Current Hepatology Reports (2019) 18:433–443
https://doi.org/10.1007/s11901-019-00497-7

FATTY LIVER DISEASE (V AJMERA, SECTION EDITOR)

Should We Screen High-Risk Populations for NAFLD?

Cyrielle Caussy [1,2]

Published online: 8 November 2019

Abstract

Purpose of review Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide and yet remains largely underdiagnosed. However, whether a systematic screening in high-risk population for NAFLD should be performed remains debated.

Recent findings Over the past decade, a better knowledge of the natural history and epidemiology of NAFLD has identified high-risk population for NAFLD including obese and type 2 diabetes patients. Moreover, the presence of advanced fibrosis has been identified as the major determinant of overall and liver-related mortality. Moreover, several non-invasive biomarkers have been developed for the screening of advanced fibrosis while therapeutic clinical trials are intensive field of research.

Summary Screening for advanced fibrosis in high-risk population for NAFLD should be performed as it would benefit to the patients. However further studies are needed to determine the optimal strategy and cost-effectiveness of such screening.

Keywords Obesity · Nonalcoholic fatty liver disease · Type 2 diabetes · Fibrosis · Cirrhosis · Biomarkers

Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide affecting 25–30% of the adult population [1•]. NAFLD is defined by evidence of hepatic steatosis, either by imaging or histology, and lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders [2••]. NAFLD encompasses a spectrum of disease from simple hepatic steatosis to steatohepatitis (NASH) which is considered as the progressive form with an increased risk of progression towards liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [2••]. Despite its growing epidemic closely associated with the increase epidemic of obesity and type 2 diabetes mellitus (T2DM), NAFLD remains largely underdiagnosed as it remains asymptomatic until advanced stage of the disease and even patients with advanced fibrosis may have normal liver enzymes [3]. Another limitation for the diagnosis of NAFLD is the need to perform a liver biopsy which is considered as the reference standard but is expensive, invasive, and not applicable at the level of the population as a screening method.

Over the past decade, better knowledge of the natural history and epidemiology of NAFLD has identified high-risk population for NAFLD and especially population with high-risk of progression toward advanced fibrosis [4]. In addition, several non-invasive biomarkers have been developed, and algorithms have been proposed for the non-invasive screening of the presence of advanced fibrosis [5••, 6••]. Finally, despite the lack of FDA-approved therapy for the treatment of NAFLD, NASH, or advanced fibrosis, therapeutic clinical trials are an intensive field of research with promising results [7, 8•].

In the current review, we will discuss the need to screen for NAFLD in high-risk population based upon the most recent data on the epidemiology and natural history of NAFLD, identification of high-risk population, non-invasive strategies and modalities available, and potential cost-effectiveness for such screening.

This article is part of the Topical Collection on *Fatty Liver Disease*

✉ Cyrielle Caussy
cyrielle.caussy@chu-lyon.fr

[1] Univ Lyon, CarMen Laboratory, INSERM, INRA, INSA Lyon, Université Claude Bernard Lyon 1, 69495 Pierre-Bénite, France

[2] Hospices Civils de Lyon, Département Endocrinologie, Diabète et Nutrition, Hôpital Lyon Sud, 69495 Pierre-Bénite, France

Screening for NAFLD: Which Histological Feature Should We Screen?

Several studies have improved the knowledge of the natural history of NAFLD over the past 2 decades [3, 8•]. The presence of liver fibrosis has been consistently reported as the major factor associated with a significant increased risk of overall mortality and liver-related mortality [9–11, 12•]. A recent meta-analysis performed by Dulai et al. has shown that the risk of death from liver disease is exponentially increased in patients with NAFLD who have advanced fibrosis, defined as presence of either bridging fibrosis (stage 3) or (stage 4) cirrhosis [12•]. Based upon the natural history of NAFLD, most patients have benign hepatic steatosis and will not develop NASH, advanced fibrosis of cirrhosis. However, given the high prevalence of NAFLD in the general population (approximately 100 million in the USA), even a small proportion of patients with advanced liver fibrosis of approximately 5% will correspond to a large number of patients (approximately 5 million). Indeed, recent data have shown that NAFLD is an increased etiology of cirrhosis in the USA which is currently the second indication for liver transplantation [13, 14]. Furthermore, NAFLD-related cirrhosis is rapidly becoming an important cause of HCC [15–20]. Finally, the burden of NAFLD extends beyond liver-related morbidity, as NAFLD is also associated with an increased risk of fatal and non-fatal cardiovascular events [21, 22••].

Although NASH is considered as the progressive form with higher risk of progression towards advanced fibrosis, the lack of reliable non-invasive alternatives to liver biopsy for the diagnosis of NASH currently prevents from a systematic screening for the presence of NASH in high-risk population. However, the development of several non-invasive biomarkers for the detection of liver fibrosis associated with strong evidence of prognostic value of the presence of advanced fibrosis has led the field to mainly focus on the screening for the presence of advanced fibrosis. Ultimately, the diagnosis of advanced fibrosis would benefit to the patients as they would undergo more intensive cardiovascular preventions, screening and prophylactic intervention for the esophageal varices, surveillance for HCC, and eventually liver transplantation (Fig. 1).

High-Risk Population for NAFLD: Who Should We Screen?

Given the high prevalence of NAFLD in the general population, routine screening for NAFLD in the absence of risks factors for advanced stage of the disease may not be warranted especially when the majority of patient with NAFLD will not progress towards advanced fibrosis. Therefore, risk stratification of the patients at high-risk of developing advanced fibrosis is needed in order to improve the efficiency of a screening strategy. Several populations with high-risk for NAFLD have been identified including obese and type 2 diabetes mellitus (T2DM) patients and potentially first-degree relatives of patients with NAFLD-related cirrhosis.

