36.
  45. Di Lelio A, Cestari C, Lomazzi A, Beretta L. Cirrhosis: diagnosis with sonographic study of the liver surface. *Radiology*. 1989 Aug;172(2):389-92.
  46. Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. *J Ultrasound Med*. [Review]. 2002 Sep;21(9):1023-32; quiz 33-4.
  47. Awaya H, Mitchell DG, Kamishima T, Holland G, Ito K, Matsumoto T. Cirrhosis: modified caudate-right lobe ratio. *Radiology*. [Comparative Study]. 2002 Sep;224(3):769-74.
  48. Albrecht T, Blomley MJ, Cosgrove DO, Taylor-Robin-

- son SD, Jayaram V, Eckersley R, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. *Lancet*. [Comparative Study Research Support, Non-U.S. Gov't]. 1999 May 8;353(9164):1579-83.
49. Blomley MJ, Lim AK, Harvey CJ, Patel N, Eckersley RJ, Basilio R, et al. Liver microbubble transit time compared with histology and Child-Pugh score in diffuse liver disease: a cross sectional study. *Gut*. [Comparative Study Research Support, Non-U.S. Gov't]. 2003 Aug;52(8):1188-93.
  50. Kim CK, Lim JH, Lee WJ. Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver: accuracy of ultrasonography in transplant patients. *J Ultrasound Med*. [Evaluation Study]. 2001 Feb;20(2):99-104.
  51. Burrell M, Llovet JM, Ayuso C, Iglesias C, Sala M, Miquel R, et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. *Hepatology*. [Research Support, Non-U.S. Gov't]. 2003 Oct;38(4):1034-42.
  52. Bonkovsky HL, Rubin RB, Cable EE, Davidoff A, Rijcken TH, Stark DD. Hepatic iron concentration: noninvasive estimation by means of MR imaging techniques. *Radiology*. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1999 Jul;212(1):227-34.
  53. Lieber CS, Weiss DG, Morgan TR, Paronetto F. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. *Am J Gastroenterol*. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. 2006 Jul;101(7):1500-8.
  54. Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. *Hepatology*. [Comparative Study Validation Study]. 2005 Jun;41(6):1376-82.
  55. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2003 Aug;38(2):518-26.
  56. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*. [Meta-Analysis Research Support, Non-U.S. Gov't Review]. 2011 Mar;53(3):726-36.
  57. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology*. 2007 Jul;46(1):32-6.
  58. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. [Comparative Study Research Support, N.I.H., Extramural]. 2006 Jun;43(6):1317-25.
  59. Suh B, Yun JM, Park S, Shin DW, Lee TH, Yang HK, et al. Prediction of future hepatocellular carcinoma incidence in moderate to heavy alcohol drinkers with the FIB-4 liver fibrosis index. *Cancer*. [Research Support, Non-U.S. Gov't]. 2015 Nov 1;121(21):3818-25.
  60. Salkic NN, Jovanovic P, Hauser G, Brcic M. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. *Am J Gastroenterol*. [Meta-Analysis Review]. 2014 Jun;109(6):796-809.
  61. Halfon P, Bourliere M, Deydier R, Botta-Fridlund D, Renou C, Tran A, et al. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. *Am J Gastroenterol*. [Comparative Study Multicenter Study]. 2006 Mar;101(3):547-55.
  62. Myers RP, De Torres M, Imbert-Bismut F, Ratziu V, Charlotte F, Poynard T. Biochemical markers of fibrosis in patients with chronic hepatitis C: a comparison with prothrombin time, platelet count, and age-platelet index. *Dig Dis Sci*. [Comparative Study Research Support, Non-U.S. Gov't]. 2003 Jan;48(1):146-53.
  63. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. [Comparative Study]. 2005 Feb;128(2):343-50.
  64. Kelleher TB, Mehta SH, Bhaskar R, Sulkowski M, Assemborski J, Thomas DL, et al. Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: the SHASTA index. *J Hepatol*. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. 2005 Jul;43(1):78-84.
