|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| bs\_bs\_banner | |  | | --- | |  | |  |  |

doi:10.1111/jgh.13857

REVIEW

Asia–Pacific Working Party on Non-alcoholic Fatty Liver

Disease guidelines 2017—Part 1: Definition, risk factors and

assessment

Vincent Wai-Sun Wong,\*,†Wah-Kheong Chan,‡Shiv Chitturi,§Yogesh Chawla,¶Yock Young Dan,\*\*

Ajay Duseja,¶Jiangao Fan,††Khean-Lee Goh,‡Masahide Hamaguchi,‡‡Etsuko Hashimoto,§§

Seung Up Kim,¶¶Laurentius Adrianto Lesmana,\*\*\* Yu-Cheng Lin,†††Chun-Jen Liu,‡‡‡Yen-Hsuan Ni,†††

Jose Sollano,§§§Simon Kin-Hung Wong,¶¶¶Grace Lai-Hung Wong,\*,†Henry Lik-Yuen Chan\*,†and Geoff Farrell§

\*Department of Medicine and Therapeutics,†State Key Laboratory of Digestive Disease and Department of Surgery,¶¶¶Department of Surgery, The Chinese

University of Hong Kong, Shatin, Hong Kong;‡Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia;§Gastroenterology and Hepatology

Unit, The Canberra Hospital, Canberra, Australian Capital Territory, Australia;¶Department of Hepatology, Postgraduate Institute of Medical Education and

Research, Chandigarh, India; \*\*Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore;††Xin Hua Hospital

Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China;‡‡Department of Diabetology, Kameoka Municipal Hospital, Kameoka and

§§Departments of Internal Medicine and Gastroenterology, Tokyo Women’s Medical University, Tokyo, Japan; ¶¶Department of Internal Medicine, Institute of

Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; \*\*\*Digestive Disease and GI Oncology Centre, Medistra Hospital, Jakarta, Indonesia;

†††Hepatitis Research Center, National Taiwan University, and ‡‡‡Department of Internal Medicine, Hepatitis Research Center and Graduate Institute of

Clinical Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan; and§§§University of Santo Tomas, Manila, The Philippines

|  |  |
| --- | --- |
| Key words  hepatocellular carcinoma, liver biopsy, liver stiffness measurement, metabolic syndrome, NAFLD, NASH, non-alcoholic steatohepatitis, obesity, transient elastography.  Accepted for publication 25 June 2017.  Correspondence  Professor Geoffrey C. Farrell, Gastroentology and Hepatology Unit, The Canberra Hospital, PO Box 11, Woden, ACT 2606, Australia.  Email: geoff.farrell@anu.edu.au  Dr Vincent Wai-Sun Wong, Department of Medi-cine and Therapeutics, The Chinese University of Hong Kong, 9/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street,  Shatin, Hong Kong.  Email: wongv@cuhk.edu.hk  Declaration of conflict of interest: Vincent Wong served as a consultant for AbbVie, Allergan, Gilead Sciences, Janssen, Perspectum Diagnostics, and Pfizer and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck. Yock  Young Dan served as an advisory board member and has received research grants from AbbVie, Bristol-Myers Squibb, and Gilead Sciences. Khean- | Introduction  Since the publication of the guidelines for the assessment and management of non alco-holic fatty liver disease (NAFLD) by the Asia–Pacific Working Party on NAFLD in 2007,1our understanding of the clinical characteristics and natural history of NAFLD has improved, and there have been developments in the assessment and treatment of NAFLD. It is therefore timely to update the guidelines in light of new evidence.  This document presents the recommendations of the Asia–Pacific Working Party on NAFLD. The exercise was supported by the Journal of Gastroenterology and Hepatology Foundation. Members performed a systematic review of the literature on specified domains of interest, thereby allowing them to provide recommendations on different aspects of the clinical assessment and management of patients with NAFLD. The contents and statements were then discussed through face-to-face meetings and e-mail communications. The statements in this document follow the Grading of Recommendation Assessment, Develop-ment, and Evaluation approach (Table 1).2The final grading of evidence and recommenda-tions was determined by majority vote.  These guidelines cover various aspects in the management of NAFLD, including diagno-sis, screening, assessment, and treatment. While most evidence came from studies on adults identified to be at risk of metabolic disorder and after exclusion of other liver diseases, two special populations are included in this document. NAFLD in children and adolescents is becoming increasingly prevalent and may have devastating consequences owing to the long duration of fatty liver disease. In addition, chronic viral hepatitis is highly prevalent in Asia–Pacific countries, and the impact of concomitant fatty liver, a much discussed topic both for hepatitis B and C, is re-evaluated here for its long-term clinical significance and implications for patient care. |

Lee Goh served as an advisory board member of

|  |  |
| --- | --- |
| Gilead Sciences and a speaker for AbbVie and Gilead Sciences. Grace Wong has served as an advisory committee member for Otsuka and  Gilead. She has also served as a speaker for  Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, Janssen, Otsuka, and Roche. Henry Chan served as an advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Roche and a speaker for AbbVie, Bristol-Myers Squibb, | Definitions  The need for a definition. A clear, reproducible definition of NAFLD is required for clinical practice and epidemiological studies because there are several causes of fatty liver and steatohepatitis, each with differing management implications and clinical out-comes. An unresolved definitional and semantic challenge is that two or more etiological factors commonly interact to influence the incidence, severity, and outcome of fatty liver. |

Echosens, Gilead, Novartis, and Roche.

Financial support: This project was supported Established “negative” definition of NAFLD (e.g. AASLD 2012). The

by a grant from the Journal of Gastroenterology current established “negative” definition of NAFLD requires (i) evidence of hepatic

and Hepatology Foundation. steatosis by either imaging or histology and (ii) absence of other causes of hepatic fat

70 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

Table 1 Grading of evidence and recommendations (adapted from the Grading of Recommendation Assessment, Development, and Evaluation sys-tem 0)2

|  |  |
| --- | --- |
| Grading of evidence | Description |
| A | High-quality evidence from meta-analysis or randomized controlled trials without major limitations or, in the |

case of non-interventional studies, evidence from high-quality observational studies. Further research is unlikely to change our confidence in the estimate of effect.

B Moderate-quality evidence from meta-analysis or randomized controlled trials with obvious limitations or observational studies. Further research is likely to have an important impact on our confidence in the estimate of effect.

C Low-quality or very low-quality evidence from randomized controlled trials or observational studies with major limitations, case series, and case reports. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

|  |  |
| --- | --- |
| Grading of recommendations | Description |
| 1  2 | Strong recommendation based on the quality of evidence, presumed patient-important outcomes, and costs. Weaker recommendation because of variability in preferences and values, uncertainty, and higher cost or |

resource consumption.

|  |  |
| --- | --- |
| accumulation from conditions such as significant alcohol con-sumption, hepatitis C, medication use, or hereditary disorders. | alcohol-related liver disease, and haemochromatosis needs to be recognized. (A1) |

While it has been acknowledged that “in the majority of

patients” NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia, this fails to identify overnutrition (as opposed to established obesity) as pivotal, or to account for the approximately 25% of patients in Asian cohorts who have fatty liver but are not obese. However, the vast majority of such “non-obese NAFLD” patients exhibit insulin resistance. In this respect, it is also critical to note that family history of diabetes (genetic predisposition) and prediabetes as well as established diabetes are commonly associated with NAFLD. Finally, it has now been clearly demonstrated that loss of 10% of bodyweight (in overweight persons) completely reverses all elements of non-alcoholic steatohepatitis (“NASH”) pathology, including liver fibrosis. This cements the role of overnutrition in the causation of NAFLD.

Proposed “positive” definition of NAFLD. Review articles from Europe have tended towards a more positive defini-tion of NAFLD, as did the original Asia–Pacific Guidelines of 2007. The recommended definition for the 11th Revision of the International Classification of Diseases is  
 “NAFLD is characterized by fatty liver (defined as earlier) related to over-nutrition in the absence of excessive alcohol

Pathological subtypes and outcomes of NAFLD. The majority of cases of NAFLD show steatosis with no or mini-mal liver inflammation. The term favored by the American Asso-ciation for the Study of Liver Diseases (AASLD) for this, non-alcoholic fatty liver, has not been adopted by the 11th Revision of the International Classification of Diseases as it seems ambigu-ous. Specifically, all NAFLD cases have fatty liver, whether steatohepatitis (NASH) is present or not. Instead, if the pathology is known, the terminology should be “NAFLD without NASH” or“simple steatosis,” “NASH,” and “with or without fibrosis or cirrhosis” for either category.

Between 10% and 25% of NAFLD cases show steatohepatitis, that is, NASH. The hallmarks are conspicuous hepatocyte injury (especially ballooning and apoptosis) and substantial liver inflam-mation. NASH is more likely to be associated with liver fibrosis than cases showing only steatosis. Notwithstanding the likely im-portance of NASH in leading to fibrosis, it is the presence of fibrosis (with or without NASH) that predicts progression to cirrhosis in clinical outcome studies. Hepatocellular carcinoma (HCC) is a complication of NAFLD, but not exclusively among cases that progressed to cirrhosis (including cases of “crypto-genic cirrhosis”). Besides, it is unclear if a patient must have

consumption.” NASH before progressing to NAFLD-related HCC.

We therefore recommend the following language:

2.1 Non-alcoholic fatty liver disease (NAFLD) is a form of fatty liver disease (as previously defined – see 2007 Guidelines and the 2012 American Guidelines) that can reasonably be attributed to over-nutrition and its complications, such as weight gain, central obesity, insulin resistance, glucose intolerance, atherogenic dyslipidemia and arterial hypertension (metabolic syndrome), particularly in genetically predisposed individuals. For a strict definition of NAFLD, significant (or excessive) alcohol consump-tion and other diseases must be excluded. However, the interaction between over-nutrition and other liver disorders commonly causing fatty liver disease, including hepatitis C, hepatitis B,

Alcohol exclusion criteria. No more than one standard drink per day (i.e. 70 g ethanol per week) for women and no more than two standard drinks per day (i.e. 140 g ethanol per week) for men have been used by the National Institutes of Health NASH clinical research network and widely adopted for clinical studies. The relevance of this standard to the populations in the Asia–Pacific region was discussed in the 2007 Guidelines. The proposed levels of alcohol intake are based on evidence about daily alcohol intake and risk of cirrhosis. The “cut-off” values have been set lower than the apparent “threshold levels” so as to avoid the issue of overlap between alcoholic liver disease and obesity, type 2 diabetes (T2DM), and metabolic syndrome in progression to

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 71

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

cirrhosis. Patients who may be drinking at safe levels at the time of presentation with liver disease may have a past history of chronic excessive alcohol intake for a prolonged period of time and may have cirrhosis. Lifetime alcohol intake is therefore important and needs to be incorporated into history taking.

Epidemiology

320 HCC cases (5.3%) were either associated with NASH or had unknown (“cryptogenic”) etiology.8“Cryptogenic” HCC also accounted for 5.4% of all HCCs in Korea. Metabolic syndrome and its components (i.e. obesity and T2DM) are very common in cryptogenic cirrhosis and HCC patients. Recent literature from Asia also suggests a strong association between NAFLD and HCC in non-cirrhotic livers (see comments under Definition). The majority of NASH-related HCC patients either did not have

Adults definite cirrhosis or cirrhosis was well compensated (Child–Pugh

A), compared with Child B and C cirrhosis with other etiologies.

