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Clinical Assessment & Management of Nonalcoholic Fatty Liver Diseases (NAFLD)

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Health Sciences North
Horizon Santé-Nord

Disclosures

I have received funded grants and/or I have served as a consultant and/or speaker for:

- **AbbVie.**
- **Janssen.**
- **Takeda.**
- **McKesson.**
- **Biojamp.**

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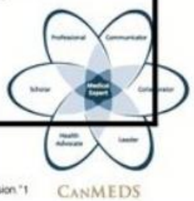
CanMEDS Roles Covered

★	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
★	**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
★	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
★	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
★	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
★	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
★	**Professional** (as *Professionals*, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)



Learning Objectives

- Definitions.
- Epidemiology and natural History.
- Comorbid conditions.
- Initial evaluation.
- Management in primary care setting.
- Treatment.

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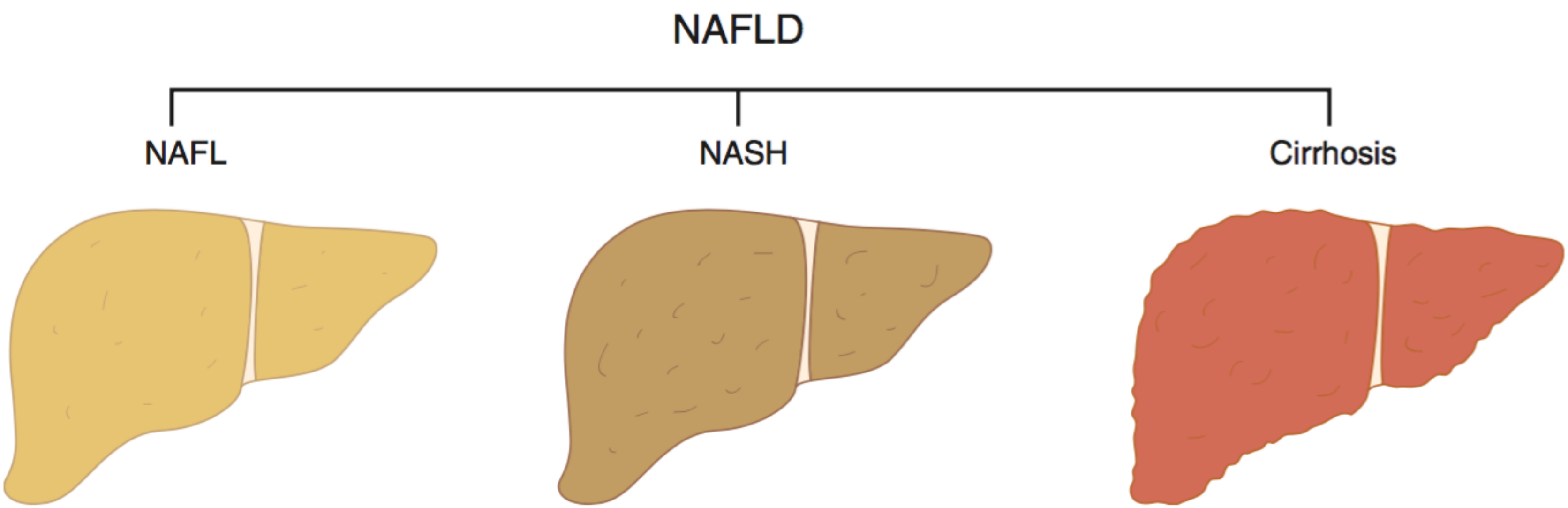
Definitions

- ≥ 5% of hepatocytes display macrovesicular steatosis in the absence of alternative cause of steatosis in individuals who drink little or no alcohol.



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Epidemiology

cmajOPEN

Research

Burden of nonalcoholic fatty liver disease in Canada, 2019–2030: a modelling study

Mark G. Swain MD, Alnoor Ramji MD, Keyur Patel MD PhD, Giada Sebastiani MD, Abdel Aziz Shaheen MBBCh, Edward Tam MD, Paul Marotta MD, Magdy Elkhashab MD, Harpreet S. Bajaj MD, Chris Estes MPH, Homie Razavi PhD