  65. Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. *Scand J Gastroenterol*. [Comparative Study]. 2005 Jul;40(7):867-72.
  66. Schiavon LL, Schiavon JL, Filho RJ, Sampaio JP, Lanzoni VP, Silva AE, et al. Simple blood tests as noninvasive markers of liver fibrosis in hemodialysis patients with chronic hepatitis C virus infection. *Hepatology*. [Research Support, Non-U.S. Gov't]. 2007 Aug;46(2):307-14.
  67. Singal AG, Thomassen LV, Gretch DR, Shuhart MC. Use of the AST to platelet ratio index in HCV/HIV co-infected patients. *Aliment Pharmacol Ther*. [Research Support, N.I.H., Extramural]. 2011 Mar;33(5):566-77.
  68. Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwittaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2013 Oct;145(4):782-9 e4.
  69. Myers RP, Benhamou Y, Imbert-Bismut F, Thibault V, Bochet M, Charlotte F, et al. Serum biochemical markers accurately predict liver fibrosis in HIV and hepatitis C virus co-infected patients. *Aids*. [Research Support, Non-U.S. Gov't]. 2003 Mar 28;17(5):721-5.
  70. Rossi E, Adams L, Prins A, Bulsara M, de Boer B, Garas G, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients.

- Clin Chem. [Research Support, Non-U.S. Gov't Validation Study]. 2003 Mar;49(3):450-4.
71. Adams LA, Bulsara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem. [Comparative Study Research Support, Non-U.S. Gov't Validation Study]. 2005 Oct;51(10):1867-73.
  72. Becker L, Salameh W, Sferruzza A, Zhang K, ng Chen R, Malik R, et al. Validation of hepascore, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. Clin Gastroenterol Hepatol. [Comparative Study Research Support, Non-U.S. Gov't Validation Study]. 2009 Jun;7(6):696-701.
  73. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol. [Comparative Study]. 1998 Jan;93(1):44-8.
  74. Imperiale TF, Said AT, Cummings OW, Born LJ. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. Am J Gastroenterol. [Comparative Study]. 2000 Sep;95(9):2328-32.
  75. Reedy DW, Loo AT, Levine RA. AST/ALT ratio > or = 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. Dig Dis Sci. [Research Support, Non-U.S. Gov't]. 1998 Sep;43(9):2156-9.
  76. Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med. [Validation Study]. 2003 Jan 27;163(2):218-24.
  77. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. [Validation Study]. 2007 Apr;45(4):846-54.
  78. Poynard T, Aubert A, Bedossa P, Abella A, Naveau S, Paraf F, et al. A simple biological index for detection of alcoholic liver disease in drinkers. Gastroenterology. 1991 May;100(5 Pt 1):1397-402.
  79. Oberti F, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Aube C, et al. Noninvasive diagnosis of hepatic fibrosis or cirrhosis. Gastroenterology. [Research Support, Non-U.S. Gov't]. 1997 Nov;113(5):1609-16.
  80. Koda M, Matunaga Y, Kawakami M, Kishimoto Y, Suou T, Murawaki Y. FibroIndex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. Hepatology. [Validation Study]. 2007 Feb;45(2):297-306.
  81. Fornis X, Ampurdanes S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology. 2002 Oct;36(4 Pt 1):986-92.
  82. Cales P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konate A, et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology. [Research Support, Non-U.S. Gov't]. 2005 Dec;42(6):1373-81.
  83. Leroy V, Hilleret MN, Sturm N, Trocme C, Renversez JC, Faure P, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. J Hepatol. [Comparative Study Research Support, Non-U.S. Gov't]. 2007 May;46(5):775-82.
  84. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut. [Multicenter Study Validation Study]. 2008 Oct;57(10):1441-7.
  85. Patel K, Gordon SC, Jacobson I, Hezode C, Oh E, Smith KM, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol. [Evaluation Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Validation Study]. 2004 Dec;41(6):935-42.
  86. Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology. [Clinical Trial Research Support, Non-U.S. Gov't]. 2004 Dec;127(6):1704-13.