Prevalence of NAFLD. Over the past three decades, changing Western lifestyles and dietary habits, in addition to relatively high rates of genetic predisposition in several community groups, have increased the prevalence of NAFLD in the Asia–Pacific region. On the basis of hepatic imaging, recent studies suggest that a quarter (95% confidence interval [CI]: 23.3–31.9%) of the general popula-tion in Asia has NAFLD, but the proportion of patients with ad-vanced liver fibrosis diagnosed by transient elastography (TE) appears to be low (3.7% among NAFLD patients).3Obesity, dys-lipidemia, T2DM, and metabolic syndrome are established risk factors for developing NAFLD. In addition, several other risk factors for NAFLD have been identified in the Asia–Pacific re-gion. These include hypothyroidism, polycystic ovary syndrome, obstructive sleep apnea, hypopituitarism, and hypogonadism.

There may be subtle differences in the phenotype distribution of NAFLD between Asia–Pacific and Western countries. Of particu-lar interest are more frequent “lean NAFLD” and the urban–rural differences of prevalence rates of NAFLD in Asia.4In addition, Asian people are particularly susceptible, partly owing to body composition differences in fat and muscle and genetic suscep-tibility via predisposition to T2DM, PNPLA3 SNPs, and polymor-phisms in apolipoprotein 3.5On the other hand, the natural history of NAFLD and its progression to cirrhosis and HCC (when this occurs) is over several decades; the fact that NAFLD in Asian countries may be more recent than in North and South America, for example, may also influence the present distribution of disease phenotypes towards the milder end of the pathological spectrum.

Prevalence of NASH and incidence of NAFLD. There are limited studies evaluating the incidence of NAFLD and the pre-valence of NASH in the general population. In Japan, pooled regional NAFLD incidence rate estimates are 52.3 (95%CI: 28.1–96.8) per 1000 person-years.6Incident NAFLD is not uncommon among Chinese people who are not obese; for instance, 8.9% of lean subjects developed NAFLD during a 5-year follow-up.6Because the diagnosis of NASH requires a liver biopsy, the population prev-alence of NASH in Asia is currently unknown. Among Asian liver biopsy series, NASH can be found in 63.5% (95%CI: 47.7–76.8). In natural history studies involving paired liver biopsies, around 25% of patients may progress from simple steatosis to NASH in 3 years.7

Prevalence of NASH-related cirrhosis and HCC. Non-alco-holic steatohepatitis is the most common cause of cirrhosis and HCC in patients without other known etiological causes of liver disease worldwide. Thus, 63.3% of formerly designated crypto-genic cirrhosis cases could finally be attributed to NAFLD because cryptogenic cirrhosis is more associated with metabolic syndrome than other causes of cirrhosis. A study from Japan found that 17 of

However, data from carefully controlled long-term studies from this region, with better documentation of liver disease, are required to determine the prevalence and incidence of HCC in NAFLD pa-tients, especially in non-cirrhotic NASH patients in Asia. Another general need is to better understand the relative importance of in-dividual host and environmental factors in determining the preva-lence of NAFLD and its liver complications in different ethnic groups across geographical areas of the vast Asia–Pacific region.

Children and adolescents

The prevalence of NAFLD in children and adolescents. Es-timates of the prevalence of NAFLD in children and adolescents vary widely between epidemiologic studies. Using liver ultraso-nography, Tominaga et al. reported that the prevalence of NAFLD was 2.6% in 810 Japanese children aged 4 to 12 years.9Another study from Shanghai showed the prevalence was 2.1% in 6- to 12-year-old schoolchildren in China.10To clarify the prevalence of NAFLD in obese children (defined as the body mass index [BMI] value >95 percentile by age-specific and gender-specific cut-off points), Lin et al. reported that 22.8% of 832 obese Taiwan-ese children and adolescents had ultrasound-defined NAFLD.11 However, the true prevalence of NAFLD may be underestimated by this method because liver ultrasonography is relatively insensi-tive for detecting cases with hepatic fat content below 30%.12 Serum alanine transferase (ALT) is frequently used to assess NAFLD prevalence. The prevalence of elevated ALT levels (>40 U/L) was 8% in 1594 adolescents aged 10 to 19 years in the Korean National Health and Nutrition Examination Survey 1998.13A Japanese study of 228 obese children aged 6–15 years reported a prevalence of ALT >35 U/L of 24.1% (the “normal”value for ALT in the general population is likely to be 25.8 U/L in boys and <22.1 U/L in girls).14,15There are some limitations when using ALT as a screening measure for NAFLD as the upper limit of normal ALT is not well established and ALT levels do not parallel the histological severity of NAFLD in children or adults.16

Prevalence of NASH and NASH-related cirrhosis. The stan-dard diagnosis of NASH relies on liver histological features. There were no studies to estimate NASH prevalence by this method in the Asia–Pacific region. In the USA, Schwimmer et al. used au-topsy data to assess liver steatosis. They found that the prevalence of NAFLD and NASH was 13% and 3%, respectively, among children, regardless of the cause of death.17Another study in Poland surveyed children whose death was caused by trauma; prevalences of NAFLD and NASH were 5.3% and 0.3%, respec-tively.18NASH-related cirrhosis has been reported in children as young as 10 years of age.19

72 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

Geographical difference. A recent meta-analysis reported that the pooled prevalence estimates did not differ by geographical re-gion in the general population among children and adolescents. In contrast, in clinical studies of obese population, the prevalence es-timates varied by geographical region, being higher in the studies from Asia (62.3%) than studies from Europe (29.8%) and North America (39.2%).20It should be emphasized that diagnostic methods used in different studies could significantly affect NAFLD prevalence estimates.

Risk factors of NAFLD. Overnutrition and insulin resis-tance are dominant risk factors for the development of NAFLD (Table 2). The condition of gut microbiota, genetic variations, and epigenetic regulation induced by microRNAs (miR), DNA methylation, histone modification, and ubiquitination may alter the susceptibility to NAFLD. Although the prevalence of NAFLD increases with age and with the male gender,21the direct relation-ships among age, gender, and susceptibility to NAFLD remain unsettled.22

Fatty liver can also be triggered by exogenous factors including certain medications and malnutrition,23–25although the liver pathology in such cases may be indistinguishable from NAFLD secondary to overnutrition and obesity.

Overnutrition and insulin resistance. Overnutrition or inap-propriate diet, such as excessive carbohydrate intake and/or exces-sive fat intake, induces insulin resistance and bodyweight gain.26 Excessive carbohydrate intake and/or excessive fat intake also lead to increased circulating concentrations of both glucose and free fatty acids. Moreover, insulin resistance reduces glucose uptake by adipose tissue and muscle and reduces the hydrolysis of triglyc-erides in adipose tissue.27,28   
 Insulin programs hepatic uptake of free fatty acid and free cholesterol,29which consist of the majority of liver fat. De novo lipogenesis is also increased by insulin, which leads to an in-creased conversion of glucose to fatty acids in the liver.30Thus, in-sulin resistance with resultant hyperinsulinemia, combined with the increased circulating concentrations of both glucose and free

|  |  |  |
| --- | --- | --- |
| Table 2 | Risk factors for NAFLD | fatty acid, contributes to an excessive accumulation of neutral |
| lipids in the liver.31–33 |

1. NAFLD   
 Overnutrition (invariable)   
 Insulin resistance (invariable with NASH)   
 Gut microbiota (mainly experimental data)   
 Genetic variations in addition to family history of T2DM, cirrhosis, and fatty liver disease:   
 PNPLA3, TM6SF2, LEPR, PPAR, SREBP, MTTP, positions308 or238 of TNF-α, MnSOD, MBOAT7, TMC4, and FDFT1†  
2. Fatty liver attributable to causes other than alcohol or overnutrition (“secondary NAFLD”)‡  
 Medications   
 Valproic acid, estrogens, tamoxifen, corticosteroids, tetracycline, amiodarone, perhexiline maleate, methotrexate, 4,40-  
diethylaminoethoxyhexesterol, chloroquine, calcium channel blockers, and L-asparaginase   
 Occupational exposure to hepatoxins   
 Malnutrition (especially kwashiorkor)   
 Total parenteral nutrition, rapid weight loss   
 Surgically altered bowel anatomy:   
 Jejunoileal bypass, jejunocolic bypass, gastroplasty, and extensive small bowel resection   
 Polycystic ovary syndrome   
 Wilson’s disease   
 Weber Christian disease   
 Severe insulin resistance with lipodystrophies

It is widely accepted that obesity/overweight is the most signif-icant risk factor for incident NAFLD.34–38However, weight gain

that has not yet led to obesity is also an important determinant of NAFLD incidence.31,39Thus, bodyweight gain after 20 years of

age as well as bodyweight gain from baseline to onset are both risk

factors for incident NAFLD, in both obese and non-obese individuals.40

Gut microbiota. Several studies in mice indicate that the gut

microbiome influences both sides of the energy balance equation

by contributing to nutrient absorption and increasing metabolic endotoxemia, which increases hepatic steatosis.41–43Small intesti-nal bacterial overgrowth increases intestinal permeability23and could induce endotoxemia.44Although a specific gut microbiota

might be involved in incident NAFLD, no consensus has yet been

reached about this.

Genetic variations. The G allele of PNPLA3 rs738409 is asso-ciated with the degree of hepatic steatosis,45while the T allele of

PNPLA3 rs6006460 is associated with lower hepatic triglyceride content.45The variant of TM6SF2 is associated with the hepatic triglyceride content.46A relationship between the gene polymor-

phisms of APOC3 and hepatic triglyceride content has been re-ported,47but so have contrary findings; a meta-analysis found no

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| †45, 46 | FDFT1, | farnesyl | diphosphate | farnesyl | significant association between APOC3 polymorphisms and risk |
| ‡25, 37 | of NAFLD.48 |
| APOC3, apolipoprotein C3; |

transferase 1; LEPR, leptin receptor; MBOAT7, the membrane-bound O-acyltransferase domain-containing 7; MnSOD, manganese superoxide dismutase; MTTP, microsomal triglyceride transfer protein; NAFLD, non alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCOS, polycystic ovary syndrome; PNPLA3, the patatin-like phos-pholipase domain-containing protein 3; PPAR, peroxisome proliferator-activated receptors; SREBP, sterol regulatory element-binding proteins; TM6SF2, transmembrane 6 superfamily member 2; TMC4, transmem-brane channel-like 4; TNF-α, tumor necrosis factor-alpha; T2DM, type 2

Natural history. NAFLD is associated with an increase in the standardized mortality ratio compared with the general population because of an increased liver-related—and cardiovascular-related—mortality rate.49–54The most common causes of death in patients with NAFLD are cardiovascular disease and malignancy, followed by liver-related disease. Overall, NAFLD appears to be slowly pro-gressive with liver-related morbidity and mortality occurring in a small number of patients. The reported risk factors for the develop-

diabetes. ment of advanced fibrosis or cirrhosis are advanced age, diabetes,

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 73

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

morbid obesity, and transaminase elevation.55–58Prospective follow-up studies for the incidence and remission of NAFLD in

Recommendation Statements   
3.1 NAFLD-related HCC is becoming increasingly prevalent in

the general population showed that the incidence rate of NAFLD Asia. (B1)

was around 7–20% during a 1- to 7-year follow-up period, and 16–37% of patients with NAFLD had remission during that period.

