

EXECUTIVE SUMMARY

Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: Executive summary

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Overview

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western industrialized countries,^{1,2} affecting 20–30% of the general population, and recent studies indicate that fatty liver is an emerging problem in the Asia-Pacific region.³ A comprehensive review of available data reveals that the overall prevalence of NAFLD in the Asia-Pacific region is broadly similar to that in North America, affecting between 12% and 24% of community subgroups.^{4,5} The prevalence varies by age, gender, ethnicity, and locality (urban versus rural), as well as with criteria used for disease definition.⁵ There is strong evidence that the prevalence of NAFLD in this region has increased substantially during the last 15 years in parallel with regional trends in over-nutrition (decreased physical activity with disproportionate food intake), central and overall obesity, type 2 diabetes mellitus (T2DM), and the metabolic syndrome.^{6–8} Present trends in the obesity and diabetes pandemic indicate that a further increase in NAFLD prevalence is likely in the immediate future.^{9,10}

The inextricable relationship between NAFLD and central (visceral) obesity, insulin resistance, and metabolic syndrome is evident in community studies from China,⁶ Japan,⁸ and Korea,⁷ which are the largest reported worldwide. With remarkable reproducibility, the data show changes in the age and gender-specific

prevalence of NAFLD in parallel with central obesity, diabetes, and metabolic syndrome.⁵ In South-East Asia, early observations indicate that ethnic predisposition to NAFLD is similar to that of metabolic syndrome (Indians > Malays > Chinese).^{4,5} The strength of associations between NAFLD and metabolic risk factors is not fully appreciated unless Asian rather than Caucasian anthropometric standards are used for central obesity and body mass index (BMI). Those of the International Diabetes Federation (IDF) published in 2005 are used in the present guidelines.^{11,12}

The full range of histological manifestations of NAFLD has been demonstrated in Asian patients, from steatosis through non-alcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma (HCC).¹³ The present natural history data are limited, but the course of NAFLD also appears to be similar in Asian as in European populations. Fatty liver attributable to metabolic factors is common in persons affected by other common liver diseases, particularly hepatitis C, hepatitis B, and alcoholic liver disease. This important aspect is touched on only briefly in these guidelines in so much as it impacts on definition and routine clinical assessment. More detailed considerations of the influence of steatosis and metabolic factors on liver pathology, disease outcomes, and treatment efficacy would be worthy subjects for future working parties.

This document summarizes proposals by the Asian-Pacific Working Party for NAFLD (APWP-NAFLD) for the definition of NAFLD, and suggests clinical guidelines for the initial assessment and management of affected patients within the Asia-Pacific region. The accompanying four reviews annotate and summarize the evidence and logic that support these proposals.^{4,5,13,14} They canvass suggestions to improve prevention, early recognition, and management of fatty liver disease in clinical practice, as well as early detection and correction of metabolic disorders in the numerous individuals with NAFLD.¹⁴ These perspectives have particular public health relevance to the world's most populous region.

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Proposal 1: Operational definition of NAFLD

For research studies and clinical practice settings, an operational definition of NAFLD is required because pathological definition is often not possible.

1A Defining fatty liver

Fatty liver can be defined by the presence of at least two of three abnormal findings on abdominal ultrasonography: diffusely

increased echogenicity ('bright') liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal.¹⁵ NAFLD is highly likely provided that the other causes of liver disease (detailed in Proposal 2) have been rigorously excluded, particularly significant alcohol intake (more than 140 g weekly in men, 70 g weekly in women) and medication use.

1B Patients with otherwise unexplained ALT elevation

In patients with otherwise unexplained ALT elevation, NAFLD is highly likely to be the cause if hepatic imaging results are compatible with fatty liver, and metabolic risk factors are present.

Proposal 2: Exclusion criteria

2A Alcohol

It is critical to exclude persons with excess alcohol intake (more than 40 g daily or 280 g weekly for women; 60 g daily or 420 g weekly for men), who are regarded as having *fatty liver consistent with alcoholic liver disease*. Intake levels of two standard drinks (20 g ethanol daily, 140 g weekly) for men and one standard drink daily (70 g weekly) for women are endorsed as the acceptable threshold to define *non-alcoholic*.¹⁶

For purposes of disease definition, intake between that defined as 'excessive' or 'consistent with non-alcoholic disease' should be regarded as 'indeterminate'. Individual patient management should consider the potential roles of both alcohol and metabolic factors, and the lifetime history of alcohol exposure may be a relevant factor.

2B NAFLD or serum ALT elevation secondary to other causes

Patients with a history of systemic illnesses known to cause fatty liver disease, and those who are receiving or have recently received drugs (including herbal medicines) known to raise ALT and GGT or cause fatty liver disease should not be regarded as having NAFLD. Some pertinent conditions and agents are listed elsewhere.^{13,17} Preferred nomenclatures include the known causative factor and the resultant pathology, e.g. total parenteral nutrition-induced steatosis; tamoxifen-induced steatohepatitis, rather than 'secondary NASH'.¹⁷

2C Other liver diseases

All common (hepatitis B virus [HBV], hepatitis C virus [HCV]) and less common (autoimmune, celiac disease, genetic disorders such as Wilson's disease, and alpha-1-antitrypsin deficiency) liver diseases, hepatic malignancies, hepatobiliary infections, and biliary tract disease should be excluded before ascribing abnormal liver tests to NAFLD. In HBsAg-positive patients with serum HBV DNA level below 10⁴ IU/mL, abnormal liver tests may be due to fatty liver disease if metabolic risk factors are present.

