

GUIDELINES

Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China)

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KEYWORDS: diagnosis, guidebooks, metabolic syndrome, nonalcoholic fatty liver diseases, nonalcoholic steatohepatitis, therapy

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an acquired metabolic stress-induced liver disease associated closely with genetic susceptibility and insulin resistance (IR), the spectrum of the disease includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and related liver cirrhosis, and hepatocellular carcinoma (HCC).^{1,2} NAFLD not only causes liver disease-related morbidity and mortality, but is also closely associated with a high incidence of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease, and even extrahepatic malignancy. Due to the increasing prevalences of obesity and MetS, NAFLD now ranks the leading cause of chronic liver disease and abnormal liver function tests in "healthy" population in China. Furthermore, its prevalence is increasing in hepatitis B virus (HBV)-infected patients as well.^{3–5} NAFLD with and without chronic hepatitis B (CHB) thus becomes a serious health concern in China.

In order to standardize the diagnosis, management, screening and follow-up of NAFLD patients, the Chinese National Consensus Workshop on NAFLD had organized concerned experts and established the

first guidelines on NAFLD in 2006, which was updated in 2010.⁶ With reference to the latest global advances in NAFLD,^{7–10} the National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association in conjunction with the Fatty Liver Disease Expert Committee, Chinese Medical Doctor Association again revised the guidelines.

The recommendations in the updated guidelines are intended to aid the physicians in the diagnosis, management, screening and follow-up of NAFLD patients; however, they are not mandatory standards and cannot cover or resolve all issues related to NAFLD in clinical setting. When facing a specific patient, clinicians should be able to make reasonable diagnostic and therapeutic strategies based on a full understanding of the best clinical evidence, available medical resources, a comprehensive consideration of patient's specific condition and wishes, and in accordance with their own knowledge and experiences. As the research work on NAFLD advances rapidly, the guidelines should be updated and improved continually based on the progresses of the discipline and clinical requirements in the near future. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, the evidences to support the guidelines are stratified into three categories as A, B and C, and the recommendations are grouped into two grades as 1 and 2 (Table 1).¹¹

The guidelines have been published in Chinese on the *Journal of Practical Hepatology*. 2018;21(2):177–186.

2 | TERMINOLOGY

Terminology and work definitions of NAFLD and MetS in the guidelines are listed in Tables 2 and 3.^{7–10,12,13}

3 | EPIDEMIOLOGY AND SCREENING

Nowadays, NAFLD is recognized as one of the most common chronic liver diseases worldwide. The global prevalence of NAFLD is 6.3%–45% (median 25.2%, 95% confidence interval [CI] 22.1%–28.7%) in the general population, among which NASH accounts for 10%–30%; its prevalence is the highest in the Middle East and South America, and the lowest in Africa.¹⁴ The prevalence of NAFLD in most Asian countries, including China, remains above 25%.¹⁴ According to the epidemiological surveys from Shanghai and Beijing, China, the prevalence of NAFLD diagnosed by ultrasound in general adults increased from 15% to over 31% during a 10-year period; in adults aged <50–55 years the prevalence of NAFLD is higher in men than in women, while in those aged over 50–55 years the prevalence in women increases rapidly and is even higher than that in men.^{4,8,14,15} Based on a survey conducted at a local manufactory in Shanghai, the detectable rate of NAFLD among health screening workers with elevation of serum alanine aminotransferase (ALT) level raised from 26% to above 50% from 1995 to 2001. Currently, NAFLD is the main cause for “healthy” population with elevated serum levels of ALT and gamma-glutamyl peptidase (GGT).¹⁵ A recent Hong Kong study showed that the accumulative incidence of NAFLD in adults was 13.5% during the 3–5-year follow-up, but less patients had severe hepatic steatosis or advanced liver fibrosis.¹⁶ The Ningbo (Zhejiang Province) study demonstrated that the prevalence and annual incidence of NAFLD among non-obese adults were 7.3% and 1.8%, respectively.¹⁷ In addition, the percentages of NASH and liver cirrhosis in 152 patients with liver biopsy-proven NAFLD were 41.4% and 2%, respectively.¹⁸ Similarly, in another liver biopsy-proven study with

101 patients, the presences of NASH and liver cirrhosis were 54% and 3%, respectively.¹⁹

It is well-known that NAFLD is associated with MetS and T2DM. The prevalence of NAFLD parallels the epidemic of obesity, T2DM

TABLE 2 Terminology and working definitions in non-alcoholic fatty liver disease (NAFLD)^{7–10}

Terminology	Working definitions
NAFLD	A spectrum of histopathology- or imaging-proven hepatic fat accumulation, including NAFL, NASH, and associated liver cirrhosis. No history of alcohol overconsumption (<210 g per week in men and <140 g per week in women during the past 12 months). No long-term history of taking steatogenic medications, i.e., amiodarone, methotrexate, tamoxifen and glucocorticoids. Exclusion of the diseases that can lead to fatty liver such as genotype 3 HCV infection, Wilson's disease, autoimmune hepatitis, total parenteral nutrition, hypo- β -lipoproteinemia, congenital lipodystrophy, and celiac disease.
NAFL	An early form of NAFLD, defined as significant hepatic steatosis involving $\geq 5\%$ of the hepatocytes, without evidence of hepatocellular injury and liver fibrosis. NAFL can be diagnosed either by imaging or histopathology.
NASH	A progressive form of NAFLD, defined as hepatic steatosis involving $\geq 5\%$ of the hepatocytes, lobular inflammation, and hepatocyte ballooning, without or with liver fibrosis. Liver biopsy remains the gold standard for the diagnosis of NASH and staging of fibrosis. Early NASH, advanced NASH and NASH cirrhosis are defined as F0-F1, F2-F3 and F4, respectively.
NAFLD-associated cirrhosis	A form of liver cirrhosis related to NASH in patients with metabolic syndrome, or cryptogenic cirrhosis associated with obesity, type 2 diabetes mellitus, metabolic syndrome, etc.

HCV, hepatitis C virus; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.

