The Burden of NAFLD Worldwide

2

Zobair Younossi and Linda Henry

2.1 Background

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the most common cause of chronic liver disease and is now among the top causes of cirrhosis, hepatocellular carcinoma (HCC), and indications for liver transplantation in United States and probably the rest of the world [1, 2]. However, NAFLD is not a single disease but rather a spectrum of clinico-pathologic liver diseases that include nonalcoholic fatty liver (NAFL or simple steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis, and its complications [3]. Furthermore, NAFLD is considered the hepatic manifestation of metabolic syndrome since most NAFLD patients have visceral adiposity, insulin resistance, and/or type 2 diabetes mellitus, hypertension, hypercholesteremia, and hypertriglycemia. In fact, the more components of metabolic syndrome are present in patients with NAFLD, the higher the risk of advanced fibrosis and liver-related mortality [1–4].

Z. Younossi (✉)
Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, USA

Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA
e-mail: zobair.younossi@inova.org

L. Henry
Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA

Center for Outcomes Research in Liver Diseases, Washington, DC, USA

E. Bugianesi (ed.), *Non-Alcoholic Fatty Liver Disease*,
https://doi.org/10.1007/978-3-319-95828-6_2

2.2 Global and Regional Prevalence of NAFLD and NASH

Currently, 25% of the world is thought to have NAFLD with the highest prevalence being reported from the Middle East and South America (31.79% and 30.45%, respectively) and the lowest from Africa (13.48%) [4]. The prevalence of NAFLD in North America, Europe, and Asia has been reported as 24.13%, 23.71%, and 27.37%, respectively. Other histologic-based studies from Europe have suggested a NAFLD prevalence of approximately 20% while in Asia NAFLD prevalence is thought to range from 19 to 23% [3, 4].

Among patients with type 2 diabetes, the prevalence of NAFLD is higher at 57.80% [5]. Furthermore, among the morbidly obese, NAFLD prevalence has been found to be 95% [6].

Since diagnosis of NASH is based on histology, true prevalence rates for NASH in the general population is not known. On the other hand, estimated prevalence rates for NASH in the general population is considered to range from 1.5 to 6.45% [4]. In contrast, the prevalence of NASH in patients with type 2 diabetes is higher. A recent meta-analysis suggested that the overall prevalence of NASH among biopsied diabetics is 65.26% with 15.05% of these patients having advanced fibrosis (fibrosis $\geq$ F3) [5]. Finally, the prevalence of NAFLD among very obese individuals undergoing bariatric surgery is over 95%, while 20–50% of them have NASH and about 10% have advanced fibrosis [6].

As the rates of obesity, type 2 diabetes mellitus, and insulin resistance increase among an aging population, so does the prevalence of NAFLD. Several recent global modeling analyses based on changes in adult obesity and DM in the United States have determined that the prevalence of NAFLD is set to grow exponentially over the next decade [7–9]. Similar rates are being reported from other regions of the world. In Saudi Arabia, there is projected to be 12,534,000 NAFLD cases, while for the United Arab Emirates there are projected to be approximately 372,000 cases [9]. As a result, the prevalent cases of compensated cirrhosis and advanced liver disease are projected to at least double by 2030, while an annual liver-related mortality is projected to be an annual 4800 deaths in Saudi Arabia and 140 deaths in UAE [9]. When modeling NAFLD for Asia and Europe, researchers determined that dependent on the rate of increase for obesity and diabetes, there could be a 0–30% increase in total NAFLD cases between 2016 and 2030 [8]. Due to urbanization, China is expected to experience the highest increase in NAFLD cases, incident cases of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and death. Within the European countries, Germany is expected to experience the highest increase in NASH and HCC cases by 2030, while France is projected to have the most cases of compensated and decompensated cirrhosis by 2030 [8].