Obese patients

Obesity is closely associated with the presence of NAFLD and is the most common risk factor for NAFLD [26]. The estimated prevalence of NAFLD in obese patients varies from 75 up to 92% in patients with severe obesity with BMI ≥ 40 kg/m^2. Epidemiological data of the prevalence of NAFLD in obese population mainly derives from bariatric surgery cohorts with intraoperative liver biopsy [27, 28]. In severely obese patients that underwent bariatric surgery, the median prevalence of NASH is estimated of 33% (range from 10 to 56%) and the prevalence of advanced fibrosis is estimated of 10% (range 4–16%) [28]. However, the prevalence of cirrhosis may have been underestimated in these cohorts as cirrhosis is a contraindication to bariatric surgery.

In addition, the presence of obesity increases the risk of various cancer including liver cancer [29], and a recent study performed by Hagström et al. from registry data of more than 1.2 million Swedish men has reported that high BMI in late adolescence is associated with an increased risk of developing hepatocellular carcinoma [30]. These data further support the possibility of screening the obese population for NAFLD.

Type 2 Diabetes Patients

NAFLD is a frequent finding in patients with type 2 diabetes with a reported prevalence from 60 to 80% depending on the study and diagnostic methods used [31–37]; approximately, 30 to 40% are estimated to have NASH [38, 39] and 7 to 20% are estimated to have advanced fibrosis with a higher prevalence in T2DM older than 50 years [37, 40, 41]. A recent meta-analysis including 80 studies has reported a global prevalence of NAFLD of 55% (95% CI 47.3–63.7) with a higher prevalence in Europe of 68.0% (95% CI 62.1–73.0). Only 10 studies have reported histological assessment of NAFLD in T2DM population with a prevalence of NASH of 69.75% and advanced fibrosis of 17.02% [42•].

Several studies have demonstrated that T2DM is an independent risk factor for the progression of NAFLD to NASH and advanced fibrosis which increases the risk of progression to cirrhosis, liver-related mortality, and hepatocellular carcinoma [43–46]. Although the interrelationship between T2DM and NAFLD remains unclear [47], several studies suggest that the coexistence of T2DM and NAFLD worsens the course of both diseases. Indeed, the presence of NAFLD in T2DM patients hampers to maintain an optimal glycemic control as it increases hepatic and peripheral insulin resistance [48]. Moreover, an increased risk of both macrovascular and

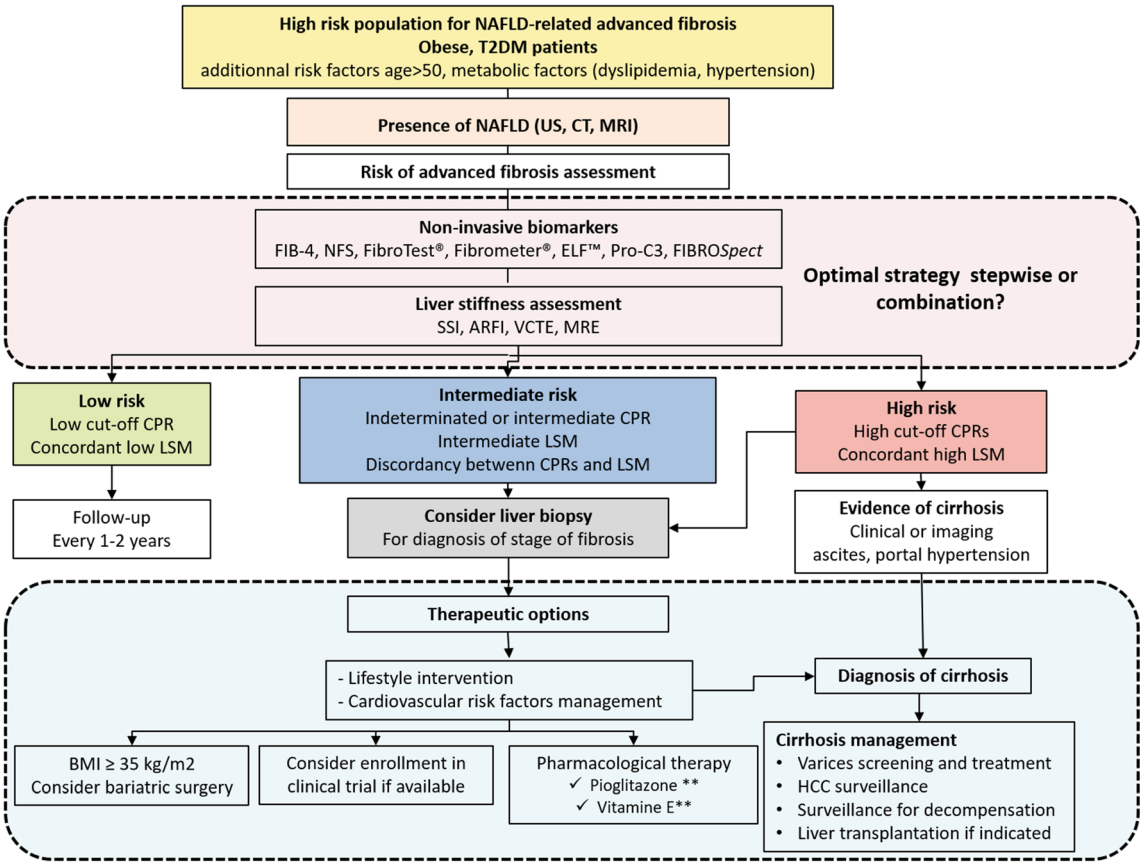

Fig. 1 Screening for advanced fibrosis in high-risk population of NAFLD. Algorithm for risk stratification of high-risk population for NAFLD and therapeutic options. High-risk population are screened for the presence of NAFLD including presence of hepatic steatosis identified using ultrasound, CT scan or MRI, and absence of other causes of hepatic steatosis [2••]. The optimal strategy for the screening of advanced fibrosis using clinical prediction rules (CPR) and imaging liver stiffness measurement (LSM) needs to be determined in order to classify patients with low risk, intermediate, and high-risk of advanced liver fibrosis. This stratification will help to determine which patients requires a liver biopsy for a confirmed diagnosis of stage of liver fibrosis unless clinical or imaging evidence of cirrhosis [23–25]. Current therapeutic options are presented based upon current AASLD guidelines [2••] and cost-effectiveness needs to be determined. **Pioglitazone may be considered in patients with biopsy-proven NASH, and vitamin E may be considered in nondiabetic patients with biopsy-proven NASH; both treatments require risks and benefits evaluation [2••]. BMI body mass index, NFS NAFLD fibrosis score, T2DM type 2 diabetes mellitus, ELF enhanced liver fibrosis, HCC hepatocellular carcinoma, US ultrasound, CT computed tomography, MRI magnetic resonance imaging

microvascular complications of T2DM has been reported in the presence of NAFLD [49–52]. In addition, several studies have reported a significant association between NAFLD and cardiovascular disease in several population including T2DM [53, 54].

