

## Clinical guidelines of non-alcoholic fatty liver disease: A systematic review

Jin-Zhou Zhu, Kelseanna Hollis-Hansen, Xing-Yong Wan, Su-Juan Fei, Xun-Lei Pang, Fan-Dong Meng, Chao-Hui Yu, You-Ming Li

Jin-Zhou Zhu, Xing-Yong Wan, Chao-Hui Yu, You-Ming Li, Department of Gastroenterology, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

Kelseanna Hollis-Hansen, Systems-oriented Global Childhood Obesity Intervention Program, Department of Epidemiology and Environmental Health, University at Buffalo, The State University of New York, Buffalo, NY 14214, United States

Su-Juan Fei, Xun-Lei Pang, Department of Gastroenterology, The Affiliated Hospital, Xuzhou Medical University, Xuzhou 221000, Jiangsu Province, China

Fan-Dong Meng, Department of Endocrinology, The Affiliated Hospital, Xuzhou Medical University, Xuzhou 221000, Jiangsu Province, China

**Author contributions:** Zhu JZ collected data; Zhu JZ and Hollis-Hansen K contributed equally to the work; Hollis-Hansen K performed analyses and wrote manuscript; Wan XY, Fei SJ and Pang XL performed systematic evaluation; Meng FD revised the manuscript; Yu CH and Li YM contributed to the study design; all authors reviewed and approved the final manuscript as submitted.

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**Correspondence to:** Dr. You-Ming Li, Professor, Department of Gastroenterology, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. [ymli.zju@live.com](mailto:ymli.zju@live.com)  
**Telephone:** +86-156-65170166  
**Fax:** +86-571-87080565

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## Abstract

### AIM

To perform a systematic review to grade guidelines and present recommendations for clinical management of non-alcoholic fatty liver disease (NAFLD).

### METHODS

A database search was conducted on PubMed for guidelines published before May 2016, supplemented by reviewing relevant websites. The Appraisal of Guidelines for Research and Evaluation (ARGEE) Instrument II was a tool designed to appraise the methodological rigor and transparency in which a clinical guideline is developed and it is used internationally. It was used to appraise the quality of guidelines in this study. The inclusion criteria include: clinical NAFLD guidelines for adults, published in English, and released by governmental agencies or key organizations.

### RESULTS

Eleven guidelines were included in this study. Since 2007, guidelines have been released in Asia (3 in China, 1 in South Korea, and 1 in Japan), Europe (1 in Italy),

America (1 in United States and 1 in Chile) and three international agencies [European associations joint, Asia-Pacific Working Party and World Gastroenterology Organization (WGO)]. Using the ARGE II instrument, we found US 2012 and Europe 2016 had the highest scores, especially in the areas of rigor of development and applicability. Additionally, Italy 2010 and Korea 2013 also presented comprehensive content, rigorous procedures and good applicability. And WGO 2014 offered various algorithms for clinical practice. Lastly, a practical algorithm for the clinical management was developed, based on the recommended guidelines.

## CONCLUSION

This is the first systematic review of NAFLD guidelines. It may yield insights for physicians and policy-makers in the development and application of guidelines.

**Key words:** Diagnosis; Management; Non-alcoholic fatty liver disease; Systematic review; Treatment

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**Core tip:** Non-alcoholic fatty liver disease (NAFLD) is one of the leading chronic liver diseases globally. A comprehensive study of NAFLD guidelines will be useful for various stakeholders to develop and utilize guidelines. This is the first systematic review to grade NAFLD guidelines and present recommendations for the clinical management of NAFLD. Through systematically evaluating the published guidelines and offering a clinical algorithm, it may yield insights for physicians and policy-makers in the development and application of guidelines.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple hepatic steatosis, to inflammatory non-alcoholic steatohepatitis (NASH) with increasing levels of fibrosis and eventually hepatic cirrhosis<sup>[1]</sup>. According to the latest guideline released in Europe<sup>[2]</sup>, it is defined by the presence of steatosis in > 5% hepatocytes, in the absence of other causes attributed to hepatic steatosis<sup>[3]</sup>. Recent advance supports NAFLD as the chronic liver disease component of metabolic syndrome<sup>[4]</sup>.

