



## Getting Ahead of Nonalcoholic Steatohepatitis (NASH)

### REFERENCES

1. Lonardo A. Back to the future: From the history of NAFLD to NAFLD to heterogeneity of disease. *Clin Transl Discov.* 2021;1(1):e9.
2. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology.* 2023;29(1):101133.
3. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology.* 2023;77(5):1797-1835.
4. 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: Co-Sponsored by the American Association for the Study of Liver Disease (AASLD). *Endocr Pract.* 2022;28(5):528-562.
5. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: Expert review. *Gastroenterology.* 2023;165:1080-1088.
6. Younossi ZM, Loomba R, Anstee QM, et al. Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. *Hepatology.* 2018;68(1):349-360.
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. *Circulation.* 2005;112:e285-e290.
8. Le MH, Devaki P, Ha NB, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. *PLoS One.* 2017;12(3):e0173499.
9. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology.* 2018;67(1):123-133.
10. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64(1):73-84.
11. Browning J, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. *Hepatology.* 2004;40(6):1387-1395.
12. Kanwal F, Kramer JR, Duan Z, Yu X, White D, El-Serag HB. Trends in the burden of nonalcoholic fatty liver disease in a United States cohort of veterans. *Clin Gastroenterol Hepatol.* 2016;14(2):301-8.e1-2.
13. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med.* 2021;385(17):1559-1569.
14. Tapper EB, Krieger N, Przybysz R, et al. The burden of nonalcoholic steatohepatitis in the United States. *BMC Gastroenterol.* 2023;23:109.
15. Stengel JZ, Harrison SA. Nonalcoholic steatohepatitis: Clinical presentation, diagnosis, and treatment. *Gastroenterol Hepatol (NY).* 2006;2(6):440-449.
16. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology.* 1994;107(4):1103-1109.



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17. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol*. 2020;5(4):362-373.
18. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology*. 2017;65(5):1557-1565.
19. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13(4):643-654.
20. Jinjuvadia R, Antaki F, Lohia P, Liangpunsakul S. The association between nonalcoholic fatty liver disease and metabolic abnormalities in the United States population. *J Clin Gastroenterol*. 2017;51(2):160-166.
21. Kanwal F, Kramer JR, Li L, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. *Hepatology*. 2020;71(3):808-819.
22. Lomonaco R, Leiva EG, Bril F, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. *Diabetes Care*. 2021;44(2):399-406.
23. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801.
24. Paik JM, Henry L, de Avila L, Younossi E, Racila A, Younossi ZM. Mortality related to nonalcoholic fatty liver disease is increasing in the United States. *Hepatol Commun*. 2019;3(11):1459-1471.
25. Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). *Medicine (Baltimore)*. 2018;97(13):e0214.
26. Duell PB, Welty FK, Miller M, et al. Nonalcoholic fatty liver disease and cardiovascular risk: A scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42(6):e168-e185.
27. Koutoukidis DA, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179:1262-1271.
28. Patel NS, Doycheva I, Peterson MR, et al. Effect of weight loss on magnetic resonance imaging estimation of liver fat and volume in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2015;13:561-568.
29. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149:367-378.
30. Patel NS, Hooker J, Gonzalez M, et al. Weight loss decreases magnetic resonance elastography estimated liver stiffness in nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2017;15:463-464.
31. Kim NH, Kim JH, Kim YJ, et al. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. *Liver Int*. 2014;34(4):604-611.
32. Hamabe A, Uto H, Imamura Y, et al. Impact of cigarette smoking on onset of nonalcoholic fatty liver disease over a 10-year period. *J Gastroenterol*. 2011;46(6):769-778.
33. Huh Y, Cho YJ, Nam GE. Recent epidemiology and risk factors of nonalcoholic fatty liver disease. *J Obes Metab Syndr*. 2022;31(1):17-27.



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34. Speliotes EK, Massaro JM, Hoffmann U, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. *Hepatology*. 2010;51(6):1979-1987.
35. Jarvis H, Craig D, Barker R, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. *PLoS Med*. 2020;17(4):e1003100.
36. Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. *Obes Rev*. 2016;17(6):510-519.
37. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. 2008;371(9615):838-851.
38. Alexander M, Loomis AK, van der Lei J, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. *BMC Medicine*. 2019;17(95).
39. Caussy C, Soni M, Cui J, et al. Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis. *J Clin Invest*. 2017;127(7):2697-2704.
40. Di Mauro S, Scamporrino A, Filippello A, et al. Clinical and molecular biomarkers for diagnosis and staffing of NAFLD. *Int J Mol Sci*. 2021;22(21):11905.
41. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2021;161(5):1657-1669.
42. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: a systematic review. *Liver Int*. 2021;41(2):261-270.
43. Shah AG, Lydecker A, Murray K, et al. Use of the FIB4 index for non-invasive evaluation of fibrosis in non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009;7(10):1104-1112.
44. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol*. 2016;65(3):570-578.
45. Sanyal AJ, Castera L, Wong VWS. Noninvasive assessment of liver fibrosis in NAFLD. *Clin Gastroenterol Hepatol*. 2023;21:2026-2039.
46. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6:33.
47. Fedchuk L, Nascimbeni F, Pais R, et al. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2014;40:1209-1222.
48. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterology*. 2009;137:865-872.
49. Poynard T, Ratziu V, Naveau S, et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. *Comp Hepatol*. 2005;4:10.
50. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. *Hepatology*. 2011;54:1082-1090.
51. Boyd A, Cain O, Chauhan A, Webb GJ. Medical liver biopsy: background, indications, procedure and histopathology. *Frontline Gastroenterol*. 2020;11(1):40-47.
52. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol*. 2014;20(2):475-485.
53. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol*. 1998;93:44-48.