TABLE 1 Evidence quality and grades of strength of recommendation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system¹¹

Grades	Symbol	Details
Evidence		
High quality	A	Further research is less likely to change the confidence in the estimated effect.
Moderate quality	B	Further research is likely to have an important impact on the confidence in the estimated effect.
Low quality	C	Further research is most likely to have an important impact on the confidence in the estimated effect and may change the estimated effect.
Recommendation		
Strong	1	The final recommendation is based on the quality of evidence, patient's prognosis and treatment costs.
Weak	2	The final recommendation is based on evidence with mixed values, uncertainties and higher costs.

TABLE 3 Terminology and working definition of metabolic syndrome (MetS)

Terminology	Working definitions
MetS	Diagnosis of MetS should meet three and more of the following metabolic risk factors: abdominal obesity, arterial hypertension, hypertriglyceridemia, low HDL-C, and hyperglycemia. These are risk factors for both cardiovascular diseases and liver diseases.
Abdominal obesity	Waist circumference >90 cm in men and >85 cm in women
Arterial hypertension	Arterial blood pressure $\geq 130/85$ mmHg or on antihypertensive therapy
Hypertriglyceridemia	Fasting serum triglycerides ≥ 1.7 mmol/L or on lipid-lowering medications
HDL-C	Fasting serum HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women
Hyperglycemia	Fasting blood glucose ≥ 5.6 mmol/L or ≥ 7.8 mmol/L at 2 hours postprandial, or with a history of type 2 diabetes mellitus

HDL-C, high-density lipoprotein cholesterol.

and MetS in China. Currently, the prevalences of overall obesity, abdominal obesity and T2DM in China reach 7.5%, 12.3% and 11.6%, respectively.^{3,4} The prevalences of NAFLD among patients with obesity, hyperlipidemia and T2DM have been reported to be 60%–90%, 27%–92% and 28%–70%, respectively.^{14,20} Therefore, many NAFLD patients have co-existing obesity (51.3%, 95% CI 41.4%–61.2%), hyperlipidemia (69.2%, 95% CI 49.9%–83.5%), arterial hypertension (39.3%, 95% CI 33.2%–45.9%), T2DM (22.5%, 95% CI 17.9%–27.9%), and MetS (42.5%, 95% CI 30.1%–56.1%).¹⁴

Major risk factors for NAFLD include obesity-related high-calorie dietary rich in saturated fat and fructose, and sedentary lifestyles. Increased waist circumference and IR have a more significant correlation with NAFLD than increased subcutaneous fat deposit and high body mass index (BMI). By using the World Health Organization (WHO) 2000 Western Pacific diagnostic criteria for overweight and obesity, more than 10% NAFLD occur in patients with BMI of <23 kg/m² ("lean" NAFLD). "Lean" NAFLD patients often have a history of recent weight gain or increasing in waist circumference. Up to one-third of the NAFLD patients with normal BMI meet the criteria of MetS. NAFLD alone has a better value in predicting MetS than BMI (overall obesity) and waist circumference (abdominal obesity).^{3,4} Sarcopenia is an independent risk factor for NAFLD in both "lean" and obese patients.⁴ The genetic susceptible genes of NAFLD in Chinese Han population were similar to other ethnic populations, as reported in the previous literatures. *PNPLA3* I148M and *TM6SF2* E167K variations are closely related to the prevalence and severity of NAFLD. This group of NAFLD patients may not have characteristics of IR and MetS.^{4,21} Other independent risk factors for the occurrence and development of NAFLD include hyperuricemia, hyperhemoglobinemia, hypothyroidism, hypopituitarism, sleep apnea syndrome and polycystic ovary syndrome.^{22–25}

Recommendations

1. Since NAFLD is the leading cause for elevated serum liver enzymes in healthy population, patients with elevated serum ALT and GGT levels should thus be screened for NAFLD. (A1)
2. In patients with obesity, hypertriglyceridemia, T2DM and MetS, serum liver enzyme tests and abdominal ultrasound should be performed to screen for NAFLD. (A1)
3. Since unhealthy lifestyle plays a significant role in the development of NAFLD, patients suspected for NAFLD should be investigated for their dietary and exercise habits. (A1)

4 | NATURE HISTORY AND FOLLOW-UP

NAFLD is a chronic liver disease with indolent onset and slow progression to cirrhosis. On average, NASH-related liver fibrosis advances one stage during every 7–10 years.^{4,14} Significant liver fibrosis (F2–F4) is an only independent prognostic factor for liver-related outcomes in NAFLD patients. In a recent meta-analysis investigating 1495 NAFLD patients with 17 452 patient-year of follow-up, the all-cause mortality, especially liver disease-related mortality, were high in

patients presenting significant fibrosis or advanced fibrosis (F3, F4).²⁶ The incidence of liver cirrhosis is only 0.6%–3% after 10–20-year follow-up in NAFL patients. However, that in NASH patients is 15%–25% after 10–15-year follow-up.^{4,15} NAFLD patients with MetS and/or persistent elevated serum ALT levels often have a high probability of liver biopsy-proven NASH. On average, about 40.8% (95% CI 34.7%–47.1%) NASH patients developed progressive liver fibrosis, with fibrosis advancing about 0.09% (95% CI 0.06%–0.12%) stage annually.¹⁵ NAFLD-associated liver cirrhosis and HCC occur more often in patients aged over 65 years with MetS and T2DM. Comparing to obese NAFLD patients, those with BMI <25 kg/m² have less severe liver inflammation and fibrosis.^{27,28} In a study from Hong Kong SAR, China on 307 liver biopsy-proven NAFLD patients and with a median follow-up of 49 months, mortality and mobility occurred only among the obese patients, including six deaths, two with HCC, and one with acute-on-chronic liver failure (ACLF).²⁷ NASH patients with fibrosis and co-existing arterial hypertension are at a high risk of developing liver disease progression. Patients with NAFLD-related cirrhosis often have a long compensatory phase. However, mortality in cirrhotic patients increases when they develop decompensation or HCC. NAFLD with and without cirrhosis are closely related to HCC. The incidence of HCC in NAFLD patients is 0.29%–0.66%. NAFLD patients with cryptogenic cirrhosis, MetS, T2DM and *PNPLA3* rs738409 C>G are at a high risk of developing HCC.^{4,8} Patients with NASH-related cirrhosis have increased risk of developing HCC, they should thus be on routine HCC surveillance. Although up to 30%–50% of HCC occurs in non-cirrhotic NASH patients, the overall risk of developing HCC in these patients is relatively low, HCC surveillance is not recommended for non-cirrhotic patients with NAFL or NASH.^{4,9,10}