3.2 The risk of HCC with NAFLD is directly related to the degree of liver fibrosis, but HCC can occur in non-cirrhotic

It is well known that weight gain is closely related to NAFLD de-patients. (C1)

velopment, and weight loss is associated with NAFLD remission.

Diagnosis

Histological progression. It is generally agreed that simple steatosis is mostly a benign, non-progressive clinical entity, while NASH can progress to cirrhosis, which in rare cases gives rise to HCC. However, recent paired-biopsy studies have demonstrated that simple steatosis has the potential to progress to NASH with the development of fibrosis7,59–61and that the presence and sever-ity of fibrosis, regardless of the diagnosis of NASH, dictate the long-term prognosis.50,62,63According to a systemic review and meta-analysis of paired-biopsy studies, the annual fibrosis progres-sion rate in patients with simple steatosis was 0.07 stages, com-pared with 0.14 stages in patients with NASH.61Fibrosis progresses rapidly in 20% of patients. A histological risk factor for such progression is more extensive necroinflammatory change on baseline liver biopsy.64The characteristic features of NASH disappear in advanced cirrhosis, a phenomenon referred to as“burned-out NASH”.65,66

Cirrhosis and liver decompensation. Previous studies have reported that patients with cirrhotic NASH/NAFLD showed a sim-ilar survival rate to patients with cirrhosis caused by the hepatitis C virus, although the rate of development of HCC was lower (5-year HCC development rate: about 10%, 5-year survival rate: 70–80%).67–70

NASH-related HCC. Non alcoholic fatty liver disease can lead to cirrhosis and result in HCC.67,71Up to 30% of HCC can be attributable to cryptogenic cirrhosis; the majority of such cases are believed to be due to NASH.72Cross-sectional studies in Asian countries such as Malaysia, Japan, and Korea suggest that the con-tribution of NASH to HCC is lower than in the West and is in the region of 7–16%.73–75   
 The incidence of HCC in NAFLD is highest in patients who have cirrhosis. In Japanese cohorts, the retrospective annual incidence of developing HCC among 6508 NAFLD patients was 0.043%, but it was 25 times more likely among those with ad-vanced fibrosis. Among cirrhotics, the incidence of HCC was 11.3% in 5 years.70In addition, obesity and diabetes mellitus are independent risk factors for HCC and increase the risk of HCC with other disorders (e.g. hepatitis B and C) 10-fold.76The obesity and diabetes pandemic has caused a sharp rise in incidence of NASH-related HCC, which has now become the most rapidly ris-ing cause for liver transplantation in the US.77Data from South

Non alcoholic fatty liver disease should be suspected as the cause of liver disease in any patient who is overweight and in whom hep-atitis B or C, alcoholic liver disease, autoimmune liver diseases, and inherited metabolic diseases have been excluded. Liver dis-ease may present with abnormal liver tests (usually minor in-creases in ALT and gamma-glutamyl transpeptidase); a clear relationship between these changes and fluctuations in bodyweight is a clue to diagnosis. Hepatic imaging (usually ultrasonography) should be used to confirm steatosis. If negative, other techniques, such as controlled attenuation parameter (CAP) by TE, may pro-vide supporting data.

Exclusions require meticulous history taking for lifetime and current alcohol exposure. A lifestyle history, including trajectory of bodyweight since young adulthood and recently, waist expan-sion, eating habits, sedentary occupation, and level of physical activity, is a prerequisite to considering NAFLD diagnosis. A personal or family history of T2DM, premature vascular disease, atherogenic dyslipidemia and high blood pressure (metabolic syn-drome), fatty liver, and cirrhosis is often informative.

In many cases, diagnosis could be made with positive recogni-tion of risk factors for NAFLD, exclusion of other disorders, and documentation of fatty liver by hepatic imaging. If biochemical changes normalize with lifestyle intervention and weight loss, a diagnosis of NAFLD is very likely. On the other hand, recommen-dation for liver biopsy will depend on the level of confidence that other conditions have been excluded (such as autoimmune hepatitis and drug-related liver disease) and whether approaches to reversing NAFLD other than weight reduction by lifestyle inter-vention or obesity surgery are being considered, such as entry into a clinical trial of novel pharmacological agents.

Exclusion criteria:

1 Significant alcohol intake [>7 standard alcoholic drinks per week (70 g ethanol) in women and >14 (140 g) in men]; 2 hepatitis B and C by serologic and virologic criteria; 3 drug-induced liver disease, including herbal medicines and dietary supplements;

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 4 | autoimmune | liver | disease—including | autoimmune |

hepatitis (three subtypes), celiac disease, primary biliary cholangitis, and primary sclerosing cholangitis;   
5 metabolic liver disorders: Wilson’s disease, alpha-1-antitrypsin deficiency, hemochromatosis, glycogen storage disorders, cholesterol storage disorders, and so forth.

|  |  |  |
| --- | --- | --- |
| Korea corroborate the same trend where NAFLD HCC has risen from 3.8% to 12% over the last decade.78  There is growing evidence that HCC can occur in patients with NASH without development of liver cirrhosis.79Japanese series  have reported that 38–49% of NASH HCC cases do not show evi-dence of liver cirrhosis,71,75,80and the risk of non-cirrhotic HCC ap-pears to be highest with NAFLD compared with other etiologies.81  74 | Diagnostic workup: | |
| 1 | Conventional liver biochemistry (include ALT and AST) |
| and platelet count | |
| 2 | Hepatic ultrasonography. If no evidence of steatosis, con- |
| sider magnetic resonance imaging (MRI) liver (more sensi-tive and quantitative but expensive).  Journal of Gastroenterology and Hepatology 33 (2018) 70–85 | |

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

(Metabolic tests for risk factors are discussed in the section on Extrahepatic manifestations of NAFLD.)   
 FibroScan (TE) or other modalities may be used to determine liver stiffness. Although the cut-offs for NASH versus not NASH and for various stages of fibrosis have not yet been agreed to, TE can be a basis for confirming the potential benefits of lifestyle intervention by observed changes, including normalization of liver stiffness. In addition, CAP measurement is an alternative approach to steatosis quantification, as discussed in detail in the Assessment section.

In patients with abnormal liver tests and/or liver stiffness mea-surement, the options are immediate liver biopsy or retesting after lifestyle changes. This is considered in detail in the section on Non-invasive tests of liver fibrosis.

hepatic steatosis and may be useful as a screening tool for NAFLD, where available, as well as for assessing progress (re-sponse to lifestyle intervention and weight loss).91Moreover, liver stiffness measurement is performed simultaneously, allowing as-sessment of the severity of liver disease at the same setting.

Despite the earlier discussion, there exist knowledge gaps in the natural history of NAFLD/NASH, optimal screening tool, long-term outcomes of treatment, and cost-effectiveness of screening (Table 3). These preclude a concrete recommendation on screen-ing for NAFLD/NASH.

Recommendation Statements

5.1 Screening of NAFLD may be considered in at risk groups such as patients with T2DM and obesity. (B2)

|  |  |
| --- | --- |
| Screening | 5.2Ultrasonography is a reasonable screening tool for NAFLD, but will not detect many cases of minor steatosis. (B1) |

Non alcoholic fatty liver disease is the most common cause of chronic liver disease and is estimated to affect up to 30% of the general population.82However, only a small proportion of the gen-eral population has severe liver disease because of NAFLD. In a population-based study on 922 subjects in Hong Kong, NAFLD

5.3 Transient elastography may be used as a screening tool where available. (B2)   
5.4 Patients with NAFLD detected by screening should receive advice and support for lifestyle interventions to reduce the risk of onset of T2DM and cardiovascular disease, and to resolve fatty

(based on proton magnetic resonance spectroscopy) was observed liver disease. (A1)

in 27.3%, while advanced fibrosis (based on liver stiffness mea-surement) was found in only 3.7%.83Nevertheless, subjects found to have NAFLD on population screening may benefit from life-style interventions, as well as assessment for, and treatment of, other components of the metabolic syndrome to reduce the risk of cardiovascular disease. However, the cost-effectiveness of such an approach is unknown. On the other hand, the prevalence of NAFLD and severe liver disease is remarkably high among

5.5 Patients with NAFLD detected by screening should be assessed for other components of metabolic syndrome (including T2DM, atherogenic dyslipidemia, and arterial hypertension) and be treated accordingly. (A1)   
5.6 Patients with NAFLD detected by screening should be assessed for severity of liver disease. (B1)

|  |  |
| --- | --- |
| patients with diabetes mellitus and obesity. In a study on 1918 pa-tients with diabetes mellitus using TE, the proportions of patients | Assessment |

with increased CAP (consistent with NAFLD) and liver stiffness measurement (consistent with advanced fibrosis) was 73% and 18%, respectively.84In a separate study, the prevalence of NAFLD (based on proton magnetic resonance spectroscopy) and advanced fibrosis (based on liver stiffness measurement) was 61% and 19%, respectively, among obese subjects.85In another study on 102 patients with morbid obesity undergoing bariatric surgery, NAFLD, NASH, and advanced fibrosis were observed in 82%, 78% and 16%, respectively.86These groups of patients would ful-fill most of the classic criteria for screening.87While the current lack of an effective drug treatment is a stumbling block to strongly recommending community screening (whether all or those with risk factors), the results of lifestyle intervention with reduction of 10% of bodyweight are now such that it can be reasoned that those

Liver histology

Who should undergo liver biopsy?. Liver biopsy is essential for the diagnosis of NASH, as opposed to the other liver pheno-types of NAFLD. However, it is an expensive and invasive proce-dure with a very low risk of morbidity and mortality. Additionally, sampling errors and variability in interpretation by pathologists may occur. Moreover, in clinics with a large number of referred

|  |  |
| --- | --- |
| Table 3 | Wilson and Jungner classic screening criteria85 |

1. The condition sought should be an important health problem. 2. There should be an accepted treatment for patients with recognized

affected by NAFLD, with their increased standardized mortality disease.

largely attributable to cardiovascular disease and common cancers, need to be appraised of the merits and importance of interrupting the health consequences of NAFLD.

Serum aminotransferase levels are not useful for screening for NAFLD as they may be normal in patients with severe liver dis-ease due to NAFLD,88, and they may be increased in some patients with only simple steatosis. Ultrasonography is a reasonable screen-ing tool. Using a scoring system, ultrasonography was found to have excellent sensitivity (92%) and specificity (100%) for the di-agnosis of NAFLD.89However, it is operator dependent and may be less accurate for mild fatty liver.90The CAP using FibroScan has been shown to be excellent for the detection of significant

3. Facilities for diagnosis and treatment should be available.

4. There should be a recognizable latent or early symptomatic stage. 5. There should be a suitable test or examination.

6. The test should be acceptable to the population.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed policy on whom to treat as patients. 9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case-finding should be a continuing process and not a “once and for all” project.

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 75

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

patients or in a community setting, a liver biopsy is not logistically suitable as a general diagnostic procedure. Accordingly, liver bi-opsies may strongly be advocated for patients with NAFLD who are suspected to have coexisting chronic liver diseases and/or when there is a need to distinguish NASH from other chronic liver diseases, especially autoimmune hepatitis.92The development and application of new imaging modalities and diagnostic scores can reduce the clinical need for liver biopsy.