  87. Guibal A, Boularan C, Bruce M, Vallin M, Pilleul F, Walter T, et al. Evaluation of shearwave elastography for the characterisation of focal liver lesions on ultrasound. Eur Radiol. 2013 Apr;23(4):1138-49.
  88. Ronot M, Di Renzo S, Gregoli B, Duran R, Castera L, Van Beers BE, et al. Characterization of fortuitously discovered focal liver lesions: additional information provided by shearwave elastography. Eur Radiol. 2015 Feb;25(2):346-58.
  89. Heide R, Strobel D, Bernatik T, Goertz RS. Characterization of focal liver lesions (FLL) with acoustic radiation force impulse (ARFI) elastometry. Ultraschall Med. 2010 Aug;31(4):405-9.
  90. Ying L, Lin X, Xie ZL, Tang FY, Hu YP, Shi KQ. Clinical utility of acoustic radiation force impulse imaging for identification of malignant liver lesions: a meta-analysis. Eur Radiol. [Meta-Analysis]. 2012 Dec;22(12):2798-805.
  91. Marginean CO, Marginean C. Elastographic assessment of liver fibrosis in children: A prospective single center experience. Eur J Radiol. [Research Support, Non-U.S. Gov't]. 2012 Aug;81(8):e870-4.
  92. Sporea I, Sirli R, Popescu A, Bota S, Badea R, Lupsor M, et al. Is it better to use two elastographic methods for liver fibrosis assessment? World journal of gastroenterology. 2011 Sep 7;17(33):3824-9.
  93. Bota S, Sporea I, Sirli R, Popescu A, Danila M, Sendroiu M. Factors that influence the correlation of acoustic radiation force impulse (ARFI), elastography with liver fibrosis. Med Ultrason. 2011 Jun;13(2):135-40.
  94. Yoon KT, Lim SM, Park JY, Kim DY, Ahn SH, Han KH, et al. Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography and effect of necroinflammation. Dig Dis Sci. [Comparative Study Research Support, Non-U.S. Gov't]. 2012 Jun;57(6):1682-91.
  95. Nahon P, Kettaneh A, Tengher-Barna I, Zioli M, de Ledinghen V, Douvin C, et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol. [Clinical Trial Validation Study]. 2008 Dec;49(6):1062-8.
  96. Fraquelli M, Rigamonti C, Casazza G, Donato MF, Ron-

- chi G, Conte D, et al. Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C. *J Hepatol. [Clinical Trial]*. 2011 Apr;54(4):621-8.
97. Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J Viral Hepat. [Comparative Study Research Support, Non-U.S. Gov't]*. 2007 May;14(5):360-9.
  98. Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology. [Research Support, Non-U.S. Gov't]*. 2008 Feb;47(2):380-4.
  99. Kuroda H, Takikawa Y, Onodera M, Kakisaka K, Yoshida Y, Kataoka K, et al. Serial changes of liver stiffness measured by acoustic radiation force impulse imaging in acute liver failure: a case report. *J Clin Ultrasound. [Case Reports]*. 2012 Feb;40(2):99-104.
  100. Wong VW, Vergniol J, Wong GL, Foucher J, Chan AW, Chermak F, et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol. [Multicenter Study Research Support, Non-U.S. Gov't]*. 2012 Dec;107(12):1862-71.
  101. de Ledinghen V, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan(R). *J Hepatol. [Comparative Study Evaluation Study Research Support, Non-U.S. Gov't]*. 2012 Apr;56(4):833-9.
  102. de Ledinghen V, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. *Liver Int. [Comparative Study Evaluation Study Research Support, Non-U.S. Gov't]*. 2012 Jul;32(6):911-8.
  103. Popescu A, Bota S, Sporea I, Sirlu R, Danila M, Racean S, et al. The influence of food intake on liver stiffness values assessed by acoustic radiation force impulse elastography-preliminary results. *Ultrasound Med Biol*. 2013 Apr;39(4):579-84.