In the general population, NAFLD diagnosed by either elevated serum levels of ALT and GGT or ultrasound increases the incidences of MetS and T2DM. After being followed up for 5–10 years, the risks for developing T2DM, MetS and cardiovascular disease in NAFLD patients are 1.86-fold (95% CI 1.76–1.95), 3.22-fold (95% CI 3.05–3.41) and 1.64-fold (95% CI 1.26–2.13), respectively.^{29–31} Comparing to the controls, the all-cause mortality is significantly high in NAFLD patients, mostly due to cardiovascular disease, extrahepatic malignancy and liver decompensation. After careful grouping of MetS and eliminating other cardiovascular risk factors, the incidence of coronary heart disease still increases significantly in NAFLD patients after liver transplantation. Therefore, coronary heart disease is an important prognostic factor in liver transplant recipients.³²

Though NAFLD is highly related to increased incidences of atherosclerotic coronary cardiovascular and cerebrovascular diseases, concurrent fatty liver may not have a prognostic effect in these patients.^{33,34} Comparing to female controls, female NAFLD patients have high incidence of coronary heart disease and stroke at earlier age. The liver disease-related mortality rates of NAFLD and NASH patients were 0.77‰ (95% CI 0.33‰–1.77‰) and 11.77‰ (95% CI 7.10‰–19.53‰), and the all-cause mortality rates were 15.44‰ (95% CI 11.72‰–20.34‰) and 25.56‰ (95% CI 6.29‰–103.80‰), respectively.¹⁴ Furthermore, NAFLD patients, especially those with NASH, have been found to be associated with high incidences of osteoporosis, chronic kidney disease, colorectal carcinoma, breast cancer

and some other chronic diseases.^{35–37} In “lean” NAFLD, especially NASH, patients with high homeostasis model assessment-IR (HOMA-IR) also have a high risk of metabolic and cardiovascular diseases and progressive liver disease.^{4,8,15}

Recommendations

4. Because obesity, arterial hypertension, T2DM and MetS are related to the poor prognosis in NAFLD patients, these patients should be monitored for the complications of metabolic, cardiovascular and liver diseases (B1). Regular follow-up is also recommended in “lean” NAFLD patients with concurrent IR and/or abdominal obesity (B2).
5. NAFLD is a well-known concomitant of T2DM. Therefore, NAFLD patients should be tested regularly for fasting blood glucose, glycated hemoglobin (HbA1c), or even oral glucose tolerance test (OGTT) to screen for possible T2DM. (A1)
6. Since NAFLD patients have high cardiovascular and cerebrovascular disease-related mortality, NAFLD patients should be regularly assessed for the risk of cardiovascular and cerebrovascular diseases. (A1)
7. NASH patients with cirrhosis should be screened for esophageal-gastric varices and hepatocellular carcinoma (B1). There is no sufficient evidence to support the screening of colorectal and breast cancers in NAFLD patients (C1).

5 | DIAGNOSIS AND EVALUATION

The diagnosis of NAFLD requires the presence of significant hepatic steatosis confirmed by imaging or histological examination, in the absence of other causes for fatty liver diseases, especially excluding overconsumption of alcohol. Since NAFLD patients are often asymptomatic, most suspected NAFLD patients only have incidental elevated serum ALT and GGT levels or imaging-confirmed diffuse fatty liver. Suspected NAFLD patients need to be evaluated for the degree of hepatic steatosis with and without inflammation, fibrosis, as well as the risk of concurrent metabolic and cardiovascular diseases, and other likely causes that may lead to chronic liver diseases.³⁸

5.1 | Definition of NAFLD

NAFLD refers to a form of fatty liver disorder that is usually attributed to over-nutrition and its complications, particularly in genetically predisposed individuals. The clinical-pathological spectrum of NAFLD includes NAFL, NASH, NASH-related cirrhosis and HCC. For strict definition of NAFLD, significant alcohol consumption (≥ 210 g/week in men and ≥ 140 g/week in women) and other causes of hepatic fat accumulation must be excluded. Therefore, in patients with histopathologic features and/or imaging of NAFLD, the following conditions should be excluded, i.e. alcoholic liver disease (ALD), genotype 3 hepatitis C virus (HCV) infection, autoimmune hepatitis, Wilson's disease, long-term use of steatogenic medications (i.e. tamoxifen, amiodarone, valproate, methotrexate, glucocorticoids, etc.), total parental nutrition, inflammatory bowel disease, celiac disease, Cushing's syndrome,

hypo- β -lipoproteinemia, lipodystrophy-induced diabetes, and Mauriac syndrome.³⁸ Similarly, other likely cause-induced liver injury need to be excluded carefully before the diagnosis of NAFLD-related abnormal liver enzymes and cryptogenic liver cirrhosis. In clinical practice, patients with other causes-related liver diseases such as chronic hepatitis B can have co-existing IR and MetS, which result in concurrent NAFLD. Comparing to the health controls, NAFLD patients are more susceptible to develop drug-induced liver injury (DILI) and superimposed other likely cause-induced ACLF. In patients co-existing with other chronic liver diseases, obesity, T2DM, MetS and related fatty liver might further deteriorate liver injury, and increase risk for liver cirrhosis and HCC.