First-Degree Relatives of Patients with NAFLD-Related Cirrhosis

Studies using a twin-study design have shown that both hepatic steatosis and liver fibrosis are heritable trait even after adjustment of common risk factors such as age, sex, BMI, and Hispanic ethnicity [55, 56]. These data along with previous retrospective family studies point towards an increased familial aggregation of NAFLD and NAFLD-related cirrhosis [57, 58]. In addition, Caussy et al. have demonstrated that first-degree relatives of probands with NAFLD-related cirrhosis have 12 times higher risk of having advanced fibrosis compared to non-NAFLD individual [59•]. This important finding suggests that first-degree relatives of patients with NAFLD-related cirrhosis should be screened for advanced fibrosis. Further studies with larger familial cohort are needed to determine if a systemic screening for advanced fibrosis in first-degree relatives is recommended and to improve future clinical guidelines.

Despite these data, NAFLD remains largely underdiagnosed in these high-risk populations. Interestingly, the screening for NAFLD and especially advanced fibrosis in patients with T2DM is recommended by the European EASL/EASD/EASO Guidelines published in 2016 [60••] and more recently by the American Diabetes Association (ADA) guidelines in 2019 [61••]. However, the latest guidelines from the American Association for the Study of Liver Diseases (AASLD) in 2018 did not recommend the systematic

screening for NAFLD in high-risk population such as diabetes and obese patients due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening. Indeed, the systematic screening of obese and T2DM would represent a large number of individuals considering the growing epidemic of these metabolic diseases. Therefore, the screening for NAFLD-related advanced fibrosis in these populations could be improved by incorporating additional risk factors for advanced fibrosis including age (e.g., greater than 50 years) and possibly presence of other metabolic disorders such as dyslipidemia or hypertension.

Modality of Screening for NAFLD: How Should We Screen High-Risk Population?

Several non-invasive modalities have been developed for the screening of advanced fibrosis in NAFLD including blood and imaging-based biomarkers.

Non-Invasive Blood-Based Biomarkers

The clinical predictive rules (CPR) derived from standard clinical parameters including FIB-4 [62] and NAFLD fibrosis score (NFS) [63] have been validated in large cohorts of patients with biopsy-proven NAFLD [6]. These CPRs are currently considered as first-line non-invasive tests for the screening of advanced fibrosis as they are easy to perform, inexpensive, and widely available. The interpretation of the CPRs uses a low and high cutoff. The advantage of these CPRs is a high negative predictive value that enables to rule out patients with low risk of having advanced fibrosis below the low cutoff. However, these tests lack specificity for the diagnosis of advanced fibrosis, and a significant number of patients fall in indeterminate "grey" zone between the low and high threshold. Other proprietary formula including enhanced liver fibrosis (ELF^{TM}) [64], FibroTest® [65], Fibrometer® [66], and FIBROSpect [67] for the non-invasive stage of fibrosis have been developed. In addition, the peptide PRO-C3 that detects the N-terminal pro-peptide of type III collagen (PIIINP) has emerged as a non-invasive biomarker of fibrogenesis [68]. PRO-C3 incorporated in clinical and biological data has recently been found to accurately detect the presence of advanced fibrosis in individuals with NAFLD [69, 70] (Table 1). However, these tests are more expensive and are currently not widely available in every center. The proprietary tests provide a reasonable accuracy for lower stage of fibrosis and detection of higher stage of fibrosis but was less

Table 1 Non-invasive tests blood-based biomarker for the detection of advanced fibrosis

NITs	Parameters	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Clinical predictive rules						
FIB-4 [62]	Age, ALT, AST, and platelets count	Low cutoff 1.3	74	71	73	72
		High cutoff 2.67	34	98	59	93
NFS [63]	Age, BMI, platelets count, albumin, AST, ALT, and IFG/diabetes	Low cutoff − 1.455	77	71	88	52
		High cutoff 0.676	43	96	80	82
BARD[71]	BMI, AST, ALT, and diabetes	2	-	-	96	43
BAAT [72]	Age, BMI, ALT, and triglycerides	2	71	80	86	61
Proprietary tests						
FibroTest® [65]	Alpha-2 macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, and GGT	Low: 0.30	92	72	98	33
		High 0.70	25	97	60	89
Fibrometer®[66]	Age, weight, glucose, AST, ALT, platelets, and ferritin	0.49	78.5	95.9	87.9	92.1
ELF™ [64]	P3NP, hyaluronate, and TIMP-1	0.3576	80	90	94	71
FIBRO*Spect* NASH [67]	alpha-2 macroglobulin, HA, and TIMP1	17	79.7	75.7	93.4	46.3
FIBC3 [70]	age, BMI, T2DM, platelets count, PRO-C3	> −0 .4	83	80	88	74
ADAPT [69]	age, presence of diabetes, PRO-C3, and platelet count	6.3287	90.9	72.6	96.6	48.4
Stepwise combination						
eLIFT-FM^{VCTE} [73]	eLIFT: age, gender, AST, GGT, platelets, PT FM^{VCTE} : fibrometer and LSM	≥ 8 ≥ 0.715	78.2	91.4	78.8	91.1

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *IFG*, impaired fasting glucose; *PT*, prothrombine time; *NAFLD*, nonalcoholic fatty liver disease; *NASH*, nonalcoholic steatohepatitis; *NIT*, non-invasive test, *NFS*, NAFLD fibrosis score; *NPV*, negative predictive value; *PPV*, positive predictive value, *TIMP* metallopeptidase inhibitor, *HA*, hyaluronic acid; *T2DM*, type 2 diabetes mellitus

extensively studied in large and independent cohort of patients with NAFLD, and further validations are needed to determine their role and utility in the risk stratification algorithm for the detection of advanced fibrosis in high-risk population [4, 6••].