What histological features should be examined and re-ported? Non-alcoholic steatohepatitis is defined as the presence of hepatic steatosis, inflammation, and hepatocyte injury (balloon-ing degeneration).93–99Simple steatosis encompasses steatosis alone or steatosis with inflammation. The histological checklist is as follows: steatosis, lobular and portal inflammation, balloon-

is important to note that steatosis does not include activity, but this is reported separately in the SAF score; this is because the degree of steatosis is not a histological marker of ongoing liver damage. Fi-brosis staging basically relies on the Kleiner classification.104On the basis of the distinctive histological pattern, a specific histolog-ical score—the pediatric NAFLD histological score—has been val-idated for better classification of children with/without NASH.101

Non-invasive tests of hepatic steatosis (Table 4) Prediction models. Several prediction models composed of common clinical and laboratory parameters have been used in clin-ical studies. While none of these allow precise estimation of liver fat content, they collectively point to simple biochemical indices for clinicians to consider the presence of NAFLD. In fact, the extent of steatosis (or its biochemical equivalent of total liver fat content) may not be relevant to the outcome of NAFLD or its sub-

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ing | degeneration, | Mallory–Denk | bodies, | megamitochondria, | type of NASH (see sections on Natural history and Liver histology). |

lipogranulomas, iron granules, glycogenated nuclei, acidophilic bodies, veno-occlusive lesions, pericellular fibrosis, and degree of fibrosis. Degree of fibrosis and portal inflammation have been reported to be very important features for prognosis but not neces-sary for the diagnosis for NASH.50,63,100In children, steatosis and portal-based chronic inflammation are more prominent than in adults, and hepatocellular ballooning and Mallory–Denk bodies are not conspicuous.101–103

What kind of histological staining should be performed? The minimum staining includes HE, picrosirius red or Mallory’s stain for the detection of fibrosis, and Perls staining for hemosiderosis.

Which scoring system, if any, should be used?. In 2005, the NASH Clinical Research Network Pathology Committee de-veloped and validated the NAFLD activity score (NAS) as a semi-quantitative instrument to judge treatment responses and disease progression in clinical studies.104NAS was not developed to diag-nose NASH; it was developed as a potential end-point for clinical trials, but even in this respect has now been replaced by the US Food and Drug Administration (FDA) and AASLD recommended end-point of NASH reversal without fibrosis worsening. The NAS system is the unweighted sum of the scores for steatosis (0–3), lob-ular inflammation (0–3), and ballooning degeneration (0–2). A score of greater than or equal to 5 correlates with a diagnosis of NASH; scores less than 3 correlate with “non-NASH”; and scores of 3 or 4 are regarded as borderline. With regard to fibrosis, stage 1 refers to perisinusoidal fibrosis in the perivenular area (delicate <1A> or dense <1B>). Detection of portal fibrosis without perisinusoidal fibrosis is defined as 1C. Stage 2 is characterized by perisinusoidal and portal/periportal fibrosis. Stage 3 is defined as bridging fibrosis, and stage 4 as cirrhosis.

The recently reported fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score increase observer agreement.105,106The FLIP algorithm is based on semi-quantitative evaluation of steatosis, hepatocellular ballooning, and lobular inflammation for segregating normal liver, NAFLD, and NASH. The SAF score consists of the semiquantitative scoring of steatosis (S), activity (A), and fibrosis (F). The activity score consists of ballooning degeneration and lobular inflammation. It

Fatty liver index is derived from serum triglyceride and gamma-glutamyltransferase (GGT) levels, BMI, and waist circum-ference.107NAFLD liver fat score estimates liver fat content (in percentage) with a formula consisting of metabolic syndrome, T2DM, fasting serum insulin, aspartate aminotransferase (AST), and the AST/ALT ratio.108SteatoTest is a complex logistic regression model of 12 parameters: α2-macroglobulin (A2M), apolipoprotein A-I (ApoA1), haptoglobin, total bilirubin, GGT, cholesterol, triglycerides, glucose, age, gender, and BMI.109The issue of SteatoTest is that some of the parameters (e.g. A2M and ApoA1) may not be readily available in local laboratories.

Abdominal ultrasonography. Abdominal ultrasonography is the most common first-line imaging modality for patients with el-evated liver enzymes or suspected NAFLD.110An increase in the echogenicity of the liver parenchyma appearing brighter than the cortex of the kidney, intrahepatic vessels blurring, and deep atten-uation are the typical imaging features of fatty liver.111A 6-point score based on these ultrasonographic features was found to corre-late well with histological steatosis.89However, ultrasonography does not perform well in morbidly obese patients112and may miss the diagnosis (because of insensitivity) if steatosis is ≤30%.113

Controlled attenuation parameter by FibroScan. Controlled attenuation parameter measures ultrasound attenuation (go and return path) using signals acquired by the M probe114or XL probe115,116of a FibroScan machine. CAP has demonstrated satis-factory diagnostic performance in detecting steatosis, with area un-der receiver operating characteristics curves (AUROC) ranging from 0.80 to 0.97 for steatosis ≥11%, 0.81 to 0.95 for steatosis≥34%, and 0.66 to 0.93 for steatosis ≥67%.91,117,118FibroScan has the advantages of being painless, rapid (usually less than 5 min), and user-friendly. CAP can be measured simultaneously with liver stiffness (see succeeding sections) and thus may be used to diagnose NAFLD by confirming the presence of steatosis and to assess its severity (albeit the uncertainty remains regarding the“cut-offs” for NASH vs SS, and for advanced fibrosis or cirrhosis vs no or other degrees of fibrosis; see earlier section).

Magnetic resonance imaging. Proton magnetic resonance spectroscopy measures proton signals from the acyl groups of

76 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| VW-S Wong et al. | | | | | | | 71 | - Modest accuracy | 54 | parameters involved | - High cost | - Modest specificity | 89% | obesity | - Operator dependent | - Cannot detect subtle changes | 79–81% | 86% | 78% | - Can grade steatosis | N.A. N.A. | S1: 100 | S2: 95 | - Long imaging time | Hepatic steatosis: S1 = ≥11%; S2 = ≥34%; S3 = ≥67%. | Asia-Pacific NAFLD guidelines | |
| AUROC, area under receiver operating characteristics curve; H1-MRS, proton magnetic resonance spectroscopy; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; N.A., | not available. |
| Specificity | | | (%) | 64 | | 86 |
| Diagnostic performance | | Sensitivity | (%) | 87 | | 61 |
| 86 | 90 | 91% | 76–91% | 89% | 100% | S1–2: 80 |
| Cut-off | 30 | | 60 | 0.640 | 0.30 | N.A. | S1: 0.80 to 0.91215–283 dB/m | S2: 0.81 to 0.95252–259 dB/m | S3: 0.66 to 0.93292–296 dB/m | 55.6 mg/g | - Need on patients cooperation |
| N.A. |
| 0.86–0.87 | 0.72–0.86 |
| N.A. | N.A. | 0.95 |
| AUROC | | | | 0.84 | | |
| - Sensitivity decreased with morbid |
| - Some uncommon laboratory |
| Disadvantages | | | | - Complex formula | | - Modest accuracy | - Sensitive but not as specific |
| - No consensus in cut-off |
| - Complex formula | - Limited availability |
| - High cost |
| Non-invasive tests of hepatic steatosis | Advantages | | | Prediction models | - Common clinical and laboratory parameters | - High applicability | - Common clinical and laboratory parameters | - High applicability | - High sensitivity and negative predictive value even | with mild steatosis (>5%) | - Inexpensive | - Widely available | - Can be used as a screening tool | - High sensitivity even with mild steatosis (>10%) | - Instant results | - Inexpensive | - High sensitivity even with mild steatosis (more than | 5–10%) | - Can differentiate tissue characterization | - Operator independent |
| Modalities | | | Fatty liver index(Bedogni) | NAFLD liver fat score(Kotronen) | SteatoTest(Poynard05) | Abdominal ultrasonography | Controlled attenuation parameter(Wong | WJH13) | H1-MRS(Szczepaniak) | MRI-PDFF (Idilman) |
| Table 4 |
| Journal of Gastroenterology and Hepatology 33 (2018) 70–85 | | | | | | |
| 77 | |

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

hepatocyte triglyceride stores directly. MRS accurately measures intrahepatic triglyceride content; the results correlate well with histological assessments of hepatic steatosis.119An intrahepatic triglyceride content cut-off of 5–5.5% is often used to define fatty liver with high sensitivity.83   
 Magnetic resonance imaging-estimated proton density fat frac-tion (MRI-PDFF) is an imaging-based biomarker that allows fat mapping of the entire liver,120whereas MRS-PDFF provides a biochemical measure of liver fat in small regions of interest.119 MRI-PDFF is potentially more suitable to quantify changes in liver fat in clinical trials as it is more sensitive than the histology-determined steatosis grade in quantifying changes in the liver fat content.121MRI-PDFF has an AUROC of 0.95 for steatosis ≥67%; nonetheless, the PDFF results were affected by the presence of fibrosis.120Despite their high degree of accuracy, the availability and cost of magnetic resonance-based techniques are the key hurdles in limiting their applicability, especially to the general population.

Non-invasive tests of NASH

Cytokeratin-18 fragment. Plasma cytokeratin-18 fragment (CK-18) reflects the degree of hepatocellular apoptotic activity, a characteristic feature of NASH.122Three ELISA-based CK-18 assays have been developed to assess NAFLD. The M30 assay detects hepatocyte apoptosis through the identification of a caspase-cleaved fragment of CK-18. In contrast, both M65 and M65ED assays detect total cell death through the identification of both caspase-cleaved and uncleaved CK-18.123   
 CK-18 level is significantly increased in NASH.124It has dem-onstrated good diagnostic accuracy for NAFLD versus healthy livers, but less satisfactory accuracy for NASH versus simple steatosis.125,126The latter is arguably the greater diagnostic need in clinical assessment. The test was also criticized for limited sensitivity at a cut-off value of 165 U/L, making it inadequate as a screening test for staging NASH.127A meta-analysis of 10 studies showed that CK-18 fragments had an AUROC of 0.8 to di-agnose NASH versus non-NASH.128Two other models combin-ing CK-18 with hyaluronic acid,129or soluble Fas,130showed better predictive value for NASH versus non-NASH in patients with NAFLD. As the diagnostic accuracy is modest, CK-18 is un-likely to be used alone but probably either as the initial screening test with a low cut-off or part of a diagnostic panel.