Recommendations

8. If a patient is suspected of having NAFLD/NASH, it is necessary to exclude other causes for fatty liver disease, including alcohol overconsumption, genotype 3 HCV infection, Wilson's disease, autoimmune hepatitis and steatogenic medications (A1). Patients with NAFLD/NASH should also be evaluated for concurrent chronic hepatitis B (B1).
9. The combination of NAFLD with chronic viral hepatitis or DILI often result in severe liver damage, and the effect of metabolic risk factors on the development of hepatic steatosis and liver injury should be evaluated objectively. (B1)
10. Pathology- and/or imaging-proven NAFLD patients should be tested for liver biochemistries as well as screened for MetS-related disorders. Additionally, physicians should take into account the patient's alcohol consumption, and evaluate the combined effect of mild drinking and metabolic risk in the development of fatty liver disease. (A1)

5.2 | Diagnosis of hepatic steatosis

Significant hepatic steatosis by histology and/or fatty liver by imaging is an important feature of NAFLD. Steatosis and its grade may predict the severity of histological features (e.g., hepatocyte ballooning and steatohepatitis) as well as the risks of MetS and T2DM in NAFLD patients. Conventional B-type ultrasound is currently the most commonly used imaging modality for the diagnosis of fatty liver disease based on the findings of liver anterior echogenicity (“bright liver”), far-field echo attenuation and unclear intrahepatic duct structure. In addition to identify diffuse, localized or non-homogenous fatty liver, the routine upper abdominal ultrasound can provide general information on liver, gallbladder, biliary ducts, pancreas, spleen and kidneys. However, ultrasound has low sensitivity for diagnosing mild steatosis and lacks specificity, because “bright liver” could be observed in patients with diffuse liver fibrosis and early cirrhosis as well.³⁹ Using vibration controlled transient elastography (VCTE) to obtain controlled attenuation parameter (CAP) is a new promising tool for quantifying hepatic fat accumulation. CAP can detect $\geq 5\%$ hepatic steatosis and is able to distinguish accurately between mild and moderate-to-severe steatosis. However, compared to ultrasound, CAP sometimes overestimates the degree of hepatic steatosis. The accuracy of CAP in diagnosing hepatic steatosis decreases when BMI is over 30 kg/m^2 , with a

skin-to-liver capsule distance of >25 mm, and the interquartile range (IQR) of CAP >40 dB/m.^{19,39–41} The diagnostic cut-off values for CAP in differing different degrees of steatosis and documenting the dynamic fatty changes in the liver remain unclear. Additionally, the diagnostic values of computed tomography (CT) and conventional magnetic resonance imaging (MRI) in fatty liver are not superior to that of ultrasound. CT and MRI are often used to confirm ultrasonic finding of fatty liver with islands of normal liver, focal fatty changes and space-occupying lesion.⁴² Magnetic resonance spectroscopy (MRS) and MRI-based proton density fat fraction (MRI-PDFF) were more accurate than CAP for detecting hepatic steatosis in patients with biopsy-proven NAFLD.^{8–10} However, MRS and MRI-PDFF are expensive and their applications are limited in clinical setting. Clinical decision aids, such as fatty liver index or hepatic steatosis index based on different calculation of BMI, waist circumference, serum levels of triglyceride (TG) and GGT, can serve as an alternative to imaging examinations in large-scale epidemiologic studies and under certain clinical circumstances. However, the diagnostic values of these parameters vary by age and ethnicity.^{8–10}

Recommendation

11. B-type ultrasound is the first choice for the imaging diagnosis of hepatic steatosis in fatty liver (A1), which can also provide additional diagnostic information. CAP is a good alternative in assessing steatosis quantitatively (B1).

5.3 | Diagnosis of steatohepatitis

NASH, a progressive form of NAFLD, is a key stage from simple hepatic steatosis to liver cirrhosis and HCC. NASH occurs in 10%–30% of the NAFLD patients, and it is important to identify these NASH patients clinically. Currently, all non-invasive imaging studies or laboratory tests cannot accurately diagnose NASH. The presences of MetS, persistent elevated serum ALT level, increased serum cytokeratin (CK)-18 fragment (M30 and M65) levels are only suggestive of possible NASH in NAFLD patients.⁴³ Serum ALT within normal range may be observed in NAFLD patients with hepatic inflammatory injury, while those with elevated ALT may not have NASH. Therefore, liver biopsy remains the clinical gold standard for diagnosing NASH and fibrosis in NAFLD patients, regardless of its invasiveness, high cost, possible complications, sampling errors, and variable intra- and inter-observer agreement.^{8–10} Biopsied liver tissues are evaluated microscopically for hepatic steatosis, lobular inflammation, ballooning hepatocytes and stage of fibrosis. The presence of hepatic steatosis with lobular/portal inflammation and hepatocellular ballooning is the prerequisite for the diagnosis of NASH in patients with NAFLD. Specific scoring systems are available to evaluate the severity of NASH and fibrotic stages in NAFLD, including Steatosis Activity Fibrosis (SAF; including hepatic steatosis, activity of both inflammation and hepatocyte ballooning, and fibrosis) score from the European Fatty Liver Inhibition of Progression (FLIP) Consortium and the NAFLD Activity Score (NAS [plus fibrotic stage]) from the American Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN).^{8–10,12,13,44} The SAF was designed for both clinical diagnosis and clinical trials,

which is easy to be used to differentiate NAFL and NASH at different fibrotic stages. The NAS only includes hepatic steatosis, inflammation and ballooning hepatocytes, and stage of fibrosis is reported separately, and NAS was primarily designed for the clinical trials of NASH.^{12,13,44}

Recommendations

12. The diagnosis of NASH requires histopathologic evidence on liver biopsy (A1), and the presence of macrovesicular steatosis with lobular inflammation and hepatocellular ballooning is the prerequisite for its diagnosis. According to the SAF scoring system, NAFLD can be categorized histologically into simple hepatic steatosis, early NASH (F0, F1), fibrotic NASH (F2, F3) and NASH cirrhosis (F4) (C2).
13. Liver biopsy should be considered in NAFLD patients with MetS, persistently high serum aminotransferases, and/or high serum levels of CK-18 fragments (M30 and M65), as they are at high risk of having NASH. (A2)