Younossi *et al*<sup>[5]</sup> estimated the global prevalence of imaging-diagnostic NAFLD arrived at 25%, although it

varied by region and age. In the United States, it was reported to be between 10% and 30%, which is similar to rates in Europe and Asia<sup>[6-8]</sup>. It is alarming that the prevalence of NAFLD worldwide is on the rise<sup>[9]</sup>, along with the associated disorders: obesity, insulin resistance, diabetes and metabolic syndrome<sup>[8]</sup>. New evidence supports NAFLD as a common liver disease presenting across the globe, which warrants the attention of physicians, researchers, and national policy makers. However, gaps between provider knowledge and awareness of clinical practice guidelines exist.

Offering continuing education and developing high-quality national guidelines may help making inroads into the problem of suboptimal NAFLD care. A comprehensive study of the existing guidelines of NAFLD might be useful for helping stakeholders, including physicians, patients, policymakers and governmental bodies to develop and implement guidelines. To our knowledge, this is the first systematic critical appraisal of published guidelines to systematically grade and comprehensively present the evidence-based recommendations for the diagnosis and treatment of NAFLD.

## MATERIALS AND METHODS

This systematic review was conducted according to the PRISMA guidelines<sup>[10]</sup>.

### Electronic database search

The database search was conducted on PubMed for guidelines published before May 2016. In the search, we used the following key words and terms: ["fatty liver"(Title)] AND [strategy\*(Title) OR guideline\*(Title) OR recommendation\*(Title) OR management\*(Title)].

### Websites searches

The literature search was supplemented by searching relevant websites (using the term "fatty liver"), including the following: (1) Australia National Health and Medical Research Council (<https://www.nhmrc.gov.au/?>); (2) American College of Physicians (<https://www.acponline.org/>); (3) American Medical Association (<http://www.ama-assn.org/ama>); (4) Institute for Clinical Systems Improvement (<https://www.icsi.org/>); (5) Institute of Medicine (<http://www.nationalacademies.org/>); (6) National Guidelines Clearinghouse (<https://www.guideline.gov/>); (7) National Institute for Health and Clinical Excellence (<https://www.nice.org.uk/>); (8) Royal College of Physicians (<https://www.rcplondon.ac.uk/>); (9) Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk/>); and (10) World Health Organization (<http://www.who.int/en/>).

### Inclusion criteria and guidelines selection

The guideline was included in this study, if it met the following criteria: (1) clinical guidelines regarding the diagnosis and management of NAFLD in adults; (2) released by governmental agencies or key health