  104. Goldschmidt I, Streckenbach C, Dingemann C, Pfister ED, di Nanni A, Zapf A, et al. Application and limitations of transient liver elastography in children. *J Pediatr Gastroenterol Nutr. [Comparative Study Research Support, Non-U.S. Gov't]*. 2013 Jul;57(1):109-13.
  105. Berzigotti A, De Gottardi A, Vukotic R, Siramolpiwat S, Abraldes JG, Garcia-Pagan JC, et al. Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension. *PLoS One. [Clinical Trial Research Support, Non-U.S. Gov't]*. 2013;8(3):e58742.
  106. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging. [Research Support, U.S. Gov't, P.H.S.]*. 1991 Apr;13(2):111-34.
  107. Parker KJ, Huang SR, Musulin RA, Lerner RM. Tissue response to mechanical vibrations for "sonoelasticity imaging". *Ultrasound Med Biol. [Research Support, U.S. Gov't, P.H.S.]*. 1990;16(3):241-6.
  108. Parker KJ, Doyley MM, Rubens DJ. Imaging the elastic properties of tissue: the 20 year perspective. *Phys Med Biol. [Historical Article Research Support, N.I.H., Extramural Review]*. 2011 Jan 7;56(1):R1-R29.
  109. Bavu E, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. *Ultrasound Med Biol*. 2011 Sep;37(9):1361-73.
  110. Muller M, Gennisson JL, Deffieux T, Tanter M, Fink M. Quantitative viscoelasticity mapping of human liver using supersonic shear imaging: preliminary in vivo feasibility study. *Ultrasound Med Biol. [Clinical Trial]*. 2009 Feb;35(2):219-29.
  111. Dietrich CF, Cantisani V. Current status and perspectives of elastography. *Eur J Radiol. [Editorial Introductory]*. 2014 Mar;83(3):403-4.
  112. Nightingale K, Bentley R, Trahey G. Observations of tissue response to acoustic radiation force: opportunities for imaging. *Ultrason Imaging. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]*. 2002 Jul;24(3):129-38.
  113. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am. [Research Support, U.S. Gov't, Non-P.H.S.]*. 2001 Jul;110(1):625-34.
  114. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). *J Hepatol. [Clinical Trial Comparative Study Multicenter Study Research Support, Non-U.S. Gov't]*. 2010 Dec;53(6):1013-21.
  115. Lupsor M, Badea R, Stefanescu H, Grigorescu M, Sparchez Z, Serban A, et al. Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. *J Gastrointest Liver Dis. [Comparative Study Research Support, Non-U.S. Gov't]*. 2008 Jun;17(2):155-63.
  116. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med. [Consensus Development Conference Practice Guideline Research Support, Non-U.S. Gov't]*. 2013 Apr;34(2):169-84.
  117. Rousselet MC, Michalak S, Dupre F, Croue A, Bedossa P, Saint-Andre JP, et al. Sources of variability in histological scoring of chronic viral hepatitis. *Hepatology*. 2005 Feb;41(2):257-64.
  118. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pylsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002 Oct;97(10):2614-8.
  119. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003 Dec;38(6):1449-57.
  120. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology. [Clinical Trial]*. 2005 Jun;128(7):1898-906.
  121. Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. *Arch Intern Med. [Research Support, U.S. Gov't, P.H.S.]*. 1979 Jun;139(6):667-9.
  122. Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J*

- Med. [Review]. 2001 Feb 15;344(7):495-500.
123. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1981 Sep-Oct;1(5):431-5.
  124. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*. [Research Support, Non-U.S. Gov't]. 1994 Jul;20(1 Pt 1):15-20.
  125. Robic MA, Procopet B, Metivier S, Peron JM, Selves J, Vinel JP, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J Hepatol*. [Comparative Study]. 2011 Nov;55(5):1017-24.
  126. Udell JA, Wang CS, Tinmouth J, FitzGerald JM, Ayas NT, Simel DL, et al. Does this patient with liver disease have cirrhosis? *Jama*. [Case Reports Meta-Analysis Research Support, Non-U.S. Gov't]. 2012 Feb 22;307(8):832-42.