2.3 Natural History of NAFLD

The data about the natural history studies of NAFLD comes from several lines of evidence. Initial studies were histologic cohorts from tertiary care centers with mortality data [9–11]. Most of these studies and their meta-analytic summaries suggested that patients with histologic NASH were predominantly progressive [12–14]. Subgroup analysis suggested that presence of type 2 diabetes and advanced histologic fibrosis at baseline predicted mortality [15, 16]. The second line of evidence also comes from tertiary care centers where repeated liver biopsies were performed during clinical follow-ups [17, 18]. These studies also suggested that patients with NASH can show progression of fibrosis [17, 18]. Furthermore, they observed that some patients whose initial liver biopsies were not consistent with NASH also progressed [17, 18]. Furthermore, some patients showed regression of fibrosis regardless of the initial histology [1, 18]. The third line of evidence comes from placebo arms of clinical trials of NASH with sequential protocol biopsies [19]. These data provide a much more dynamic picture. In fact, some patients with NASH and fibrosis progress while others regress [19]. The exact reasons for these fluctuating patterns of progression and regressions are not known. The latest evidence supporting the progressiveness of NAFLD is related to the observation that most patients with cryptogenic cirrhosis have the profile of patients with NASH and have a high recurrence of NASH post liver transplantation [20, 21]. Although this has created some controversy [22], a recent biopsy-based data confirmed that most of these patients do have the clinical profile of patients with NAFLD [23].

Although these data suggest that the exact course of a patient with NAFLD can vary and fluctuate, one can draw some generality about the natural history of NAFLD. In this context, the histologic subtype of NAFLD that can be classified as NASH is associated with highest risk for progressive liver disease [17, 18]. In fact, the risk becomes higher in those with significant hepatic fibrosis [12, 24–27]. In this context about 20–30% of patients with NAFLD will have NASH and of these 10–15% can progress to cirrhosis. As noted previously, those with increasing number of metabolic comorbidities, especially type 2 diabetes mellitus, are at the highest risk of progression [3, 5, 12, 26]. In contrast, those with early NASH and individuals with non-NASH NAFLD more commonly die of cardiovascular causes and possibly non-HCC cancers [12–15, 27, 28] (Fig. 2.1).

The time line of progression can vary due to underlying risk factors. In general, the average progression from one disease state to another can take up 7.7 years [26]. In studies using paired liver biopsies, researchers found that 30% of patients with NAFL and NASH had progressive fibrosis while 20% had NAFLD regression over 2.2–13.8 years [27]. Nevertheless, some patients may experience faster progression

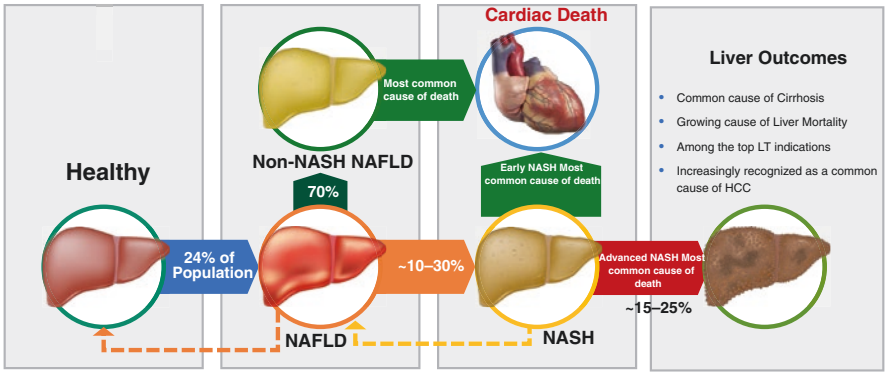

Fig. 2.1 The natural history of NAFLD

rates, especially those with visceral obesity, type 2 diabetes, older age, and possibly Hispanic ethnicity [17, 18, 28]. This last factor may be different based on the country of origin and may be affected by PNALP3 genetic predisposition [29, 30].

2.4 Hepatic Complications of NAFLD

Despite the complexity of the natural history of NAFLD, there is increasing evidence that NAFLD is becoming the most common cause of liver disease [31]. Additionally, data from the United States indicates that NASH-related cirrhosis has doubled over a decade or so [32]. Furthermore, the risk of hepatocellular carcinoma (HCC) related to NAFLD in the United States has increased substantially. In fact, the incidence of HCC among NAFLD patients is estimated to be 0.44 per 1000 person years [17, 18]. In addition, patients with NAFLD fibrosis stages 3 and 4 have almost a seven times higher risk of developing HCC compared to those without significant liver disease [17, 18, 26, 27, 33, 34]. It is interesting to note that presence of metabolic syndrome especially obesity and insulin resistance may hasten development of HCC [35–37].