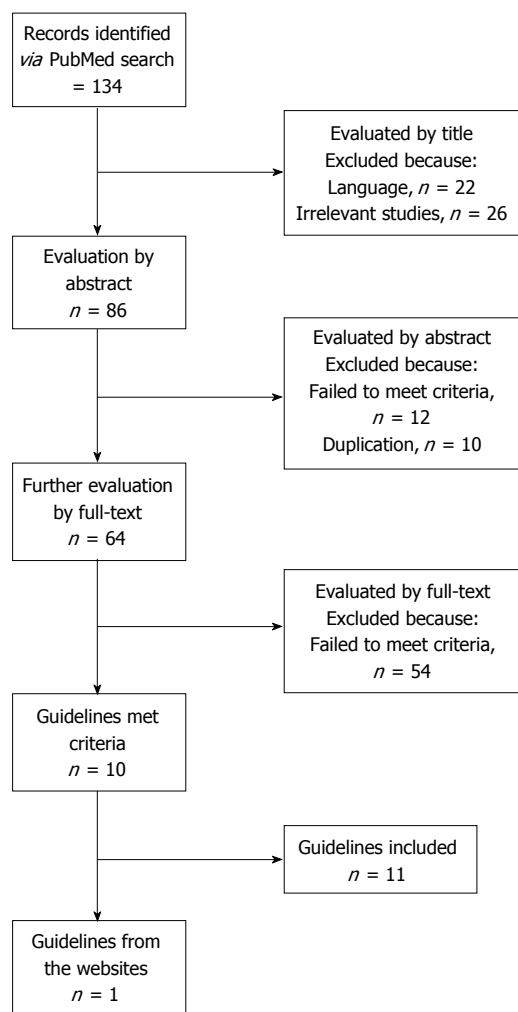


Figure 1 Flow chart of guidelines searching.

organizations; and (3) published in English. Two investigators independently performed the screen on PubMed and the websites, according to the inclusion criteria. Discrepancies were resolved by the involvement of a third reviewer.

### The Appraisal of Guidelines for Research and Evaluation Instrument II

The Appraisal of Guidelines for Research and Evaluation (AGREE) II was a tool designed to appraise the methodological rigor and transparency in which a clinical guideline is developed and it is used internationally. It consists of 23 items grouped in 6 domains, *i.e.*, scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence<sup>[11]</sup>.

## RESULTS

### Guidelines included in the study

As shown in Figure 1, eleven guidelines met the criteria and were included in the final version of this systematic review. Since 2007, five guidelines were released in

Asia (3 in China, 1 in Japan and 1 in South Korea), while three guidelines were released in the United States, Italy and Chile, respectively (Table 1). Three guidelines were released by international agencies, *i.e.* Asia-Pacific Working Party, World Gastroenterology Organization (WGO) and a joint commission of European associations.

### Guidelines quality scores

Eleven guidelines were appraised according to AGREE II, as presented in Table 1 and Figure 2. We highly recommended the two guidelines, United States 12<sup>[1]</sup> and Europe 16<sup>[2]</sup>, given the high scores and the authority of the organizations. Additionally, Italy 10<sup>[12]</sup> and South Korea 13<sup>[13]</sup> also presented comprehensive content, rigorous procedures and good applicability. Lastly, WGO 14<sup>[14]</sup> offered a variety of algorithms for clinical practice.

### Clinical algorithm

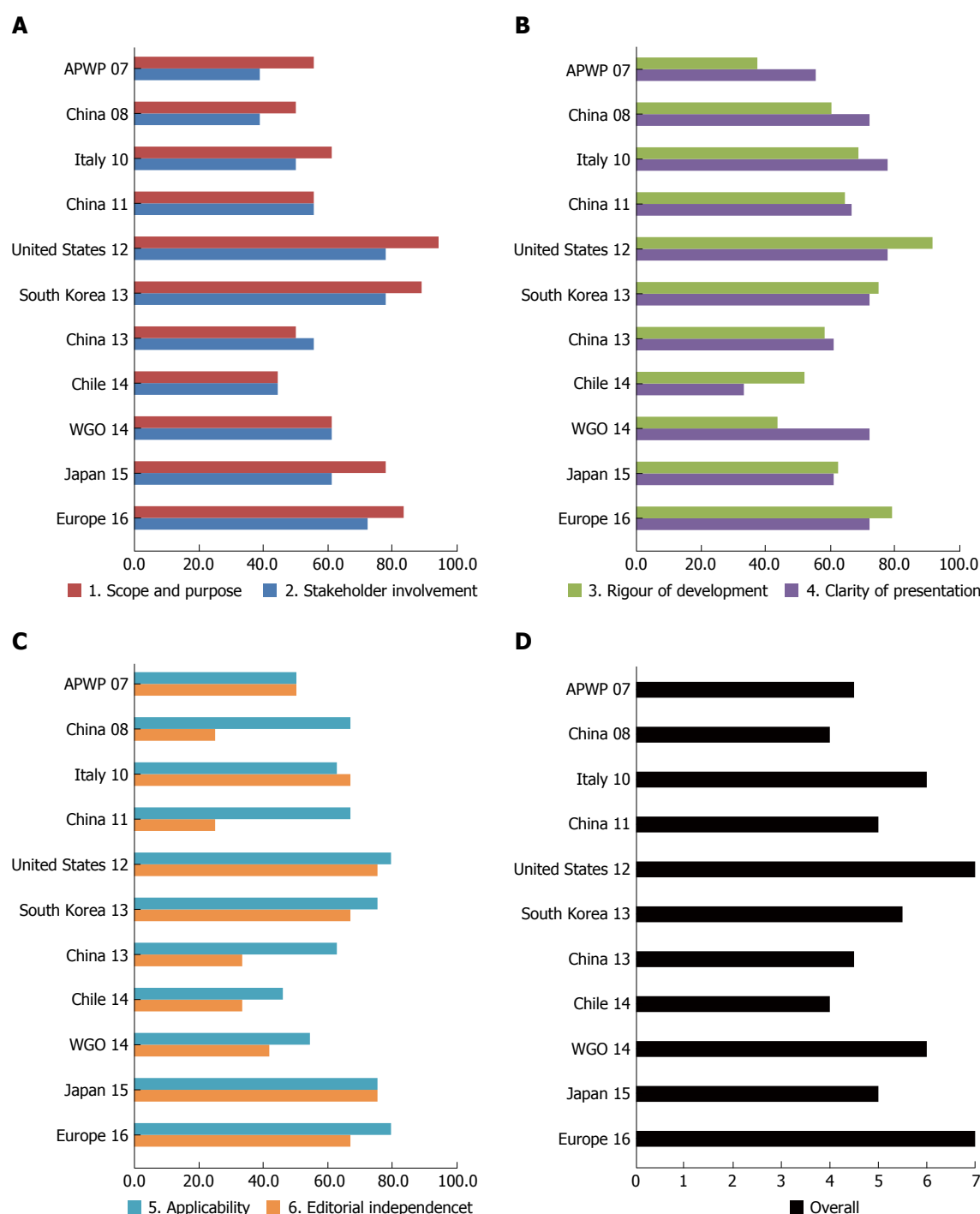
Figure 3 presented a clinical algorithm for the diagnosis and management of NAFLD in adults. Generally, the procedure of clinical practice includes diagnosis, assessment, and management.

## DISCUSSION

This is the first systematic critical appraisal to grade the guidelines and present the evidence-based recommendations for the clinical management of NAFLD. Using the ARGE II instrument, we found United States 12<sup>[1]</sup> and Europe 16<sup>[2]</sup> had the highest scores, especially in the areas of rigor of development and applicability. Additionally, we developed a clinical algorithm for the diagnosis and management of NAFLD in adults.

NAFLD is one of the leading chronic liver diseases in the world<sup>[5]</sup>. While incidence rates may possibly vary and/or be underreported<sup>[15,16]</sup>, the present situation reinforces the need for a precise and rational system of management for NAFLD. Additionally, the obesity epidemic has led to a rapidly increasing population at risk for NAFLD, and shows no signs of slowing down. Therefore, NAFLD will only become a larger problem in the future if it is not properly prevented and managed now.

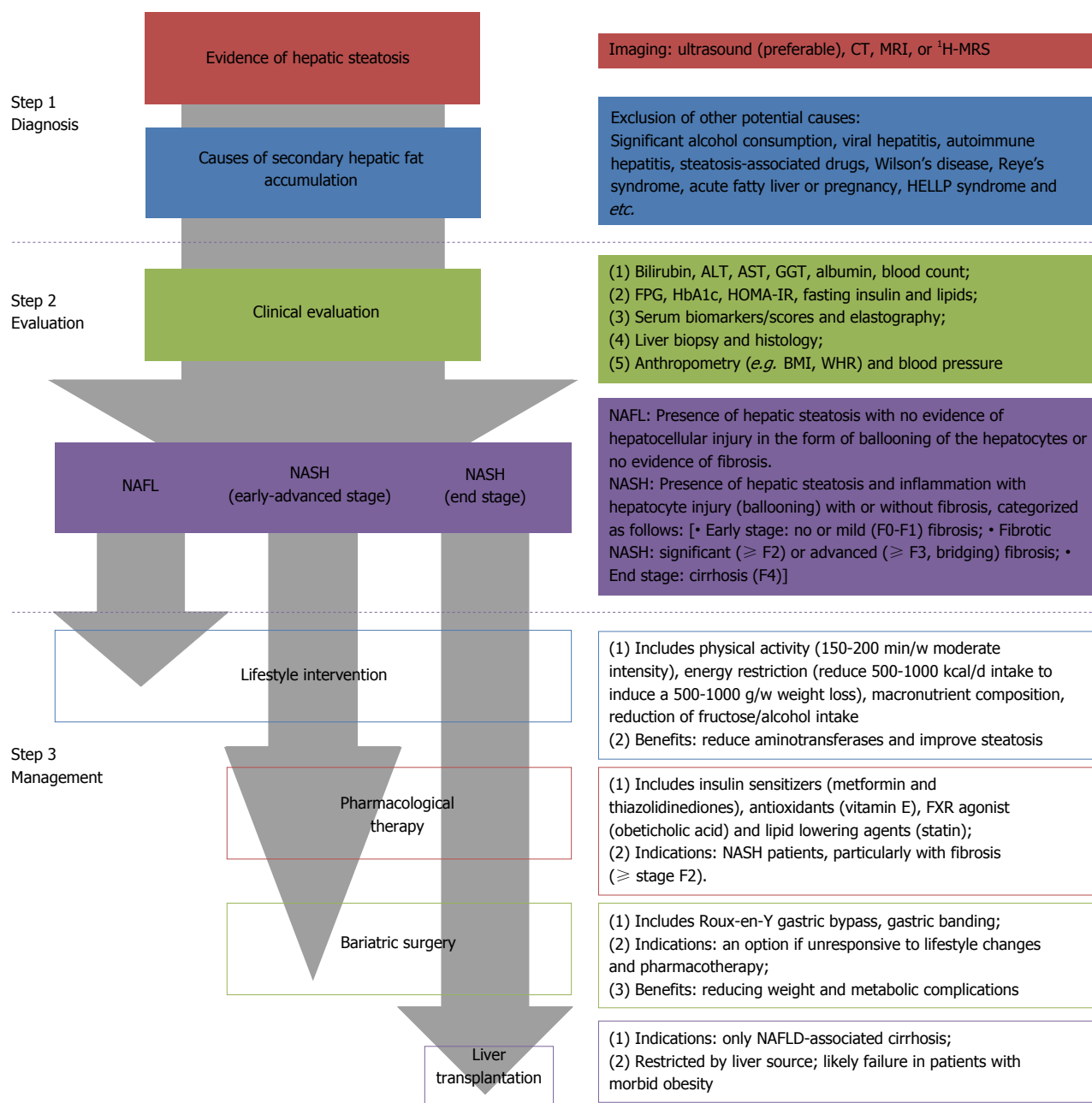
Currently, liver biopsy has still been regarded as the gold standard in the diagnostic evaluation of NAFLD<sup>[17]</sup>. However, a biopsy is an invasive practice, which carries a series of medical risks, *e.g.* hemorrhage and infection<sup>[2]</sup>. The non-invasive assessing method that is most suitable for evaluating hepatic steatosis is ultrasound, with a sensitivity of 60%-94% and a specificity of 66%-97%<sup>[18]</sup>, even though it presents less precise in milder degrees of steatosis. Given the widely availability and economic efficiency, ultrasound is recommended as a first-line diagnostic test in most guidelines, rather than liver biopsy and other



**Figure 2** Domain scores for each guideline based on the Appraisal of Guidelines for Research and Evaluation II Instrument. A-C: Each Appraisal of Guidelines for Research and Evaluation II domain score for guidelines is presented on the X-axis as a percentage of 100 (0% = the domain was not at all satisfied; and 100% = fully satisfied). D: Overall scores for guidelines. WGO: World Gastroenterology Organization.

imaging tools. Additionally, a variety of noninvasive algorithms, based on metabolic and anthropometric tests, have been developed for identifying NAFLD, e.g. the fatty liver index<sup>[19]</sup> and the hepatic steatosis index<sup>[20]</sup>. They have been utilized to screen subjects with hepatic steatosis in large epidemiologic studies or predicting potential patients in clinical practice<sup>[18]</sup>. The development of more accurate and noninvasive diagnostic tools is still a major unmet demand in the clinic.

In terms of treatment, the pathophysiological association between NAFLD and obesity-related diseases, e.g., metabolic syndrome and diabetes, supports structured programs of lifestyle intervention aimed at weight loss, before or in addition to pharmacotherapy<sup>[3,21]</sup>. The elements of a comprehensive lifestyle approach generally include energy restriction, macronutrient composition, alcohol consumption, coffee drinking and physical activity<sup>[2]</sup>. Furthermore, published guidelines suggested pharmacotherapy



**Figure 3 Clinical algorithm for the diagnosis and management of non-alcoholic fatty liver disease in adults.** The algorithm was developed according to United States 12<sup>[1]</sup>, WGO 14<sup>[13]</sup> and Europe 16<sup>[2]</sup>. <sup>1</sup>H-MRS: Proton magnetic resonance spectroscopy; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CT: Computed tomography; FPG: Fasting plasma glucose; FXR: Farnesoid X receptor; GGT: Gamma-glutamyltransferase; HbA1c: Hemoglobin a1c; HOMA-IR: Homeostasis model assessment of insulin resistance; MRI: Magnetic resonance imaging; WHR: Waist-to-hip ratio; WGO: World Gastroenterology Organization; NAFLD: Non-alcoholic fatty liver disease.

should be exclusively indicated for early-stage NASH with increased risk of advanced NASH<sup>[2,22]</sup>. The past decade has witnessed some advance in clinical pharmacotherapy trials, *e.g.*, the use of metformin, pioglitazone and vitamin E, however most NASH patients failed to respond to these methods<sup>[2,23]</sup>. When considering safety and tolerability, no drug has been approved for NAFLD by pharmacological agencies by now, while no specific drug therapy was firmly recommended in the present guidelines<sup>[2]</sup>. Therefore, it is still imperative to continue research

to improve pharmacotherapy for NASH and hepatic fibrosis. Additionally, the role of bariatric surgery in the treatment of NAFLD is still unknown. Current evidence found that NAFLD patients who undergo bariatric surgery require long-term postoperative management, due to an increased risk for fibrosis progression<sup>[1,14]</sup>.

This is the first systematic review of published NAFLD guidelines. Using AGREE II<sup>[11]</sup>, it systematically grades the guidelines and presents the evidence-based recommendations for the clinical management of NAFLD. Additionally, a clinical algorithm for the



**Table 1** Characteristics of non-alcoholic fatty liver disease guidelines included in this study

Author(s)/Organization(s)	Published Year	Region/country	Title	Recommendation
Chitturi <i>et al</i> <sup>[25]</sup> . Asia-Pacific Working Party on NAFLD (APWP 07)	2007	Asia-Pacific region	Non-alcoholic fatty liver disease in the Asia-Pacific region: Definitions and overview of proposed guidelines	Not recommended
Zeng <i>et al</i> <sup>[26]</sup> . The Chinese National Consensus Workshop on NAFLD (China 08)	2008	China	Guidelines for the diagnosis and treatment of nonalcoholic fatty liver diseases	Not recommended
Loria <i>et al</i> <sup>[12]</sup> . Italian Association for the Study of the Liver (Italy 10)	2010	Italy	Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease: A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee	Recommended but modified
Fan <i>et al</i> <sup>[27]</sup> . Chinese Association for the Study of Liver Disease (China 11)	2011	China	Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: Update 2010	Not recommended
Chalasani <i>et al</i> <sup>[1]</sup> . American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association (US 12)	2012	United States	The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association	Recommended
The Korean Association for the Study of the Liver (South Korea 13) <sup>[13]</sup>	2013	South Korea	KASL clinical practice guidelines: Management of nonalcoholic fatty liver disease	Recommended but modified
Gao <i>et al</i> <sup>[28]</sup> . Study Group of Liver and Metabolism, Chinese Society of Endocrinology (China 13)	2013	China	Diagnosis and management of non-alcoholic fatty liver disease and related metabolic disorders: Consensus statement from the Study Group of Liver and Metabolism, Chinese Society of Endocrinology	Not recommended
Arab <i>et al</i> <sup>[29]</sup> . Chilean Society of Gastroenterology (Chile 14)	2014	Chile	Management of nonalcoholic fatty liver disease: An evidence-based clinical practice review	Not recommended
LaBrecque <i>et al</i> <sup>[14]</sup> . World Gastroenterology Organization (WGO 14)	2014	World	World Gastroenterology Organization global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis	Not recommended
Watanabe <i>et al</i> <sup>[30]</sup> . Japanese Society of Gastroenterology (Japan 15)	2015	Japan	Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis	Not recommended
European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity (Europe 16) <sup>[2]</sup>	2016	Europe	EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease	Recommended

Ordered by publication year. Recommendation was developed based on AGREE II instrument. NAFLD: Non-alcoholic fatty liver disease.

clinical practice was developed, based on the highly recommended guidelines.

This study has some limitations. To begin with, only the guidelines in English were included in this review. Thus, high-quality guidelines in other languages might have been missed. Second, we chose the AGREE II instrument to evaluate the guidelines, even though there are other appraisals, *e.g.* Global Rating Scale<sup>[24]</sup>. Third, guidelines should include information on how to reduce inappropriate practice and improve the efficiency of management. Further, the application of guidelines is crucial in clinical practice. However, we failed to evaluate the acceptance and the application of the guidelines in this review, due to the limited inclusion in the literature included in this review.

In this study, a systematic review was conducted to search and integrate the published guidelines of NAFLD. Furthermore, based on the evaluation of the included guidelines, a clinical algorithm for the diagnosis and management of NAFLD was developed. We hope it will yield insights for physicians and policy-makers in the development and application of guidelines moving forward.

## COMMENTS

### Background

Non-alcoholic fatty liver disease (NAFLD) is one of the leading chronic liver diseases globally. A comprehensive study of NAFLD guidelines will be useful for various stakeholders to develop and utilize guidelines.

### Research frontiers

New evidence supports NAFLD as a common liver disease presenting across the globe, which warrants the attention of physicians, researchers, and national policy makers. However, gaps between provider knowledge and awareness of clinical practice guidelines exist. Offering continuing education and developing high-quality national guidelines may help making inroads into the problem of suboptimal NAFLD care.

### Innovations and breakthrough

A comprehensive study of the existing guidelines of NAFLD might be useful for helping stakeholders, including physicians, patients, policymakers and governmental bodies to develop and implement guidelines. The authors think, this is the first systematic critical appraisal of published guidelines to systematically grade and comprehensively present the evidence-based recommendations for the diagnosis and treatment of NAFLD.

### Applications

The systematic review included eleven published NAFLD guidelines in

the worldwide. Furthermore, we graded the guidelines, using the AGREE instrument II. Lastly, a practical algorithm for the clinical management was developed, based on the recommended guidelines.

### Terminology

The Appraisal of Guidelines for Research and Evaluation Instrument II was a tool designed to appraise the methodological rigor and transparency in which a clinical guideline is developed and it is used internationally. It consists of 23 items grouped in 6 domains, *i.e.*, scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence.

### Peer-review

The authors conducted the first systematic review of published NAFLD guidelines. It may yield insights for physicians and policy-makers in the development and application of guidelines.

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