5.4 | Assessment of liver fibrosis

The stage of liver fibrosis is the only prognostic factor, which can accurately predict patient's liver-related morbidity and mortality in NAFLD patients. In these patients, accurate staging of liver fibrosis and cirrhosis in predicting clinical outcomes has better value than distinguishing NAFL from NASH. Many factors may affect the dynamic changes in liver fibrosis in NAFLD patients. By using a combination of different clinical parameters and serum biomarkers for fibrosis, several predictive models have been established, which can roughly subdivide NAFLD patients into those without and with significant fibrosis (\geq F2) and advanced liver fibrosis (F3, F4). Among these models, NAFLD fibrosis score (NFS) might have the highest value in identifying NAFLD patients with higher likelihood of having bridging fibrosis (F3) or cirrhosis (F4). However, these non-invasive liver fibrosis predictive models do not meet the quality requirements for "Diagnostic Accuracy Reporting Standard." Recently, elastographic modalities-based biomarkers such as liver stiffness measurement (LSM) have significantly improved the predictive ability of liver fibrosis. LSM based on VCTE (FibroScan, Echosens, Paris, France) provides better predictive value for detection and quantification of liver fibrosis than NFS, aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 (FIB-4) index and other non-invasive predictive models. It can be used to differentiate NAFLD patients with no or mild fibrosis (F0, F1) from those with advanced fibrosis (F3, F4). However, up to date, there has been no acceptable threshold for the diagnosis of liver cirrhosis in NAFLD.⁴⁵ Obesity affects the performance of the FibroScan test; up to 25% of the patients fail to obtain accurate LSM values by FibroScan with M probe. Furthermore, clinicians should consider the etiology of liver disorders while interpreting LSM thresholds to determine the stage of fibrosis. Severe hepatic steatosis (CAP >310 dB/m), significant liver inflammation (serum transaminases >5 \times upper limit of normal [ULN]), liver congestion or cholestasis will increase LSM values and result in overestimation of fibrotic stage.^{45,46} Compared to VCTE, real-time MRI-based elastography (MRE) has a similar positive

predictive value (PPV) but higher negative predictive value (NPV) in diagnosing NAFLD patients with cirrhosis.⁴⁷ Liver biopsy should be considered in NAFLD patients with high NFS or FIB-4 index, or in those at high risks for advanced fibrosis and cirrhosis based on liver stiffness measured by VCTE or MRE. However, MRE is not available in routine clinical practice. In contrast to the abovementioned non-invasive biomarkers, liver biopsy for histopathologic assessment provides accurate stage of liver fibrosis. By using NAS CRN (NAS plus fibrotic stage) or SAF staging system, histopathologic assessment will provide information on the location and amount of fibrosis, and presence or absence of liver cirrhosis.^{8–10,12,13,44} Additionally, liver biopsy can confirm the type of cirrhosis (NASH-related, steatotic or NAFLD-related cryptogenic cirrhosis).

Recommendations

14. Serum biomarkers and related scoring system, as well as liver stiffness by elastographic modalities, should be used to exclude NAFLD patients with advanced liver fibrosis (A2) and monitor the progression of liver fibrosis (C2). However, these non-invasive diagnostic methods, even used in combination, still have low accuracy in diagnosing septa fibrosis and cirrhosis. Liver biopsy for histopathologic assessment is recommended for NAFLD patients at a high risk of advanced fibrosis (B2).
15. Liver biopsy is recommended when non-invasive methods are not able to determine whether patients have steatohepatitis or the potential causes of abnormal liver enzymes (B1). Before considering NAFLD as the cause for cryptogenic cirrhosis, liver disorders attributed to other likely causes should be carefully excluded (C2).

5.5 | Assessment of metabolic and cardiovascular risk factors

The relationship between NAFLD and metabolic and cardiovascular risk factors and their complications are quite close.^{1–4} Metabolic disorder is not only related to high-incidence T2DM and cardiovascular diseases, but also directly involved in the occurrence and development of NAFLD and NASH. Patients suspicious for NAFLD should be assessed thoroughly for their changes in anthropometric indexes and blood biochemical indexes including serum lipid profiles. The modified International Diabetes Federation criteria of MetS can be used to diagnose obesity and MetS in Chinese.⁴⁸ Since NAFLD patients, regardless of NAFL or NASH, are at high risks for cardiovascular events and mortality, aggressive assessment of risk factors related to cardiovascular diseases should thus be considered in all patients with NAFLD. In addition, NAFLD patients should also test their serum fasting glucose and HbA1c regularly. When needed, these patients should also have a standard OGTT of 75 g glucose to screen for impaired glucose tolerance and T2DM.^{8,48} Except for polymorphism *PNPLA3* I148M-associated NAFLD, IR is the most common feature in both NAFLD and NASH patients. HOMA-IR index can be used to evaluate IR in the general population, as calculated using the following formula: (fasting plasma glucose [FPG; mmol/L] × fasting serum insulin [FINS; mIU/L])/22.5. In healthy adults, the HOMA-IR index is around

1. In NAFLD patients without glucose regulatory impairment or diabetes, HOMA-IR index can be used to evaluate insulin sensitivity. In “lean” fatty liver patients with evidence of IR, the diagnosis of NAFLD can be established even without metabolic risk factors. During the follow-up period, decrease in HOMA-IR index might indicate the improvement of metabolic disorders and the attenuation of liver injury in patients with NAFLD. Body composition analysis helps identify “lean” patients with occult obesity (increase in body fat mass and/or its percentage of body weight) and sarcopenia.

Recommendation

16. Metabolic and cardiovascular risk factors should be evaluated in all patients with NAFLD (A1). HOMA-IR is an alternative in assessing IR in non-diabetic population (A1), which is helpful for diagnosing NAFLD in “lean” patients without metabolic risk factors (B2).