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54. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: A systematic review. *Hepatology*. 2007;46:912–921.
55. Treeprasertsuk S, Björnsson E, Enders F, Suwanwalaikorn S, Lindor KD. NAFLD fibrosis score: a prognostic predictor for mortality and liver complications among NAFLD patients. *World J Gastroenterol*. 2013;19(8):1219-1229.
56. Nielsen MJ, Leeming DJ, Goodman Z, et al. Comparison of ADAPT, FiB-4 and APRI as non-invasive predictors of liver fibrosis and NASH within the CENTAUR screening population. *J Hepatol*. 2021;75(6):1292-1300.
57. Gudowska M, Gruszewska E, Panasiuk A, et al. Hyaluronic acid concentration in liver diseases. *Clin Exp Med*. 2016;16(4):523-528.
58. Rosenberg WMC, Voelker M, Theil R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology*. 2004;127:1704-1713.
59. Poynard T, Lebray P, Ingiliz P, et al. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). *BMC Gastroenterol*. 2010;10:40.
60. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24(7):908-922.
61. Nguyen TAT, Sanyal AJ. Pathophysiology guided treatment of nonalcoholic steatohepatitis. *J Gastroenterol Hepatol*. 2012;Suppl 2:58-64.
62. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendl RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes*. 2005;54(3):603-608.
63. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. 2012;57(1):157-166.
64. Idalsoaga F, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic fatty liver disease and alcohol-related liver disease: two intertwined entities. *Front Med (Lausanne)*. 2020;7:448.
65. Ekstedt M, Franzen LE, Holmqvist M, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol*. 2009;44(3):366-374.
66. Sharma M, Premkumar M, Kulkarni AV, Kumar P, Reddy DN, Rao NP. Drugs for non-alcoholic steatohepatitis (NASH): Quest for the Holy Grail. *J Clin Transl Hepatol*. 2021;9(1):40-50.
67. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679-690.
68. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124.
69. Gastaldelli A, Cusi K, Lando LF, Bray R, Brouwers B, Rodriguez A. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406.
70. Petit JM, Cercueil JP, Loffroy R, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: The Lira-NAFLD study. *J Clin Endocrinol Metab*. 2017;102(2):407-415.
71. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomize controlled trial (D-LIFT trial). *Diabetologia*. 2020;63(11):2434-2445.



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72. Flint A, Andersen G, Hockings P, et al. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. *Aliment Pharmacol Ther.* 2021;54(9):1150-1161.
73. Newsome PN, Buchholtz K, Cusi K, et al; for NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384(12):1113-1124.
74. Hartman ML, Sanyal AJ, Loomba R, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. *Diabetes Care.* 2020;43(6):1352-1355.
75. Qiao P, Jia Y, Ma A, et al. Dapagliflozin protects against nonalcoholic steatohepatitis in db/db mice. *Front Pharmacol.* 2022;13:934136.
76. Zhang Y, Liu X, Zhang H, Wang X. Efficacy and safety of empagliflozin on nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2022;13:836455.
77. Itani T, Ishihara T. Efficacy of canagliflozin against nonalcoholic fatty liver disease: a prospective cohort study. *Obes Sci Pract.* 2018;4(5):477-482.
78. Phruksotsai S, Pinyopornpanish K, Euathrongchit J, et al. The effects of dapagliflozin on hepatic and visceral fat in type 2 diabetes patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol.* 2021;36(10):2952-2959.
79. Kahl S, Gancheva S, Straburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: A randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care.* 2020;43(2):298-305.
80. Inoue M, Hayashi A, Taguchi T, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease. *J Diabetes Investig.* 2019;10(4):1004-1011.
81. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet.* 2019;394(10215):2184-2196.
82. Rowe IA, Wong VWS, Loomba R. Treatment candidacy for pharmacologic therapies for NASH. *Clin Gastroenterol Hepatol.* 2022;20(6):1209-1217.
83. Molla A, Motohashi K, Marjot T, et al. A multidisciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health. *Frontline Gastroenterol.* 2019;10(4):337-346.
84. Porayko MK, Articolo A, Cerenzia W, Coleman B, Patel D, Stacy S. Differences in NAFLD/NASH management by provider specialty: opportunities for optimizing multidisciplinary care. *J Multidisciplin Healthc.* 2022;15:1533-1545.
85. Lazarus JV, Anstee QM, Hagstrom H, et al. Defining comprehensive models of care for NAFLD. *Nat Rev Gastroenterol Hepatol.* 2021;18(10):717-729.