Finally, the major limitation for the application of these non-invasive tests for the screening of high-risk population is that these tests have been developed in a different context of use using population with a biopsy-proven NAFLD as inclusion criteria and therefore were not developed in the context of screening patients with and without any indication for a liver biopsy. In addition, some of them include the presence of T2DM or BMI in their formula and therefore it is not best suited in obese and T2DM population as it provides a high rate of indeterminate score. In addition, a study performed by Bril et al. suggests that the performance of non-invasive tests developed from studies in non-diabetic populations should not be directly extrapolated to patients with T2DM but warrants specific validation [74]. Hence, patients with T2DM may need different non-invasive tests, specifically developed for this population.

Non-Invasive Imaging Biomarkers

Imaging modalities that assess liver stiffness as a surrogate for liver fibrosis are also useful tools for the risk stratification of patients, recently reviewed in reference [5••]. Several modalities are available including ultrasound-based methods including supersonic shear-wave imaging (SSI) [75], vibration-controlled transient elastography (VCTE) using FibroScan [76–78], and acoustic radiation force impulse (ARFI) (Table 2). These modalities have a higher diagnostic accuracy for the detection of liver fibrosis and especially for the detection of cirrhosis. Several cutoffs depending on the methods used, etiology of liver disease, and geographical origin have been proposed (Table 2). Further validation in large and multicenter cohort of patients with NAFLD will help to better define the cutoff for the detection of advanced fibrosis and how to incorporate these ultrasound-based modalities in clinical practice for the screening of advanced fibrosis depending on their availability. Finally, magnetic resonance elastography [81] has emerged as the most reliable and accurate non-invasive modality for the detection of liver fibrosis especially in intention to diagnose. MRE generally outperforms all ultrasound-based modalities including ARFI [79] and (VCTE) [82–84] and have lower risk of failure than ultrasound-based elastography especially when BMI increases [79, 81, 85]. However, its cost and lack of availability in point of care make it less practical for the screening of high-risk population.

While several non-invasive biomarkers are available for the detection of liver fibrosis, the optimal clinical approach for non-invasive screening of advanced fibrosis in T2DM and obese patients remains unclear. The recent ADA guidelines in favor for the screening for NAFLD in patients with T2DM did not provide any recommendation regarding the strategy for such screening [61••]. In addition, the strategy proposed by the EASL/EASO/EASD European guidelines for the screening of advanced fibrosis using clinical predictive rules such as FIB-4 or NAFLD fibrosis score lack of specificity and have been questioned by tertiary center expert in the clinical management of patients with T2DM and obesity [86, 87] suggesting that they would lead to an over-referral of patients which may lead to substantial pejorative impact including unjustified increase of health cost and more importantly source of anxiety for patients. Overall, further studies assessing the diagnostic performance of single non-invasive

Table 2 Non-invasive imaging biomarkers for the detection of advanced fibrosis in NAFLD

Modality	Geographical origin	Cutoff* ≥ F3	AUROC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Ultrasound-based biomarkers							
VCTE	UK [76] (M and XL probe)	9.7 kPa	0.80	71	75	81	63
	USA [77] (M and XL probe)	8.6 kPa	0.83	80	74	89	59
	France and China [78] (M probe)	8.7 kPa	0.93	83.9	83.2	94.6	59.5
ARFI	France [75]	1.26 m/s	0.84	81	78	-	-
	USA [79]	1.34 m/s	0.90	95	74	43	99
	Japan [80]	1.77 m/s	0.97	100	91	100	71
SSI	France [75]	9.3 kPa	0.86	84	83	-	-
Magnetic resonance imaging							
MRE	Japan-USA [81]	3.62 kPa	0.93	82.5	83.2	93.3	61.8

UK United Kingdom, *USA* United State of America, *VCTE* vibration controlled transient elastography, *SSI* supersonic shear-wave imaging, *NPV*, negative predictive value; *PPV*, positive predictive value.

*Optimal cutoff determined by Younden Index for the detection of advanced fibrosis stage fibrosis F3-F4

tests or combination of blood-based and ultrasound-based biomarkers are needed to determine the optimal algorithm and strategy for the screening of advanced fibrosis in high-risk population including T2DM and obese population.

Ultimately, liver biopsy remains the reference standard to diagnose the presence of NASH and liver fibrosis and is recommended to formally establish the presence of advanced fibrosis and cirrhosis unless imaging evidence for the diagnosis of NAFLD-cirrhosis [23–25] (Fig. 1).

Which therapeutic intervention options are available for patients screened for NAFLD-related advanced fibrosis?

The screening for advanced fibrosis in high-risk population can be considered only if a therapeutic intervention is available and may benefit the patients. Although there is currently no FDA-approved drug for the treatment of NASH or NAFLD-related fibrosis, several therapeutic interventions can be proposed once the presence of advanced fibrosis is diagnosed (Fig. 1).

Pharmacological Treatment

Pharmacological therapy for the treatment of NASH or NAFLD-related fibrosis is an intensive field of research with currently 6 phase 3 and approximately 20 phase 2 clinical trials for the treatment of NASH or liver fibrosis [7]. Recently, the interim analysis of the Phase 3 REGENERATE study met the primary endpoint of fibrosis improvement (≥ 1 stage) with no worsening of NASH in patients treated with obeticholic acid 25 mg once daily versus placebo [88••]. Hence, in a near future, specific therapeutics are expected to be available. In addition, enrollment on clinical trials may also be considered for patients screened for advanced fibrosis that underwent a liver biopsy.

