Hepatology Snapshot:
NAFLD/NASH

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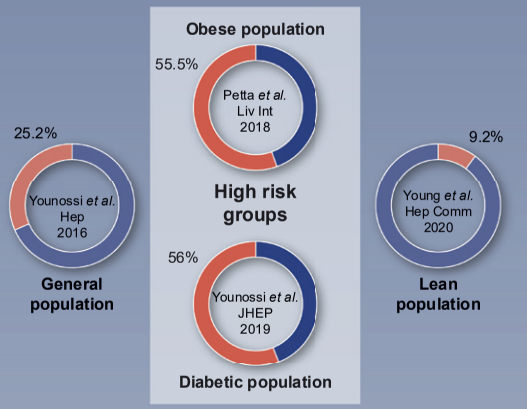
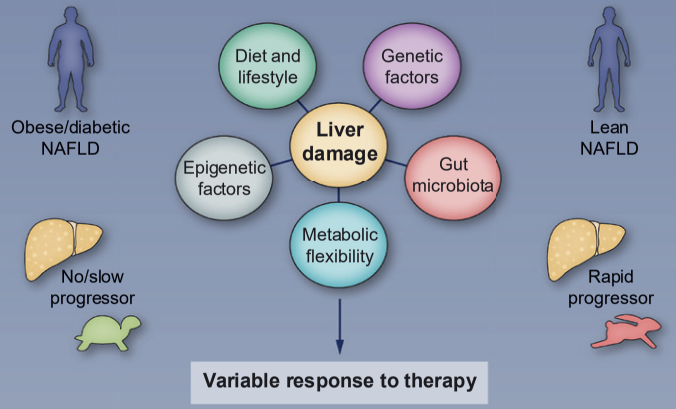
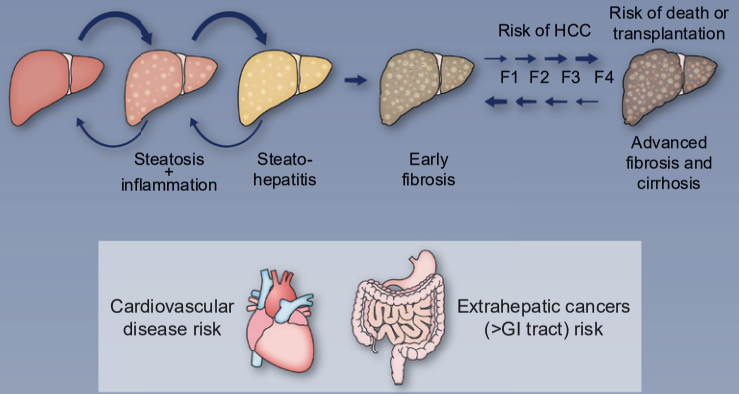
Epidemiology



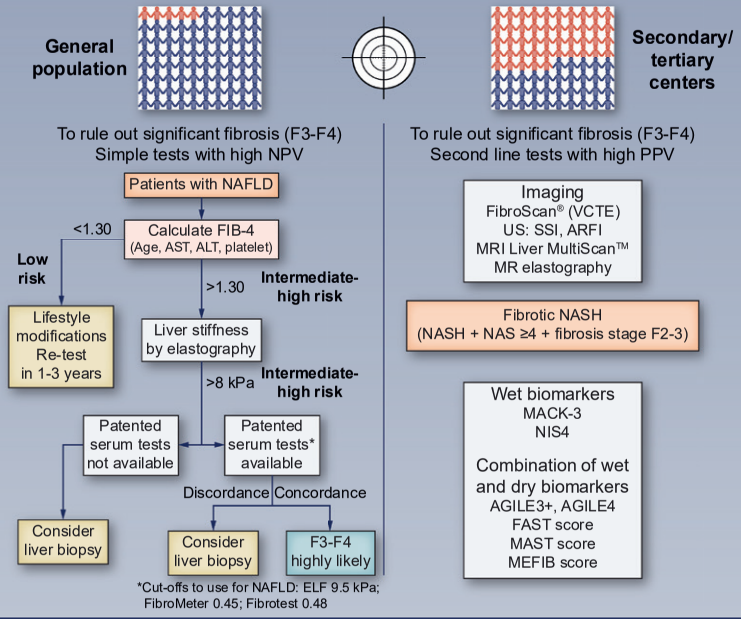
Clinical and phenotypic heterogeneity



Natural history and outcomes



Non-invasive diagnosis



NAFLD or MAFLD?

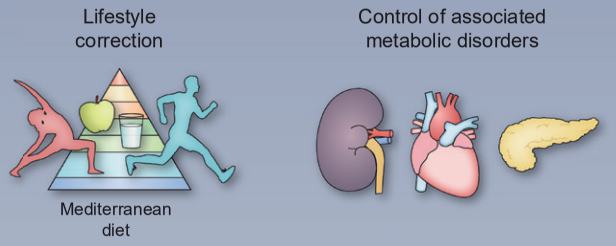
NAFLD

- Hepatic steatosis
- No alcohol intake >20 grams/day
- No other cause of liver diseases (*e.g.* viral hepatitis, autoimmune hepatitis, Wilson's disease, haemochromatosis, DILI)

MAFLD

- Hepatic steatosis
  +
- Overweight/obesity
  or
  Type 2 diabetes
  or
  at least two:
  - Visceral obesity
  - Arterial hypertension
  - High triglycerides
  - Low HDL
  - Prediabetes
  - HOMA >2.5
  - H-S PCR >2 mg/L

Management



Classes of drugs under development in phase II/III trials that target metabolic and/or inflammatory and/or fibrogenic pathways.

- Acetyl-CoA carboxylase (ACC) inhibitor
- Stearoyl-CoA desaturase (SCD) inhibitor
- Farnesoid X receptor (FXR) agonist
- Fibroblast growth factor (FGF) 19 and 21 analogs
- Peroxisome proliferator-activated receptor (PPAR) alpha and/or delta and/or gamma agonists
- Thyroid hormone receptor (THR) beta-selective agonist
- Mitochondrial pyruvate carrier (MPC) inhibitor
- Glucagon-like peptide 1 (GLP-1) agonist
- Galectin-3 inhibitor

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The current nomenclature of NAFLD supports a diagnosis "in negative", based on the exclusion of other causes of liver disease. An international consensus panel has recently suggested a new nomenclature, metabolic dysfunction-associated fatty liver disease (MAFLD),[1] based on the identification of the associated metabolic risk factors to support active case finding. The burden of the disease is large, with an estimated prevalence of 25.2% in the general population,[2] increasing to more than 50% in high-risk groups such as diabetic and obese patients.[4] Nevertheless, NAFLD can be also found in 9.2% of lean individuals,[3] a population that is usually overlooked. The complex interplay between metabolic, genetic, epigenetic, environmental factors and gut microbiota accounts for the large heterogeneity in the clinical phenotype of NAFLD, ranging from metabolic unhealthy «lean» to obese and from slow to rapid progressors. Liver damage progression is not linear and is potentially reversible up to the stage of severe liver fibrosis (F3) where disease progression is more likely to occur than regression. Older age, insulin resistance/diabetes, obesity, arterial hypertension, and common variants in *PNPLA3, TM6SF2, HSD13B17* and *MBOAT7* genes[5] can act as modulators of fibrotic changes. The severity of liver fibrosis is the main driver of hepatic complications such as liver decompensation and hepatocellular carcinoma (HCC), with growing evidence that HCC can also develop in non-cirrhotic NASH.[6] As NAFLD is a systemic disease driven by metabolic abnormalities, cardiometabolic complications and extrahepatic cancers are the most frequent events and cause of death.[7] The European guidelines advice case finding in high-risk groups of obese and diabetic patients in consideration of the 2- or 3-fold risk of developing end-stage liver disease and HCC.[8] Current non-invasive tools do not have an acceptable diagnostic accuracy for NASH. On the contrary, more robust evidence is available for the non-invasive diagnosis of advanced fibrosis (F3-F4). In the setting of primary care, where the prevalence of high-risk patients is generally low, FIB-4 can be used as first-line tool to rule out significant fibrosis. This algorithm is based on simple parameters and has a high negative predictive value. The sequential use of a second-line test such as ELF or transient elastography can streamline referrals to hepatologists.[8] In secondary or tertiary centers, where a significant proportion of patients are at high risk, more sophisticated tools can be adopted, such as magnetic resonance elastography. Recently the concept of "Fibrosing NASH" has been developed to identify patients eligible for clinical trials; in this setting, various combinations of wet and dry biomarkers are currently being tested such as MACK-3, NIS4, FAST and MAST scores.[8] The future management of NAFLD will likely involve precision medicine based on omics in combination with imaging tools and artificial intelligence. The intrinsic association between NAFLD and metabolic alterations is also crucial when considering NAFLD treatment. Lifestyle correction based on caloric restriction and Mediterranean diet plus physical activity with the goal of at least 5%-7% of weight loss should be promoted.[9] Screening for cardiometabolic comorbidities and control of associated metabolic disorders like diabetes and dyslipidemia is mandatory, as it can positively impact on liver damage. In morbidly obese patients, bariatric surgery including conventional gastric bypass, sleeve gastrectomy and innovative endoscopic techniques should be considered. Patients with fibrotic NASH or cirrhosis are deemed eligible for pharmacologic therapy by the FDA and EMA. Different classes of drugs are currently under development, such as ACC inhibitors, SCD inhibitors, FXR agonists, FGF21 and FGF19 analogs, PPAR agonists, THR beta agonists, MPC inhibitors, GLP-1 agonists and galectin-3 inhibitors.[10] This is a rapidly evolving scenario where different unsolved concerns still exist, such as the lack of head-to head comparisons among classes of drugs; the use of a single or combination therapy; the stopping rules; and, finally, the evaluation of hard extrahepatic outcomes.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Elisabetta Bugianesi and Salvatore Petta had full control of the study and preparation of article. All authors were involved in drafting the article. The final draft article was approved by all the authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.02.006.

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