6 | PREVENTION AND TREATMENT

NAFLD is the hepatic manifestation of obesity and MetS, and the majority of NAFLD patients are at the stage of NAFL without liver injury. Therefore, the primary goal for managing NAFLD is to improve IR by reducing body fat mass, and to prevent and treat MetS, T2DM as well as their associated complications, which could eventually reduce disease burden and improve patient's quality of life and prolong life expectancy. The secondary goal is to prevent the progression of hepatic steatosis to steatohepatitis and to avoid ACLF in NASH through reducing fat accumulation in the liver and avoiding “second hit”. In patients with NASH or steatotic fibrosis, the therapeutic aims should also include the prevention of liver disease progression, and treatment of liver cirrhosis, HCC, and other related complications.^{6,38}

During the treatment and follow-up of NAFLD patients, it is recommended to closely monitor changes in patient's lifestyle, body weight, waist circumference and blood pressure. Serum biochemical parameters including HbA1c should be tested every 3–6 months, and upper abdominal ultrasound examination should be repeated every 6–12 months. Drug-related adverse reactions need to be monitored as well and medications should be adjusted accordingly. The normalization of serum transaminases and the disappearance of hepatic steatosis on imaging examination do not always parallel the hepatic histological attenuation of inflammation and fibrosis. The role of dynamic observation of hepatic steatosis and fibrosis by VCTE, MRS and/or MRE in evaluating the efficacy of NAFLD treatment and identifying new drugs remains unclear. Regular liver biopsy to assess the severity of NASH and staging of fibrosis remains the only valuable method. The primary end-point for treating NASH is to reduce both the severity of steatohepatitis and stage of fibrosis, to achieving the goal that at least there is no aggravation in steatohepatitis with reduction in liver fibrosis, or alleviation of NASH without aggravation of liver fibrosis.^{9,10,38,49}

6.1 | Lifestyle modification

Weight loss and the reduction of waist circumference are the most important managements for the prevention and treatment of NAFLD

and its coexisting metabolic and cardiovascular risk factors. For NAFLD patients who are overweight, obese or with subtle gain of weight and “occult obesity”, it is recommended to correct unhealthy behaviors by introducing healthy diet and physical exercises.⁵⁰ Daily dietary calorie intake needs to be controlled and the recommended reduction in daily calorie is 2092–4184 KJ (500–1000 kcal). Adjusting major components of food, keeping balanced diet by taking adequate amounts of fat and carbohydrate, limiting sugar-sweetened soft drinks, bakeries, and refined foods, increasing whole-grain foods, omega-3 fatty acids, and dietary fiber intake. NAFLD patients should be encouraged to stay with three meals a day that are taking on time and with regular amounts, especially to control strictly calorie intake at dinner and avoid postprandial food intake.^{51,52} Patients should avoid sedentary lifestyle and have regular physical exercise to increase skeletal muscle mass and prevent sarcopenia. Depending on personal interests, patients should have moderate aerobic exercise for 30 minutes per day, five times a week, or have intensive aerobic exercise for 20 minutes per day, three times a week, and additional 8–10 sets of resistance training twice weekly.⁵³ Within 1 year, weight loss of 3%–5% of body weight in NAFLD patients can improve MetS and reverse simple hepatic steatosis, that of 7%–10% can markedly reduce serum levels of transaminases and improve NASH. However, liver fibrosis can only be reversed when weight loss reaches at least 10% and maintains for 1 year.⁵⁴ Unfortunately, less than 10% of obese patients can achieve a weight loss of 10% within 1 year of intensive lifestyle modification. Therefore, multidisciplinary approaches, including dietitians, and sports rehabilitation therapists, play a significant role in motivating NAFLD patients for long-term lifestyle modification. The implementation of ‘Health China 2030’ is expected to control the prevalences of obese, T2DM and NAFLD in China.⁴

Recommendations

17. Patients with NAFLD should adapt their lifestyle by adhering to healthy diet and increased physical activity (C2), and weight loss of at least 5%–7% of body weight within 1 year may improve serum biochemistry indexes and histopathological changes of NAFLD (B1).
18. Dietary guidelines should consider restricting calorie intake (daily reduction by 500–1000 kcal), adjusting dietary structure and avoiding poor dietary behaviors (B1). Hypocaloric diet with or without excise can result in weight loss and is likely to reduce liver fat deposit (A1).
19. Moderate aerobic exercise and/or resistance training can reduce liver fat content, patients can choose exercise types depending on their interests according to the principle of long-term adherence. (B2)

6.2 | Drug therapy for metabolic disorders

When patients with NAFLD fail to lose weight or control their metabolic risk factors effectively after 3–6-month lifestyle intervention, they are recommended to take one or multiple medications, according to the relevant guidelines, for obese, arterial hypertension, T2DM, dyslipidemia, and gout arthritis. Currently, there has been inadequate

evidence of these drugs for improvement in serum aminotransferases and liver histology in Chinese patients with NAFLD and NASH. Therefore, these drugs should not be used as specific treatment of NAFLD or NASH. In adults, BMI ≥ 30 kg/m², or BMI ≥ 27 kg/m² combined with arterial hypertension, T2DM and dyslipidemia, should consider taking weight-loss medications such as orlistat to control body weight. However, these patients need to be monitored closely for medication-related adverse effects, and should avoid long-term use of these medications as well. Angiotensin II receptor antagonists are safe in treating arterial hypertension in NAFLD and NASH patients. Although omega-3 polyunsaturated fatty acids may be safe for managing hypertriglyceridemia in NAFLD patients, it may not be effective for patients with serum TG >5.6 mmol/L. Under this circumstance, fibrates should be used with caution of liver toxicity to lower serum TG and to prevent acute pancreatitis.⁵⁵ Unless patients develop liver failure or decompensated cirrhosis, statins are safe for both NAFLD and NASH patients to lower serum low-density lipoprotein cholesterol (LDL-C) levels in order to prevent cardiovascular events. Currently, no evidence supports that statins can improve NASH and liver fibrosis.⁵⁶ While using statins, patients may develop asymptomatic and isolated elevation of serum ALT level, which usually returns to normal range without dose reduction or drug withdrawn.^{56,57} Although metformin does not have any effect on NASH, it can be used to improve IR, lower blood glucose in T2DM, and assist weight loss. For NAFLD patients with IR, metformin should be used to prevent and treat T2DM. Human glucagon-like peptide 1 (GLP-1) analogue, liraglutide has hypoglycemic effect with weight loss and IR improvement, liraglutide is thus an ideal therapy for obese patients with T2DM.⁵⁸ Pioglitazone might be effective in improving serum biochemistry and liver histopathology in NASH patients. However, long-term efficacy and safety of this drug in Chinese patients remain to be clarified. Pioglitazone is recommended to be used in NASH patients with T2DM.⁵⁹