The American Association for the Study of Liver Diseases (AASLD) [2••] and European Association for the Study of Liver (EASL) [60••] guidelines recommend that pioglitazone can be considered for use in patients with biopsy-proven NASH. However, this medication has the inconvenient of weight gain, fluid retention, and increase risk of bone fracture; and risk and benefit should be discussed with the patients. Likewise, vitamin E at a daily dose of 800 IU/day improves liver histology in non-diabetic and possibly diabetic adults with biopsy-proven NASH [89, 90] but has been associated with increased risk of prostate cancer and therefore may be considered for nondiabetic patients with biopsy-proven NASH after discussion of risks and benefit according to AASLD guidelines [2••].

Lifestyle Intervention

Lifestyle intervention remains the cornerstone of the treatment of NASH, and advanced fibrosis remains lifestyle intervention including diet modification and increase in physical activity [91•]. Studies have demonstrated that weight loss of 10% is associated with improvement of histological features of NASH and liver fibrosis. The main inconvenient is that this goal is difficult to achieve, requires usually specific coaching, and is met by approximately 20% of the patients [89].

Cardiovascular Prevention

Given the strong association between the presence of advanced fibrosis and cardiovascular outcomes, patients identified with the presence of advanced fibrosis would also benefit from more intensive cardiovascular prevention. Whether the presence of advanced fibrosis should modify the cardiovascular risk stratification of these patients needs to be established as there is currently not enough evidence available. However, optimization and more intensive modification of associated conventional cardiovascular risk factors such as statin treatment for dyslipidemia, hypertension control, smoking cessation, and control of type 2 diabetes would benefit to patients identified with advanced liver fibrosis [92].

Bariatric Surgery

In obese patients with BMI ≥ 35 kg/m^2, bariatric surgery can be considered as it has demonstrated to improve and reverse feature of NAFLD including hepatic steatosis, NASH and liver fibrosis in several retrospective studies [93], and in a large prospective study including 5-year follow-up [94, 95]. Inconvenient of bariatric surgery is that it is not recommended for patient with decompensated cirrhosis due to significant increased risk or mortality and may be considered in compensated cirrhosis by trained surgeon after careful evaluation of the risk and benefit balance [96].

Management of cirrhosis

The early detection of cirrhosis at asymptomatic stage and before decompensation would also benefit to the patients as they will undergo specific management and surveillance. Indeed, screening for varices should be initiated at the diagnosis of cirrhosis, and specific follow-up will be initiated depending on presence and the characteristic of varices or high-risk signs of bleeding. In addition, patients with large varices will benefit from prophylactic intervention to prevent bleeding either by variceal band ligation or nonselective β-blocker. Moreover, closer surveillance of signs of decompensation and screening for the development of HCC will be initiated.

Finally, for the patients with decompensated cirrhosis, referral for liver transplantation evaluation will be considered.

Is the Screening for NAFLD in High-Risk Population: Cost-Effective?

The systematic screening for advanced fibrosis in high-risk population should be recommended only if it is cost-effective. However, there are currently very limited data available on the cost-effectiveness assessment of screening strategy applied to high-risk population such obese of T2DM.

However, there is a lack of real-world data on the true economic burden of NAFLD [97•]. Recent study have reported that the costs associated with the care of patients with NAFLD have recently been found to be very high [97•, 98] with an annual direct costs associated with NAFLD in the USA estimated of approximately $103 billion [99]. A cost-effectiveness analysis performed by Zhang et al. has reported that screening for NASH may be cost-effective especially in high-risk population including obese and T2DM population [100] whereas Corey et al. have reported that screening for NASH in patients with type 2 diabetes is not cost-effective at present mainly due to side effects of current available therapy. However, bariatric surgery for the treatment of NASH was demonstrated as cost-effective in obese patients [101].

Overall, the cost-effectiveness would need to be evaluated considering the cost of the future therapy and long-term follow-up with large cohort to be able to assess treatment outcomes in the liver and in cardiovascular events.

Conclusion

NAFLD has become an important health concern affecting approximately one-third of worldwide population and is expected to increase along with increase of global obesity epidemic. Epidemiological studies have enabled a better understanding of the natural history of NAFLD and have demonstrated that the presence of advanced liver fibrosis is associated with increased risk of liver and overall mortality. Moreover, high-risk population of progression towards advanced fibrosis has been identified including obese, T2DM patients, and potentially first-degree relatives of patients with NAFLD-cirrhosis that would benefit from screening program for advanced fibrosis. However, the optimal strategy for such screening needs to be better defined in order to perform an efficient screening in primary care setting or in endocrinology and obesity clinics and avoid over-referral in hepatology clinics. Finally, based upon this optimal strategy, current and future therapeutic options, the cost-effectiveness would need to be confirmed to subsequently recommend a systematic screening of high-risk population of NAFLD and NAFLD-related advanced fibrosis.

Compliance with Ethical Standards

Conflict of Interest Cyrielle Caussy is a consultant for Gilead, NovoNordisk, Liponexus, AstraZeneca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global Perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69(6):2672–82. https://doi.org/10.1002/hep.30251 **Important article highligthing the importance of the prevalence of NAFLD and expected increase burden.**

2.•• Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57. https://doi.org/10.1002/hep.29367 **Most recent pratice guideline for the management of NAFLD.**

3. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313(22):2263–73. https://doi.org/10.1001/jama.2015.5370.

4. Cheung A, Figueredo C, Rinella ME. Nonalcoholic fatty liver disease: identification and management of high-risk patients. Am J Gastroenterol. 2019;114(4):579–90. https://doi.org/10.14309/ajg.0000000000000058.