Other biomarkers. Adiponectin is an adipokine that is exclu-sively synthesized by adipose tissue with roles in glucose and lipid metabolism.131Hypoadiponectinemia is associated with NAFLD and NASH.132Nonetheless, the large variations in adiponectin levels observed in different studies make it unsuitable to be the sole diagnostic biomarker in NAFLD/NASH.7Leptin is another potential biomarker that is often studied with adiponectin; a model combining serum suboptimal adiponectin and elevated leptin was used to predicted NASH or borderline NASH.133Nonetheless, conflicting data exist concerning its relationship with NASH or just with morbid obesity independent of liver disease.134Other biomarkers including resistin, ghrelin, and retinol-binding protein 4 may be appropriate biomarkers of NASH, but are unlikely to serve as diagnostic markers on their own.135

NashTest is made by the same manufacturer as SteatoTest, using patented algorithms combining 13 parameters: age; sex; height; weight; and serum levels of triglycerides, cholesterol, A2M, ApoA1, haptoglobin, GGT, ALT, AST, and total bilirubin. It has modest diagnostic accuracy for NASH (AUROC 0.79) and borderline NASH (AUROC 0.69).136It has poor concordance with histological NAS and so cannot be recommended.137   
 MicroRNAs are highly conserved, small non-coding RNAs of sizes 18–25 nucleotides that regulate gene expression at the post-transcriptional level.138Each miR can regulate hundreds of target genes. miRs have been increasingly recognized in the pathogene-sis and diagnosis of NAFLD and NASH.139The miR-122 and miR-34a levels were higher in NASH group compared with patients with simple steatosis.140

Non-invasive tests of liver fibrosis (Table 5) Because fibrosis is the most powerful (and possibly the only independent) prognostic factor for liver-related outcomes in NAFLD, including HCC development and mortality,62,141fibrosis assessment is of paramount clinical importance. Screening for varices and HCC should be offered in case of cirrhosis. Because of the pitfalls of liver biopsy discussed in the Liver histology section, non-invasive serological and physical tests have been developed to assess liver fibrosis.

Serum tests. Over the past several decades, panels of tests (often with clinical variables) including NAFLD fibrosis score, FIB-4, BARD score (BMI, AST/ALT ratio and diabetes), enhanced liver fibrosis panel, FibroTest, FibroMeter, and HepaScore have shown reasonable diagnostic accuracy (AUROC >0.8) when used to assess the extent of liver fibrosis.93,142–144In addition, some of these tests predict long-term prognoses such as the risk of incident diabetes and overall, cardiovascular-related, and liver-related mortality.145–147However, each of the reported studies appears to have used its own cut-off values; as a result of which, no widely accepted cut-off values to separate patients at low and high risk have been defined.

Physical tests. Recent tools to assess liver stiffness include TE, acoustic radiation force impulse elastography, and magnetic reso-nance elastography (MRE). A recent meta-analysis showed that TE had high sensitivity and specificity when used to identify fibro-sis in patients with NAFLD.148However, up to 20% of TE exam-inations yielded unreliable results, especially among patients with high BMI.149,150The use of XL probe can increase the success rate of examination in obese patients, but proper training is required.151 Acoustic radiation force impulse elastography has also afforded acceptable accuracy in patients with NAFLD (AUC >0.8).152–156 MRE was the most accurate of the non-invasive physical assess-ment tools.157However, MRE is not widely available and is rarely used in clinical practice because of the high cost.

Investigations in the Asia–Pacific region. Several studies in this region have assessed the cross-sectional accuracy of non-invasive surrogates of liver biopsy among Asian patients with NAFLD.150,157–159Some have suggested that the combined use of serum tests and physical tools can yield more reliable data than that afforded by either method alone.160–163However, cut-off

78 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

thresholds remain undefined, and as a result, the prognostic impli-cations of various values have not yet been adequately investi-gated. Thus, at the present time, the clinical use of such tools to avoid liver biopsy remains undefined.164,165

Limitations. A major limitation of non-invasive testing is that most investigations have been performed in studies featuring a

cross-sectional design. Thus, the ability of the tests to monitor the natural history of disease and to predict outcomes or responses to therapeutic intervention remains unclear.

HCC screening. The annual incidence of developing HCC in NASH cirrhosis is 2.26%, and the mortality of such cases is 47% HCC-related deaths over 5.3 years.70Cost-effectiveness data from

|  |  |  |  |
| --- | --- | --- | --- |
| Table 5 | Comparison of different tests for NAFLD to assess the degree of liver fibrosis | |  |
| Pros | | | Cons  Not specific for liver |
| Serum tests | | Good reproducibility |

High applicability, readily available   
No additional cost, if not patented   
Acceptable accuracy to exclude advanced

Not immediate result acquisition   
High cost and limited availability, if patented   
Inappropriate to discriminate between intermediate

fibrosis and cirrhosis stages of fibrosis Has prognostic value   
Physical tests

|  |  |  |
| --- | --- | --- |
| Transient elastography | Specific for liver—check pure physical property | Needs a high-cost tool |
| Short learning curve | Reliable results only 75% in obese subjects despite |

of XL probe   
Fast acquisition False positivity with high ALT, ascites, cholestasis, and heart failure   
Immediate results Inappropriate to discriminate between intermediate stages of fibrosis   
Good reproducibility   
Low intra-observer and inter-observer variability   
Good performance to exclude advanced fibrosis   
and cirrhosis   
Has prognostic value

|  |  |  |
| --- | --- | --- |
| ARFI elastography | Specific for liver—check pure physical property | Needs a high-cost tool |
| Fast acquisition | Limited data |
| Immediate results | Narrow range |
| Simultaneous acquisition of hepatic and tumor | Smaller ROI than transient elastography |

information   
Good performance to exclude advanced fibrosis No quality criteria   
and cirrhosis   
Inappropriate to discriminate between intermediate stages of fibrosis

|  |  |  |
| --- | --- | --- |
| Shear wave elastography | Specific for liver—check pure physical property | Needs a high-cost tool |
| High intra-observer reliability | Limited data |
| Fast acquisition | ~15% of failure rates |
| Immediate results | No quality criteria |
| Simultaneous acquisition of hepatic and tumor | Inappropriate to discriminate between intermediate |
| information | stages of fibrosis |

Good performance to exclude advanced fibrosis and cirrhosis

Reliable results only in 73% of patients with BMI ≥30 kg/m2

|  |  |  |
| --- | --- | --- |
| MRE | Specific for liver—check pure physical property | Needs a high-cost tool |
| Estimation of the entire liver | Limited data |
| Not affected by obesity | Not immediate result acquisition |
| Simultaneous acquisition of hepatic and tumor | Needs a specific facility |

information   
Simultaneous MRS for steatosis High cost   
Probably more accurate than transient Time-consuming   
elastography   
Inaccurate in iron overload   
Cannot be used in patients with implantable devices

ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; BMI, body mass index; MRE, magnetic resonance elastography; MRS, mag-netic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; ROI, region of interest.

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 79© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

the West suggest that twice yearly ultrasound for HCC surveil-lance is cost-effective when the risk of developing HCC is >1.5% per year.166Hence, all NASH patients with cirrhosis should undergo HCC surveillance similar to patients with cirrhosis from other etiologies.

Ultrasound every 6 months is the most practical screening modality, although the sensitivity and specificity of ultrasound in the echogenic fatty liver is not known. This may result in addi-tional need for cross-sectional imaging and affect the cost-utility of surveillance.167The benefit of adding serum α-fetoprotein remains unclear.168   
 The issue of HCC occurring in non-cirrhotic livers of patients with NAFLD was considered in the section on NASH-related HCC. However, the exact risk for each fibrosis stage is unknown, so it is not possible to calculate cost-effectiveness of HCC surveil-lance for non-cirrhotic patients in the Asian context or elsewhere. The risk of developing HCC in patients with steatosis/steatosis without advanced fibrosis is probably low with prospective popu-lation studies showing that the incidence of HCC being 0.25% HCC after 5.6 years.169   
 Markers that independently predict increased risk of HCC in non-cirrhotic NASH include PNPLA3 rs738409 C>G gene poly-morphism,170diabetes, obesity, hypertension, cigarette smoking, and family history. These factors may potentially select higher risk

in NAFLD patients have been performed to support screening beyond the current cancer screening guidelines.

Non alcoholic fatty liver disease is independently associated with obstructive sleep apnea and osteoporosis. A meta-analysis of 18 studies using polysomnography to define obstructive sleep apnea found a twofold to threefold increased risk of NAFLD including NASH and advanced fibrosis with obstructive sleep ap-nea.190Conversely, the risk of obstructive sleep apnea among NAFLD patients is not known. Korean women with ultrasound-diagnosed NAFLD have been reported to have lower bone mineral density than those without NAFLD,191while the prevalence of os-teoporotic fractures in Chinese men was increased among those with NAFLD.192   
 Recommendation Statements   
6.1 Liver biopsy should be performed in NAFLD patients whose diagnosis is unclear, or where there is a suspected possibility of co-existing chronic liver diseases. (B1)   
6.2 The NAFLD Activity Score was designed to document histo-logical changes over time in clinical studies and should not be used as a diagnostic tool. In contrast, the FLIP algorithm was de-signed to diagnose NASH. Data on their performance in the Asia-Pacific population are scarce. (B2)   
6.3 CAP by FibroScan or MR-based techniques are accurate alternatives to abdominal ultrasonography for the detection of

groups for screening, thereby improving cost-effectiveness. steatosis, by virtue of their higher sensitivity. However, their

However, as yet there is insufficient modeling or validation data applicability depends on the availability and local cost of the

to make any recommendations, and this is an important area for modality. (B1)

future study. 6.4 Prediction models for NAFLD may be used in epidemiological

studies. Their application at the individual patient level is unclear.

Extrahepatic manifestations of NAFLD. Insulin resis-(B2)

tance is central to the pathogenesis of both NAFLD and metabolic syndrome. Multiple studies have demonstrated that patients with NAFLD have a higher prevalence of features of metabolic syn-drome including obesity, T2DM, and hyperlipidemia.3,171,172In Asian cohorts, NAFLD independently increases the risk of inci-dent diabetes mellitus by twofold to fivefold.173–176The combina-tion of diabetes mellitus with NAFLD significantly increases metabolic complications and all-cause mortality.177   
 Cohort studies of NAFLD patients show that advanced fibrosis (NASH) have an increased mortality from cardiovascular causes.146Several Asian studies have shown that NAFLD is an in-dependent risk factor for coronary atherosclerosis178,179as well as coronary artery disease.180–182However, the efficacy of screening for NAFLD in patients with coronary artery disease or coronary artery disease in NAFLD patients is yet to be proven.183   
 Non alcoholic fatty liver disease, especially NASH, is indepen-dently associated with a higher prevalence of chronic kidney disease.184Although the strength of this association varies between different cohorts of NAFLD patients, among Asian NAFLD patients defined by ultrasound or raised liver enzymes, a strong independent association with 1.5-fold to 2-fold increase in incident-adjusted risk has been found consistently.182,185,186 Three large Asian studies have reported increased risk of colo-rectal adenomas in NAFLD patients.187–189In both retrospective and prospective cohorts, the risk of colorectal adenoma and carci-noma in NAFLD patients is up to 1.5-fold and 3-fold higher, respectively, compared with patients without NAFLD. These asso-ciations appear stronger in NASH patients than among those with simple steatosis. However, no prospective cancer screening trials

6.5 Biomarkers for NASH are not yet ready to replace liver biopsy as a reliable diagnostic tool. (B2)   
6.6 Biomarkers for NASH, with cut-off values of high sensitivity, may be used as the initial screening strategy to reduce the need for liver biopsy. Further research is needed to develop better bio-markers or diagnostic algorithms. (B2)   
6.7 Noninvasive serum and physical tests afford modest but possibly acceptable accuracies when used to measure the fibrotic burden in patients with NAFLD. (A2)   
6.8 Appropriate cut-off values for identifying patients who are at low and high risk of developing liver-related complications are required. Also, the prognostic performance of noninvasive tests used for monitoring changes in the fibrotic burden requires further validation. (C2)   
6.9 Liver biopsy should be considered when assessment of liver fibrosis using noninvasive tests is inconclusive. (B1)   
6.10 Patients with NASH cirrhosis are at increased risk of develop-ing hepatocellular carcinoma and should undergo regular surveil-lance with ultrasound examination every 6 months. (A1)   
6.11 The role of serum AFP is yet to be evaluated in NASH- HCC.