Proposal 3: Initial assessment

NAFLD should be suspected among those with metabolic risk factors (central obesity, T2DM, dyslipidaemia, metabolic syndrome), and sought by determining liver function tests and hepatic ultrasonography. In patients with abnormal liver tests and/or changes on hepatic imaging consistent with fatty liver,¹⁵ further examination and baseline tests should be performed to:

- allow definition of NAFLD (see Proposal 1)
- identify the underlying metabolic factors⁵
- exclude other disorders, and
- assess the likely severity of NAFLD/NASH.

These tests encompass biochemical and hematological indices, anthropometry, hepatic imaging, and determination of insulin sensitivity. For logistic reasons discussed in reference 13, these have been subdivided into those regarded as essential for minimal assessment (3A), and optional additional tests for once the diagnosis has been made (3B).

3A Minimal assessment

- Biochemical tests: bilirubin, serum ALT, AST, GGT, albumin, globulin, and fasting serum lipids
- Haematological tests: complete blood count (platelet count)
- Serology: Anti-HCV, HBsAg, antinuclear antibody (ANA)
- Insulin sensitivity: fasting blood glucose (FBG); if FBG is ≥ 5.6 mmol/L, 75G oral glucose tolerance test (OGTT) (in patients without a previous diagnosis of T2DM), as recommended by the IDF¹¹
- Anthropometry: height (m), weight (kg), BMI (kg/m²), waist circumference (cm). Reference to normal values should use Asia-Pacific standards, such as those of the IDF, as supported in these guidelines.^{5,11}
- Blood pressure measurement
- Imaging: abdominal ultrasound, assessed for the three criteria of Proposal 1A

3B Optional tests after diagnosis of NAFLD

Once the diagnosis of NAFLD is established, optional tests include:

- Abdominal CT, if properly conducted ultrasound is not informative
- Liver biopsy is not usually required for diagnosis of NAFLD. However, it should be considered in cases where:
 - i. there is diagnostic uncertainty
 - ii. patients are at risk of advanced hepatic fibrosis (in the absence of clinical or imaging evidence of cirrhosis)
 - iii. in those enrolled in clinical trials, and
 - iv. (because of reduced risk and greater convenience) in those subjected to laparoscopy for another purpose (e.g. cholecystectomy, gastric banding).
- Insulin sensitivity: in those with normal FBG (<5.6 mmol/L), 75G OGTT; fasting and postprandial serum insulin (the latter measured at 120 min of a 75G OGTT); C-peptide
- Prothrombin time

- Additional tests (specialized imaging and serum biomarkers): The following are relevant only to research studies: quantitation of hepatic triglycerides by proton magnetic resonance spectroscopy; determination of body fat distribution by DEXA scan or abdominal CT; use of biomarkers to distinguish NASH from steatosis and to estimate fibrotic severity.

Proposal 4: Liver biopsy assessment

- While refinement in the diagnostic categories is anticipated, the United States of America National Institutes of Health (NIH) non-alcoholic steatohepatitis (NASH) Clinical Research Network (CRN) criteria should be adopted for initial diagnosis and for use in therapeutic trials.¹⁸
- Use of the NAFLD Activity Score (NAS) and fibrosis score should be encouraged for routine reporting as well as research studies.¹⁸
- In the absence of any histological characteristics of steatohepatitis, caution should be exercised before attributing cases of cryptogenic cirrhosis to NAFLD/NASH.¹⁹ In such cases, clinicians should search for other causes of cirrhosis.

Proposal 5: Management

The following principles are endorsed:¹⁴

- Lifestyle measures such as diet and increasing physical activity through aerobic exercise should be encouraged in all patients with NAFLD. Some weight reduction is usually required. The most effective regime and how to achieve long-term adherence to it are crucial subjects of future research.
- Metabolic risk factors should be identified and treated, including optimal glycaemic and lipid control of T2DM, and treatment of dyslipidaemia.
- Use of 'statins' (HMG-CoA reductase inhibitors) in patients with NAFLD is safe and is recommended for usual indications. Frequent ALT monitoring is not required.
- Follow-up of patients with NAFLD should consider not only changes in liver disease (such as ALT normalization), but include monitoring of abdominal girth (central obesity) and body weight, FBG, serum lipids, blood pressure, and screening for cancers whose incidence is increased by metabolic syndrome.
- If patients are obese and do not respond to attempted lifestyle measures, they should be referred to centers specializing in obesity management. In those refractory to medical measures, consideration should be given to bariatric surgery or gastric ballooning.
- The role of pharmacotherapy is currently investigational and is not recommended for routine clinical practice.

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