5.•• Loomba R. Role of imaging-based biomarkers in NAFLD: Recent advances in clinical application and future research directions. J Hepatol. 2018;68(2):296–304. https://doi.org/10.1016/j.jhep.2017.11.028 **Important review article ot the different non-invasive imaging modalities available for the detection of liver fibrosis.**

6.•• Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. J Hepatol. 2018;68(2):305–15. https://doi.org/10.1016/j.jhep.2017.11.013 **Important review article ot the different non-invasive blood-based modalities available for the detection of liver fibrosis.**

7. Konerman MA, Jones JC, Harrison SA. Pharmacotherapy for NASH: current and emerging. J Hepatol. 2018;68(2):362–75. https://doi.org/10.1016/j.jhep.2017.10.015.

8.• Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2018;68(1):361–71. https://doi.org/10.1002/hep.29724 Most recent review article exposing the current and drug under development for the treatment of NAFLD.

9. Hagstrom H, Nasr P, Ekstedt M, Hammar U, Stal P, Hultcrantz R, et al. 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.

10. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149(2):389–97 e10. https://doi.org/10.1053/j.gastro.2015.04.043.
11. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. 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. https://doi.org/10.1002/hep.27368.
12.• 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(5):1557–65. https://doi.org/10.1002/hep.29085 **Important meta-analysis demonstating the prognostic value of advanced fibrosis in overall and liver-related mortality.**
13. 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. 2015;148(3):547–55. https://doi.org/10.1053/j.gastro.2014.11.039.
14. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014;59(6):2188–95. https://doi.org/10.1002/hep.26986.
15. Hui JM, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, et al. Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology. 2003;38(2):420–7. https://doi.org/10.1053/jhep.2003.50320.
16. Kojima H, Sakurai S, Matsumura M, Umemoto N, Uemura M, Morimoto H, et al. Cryptogenic cirrhosis in the region where obesity is not prevalent. World Journal of Gastroenterology. 2006;12(13):2080–5.
17. Ratziu V, Bonyhay L, Di Martino V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. Hepatology. 2002;35(6):1485–93. https://doi.org/10.1053/jhep.2002.33324.
18. Yatsuji S, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. Journal of Gastroenterology and Hepatology. 2009;24(2):248–54. https://doi.org/10.1111/j.1440-1746.2008.05640.x.
19. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43(4):682–9. https://doi.org/10.1002/hep.21103.
20. Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scandinavian journal of gastroenterology. 2009;44(10):1236–43. https://doi.org/10.1080/00365520903171284.
21. Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis. 2013;230(2):258–67. https://doi.org/10.1016/j.atherosclerosis.2013.07.052.
22.•• Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J Hepatol. 2016;65(3):589–600. https://doi.org/10.1016/j.jhep.2016.05.013 **Important meta-analysis underlying the assocation between NAFLD and increase risk of cardiovascular disease.**
23. Harbin WP, Robert NJ, Ferrucci JT Jr. Diagnosis of cirrhosis based on regional changes in hepatic morphology: a radiological and pathological analysis. Radiology. 1980;135(2):273–83. https://doi.org/10.1148/radiology.135.2.7367613.
24. Ito K, Mitchell DG, Hann HW, Kim Y, Fujita T, Okazaki H, et al. Viral-induced cirrhosis: grading of severity using MR imaging. AJR Am J Roentgenol. 1999;173(3):591–6. https://doi.org/10.2214/ajr.173.3.10470885.
25. Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, et al. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. A multicenter collaborative study. Intervirology. 2008;51(Suppl 1):17–26. https://doi.org/10.1159/000122595.
26. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol. 2013;10(11):686–90. https://doi.org/10.1038/nrgastro.2013.171.
27. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274–85. https://doi.org/10.1111/j.1365-2036.2011.04724.x.
28. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. J Hepatol. 2006;45(4):600–6. https://doi.org/10.1016/j.jhep.2006.06.013.
29. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38. https://doi.org/10.1056/NEJMoa021423.
30. Hagstrom H, Tynelius P, Rasmussen F. High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. Gut. 2018;67(8):1536–42. https://doi.org/10.1136/gutjnl-2016-313622.
31. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140(1):124–31. https://doi.org/10.1053/j.gastro.2010.09.038.
32. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30(5):1212–8. https://doi.org/10.2337/dc06-2247.
33. Williamson RM, Price JF, Hayes PC, Glancy S, Frier BM, Johnston GI, et al. Prevalence and markers of advanced liver disease in type 2 diabetes. QJM. 2012;105(5):425–32. https://doi.org/10.1093/qjmed/hcr233.
34. Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab. 2015;100(6):2231–8. https://doi.org/10.1210/jc.2015-1966.
35. Leite NC, Villela-Nogueira CA, Pannain VL, Bottino AC, Rezende GF, Cardoso CR, et al. Histopathological stages of non-alcoholic fatty liver disease in type 2 diabetes: prevalences and correlated factors. Liver Int. 2011;31(5):700–6. https://doi.org/10.1111/j.1478-3231.2011.02482.x.
36. Byrne CD, Olufadi R, Bruce KD, Cagampang FR, Ahmed MH. Metabolic disturbances in non-alcoholic fatty liver disease. Clin Sci (Lond). 2009;116(7):539–64. https://doi.org/10.1042/CS20080253.
37. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment

Pharmacol Ther. 2016;43(1):83–95. https://doi.org/10.1111/apt.13405.
38. Lomonaco R, Ortiz-Lopez C, Orsak B, Finch J, Webb A, Bril F, et al. Role of ethnicity in overweight and obese patients with nonalcoholic steatohepatitis. Hepatology. 2011;54(3):837–45. https://doi.org/10.1002/hep.24483.
39. Lomonaco R, Bril F, Portillo-Sanchez P, Ortiz-Lopez C, Orsak B, Biernacki D, et al. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. Diabetes Care. 2016;39(4):632–8. https://doi.org/10.2337/dc15-1876.
40. Arab JP, Barrera F, Gallego C, Valderas JP, Uribe S, Tejos C, et al. High prevalence of undiagnosed liver cirrhosis and advanced fibrosis in type 2 diabetic patients. Ann Hepatol. 2016;15(5):721–8. https://doi.org/10.5604/16652681.1212434.
41. Yeung MW, Wong GL, Choi KC, Luk AO, Kwok R, Shu SS, et al. Advanced liver fibrosis but not steatosis is independently associated with albuminuria in Chinese patients with type 2 diabetes. J Hepatol. 2017. https://doi.org/10.1016/j.jhep.2017.09.020.
42.• Younossi ZM, Golabi P, de Avila L, Minhui Paik J, Srishord M, Fukui N, et al. The Global Epidemiology of NAFLD and NASH in Patients with type 2 diabetes: A Systematic Review and Meta-analysis. J Hepatol. 2019. https://doi.org/10.1016/j.jhep.2019.06.021 **Recent meta-analysis of the prevalence of NAFLD and NASH in patients with T2DM.**
43. Neuschwander-Tetri BA, Clark JM, Bass NM, Van Natta ML, Unalp-Arida A, Tonascia J, et al. Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. Hepatology. 2010;52(3):913–24. https://doi.org/10.1002/hep.23784.
44. 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.
45. 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. https://doi.org/10.1016/j.jhep.2014.11.034.
46. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2012;28(2):109–22. https://doi.org/10.1002/dmrr.1291.
47. Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. J Hepatol. 2015;62(1 Suppl):S65–75. https://doi.org/10.1016/j.jhep.2015.02.041.
48. Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology. 2014;59(2):713–23. https://doi.org/10.1002/hep.26672.
49. Bril F, Sninsky JJ, Baca AM, Superko HR, Portillo Sanchez P, Biernacki D, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. J Clin Endocrinol Metab. 2016;101(2):644–52. https://doi.org/10.1210/jc.2015-3111.
50. Targher G, Bertolini L, Rodella S, Zoppini G, Lippi G, Day C, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. Diabetologia. 2008;51(3):444–50. https://doi.org/10.1007/s00125-007-0897-4.
51. Targher G, Bertolini L, Rodella S, Lippi G, Zoppini G, Chonchol M. Relationship between kidney function and liver histology in subjects with nonalcoholic steatohepatitis. Clin J Am Soc Nephrol. 2010;5(12):2166–71. https://doi.org/10.2215/CJN.05050610.
52. Li Y, Zhu S, Li B, Shao X, Liu X, Liu A, et al. Association between non-alcoholic fatty liver disease and chronic kidney disease in population with prediabetes or diabetes. Int Urol Nephrol. 2014;46(9):1785–91. https://doi.org/10.1007/s11255-014-0796-9.
53. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10(6):330–44. https://doi.org/10.1038/nrgastro.2013.41.
54. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol. 2018;14(2):99–114. https://doi.org/10.1038/nrendo.2017.173.
55. Cui J, Chen CH, Lo MT, Schork N, Bettencourt R, Gonzalez MP, et al. Shared genetic effects between hepatic steatosis and fibrosis: a prospective twin study. Hepatology. 2016;64(5):1547–58. https://doi.org/10.1002/hep.28674.
56. Loomba R, Schork N, Chen CH, Bettencourt R, Bhatt A, Ang B, et al. Heritability of hepatic fibrosis and steatosis based on a prospective twin study. Gastroenterology. 2015;149(7):1784–93. https://doi.org/10.1053/j.gastro.2015.08.011.
57. Abdelmalek MF, Liu C, Shuster J, Nelson DR, Asal NR. Familial aggregation of insulin resistance in first-degree relatives of patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2006;4(9):1162–9. https://doi.org/10.1016/j.cgh.2006.06.001.
58. Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol. 2001;96(10):2957–61. https://doi.org/10.1111/j.1572-0241.2001.04667.x.
59.• Caussy C, Soni M, Cui J, Bettencourt R, Schork N, Chen CH, et al. Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis. J Clin Invest. 2017;127(7):2697–704. https://doi.org/10.1172/JCI93465 **First prospective study to determine a higher risk of advanced fibrosis among first-degree relatives of patients with NAFLD-cirrhosis.**
60.•• European Association for the Study of the Liver. Electronic address eee, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004 **Most recent European guidelines that recommend the systematic screening for advanced fibrosis in high-risk population for NAFLD.**
61.•• American Diabetes A. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S34–45. https://doi.org/10.2337/dc19-S004 **Most recent practice guideline from American Diabetes Association that recommend the screening for NAFLD in patients with T2DM.**
62. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265–9. https://doi.org/10.1136/gut.2010.216077.
63. 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. 2007;45(4):846–54. https://doi.org/10.1002/hep.21496.
64. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology. 2008;47(2):455–60. https://doi.org/10.1002/hep.21984.
65. Poynard T, Morra R, Halfon P, Castera L, Ratziu V, Imbert-Bismut F, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. BMC Gastroenterol. 2007;7:40. https://doi.org/10.1186/1471-230X-7-40.