(C2)   
6.12 Although HCC can occur in non-cirrhotic NASH patients, the overall risk is low, especially for those with simple steatosis. At present, no recommendations for screening can be made. (B2) 6.13 NAFLD is associated with increased risk of cardiovascular disease, chronic kidney disease and colorectal neoplasm. Other possible associations include obstructive sleep apnoea and osteo-porosis. However, there is insufficient prospective data available to support screening patients with these associated disorders. Risk

80 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

assessment for patients with such conditions should be individual-ized. (B1)   
6.14 There is a need to define Asian patients with NAFLD who are at the greatest risk of developing metabolic complications and for whom, cost effective interventional therapies can be tested. (C1)

Acknowledgment

The authors would like to thank Mr Michael Lau for his editorial support. The preparation of this manuscript was supported by the Journal of Gastroenterology and Hepatology Foundation.

References

pediatric chronic liver disease. Gastroenterology 2010; 138: 1357-64–64 e1-2.

16 Molleston JP, Schwimmer JB, Yates KP et al. Histological   
abnormalities in children with nonalcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. J. Pediatr. 2014; 164: 707–13 e3.

17 Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics 2006; 118: 1388–93.

18 Rorat M, Jurek T, Kuchar E, Szenborn L, Golema W, Halon A. Liver steatosis in Polish children assessed by medicolegal autopsies. World J. Pediatr. 2013; 9: 68–72.

19 Molleston JP, White F, Teckman J, Fitzgerald JF. Obese children with steatohepatitis can develop cirrhosis in childhood. Am. J.

Gastroenterol. 2002; 97: 2460–2.

20 Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PLoS One 2015;

1 Farrell GC, Chitturi S, Lau GK, Sollano JD, Asia-Pacific Working 10 e0140908.

Party on N. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia–Pacific region: executive summary. J. Gastroenterol. Hepatol. 2007; 22: 775–7.

2 Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490.

3 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes.

Hepatology 2016; 64: 73–84.

4 Farrell GC, Wong VW, Chitturi S. NAFLD in Asia—as common and important as in the West. Nat Rev Gastroenterol Hepatol. 2013; 10:

21 Koehler EM, Schouten JN, Hansen BE et al. Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: results from the Rotterdam study. J. Hepatol. 2012; 57: 1305–11.

22 Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr. Opin. Gastroenterol. 2015; 31: 184–91.

23 Nazim M, Stamp G, Hodgson HJ. Non-alcoholic steatohepatitis associated with small intestinal diverticulosis and bacterial overgrowth. Hepato-Gastroenterology 1989; 36: 349–51.

24 Raman M, Allard J. Non alcoholic fatty liver disease: a clinical approach and review. Can. J. Gastroenterol. 2006; 20: 345–9.

25 Younossi ZM. Nonalcoholic fatty liver disease. Curr Gastroenterol

307–18. Rep. 1999; 1: 57–62.

5 Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am. J.

Gastroenterol. 2013; 108: 1299–304.

6 Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J. Gastroenterol. Hepatol. 2013; 28: 11–7.

7 Wong VW, Wong GL, Choi PC et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 2010; 59: 969–74.

8 Tokushige K, Hashimoto E, Kodama K. Hepatocarcinogenesis in

26 Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. Am. J. Clin. Nutr. 2007; 86: 285–300.

27 Angulo P, Lindor KD. Insulin resistance and mitochondrial abnormalities in NASH: a cool look into a burning issue.

Gastroenterology 2001; 120: 1281–5.

28 Salmenniemi U, Ruotsalainen E, Pihlajamaki J et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion   
molecules in subjects with metabolic syndrome. Circulation 2004;

non-alcoholic fatty liver disease in Japan. J. Gastroenterol. Hepatol. 110: 3842–8.

2013; 28: 88–92.

9 Tominaga K, Kurata JH, Chen YK et al. Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological

29 Wong VW-S, Chitturi S, Wong GL-H, Yu J, Chan HL-Y, Farrell GC. Pathogenesis and novel treatment options for non-alcoholic steatohepatitis. Lancet Gastroenterol. Hepatol. 2016;

ultrasonographic survey. Dig. Dis. Sci. 1995; 40: 2002–9. 1: 56–67.

10 Wan YP, Xu RY, Fang H, Lu LP, Zhang XM, Cai W. The prevalence 30 Timlin MT, Parks EJ. Temporal pattern of de novo lipogenesis in

of non-alcoholic fatty liver disease and its related risk factors in 1180 the postprandial state in healthy men. Am. J. Clin. Nutr. 2005; 81:

school children in Shanghai. Zhonghua Gan Zang Bing Za Zhi 2007; 35–42.

15: 644–8. 31 Hamaguchi M, Kojima T, Takeda N et al. The metabolic syndrome as

11 Lin Y-C, Chang P-F, Lin H-F, Liu K, Chang M-H, Ni Y-H. Variants a predictor of nonalcoholic fatty liver disease. Ann. Intern. Med. 2005;

in the autophagy-related gene IRGM confer susceptibility to non- 143: 722–8.

alcoholic fatty liver disease by modulating lipophagy. J. Hepatol. 2016; 65: 1209–16.

12 Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R,   
McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J. Hepatol. 2009; 51: 1061–7.

32 Byrne CD, Targher G. Ectopic fat, insulin resistance, and nonalcoholic fatty liver disease: implications for cardiovascular disease. Arterioscler. Thromb. Vasc. Biol. 2014; 34: 1155–61.

33 Loria P, Lonardo A, Carulli L et al. Review article: the metabolic syndrome and non-alcoholic fatty liver disease. Aliment. Pharmacol.

13 Park HS, Han JH, Choi KM, Kim SM. Relation between elevated Ther. 2005; 22: 31–36.

serum alanine aminotransferase and metabolic syndrome in Korean adolescents. Am. J. Clin. Nutr. 2005; 82: 1046–51.

14 Kawasaki T, Hashimoto N, Kikuchi T, Takahashi H, Uchiyama M.

34 Chitturi S, Farrell GC, Hashimoto E et al. Non-alcoholic fatty liver disease in the Asia–Pacific region: definitions and overview of proposed guidelines. J. Gastroenterol. Hepatol. 2007; 22:

The relationship between fatty liver and hyperinsulinemia in obese 778–87.

Japanese children. J. Pediatr. Gastroenterol. Nutr. 1997; 24: 317–21. 15 Schwimmer JB, Dunn W, Norman GJ et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of

35 Koh JC, Loo WM, Goh KL et al. Asian consensus on the relationship between obesity and gastrointestinal and liver diseases.   
J. Gastroenterol. Hepatol. 2016; 31: 1405–13.

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 81

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

36 Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease:   
evidenceo from a meta-analysis of 21 cohort studies. Obes. Rev. 2016;

57 Hashimoto E, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. J. Gastroenterol. Hepatol. 2013; 28: 64–70.

58 Okanoue T, Umemura A, Yasui K, Itoh Y. Nonalcoholic fatty liver

17: 510–19. disease and nonalcoholic steatohepatitis in Japan. J. Gastroenterol.

37 Neuschwander-Tetri BA. Fatty liver and nonalcoholic steatohepatitis. Clin. Cornerstone. 2001; 3: 47–57.

38 Than NN, Newsome PN. A concise review of non-alcoholic fatty liver disease. Atherosclerosis 2015; 239: 192–202.

39 Zelber-Sagi S, Lotan R, Shlomai A et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. J. Hepatol. 2012; 56: 1145–51.

40 Cho JY, Chung TH, Lim KM, Park HJ, Jang JM. The impact of weight changes on nonalcoholic fatty liver disease in adult men with normal weight. Korean J. Fam. Med. 2014; 35: 243–50.

41 Abu-Shanab A, Quigley EM. The role of the gut microbiota in nonalcoholic fatty liver disease. Nat. Rev. Gastroenterol. Hepatol.

Hepatol. 2011; 26: 153–62.

59 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: 1148–55.

60 Pais R, Charlotte F, Fedchuk L et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J. Hepatol. 2013; 59: 550–6.

61 Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R.

Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin. Gastroenterol. Hepatol. 2015; 13 643-54 e1-9;

2010; 7: 691–701. quiz e39-40.

42 Backhed F, Ding H, Wang T et al. The gut microbiota as an   
environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. U. S. A. 2004; 101: 15718–23.

43 Backhed F, Manchester JK, Semenkovich CF, Gordon JI.

Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc. Natl. Acad. Sci. U. S. A. 2007; 104: 979–84.

44 Miele L, Valenza V, La Torre G et al. Increased intestinal   
permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 2009; 49: 1877–87.

45 Romeo S, Kozlitina J, Xing C et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat. Genet. 2008; 40: 1461–5.

62 Ekstedt M, Hagstrom H, Nasr P 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: 1547–54.

63 Younossi ZM, Stepanova M, Rafiq N et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011; 53: 1874–82.

64 Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J. Hepatol. 2009; 51: 371–9.

65 Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 1990; 11:

46 Kozlitina J, Smagris E, Stender S et al. Exome-wide association study 74–80.

identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat. Genet. 2014; 46: 352–6.

47 Petersen KF, Dufour S, Hariri A et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N. Engl. J. Med. 2010;

66 Yoshioka Y, Hashimoto E, Yatsuji S et al. Nonalcoholic   
steatohepatitis: cirrhosis, hepatocellular carcinoma, and burnt-out NASH. J. Gastroenterol. 2004; 39: 1215–8.

67 Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein

362: 1082–9. NN. The incidence and risk factors of hepatocellular carcinoma in 48 Zhang H, Chen L, Xin Y, Lou Y, Liu Y, Xuan S. Apolipoprotein C3 patients with nonalcoholic steatohepatitis. Hepatology 2010; 51: gene polymorphisms are not a risk factor for developing non-alcoholic 1972–8.

fatty liver disease: a meta-analysis. Hepat. Mon. 2014; 14 e23100. 68 Hui JM, Kench JG, Chitturi S et al. Long-term outcomes of cirrhosis 49 Adams LA, Lymp JF, St Sauver J et al. The natural history of in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology nonalcoholic fatty liver disease: a population-based cohort study. 2003; 38: 420–7.

Gastroenterology 2005; 129: 113–21.

50 Angulo P, Kleiner DE, Dam-Larsen S et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;

69 Sanyal AJ, Banas C, Sargeant C et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology 2006; 43: 682–9.

70 Yatsuji S, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori

149: 389–97 e10. K. Clinical features and outcomes of cirrhosis due to non-alcoholic

51 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. Scand. J. Gastroenterol. 2009; 44: 1236–43.

52 Ekstedt M, Franzen LE, Mathiesen UL et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;

steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J. Gastroenterol. Hepatol. 2009; 24: 248–54.

71 Yasui K, Hashimoto E, Komorizono Y et al. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin. Gastroenterol. Hepatol. 2011; 9: 428–33 quiz e50.