Recommendation

20. Angiotensin II receptor antagonists, omega-3 fatty acids, statins, metformin, and pioglitazone are safe to control metabolic and cardiovascular risk factors in patients with NAFLD and NASH, except for patients with liver failure or decompensated cirrhosis. (C1)

6.3 | Bariatric surgery

Bariatric surgery, also known as metabolic surgery, can not only maximize the effect of weight loss and long-term maintenance of ideal body weight, but also effectively treat MetS and T2DM. According to the International Diabetes Federation guidelines, bariatric surgery should be considered in T2DM patients with severe obesity (BMI ≥ 40 kg/m²), and in T2DM patients with moderate obesity (35 kg/m² \leq BMI ≤ 39.9 kg/m²) whose blood glucose level cannot be controlled effectively by conservative treatment.⁶⁰ Patients with mild obesity (BMI 30 – 34.9 kg/m²) may also consider bariatric surgery if metabolic and cardiac risk factors cannot be effectively controlled by medical therapy. While considering BMI as an indicator for bariatric surgery, the BMI threshold for Asian population should be lowered for

2.5 kg/m². In the past decade, the number of bariatric surgeries has been increasing worldwide. Regardless of its procedural type, bariatric surgery has a better effect than non-surgical treatments in controlling obesity and T2DM. Sleeve gastrectomy is the most commonly used bariatric surgery in Asia. Obese patients with NASH or compensated cirrhosis should still be considered as candidates for bariatric surgery. Bariatric surgery not only reduces cardiovascular mortality and all-cause mortality, but also improves histological changes of NASH. However, its role in reversing liver fibrosis and reducing liver mortality remains unclear.⁶¹ Currently, there is no enough evidence to recommend bariatric surgery as the routine treatment of NASH. However, bariatric surgery should be considered for NASH patients with severe or refractory obesity or those having post-liver transplantation recurrent NASH.

Recommendations

21. Bariatric surgery for obesity, MetS and T2DM is effective to improve liver histopathology in patients with NASH (B1). Currently, there is no sufficient evidence to recommend bariatric surgery for the treatment of NASH (B1).
22. NAFLD/NASH is not a contraindication to bariatric surgery in obese patients unless they have advanced cirrhosis. (A1)

6.4 | Drug therapy for steatohepatitis and fibrosis

Since lifestyle modification and drug use targeting MetS and T2DM, even bariatric surgery, often cannot significantly reverse liver fibrosis, it is necessary to use hepatoprotective drugs including anti-oxidants and herb or plant extracts with anti-inflammatory and anti-fibrotic effects.⁶² Data from clinical trials in the United States have shown that oral vitamin E (α -tocopherol) at a daily dose of 800 IU for 2 years improves serum transaminases and liver histology in non-diabetic adults with biopsy-proven NASH.⁶³ In China, vitamin E is not listed as a medical treatment option for chronic liver disease, and the safety of long-term high-dose vitamin E remains a concern worldwide. A clinical trial from the United States has shown that obeticholic acid significantly reduces liver fibrosis in NASH patients, although it has some adverse effects on lipid metabolism and causes itch of skin. However, data from a clinical trial in Japan did not confirm the efficacy of obeticholic acid in treating NASH.⁶⁴ In China, the following medications have been widely and safely used in treating liver injury in patients with chronic liver diseases, i.e., silymarin, bicyclol, polyene phosphatidylcholine, glycyrrhizic acid diamine, reduced glutathione, S-adenosyl-methionine, ursodeoxycholic acid, and so on. Some of the listed medications are proven to be effective in patients with DILI and cholestatic liver disease as well.^{65,66} However, therapeutic effects of these drugs on steatohepatitis and fibrosis in NAFLD remains unclear and need to be further confirmed by using clinical trials.

Currently, hepatoprotective drugs are recommended to be used as adjuvant therapy for the following NAFLD patients: (a) liver biopsy-confirmed NASH or steatoic fibrosis; (b) clinical features, laboratory tests and imaging suggesting the presence of NASH and/or advanced liver fibrosis, i.e. patients with MetS, T2DM, persistently elevated serum transaminases and/or high CK-18 fragment (M30 and M65)

levels, and significantly increased LSM values; (c) patients developing elevated liver enzymes whilst receiving drugs for controlling MetS and T2DM; (d) patients with co-existing DILI, autoimmune hepatitis, chronic viral hepatitis and other liver diseases. There is no sufficient evidence to recommend a specific type of hepatoprotective drug and the best treatment course for NAFLD and NASH patients. The aforementioned patient with NAFLD should choose one hepatoprotective drug according to the type and extent of liver injury as well as the efficacy and medical cost of the medication, and the drug should be taken orally for at least 1 year. If there is no reduction of serum ALT level after 6-month treatment of the drug, patients should be switched to another hepatoprotective drug. Up to now, there is no effective hepatoprotective drug for preventing cirrhosis or HCC in NASH patients. Clinical trials are needed to confirm the hepatoprotective effect of coffee, aspirin, metformin, and statins in patients with NAFLD.