Obviously, development of cirrhosis, its complications, and HCC lead to increased risk of liver-related mortality. Liver-specific mortality among those with NAFLD has also been reported to be 0.77 per 1000 person years [38, 39]. This rate is almost 10 times higher in patients who develop NASH with a reported rate of 11.77 per 1000 person years [38, 39]. Similarly, the overall mortality per 1000 person years was reported to be 15.44 for those with NAFLD and 25.56 for those with NASH, whereas others have reported that patients with fibrosis stages 3 and 4 had an overall mortality risk three times greater than those without liver disease [34, 38]. An important issue related to NASH-HCC was observed by Surveillance, Epidemiology, and End Results Database (SEERS) study which suggested that, although NAFLD was among the top three causes of HCC, those with NAFLD HCC incurred a higher mortality at 1 year post-diagnosis [35].

As noted previously, for the entire cohort of individuals with NAFLD, cardiovascular mortality remains the most common cause of death [40]. In this context, liver-related death is the third cause of death after cardiac and cancer-related deaths [9]. On the other hand, for patients with NASH and advanced fibrosis, liver-related mortality predominates [23]. Although NAFLD and cardiovascular diseases (CVD) share common comorbidities, the exact reason for high prevalence of CVD in NAFLD patients is not known. Some investigators believe that endothelial dysfunction in patients with NAFLD may be contributing to the increased risk of cardiovascular mortality, but the exact mechanisms have not been clarified [40].

In addition to mortality, listing for liver transplantation is an important outcome for patients with liver disease. In this context, NAFLD/NASH is rapidly becoming a major indication for liver transplantation in the United States [2, 41]. A recent analysis of the United States Scientific Registry of Transplant Recipients (SRTR) from 2012 to 2016 found that NASH was the fastest increasing indication for liver transplantation among those listed positioning NASH to become the most common cause for liver transplantation in the near future [41]. Another analysis of SRTR suggests that NASH-related is the fasting growing indication for HCC listing for liver transplantation in the United States [1]. Given the lack of systematic screening or failure of screening for HCC in these individuals, it is possible that most cases of NASH-related HCC do not get listed for liver transplantation or die while waiting for an organ [42, 43].

2.5 Differences in Outcomes of Western NAFLD from Eastern NAFLD

Although most patients with NAFLD are obese, some are considered lean [44–50]. As previously noted, prevalence of lean NAFLD in the United States is about 7% [50]. In contrast, these rates are higher in some Asian countries. Using region-specific BMI thresholds, the prevalence of lean NAFLD has been reported to be 20% in India, 15.2% in Japan, 15% in China, 12% in Greece, 12.6% South Korea, and Iceland [44–49].

Although lean NAFLD is metabolically less abnormal than obese and overweight NAFLD, they still have higher rates of insulin resistance and diabetes than lean controls without NAFLD [50]. In a study of lean Korean NAFLD patients, there was an increased prevalence of hypertriglyceridemia, hyperuricemia, insulin resistance, and central obesity but a lower prevalence of diabetes, hypertension, hypertriglyceridemia, low-HDL cholesterol, central obesity, and metabolic syndrome than in other studies of lean NAFLD [48]. Others have found both lean and obese NAFLD have excess abdominal adipose tissue. On the other hand, the exact mechanism by which the genetic and environment factors influence progression of NAFLD lean individuals needs further study [51, 52]. Others have reported using data from a large multicenter, biopsy-proven cohort was that there was an increased overall mortality rate in lean patients compared to those that are overweight or obese with NAFLD

[53]. On the other hand, another study also using biopsy-proven NAFLD over a long-term follow-up of a median of 19.9 years (range 0.4–40 years) representing 12,631 person years found that patients with lean NAFLD were at a higher risk for development of severe liver disease compared to patients with NAFLD and a higher BMI [54]. This finding is especially important as it has been recently found that it is the stage of fibrosis not the presence of NASH that predicts mortality and time to development of severe liver disease [25, 55]. Although still controversial, this study suggests that lean NAFLD patients may have a more aggressive course of NAFLD that may require more close surveillance. However, further study is warranted to determine appropriate timing of surveillance especially as the most accurate non-invasive method to diagnosis NAFLD is still under debate [56].