44: 865–73. 72 White DL, Kanwal F, El-Serag HB. Association between

53 Haflidadottir S, Jonasson JG, Norland H et al. Long-term follow-up nonalcoholic fatty liver disease and risk for hepatocellular cancer,

and liver-related death rate in patients with non-alcoholic and based on systematic review. Clin. Gastroenterol. Hepatol. 2012; 10:

alcoholic related fatty liver disease. BMC Gastroenterol. 2014; 1342–59 e2.

14: 166. 73 Goh KL, Razlan H, Hartono JL et al. Liver cancer in Malaysia:

54 Soderberg C, Stal P, Askling J et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up.

Hepatology 2010; 51: 595–602.

55 Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J. Hepatol. 2005; 42:

epidemiology and clinical presentation in a multiracial Asian population. J. Dig. Dis. 2015; 16: 152–8.

74 Lee SS, Jeong SH, Byoun YS et al. Clinical features and outcome of cryptogenic hepatocellular carcinoma compared to those of viral and alcoholic hepatocellular carcinoma. BMC Cancer 2013; 13: 335.

75 Tokushige K, Hashimoto E, Horie Y, Taniai M, Higuchi S.

132–8. Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty

56 Fan JG, Saibara T, Chitturi S et al. What are the risk factors and liver disease, alcoholic liver disease, and chronic liver disease of

settings for non-alcoholic fatty liver disease in Asia–Pacific? unknown etiology: report of the nationwide survey. J. Gastroenterol.

J. Gastroenterol. Hepatol. 2007; 22: 794–800. 2011; 46: 1230–7.

82 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

76 Polesel J, Zucchetto A, Montella M et al. The impact of obesity and 95 Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA,

diabetes mellitus on the risk of hepatocellular carcinoma. Ann. Oncol. Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and

2009; 20: 353–7. staging the histological lesions. Am. J. Gastroenterol. 1999; 94:

77 Wong RJ, Aguilar M, Cheung R et al. Nonalcoholic steatohepatitis is 2467–74.

the second leading etiology of liver disease among adults awaiting 96 Hashimoto E, Tokushige K, Ludwig J. Diagnosis and classification of

liver transplantation in the United States. Gastroenterology 2015; 148: non-alcoholic fatty liver disease and non-alcoholic steatohepatitis:

547–55. current concepts and remaining challenges. Hepatol. Res. 2015; 45:

78 Cho EJ, Kwack MS, Jang ES et al. Relative etiological role of prior 20–28.

hepatitis B virus infection and nonalcoholic fatty liver disease in the development of non-B non-C hepatocellular carcinoma in a hepatitis B-endemic area. Digestion 2011; 84: 17–22.

79 Bhala N, Angulo P, van der Poorten D et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology 2011;

97 Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC,   
 McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116: 1413–9. 98 Sakamoto M, Tsujikawa H, Effendi K et al. Pathological findings of nonalcoholic steatohepatitis and nonalcoholic fatty liver disease.

Pathol. Int. 2017; 67: 1–7.

54: 1208–16. 99 Yeh MM, Brunt EM. Pathological features of fatty liver disease.

80 Kawada N, Imanaka K, Kawaguchi T et al. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis.

J. Gastroenterol. 2009; 44: 1190–4.

81 TM YJHWT. Comparison of clinical features of NASH associated HCC with versus without liver cirrhosis. In: 10th Annual Conference of the International Liver Cancer Association. Canada: Vancouver, ss.

82 Wah-Kheong C, Khean-Lee G. Epidemiology of a fast emerging disease in the Asia–Pacific region: non-alcoholic fatty liver disease. Hepatol. Int. 2013; 7: 65–71.

83 Wong VW, Chu WC, Wong GL et al. Prevalence of non-alcoholic

Gastroenterology 2014; 147: 754–64.

100 Loomba R, Chalasani N. The hierarchical model of NAFLD: prognostic significance of histologic features in NASH.

Gastroenterology 2015; 149: 278–81.

101 Alkhouri N, De Vito R, Alisi A et al. Development and validation of a new histological score for pediatric non-alcoholic fatty liver disease. J. Hepatol. 2012; 57: 1312–8.

102 Nobili V, Alisi A, Newton KP, Schwimmer JB. Comparison of the phenotype and approach to pediatric vs adult patients with   
nonalcoholic fatty liver disease. Gastroenterology 2016; 150:

fatty liver disease and advanced fibrosis in Hong Kong Chinese: a 1798–810.

population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012; 61: 409–15.

84 Kwok R, Choi KC, Wong GL et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016; 65: 1359–68.

85 Wei JL, Leung JC, Loong TC et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am. J.

Gastroenterol. 2015; 110: 1306–14 quiz 15.

86 Seki Y, Kakizaki S, Horiguchi N et al. Prevalence of nonalcoholic steatohepatitis in Japanese patients with morbid obesity undergoing bariatric surgery. J. Gastroenterol. 2016; 51: 281–9.

87 Wilson JM, Jungner YG. Principles and practice of mass screening for disease. Bol. Oficina Sanit. Panam. 1968; 65: 281–393.

88 Wong VW, Wong GL, Tsang SW et al. Metabolic and histological features of non-alcoholic fatty liver disease patients with different serum alanine aminotransferase levels. Aliment. Pharmacol. Ther. 2009; 29: 387–96.

89 Hamaguchi M, Kojima T, Itoh Y et al. The severity of

103 Schwimmer JB, Behling C, Newbury R et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology 2005; 42: 641–9. 104 Kleiner DE, Brunt EM, Van Natta M et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease.

Hepatology 2005; 41: 1313–21.

105 Bedossa P, Consortium FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014; 60: 565–75.

106 Bedossa P, Poitou C, Veyrie N et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology 2012; 56: 1751–9.

107 Bedogni G, Bellentani S, Miglioli L et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006; 6: 33.

108 Kotronen A, Peltonen M, Hakkarainen A et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology 2009; 137: 865–72.

109 Poynard T, Ratziu V, Naveau S et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Comp.

ultrasonographic findings in nonalcoholic fatty liver disease reflects Hepatol. 2005; 4: 10.

the metabolic syndrome and visceral fat accumulation. Am. J.

Gastroenterol. 2007; 102: 2708–15.

90 Saadeh S, Younossi ZM, Remer EM et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;

110 Palmentieri B, de Sio I, La Mura V et al. The role of bright liver echo pattern on ultrasound B-mode examination in the diagnosis of liver steatosis. Dig. Liver Dis. 2006; 38: 485–9.

111 Quinn SF, Gosink BB. Characteristic sonographic signs of hepatic

123: 745–50. fatty infiltration. AJR Am. J. Roentgenol. 1985; 145: 753–5.

91 Chan WK, Nik Mustapha NR, Mahadeva S. Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease. J. Gastroenterol. Hepatol. 2014; 29:

112 Wu J, You J, Yerian L, Shiba A, Schauer PR, Sessler DI. Prevalence of liver steatosis and fibrosis and the diagnostic accuracy of   
ultrasound in bariatric surgery patients. Obes. Surg. 2012; 22: 240–7.

1470–6. 113 Ryan CK, Johnson LA, Germin BI, Marcos A. One hundred

92 Yatsuji S, Hashimoto E, Kaneda H, Taniai M, Tokushige K, Shiratori K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease: is the International Autoimmune Hepatitis Group scoring system useful? J. Gastroenterol. 2005; 40: 1130–8.

93 Bedossa P, Patel K. Biopsy and noninvasive methods to assess progression of nonalcoholic fatty liver disease. Gastroenterology 2016; 150: 1811–22 e4.

94 Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. Semin. Liver Dis. 2001; 21: 3–16.

consecutive hepatic biopsies in the workup of living donors for right lobe liver transplantation. Liver Transpl. 2002; 8: 1114–22.

114 Sasso M, Beaugrand M, de Ledinghen V et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med. Biol. 2010; 36: 1825–35.

115 Sasso M, Audiere S, Kemgang A et al. Liver steatosis assessed by controlled attenuation parameter (CAP) measured with the xl probe of

Journal of Gastroenterology and Hepatology 33 (2018) 70–85 83

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

Asia-Pacific NAFLD guidelines VW-S Wong et al.

the FibroScan: a pilot study assessing diagnostic accuracy.

Ultrasound Med. Biol. 2016; 42: 92–103.

116 Chan WK, Mustapha NRN, Wong GL, Wong VW, Mahadeva S.

Controlled attenuation parameter using the FibroScan® XL probe for quantification of hepatic steatosis for non-alcoholic fatty liver disease in an Asian population. United Eur. Gastroenterol. J. 2017; 5: 76–85. 117 de Ledinghen V, Wong GL, Vergniol J et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J. Gastroenterol. Hepatol. 2016; 31: 848–55.

118 Wong GL. Transient elastography: kill two birds with one stone? World J. Hepatol. 2013; 5: 264–74.

135 Neuman MG, Cohen LB, Nanau RM. Biomarkers in nonalcoholic fatty liver disease. Can. J. Gastroenterol. Hepatol. 2014; 28: 607–18.

136 Poynard T, Ratziu V, Charlotte F et al. Diagnostic value of   
biochemical markers (NashTest) for the prediction of non alcoholo steato hepatitis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol. 2006; 6: 34.

137 Lassailly G, Caiazzo R, Hollebecque A et al. Validation of noninvasive biomarkers (FibroTest, SteatoTest, and NashTest) for prediction of liver injury in patients with morbid obesity. Eur. J.

Gastroenterol. Hepatol. 2011; 23: 499–506.

138 Ambros V. The functions of animal microRNAs. Nature 2004; 431:

119 Szczepaniak LS, Nurenberg P, Leonard D et al. Magnetic resonance 350–5.

spectroscopy to measure hepatic triglyceride content: prevalence of 139 Szabo G, Csak T. Role of microRNAs in NAFLD/NASH. Dig. Dis. hepatic steatosis in the general population. Am. J. Physiol. Sci. 2016; 61: 1314–24.

Endocrinol. Metab. 2005; 288: E462–E468. 140 Cermelli S, Guo Y, Gross SP, Welte MA. The lipid-droplet proteome 120 Idilman IS, Aniktar H, Idilman R et al. Hepatic steatosis: reveals that droplets are a protein-storage depot. Curr. Biol. 2006; 16: quantification by proton density fat fraction with MR imaging versus 1783–95.

liver biopsy. Radiology 2013; 267: 767–75. 141 Angulo P, Machado MV, Diehl AM. Fibrosis in nonalcoholic fatty 121 Noureddin M, Lam J, Peterson MR et al. Utility of magnetic resonance liver disease: mechanisms and clinical implications. Semin. Liver Dis. imaging versus histology for quantifying changes in liver fat in 2015; 35: 132–45.

nonalcoholic fatty liver disease trials. Hepatology 2013; 58: 1930–40. 122 Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN,   
 McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology 2009; 50: 1072–8.

142 Cales P, Laine F, Boursier J et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J. Hepatol. 2009; 50: 165–73.

143 Festi D, Schiumerini R, Marasco G, Scaioli E, Pasqui F, Colecchia A.

Non-invasive diagnostic approach to non-alcoholic fatty liver disease: current evidence and future perspectives. Expert. Rev. Gastroenterol.

123 Joka D, Wahl K, Moeller S et al. Prospective biopsy-controlled 2015; 9: 1039–53.

evaluation of cell death biomarkers for prediction of liver fibrosis and nonalcoholic steatohepatitis. Hepatology 2012; 55: 455–64.