Recommendations

23. In patients with biopsy-proven NAFL, dietary adjustment and increased physical activity suffice to reduce liver fat deposition (B2). However, liver biopsy-proven NASH, especially with advanced fibrosis, should take oral hepatoprotective drug (B1).
24. NAFLD patients highly suspected of NASH or advanced fibrosis in the absence of biopsy may also be considered for hepatoprotective therapy. (C1)
25. No established hepatoprotective drug is available at the moment for routine treatment of NASH. The therapeutic effects of bicyclol, silymarin, polyene phosphatidylcholine, glycyrrhizin, and vitamin E on NASH need to be confirmed by further clinical trials. (C1)
26. There is no sufficient evidence to recommend a best treatment course for NASH. It is recommended to use one hepatoprotective drug for at least 1 year, and it should be replaced by another hepatoprotective drug if serum aminotransferase levels do not significantly decline after 6-month treatment. (C1)

6.5 | Liver transplantation for end-stage liver diseases

The impact of NAFLD on liver transplantation affects both donors and recipients. Both the risk of donor fatty liver-associated post-transplantation primary non-functional liver graft and the number of patients with NASH-related decompensated cirrhosis and HCC requiring liver transplantation are rising in the world including China. The long-term outcomes of NASH patients who undergo liver transplantation are similar to those of other indications. For the recipients, aging, obesity and co-existing metabolic diseases could affect perioperative or short-term postoperative prognosis. The prevalence of recurrent NAFLD in post-transplantation reaches up to 50%, these patients often have high incidence of cardiovascular complications.^{67,68} It is important to properly evaluate and manage NASH patients on the liver transplantation waiting list to reach the best condition. Patients with NASH-related cirrhosis have high prevalence of cardiovascular disease and high post-transplantation cardiovascular mortality. In post-transplantation patients, it is necessary to control body weight

and prevent glucose and lipid metabolic disorder in order to reduce post-transplant cardiovascular complications.

Recommendation

27. NASH patients with end-stage liver disease and hepatocellular carcinoma should be considered for liver transplantation, their overall survival rate is similar to that obtained for other diseases, although their mortality due to cardiovascular diseases is higher. (A1)

6.6 | Avoiding additional liver injury

For patients with NAFLD, especially NASH patients, it is recommended to avoid very-low-calorie diet to lose weight, avoid potential liver damage medications including Chinese herbal medications. One should also be cautious about the use of natural health products. NAFLD patients need to restrict alcohol intake and surely to avoid excessive alcohol consumption, since alcohol can induce acute liver injury and accelerate liver fibrosis in patients with NAFLD. Additionally, long-term alcohol consumption, even at a low dose, can increase HCC risk in NAFLD patients with liver fibrosis.⁶⁹ Consumption of coffee and tea drinking may help recovery for NAFLD patients. Early detection and treatment are warranted to the coexisting diseases such as sleep apnea, hypothyroidism, intestinal bacterial overgrowth and some factors known to possibly exacerbate liver injury in NAFLD patients.

Recommendation

28. Patients with NAFLD should restrict alcohol intake and avoid occasionally heavy consumption of alcohol (B1). More coffee and tea consumption might be helpful for NAFLD patient (C1).

7 | EXISTING PROBLEMS AND PROSPECTS

NAFLD is a metabolic disease involving multi-systems, its relationship with MetS and T2DM is reciprocal causation. Concurrent with MetS and T2DM, NAFLD is related to high risks of liver cirrhosis, HCC, coronary heart disease, chronic renal disease, colorectal carcinoma and other types of extrahepatic malignant tumors. Currently, in China, the prevalences of obesity and MetS are increasing alarmingly and that of NAFLD is already higher than those of Europe and the United States. Nowadays, NAFLD has become a new public health issue in China and poses a serious threat to the national health and social development. The prevention and treatment of NAFLD is not only a clinical medical issue, but also a major challenge to preventive and social medicine as well as for the healthcare system. The promotion and implementation of 'Healthy China 2030' is expected to control the epidemic of NAFLD and its related diseases. The successful completion of major key research projects funded by the State Ministry of Science and Technology, the National Natural Science Foundation of China, the State Health Commission and other departments will eventually help the society understand the genetic characteristics, pathogenesis, new therapeutic agents and non-invasive diagnosis of NAFLD and its related cirrhosis and HCC.

Currently, clinicians should strengthen to conduct prospectively multicenter cohort studies on patients with imaging- and/or liver biopsy-proven NAFLD, and large-sample survey on clinical setting and natural history of chronic hepatitis B in combination with NAFLD, and fatty liver in children. Translational medical research should also be conducted to further explore molecular mechanism of NAFLD-related HCC and the potential tumor biomarkers. Non-invasive diagnostic methods remain unable to replace liver biopsy for the diagnosis of NASH and staging of liver fibrosis. It is important to further develop serum biomarkers, genomics, proteomics, glycomics, metabolomics, new imaging techniques, and their clinical applications in order to make a great progress in this field. The idea of stabilizing and monitoring intestinal homeostasis structure and function might be another method in the diagnosis of management of NASH. Further clinical trials are needed to evaluate the effects of traditional Chinese dietary and exercise methods as well as the use of prebiotics and probiotics, berberine and widely used hepatoprotective drugs in treating NASH and advanced fibrosis. It is also important to improve efficacy and safety of bariatric surgery in managing patients with NASH. Clinical research on perioperative care in NASH patients with liver transplantation is also of importance. All abovementioned investigatory studies are necessary in order to further improve diagnosis and treatment of NAFLD as well as to establish healthcare policies in China.

In addition, many national and international updated guidelines on NAFLD result in confusion about the best clinical practice. Domestic and international guidelines all point to differences in relation to medications to be used, lifestyle intervention as well as to healthcare-delivering models and insurance. In Europe and the United States, over 90% of enrolled patients in clinical trials are European and American descendants. Efficacy and safety of the recommended drugs need to be validated in Chinese patients. It is critical for the healthcare professionals and public to understand the value of education in preventing and managing NAFLD. Timely updating in popular scientific tools on how to prevent NAFLD are more than welcome. Clinicians should understand and follow the recommendations on the management of NAFLD patients. Additionally, they should combine their own clinical experiences and patient's conditions to further improve treatment algorithms. In summary, China has still a long way to go for the prevention and control of NAFLD. With the support of different governmental bodies and pharmaceutical companies, the multidisciplinary approach to this "new disease" in both primary and tertiary care facilities will eventually allow to set up a Chinese model in preventing and managing NAFLD patients.

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ACKNOWLEDGEMENT

We thank Jimin LIU MD from the Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University for her great help and constructive suggestions in writing this manuscript.

CONFLICT OF INTEREST

None.

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How to cite this article: Fan JG, Wei L, Zhuang H, On behalf of the National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association; Fatty Liver Disease Expert Committee, Chinese Medical Doctor Association. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). *J Dig Dis*. 2019;20:163-173. <https://doi.org/10.1111/1751-2980.12685>