66. Cales P, Laine F, Boursier J, Deugnier Y, Moal V, Oberti F, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J Hepatol. 2009;50(1):165–73. https://doi.org/10.1016/j.jhep.2008.07.035.
67. Loomba R, Jain A, Diehl AM, Guy CD, Portenier D, Sudan R, et al. Validation of serum test for advanced liver fibrosis in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2019;17(9):1867–76 e3. https://doi.org/10.1016/j.cgh.2018.11.004.
68. Caussy C, Bhargava M, Villesen IF, Gudmann NS, Leeming DJ, Karsdal MA, et al. Collagen formation assessed by N-terminal propeptide of type 3 procollagen is a heritable trait and is associated with liver fibrosis assessed by magnetic resonance elastography. Hepatology. 2019;70(1):127–41. https://doi.org/10.1002/hep.30610.
69. Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, et al. ADAPT: an algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. Hepatology. . https://doi.org/10.1002/hep.30163.
70. Boyle M, Tiniakos D, Schattenberg JM, Ratziu V, Bugianessi E, Petta S, et al. Performance of the PRO-C3 collagen neo-epitope biomarker in non-alcoholic fatty liver disease. JHEP Reports. 2019. https://doi.org/10.1016/j.jhepr.2019.06.004.
71. 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. 2008;57(10):1441–7. https://doi.org/10.1136/gut.2007.146019.
72. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, et al. Liver fibrosis in overweight patients. Gastroenterology. 2000;118(6):1117–23. https://doi.org/10.1016/s0016-5085(00)70364-7.
73. Boursier J, de Ledinghen V, Leroy V, Anty R, Francque S, Salmon D, et al. A stepwise algorithm using an at-a-glance first-line test for the non-invasive diagnosis of advanced liver fibrosis and cirrhosis. J Hepatol. 2017;66(6):1158–65. https://doi.org/10.1016/j.jhep.2017.01.003.
74. Bril F, Millan L, Kalavalapalli S, McPhaul MJ, Caulfield MP, Martinez-Arranz I, et al. Use of a metabolomic approach to non-invasively diagnose non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2018;20(7):1702–9. https://doi.org/10.1111/dom.13285.
75. Cassinotto C, Boursier J, de Ledinghen V, Lebigot J, Lapuyade B, Cales P, et al. Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology. 2016;63(6):1817–27. https://doi.org/10.1002/hep.28394.
76. Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156(6):1717–30. https://doi.org/10.1053/j.gastro.2019.01.042.
77. Siddiqui MS, Vuppalanchi R, Van Natta ML, Hallinan E, Kowdley KV, Abdelmalek M, et al. Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019;17(1):156–63 e2. https://doi.org/10.1016/j.cgh.2018.04.043.
78. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51(2):454–62. https://doi.org/10.1002/hep.23312.
79. Cui J, Heba E, Hernandez C, Haufe W, Hooker J, Andre MP, et al. Magnetic resonance elastography is superior to acoustic radiation force impulse for the diagnosis of fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease: A prospective study. Hepatology. 2016;63(2):453–61. https://doi.org/10.1002/hep.28337.
80. Yoneda M, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, et al. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. Radiology. 2010;256(2):640–7. https://doi.org/10.1148/radiol.10091662.
81. Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol. 2019;17(4):630–7 e8. https://doi.org/10.1016/j.cgh.2018.05.059.
82. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology. 2016;150(3):626–37 e7. https://doi.org/10.1053/j.gastro.2015.11.048.
83. Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. Gastroenterology. 2017;152(3):598–607 e2. https://doi.org/10.1053/j.gastro.2016.10.026.
84. Chen J, Yin M, Talwalkar JA, Oudry J, Glaser KJ, Smyrk TC, et al. Diagnostic performance of MR elastography and vibration-controlled transient elastography in the detection of hepatic fibrosis in patients with severe to morbid obesity. Radiology. 2017;283(2):418–28. https://doi.org/10.1148/radiol.2016160685.
85. Caussy C, Chen J, Alquiraish MH, Cepin S, Nguyen P, Hernandez C, et al. Association between obesity and discordance in fibrosis stage determination by magnetic resonance vs transient elastography in patients with nonalcoholic liver disease. Clin Gastroenterol Hepatol. 2018;16(12):1974–82 e7. https://doi.org/10.1016/j.cgh.2017.10.037.
86. Blond E, Disse E, Cuerq C, Drai J, Valette PJ, Laville M, et al. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral? Diabetologia. 2017;60(7):1218–22. https://doi.org/10.1007/s00125-017-4264-9.
87. Sberna AL, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, et al. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with type 2 diabetes. Diabet Med. 2017. https://doi.org/10.1111/dme.13565.
88.•• Younossi Z, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. GS-06-Positive results from REGENERATE: a phase 3 international, randomized, placebo-controlled study evaluating obeticholic acid treatment for NASH. Journal of Hepatology. 2019;70(1):e5. https://doi.org/10.1016/S0618-8278(19)30006-4 **Interim analysis of the first phase 3 clinical trial for the treatment of NASH with positive results presented in International Liver Congress in Vienna 2019.**
89. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675–85. https://doi.org/10.1056/NEJMoa0907929.
90. Kowdley K, Wilson LA, Van Natta ML, Pai RK, Sanyal AJ. Efficacy and safety of vitamin E in nonalcoholic steato- hepatitis patients with and without diabetes: Pooled analysis from the PIVENS and FLINT NIDDK NASH CRN Trials. Hepatology. 2015;62(S1):264A. https://doi.org/10.1002/hep.28183.

91.• Romero-Gomez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017;67(4):829–46. https://doi.org/10.1016/j.jhep.2017.05.016 **Important review article of the impact of diet and physical activity for the treatment of NAFLD.**

92. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138–53. https://doi.org/10.1136/gutjnl-2017-313884.

93. Shouhed D, Steggerda J, Burch M, Noureddin M. The role of bariatric surgery in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Expert Rev Gastroenterol Hepatol. 2017;11(9):797–811. https://doi.org/10.1080/17474124.2017.1355731.

94. Mathurin P, Hollebecque A, Arnalsteen L, Buob D, Leteurtre E, Caiazzo R, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. Gastroenterology. 2009;137(2):532–40. https://doi.org/10.1053/j.gastro.2009.04.052.

95. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149(2):379–88; quiz e15-6. https://doi.org/10.1053/j.gastro.2015.04.014.

96. Goh GB, Schauer PR, McCullough AJ. Considerations for bariatric surgery in patients with cirrhosis. World Journal of Gastroenterology. 2018;24(28):3112–9. https://doi.org/10.3748/wjg.v24.i28.3112.

97.• Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large U. S. claims database. Hepatology. 2018;68(6):2230–8. https://doi.org/10.1002/hep.30094 **Important recent study that highlights the high economic burden of NAFLD.**

98. Sayiner M, Otgonsuren M, Cable R, Younossi I, Afendy M, Golabi P, et al. 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. https://doi.org/10.1097/MCG.0000000000000567.

99. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. 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.

100. Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of nonalcoholic steatohepatitis screening. Eur Radiol. 2015;25(11):3282–94. https://doi.org/10.1007/s00330-015-3731-2.

101. Klebanoff MJ, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: a clinical and cost-effectiveness analysis. Hepatology. 2017;65(4):1156–64. https://doi.org/10.1002/hep.28958.