  127. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology*. [Research Support, Non-U.S. Gov't]. 1987 Jan-Feb;7(1):122-8.
  128. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology*. [Multicenter Study Research Support, N.I.H., Extramural]. 2012 Dec;56(6):2328-35.
  129. Ferlitsch M, Reiberger T, Hoke M, Salzl P, Schwengerer B, Ulbrich G, et al. von Willebrand factor as new noninvasive predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis. *Hepatology*. [Comparative Study Research Support, Non-U.S. Gov't]. 2012 Oct;56(4):1439-47.
  130. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology*. 2010 Oct;139(4):1246-56, 56 e1-5.
  131. Fede G, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, et al. Renal failure and cirrhosis: a systematic review of mortality and prognosis. *J Hepatol*. [Comparative Study Meta-Analysis Review Systematic Review]. 2012 Apr;56(4):810-8.
  132. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology*. [Multicenter Study Research Support, Non-U.S. Gov't]. 2003 Jan;37(1):192-7.
  133. Fallon MB. Mechanisms of pulmonary vascular complications of liver disease: hepatopulmonary syndrome. *J Clin Gastroenterol*. [Review]. 2005 Apr;39(4 Suppl 2):S138-42.
  134. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology*. 2010 May;51(5):1675-82.
  135. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. [Evaluation Study Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2007 Aug;133(2):481-8.
  136. Blendis L, Wong F. Portopulmonary hypertension: an increasingly important complication of cirrhosis. *Gastroenterology*. 2003 Aug;125(2):622-4.
  137. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med*. 2012 Jun 19;156(12):841-7, W295.
  138. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *Jama*. [Multicenter Study Research Support, Non-U.S. Gov't]. 2012 Dec 26;308(24):2584-93.
  139. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology*. [Randomized Controlled Trial]. 2012 Nov;143(5):1253-60 e4.
  140. Iredale JP. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. *J Clin Invest*. [Research Support, Non-U.S. Gov't Review]. 2007 Mar;117(3):539-48.
  141. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol*. 2001 Sep;35(3):421-30.
  142. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. [Research Support, Non-U.S. Gov't Review]. 2003 Dec 6;362(9399):1907-17.
  143. Sherman M, Klein A. AASLD single-topic research conference on hepatocellular carcinoma: Conference proceedings. *Hepatology*. [Congress]. 2004 Dec;40(6):1465-73.
  144. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. [Review]. 2004 Nov;127(5 Suppl 1):S35-50.
  145. Sinniah R. Occurrence of mesangial IgA and IgM deposits in a control necropsy population. *J Clin Pathol*. [Research Support, Non-U.S. Gov't]. 1983 Mar;36(3):276-9.
  146. Fabrizi F, Lunghi G, Messa P, Martin P. Therapy of hepatitis C virus-associated glomerulonephritis: current approaches. *J Nephrol*. [Meta-Analysis Research Support, Non-U.S. Gov't Review]. 2008 Nov-Dec;21(6):813-25.
  147. Eshraghian A, Taghavi SA. Systematic review: endocrine abnormalities in patients with liver cirrhosis. *Arch Iran Med*. [Review Systematic Review]. 2014 Oct;17(10):713-21.
  148. 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*. [Review Systematic Review]. 2006 Jan;44(1):217-31.
  149. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general

- population: a population-based cohort study. *Liver Int.* [Comparative Study Research Support, Non-U.S. Gov't]. 2012 Jan;32(1):79-84.
150. Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin Gastroenterol Hepatol.* [Research Support, Non-U.S. Gov't]. 2006 Nov;4(11):1385-94.
  151. Krag A, Wiest R, Albillos A, Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of beta-blockers improve survival of patients with cirrhosis during a window in the disease. *Gut.* [Research Support, Non-U.S. Gov't]. 2012 Jul;61(7):967-9.