2.6 Economic Impact of NAFLD and NASH

The economic burden of NAFLD/NASH has recently been assessed using different methodology and projected to be immense [1, 7, 8]. A Markov-based model estimated that in the United States, there are over 64 million people with NAFLD accounting for an annual direct medical cost of about $103 billion ($1613 per patient). Among the four European countries, approximately 52 million people were estimated to have NAFLD with an annual cost of about €35 billion (from €354 to €1163 per patient), while the costs, prevalence, and incident rates were found to be the highest in patients aged 45–65 regardless of the country of origin [57].

In a separate Markov model focusing on NASH and advanced NASH in the USA, investigators determine that, in 2017, there were 5,527,812 adult subjects with NASH in the United States. The life time cost burden of all NASH patients in the United States was estimated to be $82,704,934,702, while the cost of those with advanced NASH was $31,526,708,220. The projections of costs for each age-specific NASH cohort have the potential to increase about 400% in the next 5 years [58].

In addition to the decision analytic models, administrative billing databases can also provide some data about resource utilization related to NAFLD and NASH. In the United States, a number of studies have used the Medicare database (a federally sponsored insurance provided to all citizens 65 years and older and others who meet certain criteria) for resource utilization estimations related to different liver diseases. One such study for patients with NAFLD, investigators found the mean yearly inflation-adjusted outpatient charges for Medicare patients with NAFLD doubled from 2005 to 2010 ($2624–$3308 in 2005 to $3608–$5132) [59]. An outpatient and inpatient follow-up study also using the Medicare database confirmed the enormous impact of NAFLD when investigators reported that the median total hospital charge for NAFLD patients was $36,289 in 2010 and increased with disease severity [60].

2.7 Conclusions

In summary, the prevalence and incidence of NAFLD is growing globally. NAFLD is not a benign disease as it can progress to advanced liver disease, hepatocellular carcinoma, liver transplantation, and death. Though the number of patients who actually progress is small on a global level, the burden is substantial. In addition to the clinical burden of NAFLD also carries a tremendous economic burden which is likely to increase as the population continues to age. Continuous study is needed to develop interventions to reverse the course of NAFLD especially as our understanding of NAFLD evolves.

Disclosures ZMY has received research funds or served as consultant to Gilead Sciences, Intercept, NovoNordisk, BMS, Terns, Viking.

Funding None.

References

1. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al.; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17(4):748–755.e3. pii: S1542-3565(18)30611-6.
2. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148(3):547–55.
3. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20. https://doi.org/10.1038/nrgastro.2017.109. Epub 2017 Sep 20.
4. 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. https://doi.org/10.1002/hep.28431. Epub 2016 Feb 22. Review.
5. Golabi P, Fukui N, de Avila L, Paik JM , Srishord M, Younossi ZM. The global epidemiology of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus (abstract), AASLD meeting 2017.
6. Ong JP, Elariny H, Collantes R, Younoszai A, Chandhoke V, Reines HD, et al. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. Obes Surg. 2005;15(3):310–5.
7. 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):123–33.
8. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018;69(4):896–904.
9. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–9.

10. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129(1):113–21.
11. Angulo P. GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2007;25(8):883–9.
12. Stepanova M, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, McCullough A, Goodman Z, Younossi ZM. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci. 2013;58(10):3017–23.
13. Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver related mortality. Hepatology. 2011;53:1874–82.
14. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology. 2017;65:1557–65.
15. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol. 2004;2(3):262–5. Erratum in: Clin Gastroenterol Hepatol. 2004 Jun;2(6):522.
16. Hossain N, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7:1224–9.
17. Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, Ratziu V, LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol. 2013;59(3):550–6.
18. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015;62(5):1148–55.
19. Younossi ZM, Stepanova M, Monge F, Alparthi L, Tan D, Abdul-Al H, et al. Independent predictors of spontaneous progression and regression in nonalcoholic steatohepatitis (NASH). Accepted Abstract for AASLD. 2018;
20. Ong J, Younossi ZM, Reddy V, Price LL, Gramlich T, Mayes J, Boparai N. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. Liver Transpl. 2001;7(9):797–801.
21. Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, Fisher RA, Ham J, Sanyal AJ. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transpl. 2001;7(4):363–73.
22. Thuluvath PJ, Hanish S, Savva Y. Waiting list mortality and transplant rates for NASH cirrhosis when compared to cryptogenic, alcoholic or AIH cirrhosis. Transplantation. 2019;103(1):113–21. https://doi.org/10.1097/TP.0000000000002355. [Epub ahead of print].
23. Younossi Z, Stepanova M, Sanyal J, Harrison SA, Ratziu V, Abdelmalek MF, et al. The conundrum of cryptogenic cirrhosis: adverse outcomes without treatment options. J Hepatol. 2018;69(6):1365–70.
24. Golabi P, Stepanova M, Pham HT, Cable R, Rafiq N, Bush H, Gogoll T, Younossi ZM. Non-alcoholic steatofibrosis (NASF) can independently predict mortality in patients with non-alcoholic fatty liver disease (NAFLD). BMJ Open Gastroenterol. 2018;5(1):e000198.
25. Younossi ZM, Stepanova M, Rafiq N, Henry L, Loomba R, Makhlouf H, Goodman Z. Nonalcoholic steatofibrosis independently predicts mortality in nonalcoholic fatty liver disease. Hepatol Commun. 2017;1(5):421–8.
26. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in non-alcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13(4):643–54.e1–9.
27. Patel YA, Gifford EJ, Glass LM, McNeil R, Turner MJ, Han B, et al. Risk factors for biopsy-proven advanced non-alcoholic fatty liver disease in the Veterans Health Administration. Aliment Pharmacol Ther. 2018;47(2):268–78. https://doi.org/10.1111/apt.14411. Epub 2017 Nov 8.

28. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism. 2016;65(8):1017–25.
29. Wang JZ, Cao HX, Chen JN, Pan Q. PNPLA3 rs738409 underlies treatment response in non-alcoholic fatty liver disease. World J Clin Cases. 2018;6(8):167–75.
30. Kleinstein SE, Rein M, Abdelmalek MF, Guy CD, Goldstein DB, Mae Diehl A, Moylan CA. Whole-exome sequencing study of extreme phenotypes of NAFLD. Hepatol Commun. 2018;2(9):1021–9. https://doi.org/10.1002/hep4.1227. eCollection 2018 Sep.
31. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, Srishord M. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011;9(6):524–530.e1.
32. Kabbany MN, ConjeevaramSelvakumar PK, Watt K, Lopez R, Akras Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of National Health and Nutrition Examination Survey Data. Am J Gastroenterol. 2017;112(4):581–7.
33. Younossi ZM, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology. 2016;150(8):1778–85.
34. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61(5):1547–54.
35. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, Hunt S. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellularcarcinoma (HCC) in the United States from 2004 to 2009. Hepatology. 2015;62(6):1723–30.
36. Seyda Seydel G, Kucukoglu O, Altinbasv A, Demir OO, Yilmaz S, Akkiz H, et al. Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries. Ann Hepatol. 2016;15(5):662–72.
37. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, May SB, Kramer JR, Richardson PA, Davila JA. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2016;14(1):124–31.e1. Epub 2015 Jul.
38. Kim D, Li AA, Perumpail BJ, Gadiparthi C, Kim W, Cholankeril G, et al. Changing trends in etiology- and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology. 2018;69:1064. https://doi.org/10.1002/hep.30161. . [Epub ahead of print].
39. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018;155(2):443–457.e17.
40. Zhou YY, Zhou XD, Wu SJ, Fan DH, Van Poucke S, Chen YP, Fu SW, Zheng MH. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: a systematic review and meta-analysis. Hepatol Commun. 2018;2(4):376–92.
41. Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri P, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. Dig Dis Sci. 2017;62(10):2915–22. https://doi.org/10.1007/s10620-017-4684-x. Epub 2017 Jul 25.
42. Tavakoli H, Robinson A, Liu B, Bhuket T, Younossi Z, Saab S, Ahmed A, Wong RJ. Cirrhosis patients with nonalcoholic steatohepatitis are significantly less likely to receive surveillance for hepatocellular carcinoma. Dig Dis Sci. 2017;62(8):2174–81. https://doi.org/10.1007/s10620-017-4595-x. Epub 2017 May 4.
43. Young K, Aguilar M, Gish R, Younossi Z, Saab S, Bhuket T, Liu B, Ahmed A, Wong RJ. Lower rates of receiving model for end-stage liver disease exception and longer time to transplant among nonalcoholic steatohepatitis hepatocellular carcinoma. Liver Transpl. 2016;22(10):1356–66. https://doi.org/10.1002/lt.24507.
44. Bhat G, Baba CS, Pandey A, Kumari N, Choudhuri G. Insulin resistance and metabolic syndrome in nonobese Indian patients with non-alcoholic fatty liver disease. Trop Gastroenterol. 2013;34(1):18–24.