124 Shen J, Chan HL, Wong GL et al. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. J. Hepatol. 2012; 56: 1363–70.

125 Shen J, Chan HL, Wong GL et al. Assessment of non-alcoholic fatty liver disease using serum total cell death and apoptosis markers.

Aliment. Pharmacol. Ther. 2012; 36: 1057–66.

126 Chan WK, Sthaneshwar P, Nik Mustapha NR, Mahadeva S. Limited

144 Leroy V, Sturm N, Faure P et al. Prospective evaluation of FibroTest®, FibroMeter®, and HepaScore® for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. J. Hepatol. 2014; 61: 28–34. 145 Chang Y, Jung HS, Yun KE, Cho J, Cho YK, Ryu S. Cohort study of non- alcoholic fatty liver disease, NAFLD fibrosis score, and the risk of incident diabetes in a Korean population. Am. J. Gastroenterol. 2013; 108: 1861–8.

146 Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology

utility of plasma M30 in discriminating non-alcoholic steatohepatitis 2013; 57: 1357–65.

from steatosis—a comparison with routine biochemical markers. PLoS One 2014; 9 e105903.

127 Cusi K, Chang Z, Harrison S et al. Limited value of plasma

147 Xun YH, Guo JC, Lou GQ et al. Non-alcoholic fatty liver disease (NAFLD) fibrosis score predicts 6.6-year overall mortality of   
Chinese patients with NAFLD. Clin. Exp. Pharmacol. Physiol. 2014;

cytokeratin-18 as a biomarker for NASH and fibrosis in patients with 41: 643–9.

non-alcoholic fatty liver disease. J. Hepatol. 2014; 60: 167–74. 128 Chen J, Zhu Y, Zheng Q, Jiang J. Serum cytokeratin-18 in the diagnosis of non-alcoholic steatohepatitis: a meta-analysis. Hepatol.

148 Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann. Med.

Res. 2014; 44: 854–62. 2011; 43: 617–49.

129 Lebensztejn DM, Wierzbicka A, Socha P et al. Cytokeratin-18 and hyaluronic acid levels predict liver fibrosis in children with non-alcoholic fatty liver disease. Acta Biochim. Pol. 2011; 58: 563–6. 130 Tamimi TI, Elgouhari HM, Alkhouri N et al. An apoptosis panel for nonalcoholic steatohepatitis diagnosis. J. Hepatol. 2011; 54:

149 Castera L, Foucher J, Bernard PH et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010; 51: 828–35.

150 Wong VW, Vergniol J, Wong GL et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver

1224–9. disease. Hepatology 2010; 51: 454–62.

131 Trujillo ME, Scherer PE. Adiponectin—journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J. Intern. Med. 2005; 257: 167–75.

132 Bechmann LP, Kocabayoglu P, Sowa JP et al. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin   
counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. Hepatology 2013; 57: 1394–406.

133 Zelber-Sagi S, Ratziu V, Zvibel I et al. The association between adipocytokines and biomarkers for nonalcoholic fatty liver disease-induced liver injury: a study in the general population. Eur. J.

Gastroenterol. Hepatol. 2012; 24: 262–9.

134 Pirvulescu I, Gheorghe L, Csiki I et al. Noninvasive clinical model for the diagnosis of nonalcoholic steatohepatitis in overweight and morbidly obese patients undergoing bariatric surgery. Chirurgia (Bucur). 2012; 107: 772–9.

151 Wong VW, Vergniol J, Wong GL et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am. J. Gastroenterol. 2012; 107: 1862–71.

152 Karlas T, Dietrich A, Peter V et al. Evaluation of transient   
elastography, acoustic radiation force impulse imaging (ARFI), and enhanced liver function (ELF) score for detection of fibrosis in morbidly obese patients. PLoS One 2015; 10 e0141649.

153 Kwok R, Tse YK, Wong GL et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease—the role of transient elastography and plasma cytokeratin-18 fragments. Aliment. Pharmacol. Ther. 2014; 39: 254–69.

154 Liu H, Fu J, Hong R, Liu L, Li F. Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: a systematic review & meta-analysis. PLoS One 2015; 10 e0127782.

84 Journal of Gastroenterology and Hepatology 33 (2018) 70–85

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd

VW-S Wong et al. Asia-Pacific NAFLD guidelines

155 Palmeri ML, Wang MH, Rouze NC et al. Noninvasive evaluation of 2 diabetes: a 4-year retrospective longitudinal study. Diabetes Care hepatic fibrosis using acoustic radiation force-based shear stiffness in 2011; 34: 727–9.

patients with nonalcoholic fatty liver disease. J. Hepatol. 2011; 55: 174 Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of 666–72. nonalcoholic fatty liver disease on the development of metabolic

156 Yoneda M, Suzuki K, Kato S et al. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. Radiology 2010; 256: 640–7.

157 Imajo K, Kessoku T, Honda Y et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography.

Gastroenterology 2016; 150: 626–37 e7.

disorders. J. Gastroenterol. Hepatol. 2007; 22: 1086–91.

175 Sung KC, Jeong WS, Wild SH, Byrne CD. Combined influence of insulin resistance, overweight/obesity, and fatty liver as risk factors for type 2 diabetes. Diabetes Care 2012; 35: 717–22.

176 Yamada T, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. J. Gastroenterol. Hepatol.

158 Sumida Y, Yoneda M, Hyogo H et al. Validation of the FIB4 index in 2010; 25: 352–6.

a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol. 2012; 12: 2.

159 Yu SJ, Kim DH, Lee JH et al. Validation of P2/MS and other

177 Adams LA, Harmsen S, St Sauver JL et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. Am. J. Gastroenterol. 2010; 105:

noninvasive fibrosis scoring systems in the Korean population with 1567–73.

nonalcoholic fatty liver disease. Korean J Gastroenterol. 2011; 57: 178 Kang MK, Kang BH, Kim JH. Nonalcoholic fatty liver disease is

19–27. associated with the presence and morphology of subclinical coronary

160 Lee HW, Park SY, Kim SU et al. Discrimination of nonalcoholic steatohepatitis using transient elastography in patients with nonalcoholic fatty liver disease. PLoS One 2016; 11 e0157358.

161 Petta S, Vanni E, Bugianesi E et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with   
nonalcoholic fatty liver disease. Liver Int. 2015; 35: 1566–73.

162 Wong GL, Chan HL. Two are better than one: noninvasive assessment of liver fibrosis in nonalcoholic fatty liver disease.

Hepatol. Int. 2015; 9: 481–3.

163 Chan WK, Nik Mustapha NR, Mahadeva S. A novel 2-step approach combining the NAFLD fibrosis score and liver stiffness measurement for predicting advanced fibrosis. Hepatol. Int. 2015; 9: 594–602.

164 European Association for Study of L, Asociacion Latinoamericana para el Estudio del H. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J. Hepatol. 2015; 63: 237–64.

165 Takamura M, Kanefuji T, Suda T et al. Value of shear wave velocity measurements for the risk assessment of hepatocellular carcinoma development in patients with nonalcoholic fatty liver disease: HCC

atherosclerosis. Yonsei Med. J. 2015; 56: 1288–95.

179 Osawa K, Miyoshi T, Yamauchi K et al. Nonalcoholic hepatic steatosis is a strong predictor of high-risk coronary-artery plaques as determined by multidetector CT. PLoS One 2015; 10 e0131138.

180 Hamaguchi M, Kojima T, Takeda N et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J.

Gastroenterol. 2007; 13: 1579–84.

181 Wong VW, Wong GL, Yip GW et al. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut 2011; 60: 1721–7.

182 Yun KE, Shin CY, Yoon YS, Park HS. Elevated alanine   
aminotransferase levels predict mortality from cardiovascular disease and diabetes in Koreans. Atherosclerosis 2009; 205: 533–7.

183 Wong VW, Wong GL, Yeung JC et al. Long-term clinical outcomes after fatty liver screening in patients undergoing coronary angiogram: a prospective cohort study. Hepatology 2016; 63: 754–63.

184 Targher G, Kendrick J, Smits G, Chonchol M. Relationship between serum gamma-glutamyltransferase and chronic kidney disease in the United States adult population. Findings from the National Health and Nutrition Examination Survey 2001–2006. Nutr. Metab. Cardiovasc.

risk assessment by VTTQ. Hepatol. Int. 2014; 8: 240–9. Dis. 2010; 20: 583–90.

166 Sangiovanni A, Prati GM, Fasani P et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology 2006; 43: 1303–10.

167 Del Poggio P, Olmi S, Ciccarese F et al. Factors that affect efficacy of ultrasound surveillance for early stage hepatocellular carcinoma in patients with cirrhosis. Clin. Gastroenterol. Hepatol. 2014; 12:

185 Chang Y, Ryu S, Sung E et al. Nonalcoholic fatty liver disease predicts chronic kidney disease in nonhypertensive and nondiabetic Korean men. Metabolism 2008; 57: 569–76.

186 Li G, Shi W, Hug H, Chen Y, Liu L, Yin D. Nonalcoholic fatty liver disease associated with impairment of kidney function in nondiabetes population. Biochem. Med. (Zagreb). 2012; 22: 92–99.

1927–33 e2. 187 Huang KW, Leu HB, Wang YJ et al. Patients with nonalcoholic fatty

168 Gopal P, Yopp AC, Waljee AK et al. Factors that affect accuracy of alpha-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. Clin. Gastroenterol. Hepatol. 2014; 12:

liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy. Color. Dis. 2013; 15: 830–5.

188 Lee YI, Lim YS, Park HS. Colorectal neoplasms in relation to non-

870–7. alcoholic fatty liver disease in Korean women: a retrospective cohort

169 Kawamura Y, Arase Y, Ikeda K et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic fatty liver disease for the onset of hepatocellular carcinoma. Am. J. Gastroenterol. 2012;

study. J. Gastroenterol. Hepatol. 2012; 27: 91–95.

189 Wong VW, Wong GL, Tsang SW et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut 2011; 60:

107: 253–61. 829–36.

170 Patterson AD, Maurhofer O, Beyoglu D et al. Aberrant lipid   
metabolism in hepatocellular carcinoma revealed by plasma   
metabolomics and lipid profiling. Cancer Res. 2011; 71: 6590–600. 171 Ma J, Hwang SJ, Pedley A et al. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. J. Hepatol. 2017; 66:

190 Musso G, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R.

Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. Obes. Rev. 2013; 14: 417–31.

191 Moon SS, Lee YS, Kim SW. Association of nonalcoholic fatty liver

390–7. disease with low bone mass in postmenopausal women. Endocrine

172 Shen YH, Yang WS, Lee TH, Lee LT, Chen CY, Huang KC. Bright 2012; 42: 423–9.

liver and alanine aminotransferase are associated with metabolic syndrome in adults. Obes. Res. 2005; 13: 1238–45.

173 Bae JC, Rhee EJ, Lee WYet al. Combined effect of nonalcoholic fatty

192 Li M, Xu Y, Xu M et al. Association between nonalcoholic fatty liver disease (NAFLD) and osteoporotic fracture in middle-aged and elderly Chinese. J. Clin. Endocrinol. Metab. 2012; 97:

|  |  |  |
| --- | --- | --- |
| liver disease and impaired fasting glucose on the development of type | 2033–8. | 85 |
| Journal of Gastroenterology and Hepatology 33 (2018) 70–85 |

© 2017 Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd