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Guidelines

Non-alcoholic fatty liver disease in adults 2021: A clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO)☆

Associazione Italiana per lo Studio del Fegato (AISF), Società Italiana di Diabetologia (SID) and Società Italiana dell'Obesità (SIO)[1]

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a common and emerging liver disease in adults, paralleling the epidemic of obesity and diabetes, and leading to worrisome events (hepatocellular carcinoma and end-stage liver disease). In the last years, mounting evidence added insights about epidemiology, natural history, diagnosis and lifestyle-based or drug treatment of NAFLD. In this rapidly evolving scenario, members of the Associazione Italiana per lo Studio del Fegato (AISF), the Società Italiana di Diabetologia (SID) and the Società Italiana dell'Obesità (SIO) reviewed current knowledge on NAFLD. The quality of the published evidence is graded, and practical recommendations are made following the rules and the methodology suggested in Italy by the Centro Nazionale per l'Eccellenza delle cure (CNEC) and Istituto Superiore di Sanità (ISS). Whenever possible, recommendations are placed within the context the Italian Healthcare system, with reference to specific experience and local diagnostic and management resources.

Level of evidence: Level of evidence of recommendations for each PICO question were reported according to available evidence.

1. Introduction

The present report is a summary of Clinical Practice Guidelines resulting from a cooperative work of the Associazione Italiana per lo Studio del Fegato (AISF), the Società Italiana di Diabetologia (SID) and the Società Italiana dell'Obesità (SIO). Current knowledge on the diagnosis and treatment of non-alcoholic fatty liver disease (NAFLD) is translated into relevant practical recommendations for management following the rules and the methodology suggested in Italy by the Centro Nazionale per l'Eccellenza delle cure (CNEC) and Istituto Superiore di Sanità (ISS). In this summary, we report the outline of disease burden and the risks associated with disease progression, followed by PICO questions and recommendations. The review of the literature at the basis of individual recommendations is uploaded as supplementary material.

2. Burden of disease and risk factors

The natural history of nonalcoholic fatty liver disease (NAFLD) has been extensively investigated in the past 20 years [1,2]. Steatosis is the hallmark of NAFLD and has been identified as an independent risk factor for the full spectrum of liver damage including inflammation, ballooning and fibrosis [3]. The diagnosis of NAFLD requires the exclusion of both secondary causes and of alcohol consumption ≥30 g *per day* for men and ≥20 g *per day* for women [4]. Recently, a consensus of experts proposed to overcome the current nomenclature "NAFLD" and adopt for a "positive" definition the acronym Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) using metabolic dysfunctions as diagnostic criteria independently of the presence of other causes of

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chronic liver disease [5]. The mean prevalence of NAFLD worldwide is 24.1%, ranging from 13.5% in Africa to 31.8% in Middle East, with differences among studies also related to diagnostic methods, age, gender and ethnicity [1]. Italian studies indicate a prevalence of 22.5–27.0% in the general population [6–9], with a 2% prevalence of noninvasively-assessed advanced fibrosis due to NAFLD [9]. The prevalence increases in patients with metabolic comorbidities *and the metabolic syndrome (MetS), defined by the presence of at least three metabolic alterations among elevated waist circumference (≥94* cm *in males; ≥80* cm *in females in Europids), elevated triglycerides (≥150* mg/dL*), reduced HDL-C (≤40* mg/dL *in males; ≤50* mg/dL *in females), elevated blood pressure (systolic pressure ≥130* mmHg *and/or diastolic pressure ≥85* mm *or antihypertensive drug treatment) and elevated fasting glucose (≥100* mg/dL *antihyperglycemic treatment)* [10]. NAFLD is observed in 54–90% [9,11] and 78.8% [12] of cases with obesity or with MetS, respectively. In the Dionysos study, the presence of steatosis was closely associated with obesity [13] and in the Dionysos and Nutrition Liver Study the risk of NAFLD was 9-fold increased by the presence of BMI ≥ 30 kg/m^2 and 6-fold by abdominal obesity (waist circumference ≥102 cm in males, ≥88 in females) [6], independently of altered liver enzymes. Raised liver enzymes, assumed as surrogate indexes of NAFLD, were reported in 21% of cases with obesity and did not increase systematically with obesity class [14]. In a more recent analysis of 890 subjects of the community-based ABCD ("Alimentazione, Benessere Cardiovascolare e Diabete") study, Petta et al. reported a NAFLD prevalence of 48%, with a relative risk for obesity of 4.02 (95% confidence interval, 2.77–5.84) [9], but the various diagnostic tools and/or settings may provide slightly different results.

The prevalence of NAFLD is as high as 70–80% in patients with type 2 diabetes mellitus (T2DM) [15,16], who are also more likely to have nonalcoholic steatohepatitis (NASH) and cirrhosis, even in the presence of fairly normal serum aminotransferase levels [16–18]. In Italian patients with diabetes NAFLD is reported in 59.0–73.2% [19,20], with about 13%-18% of them experiencing advanced fibrosis [21]. A bidirectional association exists between NAFLD and T2DM [17,22], worsening the course of both diseases; the presence of T2DM increases the risk of NAFLD progression to advanced fibrosis and cirrhosis, as well as also of incident hepatocellular carcinoma (HCC), liver-related hospital admissions and liver-related deaths [17,23–25], whereas the presence of NAFLD in T2DM is associated with a reduced probability of achieving good glycemic control, and exacerbates atherogenic dyslipidemia, further increasing the risk of chronic kidney disease and adverse CV outcomes [17,18], *particularly in the presence of NASH-fibrosis [26].*

The lifetime costs of all NASH patients in the United States in 2017 is estimated at $222.6 billion, and the cost of the advanced NASH population at $95.4 billion [27]. Data from Italian local Health Units, based on administrative data and resources utilization, calculated an average direct cost for NAFLD/NASH progressively increasing from the non-advanced stage, to advanced NAFLD disease, compensated cirrhosis, liver transplant, and hepatocellular carcinoma (HCC), also driven by comorbidities, up to over € 65.000/year [28]. Considering the projections calculated by disease modeling for the next decades, the total costs is likely to become very challenging for the National Health system [29].

3. NAFLD mortality and morbidity

Patients with NAFLD have an increased overall mortality compared to matched control populations [30,31]. According to a meta-analysis, overall mortality was reported to be 15.4 per 1,000 person-years (range, 11.7–20.3) for patients with NAFLD and 25.6 (range, 6.3–103.8) for the cohort with NASH [1]. The presence of NASH (adjusted hazard ratio$_{adj}$HR], 9.16), age ($_{adj}$HR, 1.06), and the presence of T2DM ($_{adj}$HR, 2.09) increased all-cause and liver-related mortality, after controlling for other variables. Liver-specific mortality was estimated as 0.8 (range, 0.3–1.8) in NAFLD and 11.8 (range, 7.1–19.5) in NASH [1]. Cardiovascular (CV) disease (CVD) remains the most common cause of death, independent of other metabolic comorbidities [32,33], driven by the atherogenic profile and widespread CV complications [33–35], independently of other known risk factors [36,37]. Fibrosis stage is the strongest predictor for mortality from CVD and liver-related disease in a cohort of biopsy-proven NAFLD after up to 33 years of follow-up [38].

NAFLD is also associated with an approximate 2-fold increased risk of incident T2DM, ranging from a 35% to a 5.5-fold increase, independent of overweight/obesity and other common risk factors [34,39]. The risk of incident T2DM appears to diminish over time following the improvement or resolution of NAFLD [40,41]. Patients with NAFLD also have a nearly 40% increase in the long-term risk of incident chronic kidney disease [42], as well as other recognized associations with sleep apnea, osteoporosis, psoriasis and endocrinopathies [43].

The presence of NASH increases liver-related mortality [44,45], but the most important driver of mortality is fibrosis at histology, specifically, zone 3 sinusoidal fibrosis plus periportal fibrosis (stage 2), advanced fibrosis (bridging fibrosis [stage 3] or cirrhosis [stage 4]) [2,46], associated with the multiple component of MetS [47]. Patients with stage 4 fibrosis (cirrhosis) had a nearly 10-fold risk of liver-related complications [2], with liver-related events occurring in 8.9 per 100 person-years (95% CI, 6.7–11.7]. The reported annual incidence of hepatic decompensation was 3.3 and 15.6 per 100 person-years among patients with Child Pugh (CP)-A5 and CP-A6 cirrhosis, respectively [48].

4. Hepatocellular carcinoma and extrahepatic cancers

NAFLD is the third-most common cause of HCC in the United States, after hepatitis C and alcohol-related disease, accounting for 14.1% of all cases [49]. The cumulative incidence of NAFLD-associated HCC has been reported to range from 2.4% to 12.8% over a median follow-up period of 3.2–7.2 years [50], corresponding to 0.44 (range, 0.29–0.66) per 1000 person-years and increasing at a 9% annual rate [1,49,51]. Patients with NAFLD fibrosis stages F3 and F4 have an almost 7-fold increased risk of HCC compared to people without liver disease [49] and the risk is >10 folds higher in association with T2DM and obesity [52], making NAFLD the second leading cause of liver transplantation (LT) due to HCC in U.S and the most rapidly increasing indication [53]. At diagnosis, patients with NAFLD-related HCC are older, have higher prevalence of extrahepatic comorbidities but lower prevalence of cirrhosis (absence of cirrhosis in up to 1/3 of cases), and shorter survival time [50], being more likely to die from their primary liver cancer than other HCC patients [49]. These conditions may be driven by less systematic surveillance, leading to diagnosis at later stage and less treatment [54].

Other extra-hepatic cancers are similarly increased, namely cancers of the uterus (IRR=2.3; 95%CI 1.4, 4.1), stomach (IRR=2.3; 95%CI 1.3, 4.1), pancreas (IRR=2.0; 95%CI 1.2, 3.3) and colon (IRR=1.8; 95%CI 1.1, 2.8) [54]. The association with cancer risk is stronger in NAFLD than in obesity [55].

5. Lean NAFLD

The term 'lean' NAFLD refers to patients with a BMI within the ethnic-specific cut-off of normalweight, but frequently extended to the area of overweight (30 kg/m^2 in Caucasian and 27 kg/m^2 in Asian subjects). It is conceivable that 'lean' NAFLD comprises an

heterogeneous NAFLD cohort associated with environmental and genetic factors, as well as differences in fat distribution and body composition [56], accounting for 5–26% of total NAFLD cases in the Asian population and 7–20% in the Western areas [56]. *A recent meta-analysis of 33 observational studies from 14 countries concluded for a global prevalence of NAFLD in lean individuals (BMI ≤ 23 kg/m^2 for Asian subjects and BMI ≤ 25 kg/m^2 for non-Asian subjects) of 9.7% (95% CI: 7.7–11.8%), with an upward trend between 1988 and 2017[57].* Their rate of comorbidity is lower compared to obese patients, but higher compared to healthy controls [58,59]. Data on histological severity are controversial; they can develop the full spectrum of liver disease associated with NASH [60] and similar adverse health outcomes when longitudinally examined [61,62].

6. Methods for guideline development

Following the needs of an updated guidance upon clinical management of the Non Alcoholic Fatty Liver Disease, the Scientific Societies whose members are primarily involved in its management (Italian Association for the Study of the Liver - AISF; Italian Society of Diabetology - SID; Italian Society of Obesity - SIO) commissioned to an experts panel the drafting of a new dedicated document to outline the updated clinical practice guidelines. The present document was made according to the rules dictated by the Italian Center for the Cure Excellence (Centro Nazionale per l'Eccellenza delle Cure - CNEC), an institution recently set up by the Italian National Institute of Health (Istituto Superiore di Sanità - ISS) to outline the methodologies needed to provide evidence-based clinical, diagnostic and therapeutic guidelines in Italy [63]. According to these rules, a "multi-societary" and "multi-disciplinary" committee of experts was selected by the abovementioned Scientific Societies. The committee defined the objectives, the key issues and retrieved the relevant evidences by performing a systematic review of literature. Finally, the committee members (chosen on the basis of their specific expertise) identified the guidelines' key questions and developed them following the PICO format (Population, Intervention, Comparison, Outcomes) [64]. The most relevant questions were chosen by voting among the whole committee. *The mean agreement among panel members on recommendations was 98.15%, as reported in supplementary Table 1.* For each PICO question, a systematic review of the literature was made on the most important scientific databases (Pubmed, Scopus, Embase) by performing both a free-text research and by a BOOLEAN research string formulated on purpose (see Appendix 1). The profiles of evidence were developed by applying the GRADE-Evidence to Decision (EtD) frameworks as per CNEC manual indications [63,65]. In particular, all aspects regarding the questions, the assessment of evidence and the conclusions drawings were discussed between the panel members and voted to obtain a final decision. The GRADEpro GDT online tool was used to develop the questions and make the decisions [66]. The quality of evidence was evaluated by applying the "Quality Assessment of Diagnostic Accuracy Studies version 2" (QUADAS-2) checklist for the diagnostic accuracy questions [67], the "revised tool for Risk of Bias in randomized trials" (RoB 2) [68] and the "Risk Of Bias in Non-randomized Studies - of Interventions" tool (ROBINS-I) [69] for randomized clinical trials and non-randomized studies where applicable.

The final draft was submitted for advice and revision to EpaC (Liver Patients' Association). Their comments were considered in the final version.

7. Strength and limits

The present report is a summary of Clinical Practice Guidelines resulting from a cooperative multi-society work and by using rigorous methodology suggested in Italy by the Centro Nazionale per l'Eccellenza delle cure and Istituto Superiore di Sanità. Lack of awareness for NAFLD and obstacles to apply and implement guidelines could limit their utility.

8. What is already known on this subject?

NAFLD is an emerging liver disease with a growing epidemiological and clinical burden.

National guidelines for the management of NAFLD patients are not still available.

9. What this study adds?

The present document is the first effort to provide multi-society national guidelines on NAFLD aimed to a multidisciplinary and shared management of NAFLD patients.

10. PICO Questions and recommendations

(A) Assessment of disease severity

PICO 1 - In adult patients with NAFLD, should non-invasive scores, serum markers, liver stiffness, and imaging methods be used as replacement for liver biopsy for the diagnosis of NASH?

Recommendation

- In patients with NAFLD non-invasive tests do not have acceptable accuracy for the diagnosis of NASH, and liver biopsy remains the reference standard (*B*,2).

References: [4,70–75]

PICO 2 - In adult patients with NAFLD, should non-invasive scores, serum markers, liver stiffness, and imaging methods be used as replacement for liver biopsy for the diagnosis of advanced fibrosis?

Recommendations

- In patients with NAFLD, simple noninvasive scores, namely the Fibrosis-4 score (FIB-4) and the NAFLD fibrosis score (NFS), as well as liver stiffness measurement (LSM), using transient elastography, have acceptable accuracy to identify NAFLD cases at low risk of advanced fibrosis (*A*, 1).
- A two-tier sequential combination of simple noninvasive scores like FIB-4 or NFS with imaging techniques such as LSM by transient elastography is recommended as a triage test for ruling out advanced fibrosis sparing further testing (*B*, 2).
- Magnetic resonance elastography (MRE) is the most accurate noninvasive method for estimation of liver fibrosis. This technique can be preferred in clinical trials, but it is not recommended in clinical practice, being expensive and very rarely available (*B*, 2).

References: [76–102]

Fig. 1 depicts a two-step algorithm, based on FIB-4 or NAFLD fibrosis score as first step followed by LSM, proposed for the assessment of fibrosis severity in patients with NAFLD.

PICO 3 - In adult patients with NAFLD, should non-invasive scores, liver stiffness and imaging methods be used as replacement for liver biopsy for predicting liver-related outcomes?

Recommendations

- In patients with NAFLD, non-invasive tools might acceptably rule out fibrosis progression (*C*, 2).

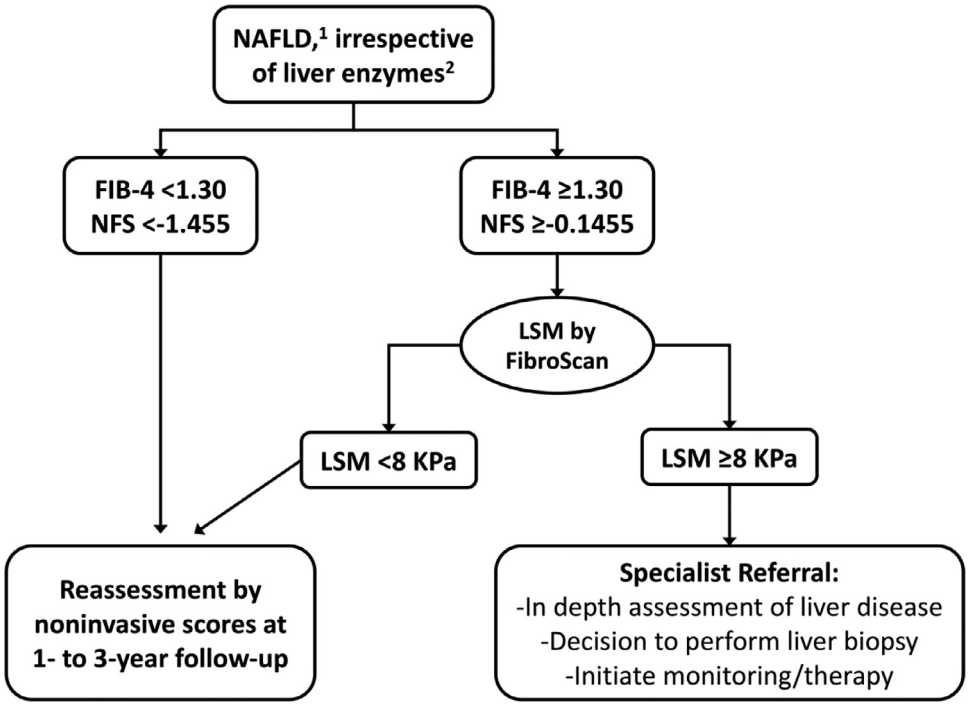

Fig. 1.
[1]NAFLD is defined by ultrasound; in case of difficult access to ultrasound, clinicians can directly screen patients with features of metabolic syndrome by liver enzymes and noninvasive scores of fibrosis.
[2]AST, ALT, GGT
Note that in patients referred to specialists (right side) follow-up will depend on disease severity/available therapeutic protocols; timing of follow-up in negative patients (left side) will depend on the presence of metabolic factors and comorbid conditions.

- In patients with NAFLD, noninvasive tools might acceptably predict the risk of occurrence of overall and liver-related events and mortality (*C*, 2).

References: [36,103–113]

PICO 4 - In adult patients with NAFLD, should genetic testing be used as an add on after usual testing in predicting the severity of histologically-assessed liver damage and liver-related outcomes?

Recommendations

- Clinicians in referral centers might consider the genetic risk profile for stratification of individual NAFLD-HCC risk, but the effectiveness of such strategy requires larger prospective studies (*C*, 2).
- We suggest that genetic risk variants be evaluated in clinical studies for stratification of disease risk progression and subphenotyping of NAFLD (*B*, 2).

References: [3,4,114–124]
Supplementary Table 2

(B) *Weight loss and behavioral intervention for NAFLD*

PICO 5 - In adult patients with NAFLD, what is the efficacy of weight loss on histologically-assessed liver damage and liver-related outcomes in comparison with no intervention?

Recommendations

- All subjects with NAFLD, including lean (non-obese) NAFLD, should be involved in lifestyle programs aimed at healthy diet and habitual physical activity to a ≥7–10% weight loss target, repeatedly associated with improved histology, including fibrosis (*B*, 1).
- The dietary approach to NAFLD should favor adherence to the principles of the Mediterranean diet, including a reduced intake of refined and industrial sugars, associated with reduced hepatic fat content and decreased cardiovascular risk (*B*, 1).
- Low-modest alcohol intake in noncirrhotic NAFLD patients should not be encouraged (C, 2) and total abstinence in NAFLD-cirrhosis is recommended (B, 1).
- In patients with NAFLD, any types of physical activity, as well as reduced sedentariness, should be counseled, in order to reduce liver fat, independently of changes in body weight (*B*, 1).
- Clinicians should recommend weight loss by intensive, structured lifestyle programs delivered under specialist control and/or pharmacotherapy and/or bariatric surgery in NAFLD subjects with obesity to reduce liver disease severity (*A*, 1).

References: [9,125–176]

(C) *Pharmacologic treatment for NAFLD*

The epidemic of NAFLD and its complications, and the discovery of different potential therapeutic targets for NASH treatment led to start an impressive number of clinical trials. International guidelines recommend that pharmacological therapy for NAFLD/NASH should be reserved to patients presenting an active disease and the presence of liver fibrosis ≥ stage 2 [177,178]. Moreover, the FDA (US Food and Drug Administration) and the EMA (European Medicines Agency) identified two endpoints for the conditional approval of drugs in patients with noncirrhotic NASH: (1) resolution of NASH without worsening of liver fibrosis, and (2) at least one stage improvement in liver fibrosis without worsening of NASH fibrosis [178]. Consistently, most of the phase 2b and phase 3 trials enrolled patients with NASH plus fibrosis stage F2-F3. However, in spite of a large number of published or ongoing clinical trials, to date neither FDA, nor EMA or AIFA have approved any pharmacological treatment for patients with NASH.

PICO 6 - In adult patients with NAFLD, what is the efficacy of pharmacological treatment on histologically-assessed liver damage and

liver-related outcomes in comparison with no pharmacological intervention?

Recommendations

- In patients with NASH pioglitazone may be used to improve NASH and fibrosis, although the drug is off-label and the risk/benefit balance *related to pioglitazone side-effects* should be discussed with each patient (*B*, 2).
- In patients with NASH vitamin E may be used to improve NASH and fibrosis, even if risks and benefits should be discussed with each patient (*B*, 2).
- *In patients with NASH standard or high-dose ursodeoxycholic acid (UDCA) should not be used to treat NASH and fibrosis, because ineffective (B, 2).*
- In patients with NASH obeticholic acid may improve fibrosis without worsening of NASH, but its use is waiting for approval by regulatory agencies, based on additional safety and efficacy data (*B*, 2).

References for pioglitazone: [179–194]
References for vitamin E: [182,195–202]
References for ursodeoxycholic acid: [203–206]
References for obeticholic acid: [207–209]

PICO 7 - In adult patients with NAFLD and type 2 diabetes mellitus, what is the efficacy of glucose-lowering treatment on histologically-assessed liver damage and liver-related outcomes?

Recommendations

- In T2DM patients with NAFLD/NASH, pioglitazone is specifically recommended to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, metformin use is safe for the liver, but it is not specifically recommended to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, DPP-4 inhibitors are safe for the liver, but their use is not specifically recommended to treat liver disease (*C*, 2).
- In T2DM patients with NAFLD/NASH, GLP-1 receptor agonists are safe for the liver, but, despite preliminary evidence that may decrease liver damage, their use is not specifically approved to treat liver disease (*B*, 2).
- In T2DM patients with NAFLD/NASH, SGLT-2 inhibitors are safe for the liver, but their use is not specifically recommended to treat liver disease (*C*, 2).

References for metformin: [185,210–215]
References for DPP-4 inhibitors: [216–220]
References for GLP-1 receptor agonists: [141,219,221–228]
References for SGLT-2 inhibitors: [229–239]

(D) *NAFLD and liver transplantation*

PICO 8 - In adult patients with NASH candidate for liver transplantation, should the evaluation of cardiometabolic comorbidities in the pre- and post-transplant phase be different from that of patients with liver disease of other etiology in order to reduce cardiovascular complications?

Recommendations

- In liver transplant candidates with NASH-related decompensated cirrhosis or NASH-HCC, both at particularly high risk of developing cardiovascular events, cardiovascular risk factors should be assessed by a multidisciplinary team, which includes a transplant cardiologist and a transplant anesthesiologist, but no universally validated algorithms are available for a comprehensive evaluation (*C*, 1).
- Thorough screening for hypertension, diabetes, and dyslipidemia is recommended in patients with NASH undergoing evaluation for liver transplantation and appropriate medical treatment in wait-listed patients is mandatory to reduce events and de-listing (*B*, 1).
- Obesity alone does not constitute a contraindication for liver transplantation. Patients with decompensated NASH-cirrhosis or NASH-HCC and morbid obesity (body mass index > 40 kg/m^2 should be listed on a highly individualized basis, especially in the presence of diabetes (*B*, 2).

References: [37,54,240–254]

PICO 9 - In adult patients with NASH and morbid obesity, candidate for liver transplantation, what is the efficacy of bariatric surgery on pre- and post-transplant outcomes in comparison with no bariatric surgery?

Recommendation

- Bariatric surgery may improve outcomes in patients with morbid obesity in the setting of liver transplantation, however in decompensated cirrhosis it is associated with higher risk of morbidity and mortality; too few data are available to recommend the procedure before, during or after transplantation (C, 2).

References: [255–263]

(E) *NAFLD ascertainment in the general population*

PICO 10 - In the adult population are non-invasive scores and imaging methods useful for the diagnosis of NAFLD?

Recommendations

- Non-invasive scores (Fatty Liver Index – FLI) may be useful in population studies for the diagnosis of steatosis (*A*, 1).
- Ultrasonography (US) is the first-line diagnostic procedure for detecting NAFLD, as it has high accuracy for moderate-severe steatosis and also provides additional diagnostic information (*A*, 1).
- ^{1}H-Magnetic Resonance Spectroscopy (MRS) is the reference standard for a quantitative estimation of liver fat. This technique should be preferred in clinical trials, but it is not recommended in clinical practice because expensive and not largely available (*A*, 2).
- Controlled Attenuation Parameter (CAP) is an alternative tool for non-invasive assessment and follow-up of steatosis but more data are needed to definitively define its role (*B*,2).

References: [264–276]

PICO 11 - In adult population with metabolic risk factors are non-invasive scores, liver stiffness and imaging methods useful for the diagnosis of advanced fibrosis?

Recommendation

- In adult individuals with one or more features of the metabolic syndrome, a combination of non-invasive fibrosis markers may help improve referral of patients with advanced liver fibrosis from primary care to specialist setting, also reducing the cost of management (*B*, 2).

References: [16,48,277–283]

11. Conclusion

In the past few years NAFLD emerged as a common liver disease in adults frequently associated with metabolic alterations, and as a leading cause of HCC and liver decompensation, finally impacting resource utilization and costs of the Healthcare systems.

Also in Italy, the cost associated with NAFLD for the National Health System is rapidly increasing [28]. The growing interest for NAFLD lead to the development of new diagnostic tools and algorithms to identify and refer patients at high risk of liver damage to liver specialists for assessment and treatment. The implementation of lifestyle programs aimed at weight loss and ongoing clinical trials with drugs targeting pathogenic pathways responsible for necroinflammation and fibrosis open new scenario in the management of NAFLD patients [284].

The present Guidelines are conceived to promote a fruitful collaboration between different specialties, in a multidisciplinary approach aimed at disseminating and improving treatment within the healthcare professionals. Given the impressive amount of research and the extraordinary advances of the past few years, the several attempts to define new treatment strategies and the large number of trials supported by pharmaceutical companies, the proposed recommendations should be considered provisional and the Writing Commission recommends systematic update of Guidelines at regular intervals.

Finally, given its epidemiological, clinical and economic burden, NAFLD should be classified as a definite liver disease by the Health Care Italian System, independently of the presence of other metabolic comorbidities, with appropriate regulations in terms of diagnosis and treatment.

Declaration of Competing Interest

Giulio Marchesini participated in NAFLD advisory boards of Astra-Zeneca, Pfizer, Gilead, Novartis and received honoraria for conference from Eli Lilly

Elisabetta Bugianesi: Consultant for Gilead, BMS, Boeringher, Intercept, Innova, Novo Nordisk

Patrizia Burra received personal fees from Biotest, Kedrion and Chiesi Farmaceutici for occasional scientific collaboration

Fabio Marra: Abbvie: consultant fees; Allergan: consultant fees; AstraZeneca: consultant fees; Gilead: speaker honoraria, consultant fees; Intercept: speaker honoraria; Menarini: consultant fees; Novartis: consultant fees; Novo Nordisk: consultant fees

Luca Miele: Advisory Board, Consultancy, Invited Speaker: Alfa-Sigma, Boehringer-Ingelheim, BMS, Echosens, Galmed, Gilead Sciences, IBSA, Intercept, MEDA, MyGenomics, Merck Sharp & Dohme, Novartis, Pfizer, ProLon, Promethera, Rottapharm-Madaus, Siemens Healthineers, Synageva

Anna Alisi: no disclosures

Piero Vajro: no disclosures

Mario Masarone: Gilead travel grants, invited speech; Abbvie: travel grants, invited speech, advisory boards

Salvatore Petta: Advisor and/or Speaker for Abbvie, Gilead, Intercept and Pfyzer

Marcello Persico acted as consultant for Abbvie and Gilead

Gianluca Svegliati-Baroni: no disclosures

Luca Valenti: Speaking: MSD, Gilead, AlfaSigma, AbbVie; Consulting: Gilead, Pfizer, Astra Zeneca, Novo Nordisk, Intercept pharmaceuticals, Diatech Pharmacogenetics, IONIS; Research: Gilead

Massimo Federici: no disclosures

Francesco Purrello: no disclosures

Ferdinando Carlo Sasso has been member of Advisory Boards for Boehringer and for Ely-Lilly and has received fees for scientific consultation and/or lectures by Jansen, Roche Diagnostics, Novo Nordisk, Sanofi, MSD, Astrazeneca

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Maria Letizia Petroni: no disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.04.029.

Appendix 1. Bibliographic research strategy

- *Identification of information needs:* scientific evidence concerning the pathogenesis, diagnosis and treatment of non-alcoholic steatosis.
- *Planning of the research strategy:* for each topic assigned, the researchers personally searched for the bibliographic sources, using digital or paper resources if necessary.
- *Choice of tools for information retrieval:* the identified articles were obtained from the online library of the Institution to which the member of the experts' panel belongs. If not available online, the article was searched among the paper volumes of institutional libraries or was obtained through a direct request to the author of the publication.
- *Identification of adequate sources of information:* only articles from journals indexed on scientific search engines (PubMed, Embase, Scopus) were included, excluding non-scientific repertoires and newspapers articles, case reports, conference abstracts not published in-extenso. The keywords used for the research were the following:

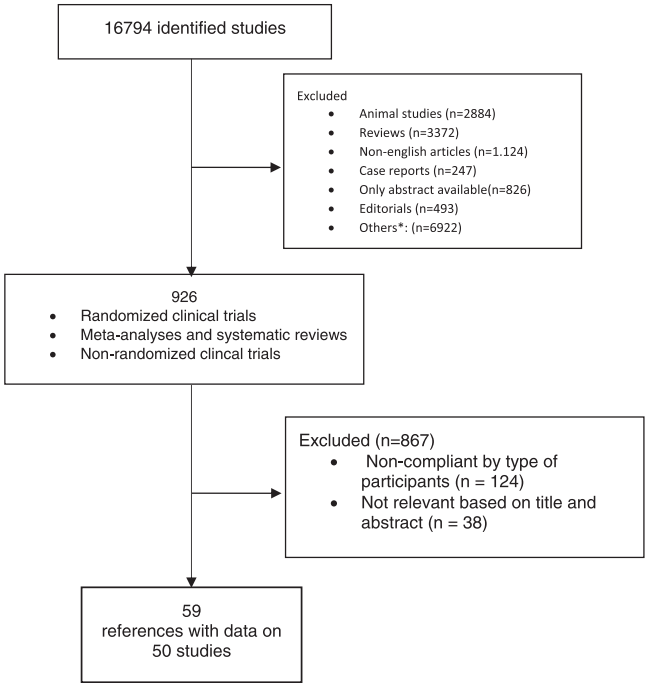
(1) Research topic: classification, diagnosis and prognosis of non-alcoholic steatosis.

Free-text research keywords: liver steatosis, non-alcoholic fatty liver, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, classification, diagnosis, prognosis.

BOOLEAN research string:

("Non-alcoholic Fatty Liver Disease" [Mesh] OR non alcoholic fatty liver disease* [Title/Abstract] OR non-alcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver* [Title/Abstract] OR non

alcoholic steatohepatitis* [Title/Abstract]) AND ("Liver Diseases" [Mesh])



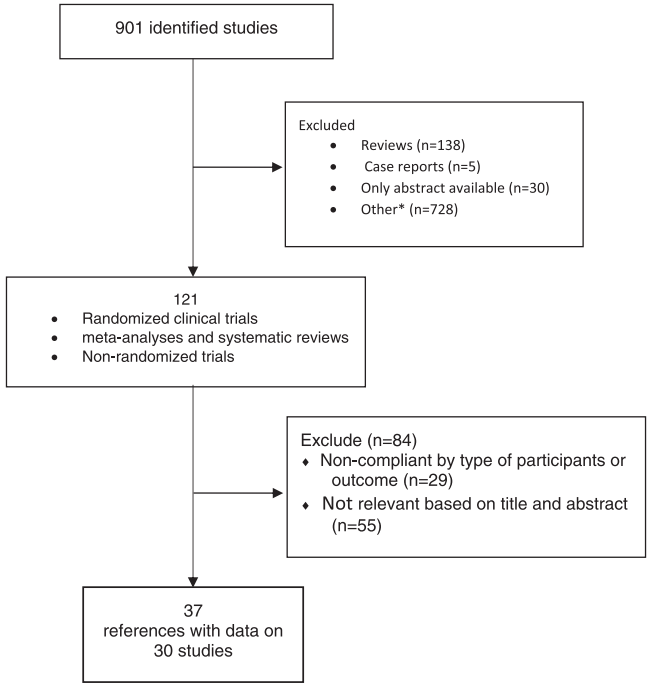
[*: Other: animal studies, letters, studies enrolling fewer than 10 subjects, articles not reporting outcomes of interest or primary data (editorial, unsystematic reviews), studies with inadequate case definition or enrolling secondary steatosis (for example: steatosis from drugs, from total parenteral nutrition etc.)]

(2) Research topic: non-invasive diagnosis of NAFLD

Free-text research keywords: non- alcoholic fatty liver disease, therapy, liver disease:

BOOLEAN research string:

("Non-alcoholic Fatty Liver Disease" [Mesh] OR non alcoholic fatty liver disease* [Title/Abstract] OR non-alcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver* [Title/Abstract] OR non alcoholic steatohepatitis* [Title/Abstract]) AND ("Liver Cirrhosis" [Mesh] OR liver fibrosis* [Title/Abstract] OR hepatic fibrosis* [Title/Abstract] OR cirrhosis* [Title/Abstract] OR cirrhoses* [Title/Abstract]) AND ((16 APRI* [Title/Abstract] OR aspartate aminotransferase to platelets ratio index* [Title/Abstract]) OR (FIB-4* [Title/Abstract] OR fibrosis-4 index* [Title/Abstract]) OR (NAFLD fibrosis score* [Title/Abstract] OR NFS* [Title/Abstract]) OR (BARD score* [Title/Abstract]) OR ("Elasticity Imaging Techniques" [Mesh] OR Elasticity Imaging Techniques [Title/Abstract]) OR (elastography* [Title/Abstract] OR elastograph* [Title/Abstract]) OR (FibroScan* [Title/Abstract] OR transient elastography* [Title/Abstract]) OR (shear wave elastography* [Title/Abstract]) OR (magnetic resonance elastography* [Title/Abstract] OR (38 MRE [Title/Abstract]))



[*: Other: animal studies, letters, studies enrolling fewer than 10 subjects, articles not reporting outcomes of interest or primary data (editorial, unsystematic reviews), studies with inadequate case definition or enrolling secondary steatosis (for example: steatosis from drugs, from total parenteral nutrition etc.), articles not in English].

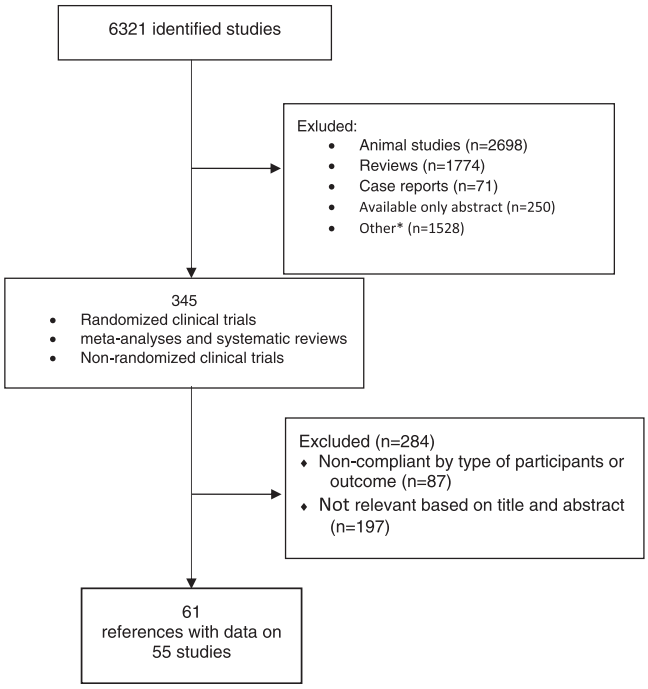
(3) Research topic: NAFLD therapy

Free-text reseach keywords: Non alcoholic fatty liver disease, therapy, liver disease

BOOLEAN research string:

("Non-alcoholic Fatty Liver Disease" [Mesh] OR non alcoholic fatty liver disease* [Title/Abstract] OR non-alcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver disease* [Title/Abstract] OR nonalcoholic fatty liver* [Title/Abstract] OR non alcoholic steatohepatitis* [Title/Abstract]) AND ((“Therapy” [MeSH] OR “Pharmacological therapy” [MeSH] OR Drug* [Title/Abstract] OR Therap* [Title/Abstract]) OR (exercise [Title/Abstract] OR resistance training [Title/Abstract] OR aerobic training [Title/Abstract] OR aerobic exercise [Title/Abstract] OR circuit training [Title/Abstract] OR walk test [Title/Abstract] OR endurance training [Title/Abstract]

OR strength training [Title/Abstract] OR weight training [Title/Abstract]))



[*: Other: animal studies, letters, studies enrolling fewer than 10 subjects, articles not reporting outcomes of interest or primary data (editorial, unsystematic reviews), studies with inadequate case definition or enrolling secondary steatosis (for example: steatosis from drugs, from total parenteral nutrition etc.), articles not in English]

Appendix 2. Members of the guidelines panel

Coordinator: Giulio Marchesini*; AISF Members:* Elisabetta Bugianesi, Patrizia Burra, Fabio Marra, Luca Miele, Anna Alisi, Piero Vajro, Mario Masarone, Salvatore Petta, Marcello Persico, Gianluca Svegliati-Baroni, Luca Valenti*; SID Members:* Massimo Federici, Francesco Purrello, Ferdinando Carlo Sasso, Giovanni Targher*; SIO Members:* Luca Busetto, Maria Letizia Petroni, Ferruccio Santini; *Metodologists:* Calogero Cammà, Agostino Colli.

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