45. Nishioji K, Sumida Y, Kamaguchi M, Mochizuki N, Kobayashi M, Nishimura T, Yamaguchi K, Itoh Y. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011-2012. J Gastroenterol. 2015;50(1):95–108.
46. Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, Sun CH. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J Gastroenterol. 2014;20(47):17932–40.
47. Margariti E, Deutsch M, Manolakopoulos S, Papatheodoridis GV. Non-alcoholic fatty liver disease may develop in individuals with normal body mass index. Ann Gastroenterol. 2012;25(1):45–51.
48. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med. 2004;164(19):2169–75.
49. Kim LJ, Nalls MA, Eiriksdottir G, Sigurdsson S, Launer LJ, Koster A, Chaves PH, Jonsdottir B, Garcia M, Gudnason V, Harris TB, AGES-Reykjavik Study Investigators. Associations of visceral and liver fat with the metabolic syndrome across the spectrum of obesity: the AGES-Reykjavik study. Obesity (Silver Spring). 2011;19(6):1265–71.
50. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, Srishord M. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore). 2012;91(6):319–27.
51. Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, et al. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease, and association with visceral obesity. Clin Gastroenterol Hepatol. 2017;15(10):1604–1611.e1.
52. Mehta R, Jeiran K, Koenig AB, Otgonsuren M, Goodman Z, Baranova A, Younossi Z. The role of mitochondrial genomics in patients with non-alcoholic steatohepatitis (NASH). BMC Med Genet. 2016;17(1):63. https://doi.org/10.1186/s12881-016-0324-0.
53. Dela Cruz AC, et al. Characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. DDW. 2014 Abstract 379.
54. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, Kechagias S. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: a long-term follow-up study. Hepatol Commun. 2017;2(1):48–57. https://doi.org/10.1002/hep4.1124. eCollection 2018 Jan.
55. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, Kechagias S. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol. 2017;67(6):1265–73. https://doi.org/10.1016/j.jhep.2017.07.027. Epub 2017 Aug 10.
56. Younossi ZM, Loomba R, Anstee QM, Rinella ME, Bugianesi E, Marchesini G, et al. Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. Hepatology. 2018;68(1):349–60.
57. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, Racila A, Hunt S, Beckerman R. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577–86. https://doi.org/10.1002/hep.28785. Epub 2016 Sep 26.
58. Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of illness and economic model for patients with non-alcoholic steatohepatitis (NASH) in the United States. Hepatology. 2019;69(2):564–72. https://doi.org/10.1002/hep.30254. [Epub ahead of print].
59. Younossi ZM, Zheng L, Stepanova M, Henry L, Venkatesan C, Mishra A. Trends in outpatient resource utilizations and outcomes for medicare beneficiaries with nonalcoholic fatty liver disease. J Clin Gastroenterol. 2015;49:222–7.
60. Sayiner M, Otgonsuren M, Cable R, Younossi I, Afendy M, Golabi P, Henry L, Younossi ZM. Variables associated with inpatient and outpatient resource utilization among medicare beneficiaries with nonalcoholic fatty liver disease with or without cirrhosis. J Clin Gastroenterol. 2017;51(3):254–60.