  152. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol.* [Comparative Study]. 2008 Dec;6(12):1418-24.
  153. Veldt BJ, Laine F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol.* [Research Support, Non-U.S. Gov't]. 2002 Jan;36(1):93-8.
  154. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. *Hepatology.* [Review]. 2010 Apr;51(4):1445-9.
  155. Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology.* [Comparative Study Research Support, Non-U.S. Gov't]. 1987 Jul-Aug;7(4):660-4.
  156. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology.* 2003 Jan;124(1):91-6.
  157. Asrani SK, Kamath PS. Natural history of cirrhosis. *Curr Gastroenterol Rep.* [Review]. 2013 Feb;15(2):308.
  158. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clin Nutr.* [Consensus Development Conference Practice Guideline]. 2006 Apr;25(2):285-94.
  159. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. *Hepatology.* [Comparative Study Randomized Controlled Trial]. 2008 Aug;48(2):557-66.
  160. Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology.* [Research Support, Non-U.S. Gov't]. 1988 Feb;94(2):482-7.
  161. Krag A, Bendtsen F, Henriksen JH, Moller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut.* [Research Support, Non-U.S. Gov't]. 2010 Jan;59(1):105-10.
  162. Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. *J Hepatol.* [Review]. 2014 Mar;60(3):643-53.
  163. Lebrech D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med.* [Clinical Trial Randomized Controlled Trial]. 1981 Dec 3;305(23):1371-4.
  164. Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med.* [Clinical Trial Randomized Controlled Trial]. 1987 Oct 1;317(14):856-61.
  165. Serste T, Francoz C, Durand F, Rautou PE, Melot C, Valla D, et al. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol.* [Clinical Trial]. 2011 Oct;55(4):794-9.
  166. Serste T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology.* [Research Support, Non-U.S. Gov't]. 2010 Sep;52(3):1017-22.
  167. Serste T, Njimi H, Degre D, Deltenre P, Schreiber J, Lepida A, et al. The use of beta-blockers is associated with the occurrence of acute kidney injury in severe alcoholic hepatitis. *Liver Int.* [Comparative Study Research Support, Non-U.S. Gov't]. 2015 Aug;35(8):1974-82.
  168. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* [Research Support, Non-U.S. Gov't]. 2015 Sep;63(3):743-52.
  169. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol.* [Lecture]. 2002;40(1):3-20.
  170. Spahr L, Coeytaux A, Giostra E, Hadengue A, Annoni JM. Histamine H1 blocker hydroxyzine improves sleep in patients with cirrhosis and minimal hepatic encephalopathy: a randomized controlled pilot trial. *Am J Gastroenterol.* [Randomized Controlled Trial]. 2007 Apr;102(4):744-53.
  171. Grabau CM, Crago SF, Hoff LK, Simon JA, Melton CA, Ott BJ, et al. Performance standards for therapeutic abdominal paracentesis. *Hepatology.* 2004 Aug;40(2):484-8.
  172. Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. *Am J Gastroenterol.* [Multicenter Study]. 2014 Sep;109(9):1436-42.
  173. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg.* 2005 Aug;242(2):244-51.
  174. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. *Ann Surg.* 1968 Sep;168(3):392-415.
  175. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med.* [Case Reports]. 1990 May 24;322(21):1505-7.
  176. Broelsch CE, Frilling A, Testa G, Malago M. Living donor liver transplantation in adults. *Eur J Gastroenterol*



- Hepatol. [Comment Review]. 2003 Jan;15(1):3-6.
177. de Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. *Oncologist*. [Review]. 2007 Nov;12(11):1321-31.
178. Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. *Liver Transpl*. 2004 Jan;10(1):7-15.
179. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2002 Apr;122(4):889-96.
180. Boyarsky BJ, Durand CM, Palella FJ, Jr, Segev DL. Challenges and Clinical Decision-Making in HIV-to-HIV Transplantation: Insights From the HIV Literature. *Am J Transplant*. [Review]. 2015 Aug;15(8):2023-30.