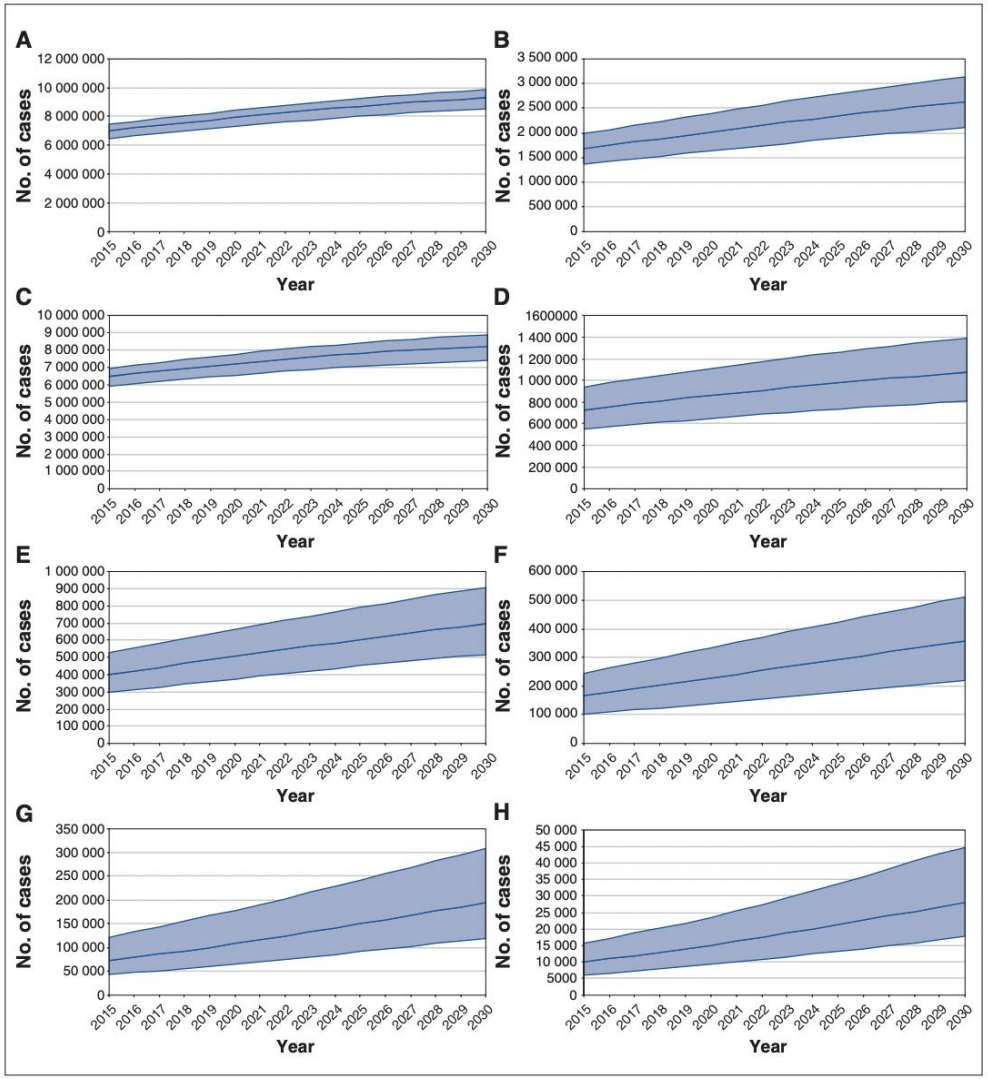


Figure 1: Model-estimated prevalent cases of nonalcoholic fatty liver disease (NAFLD) (A), nonalcoholic steatohepatitis (B), stage F0 NAFLD (C), stage F1 NAFLD (D), stage F2 NAFLD (E), stage F3 NAFLD (F), compensated cirrhosis NAFLD (G) and decompensated cirrhosis, hepatocellular carcinoma and liver transplantation related to NAFLD (H) for Canada, 2015–2030. Shaded areas represent 95% uncertainty interval.

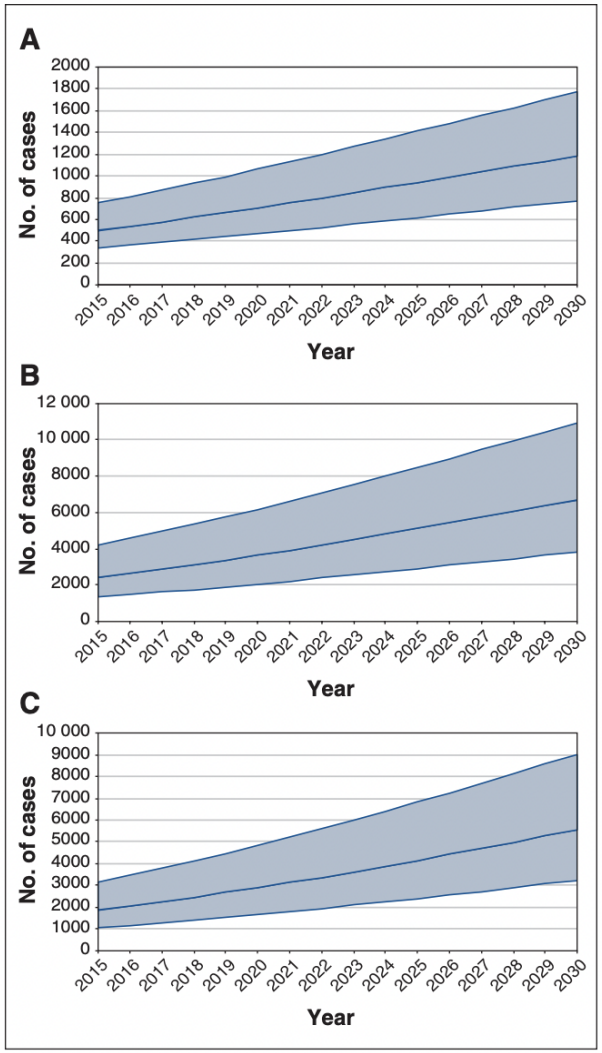
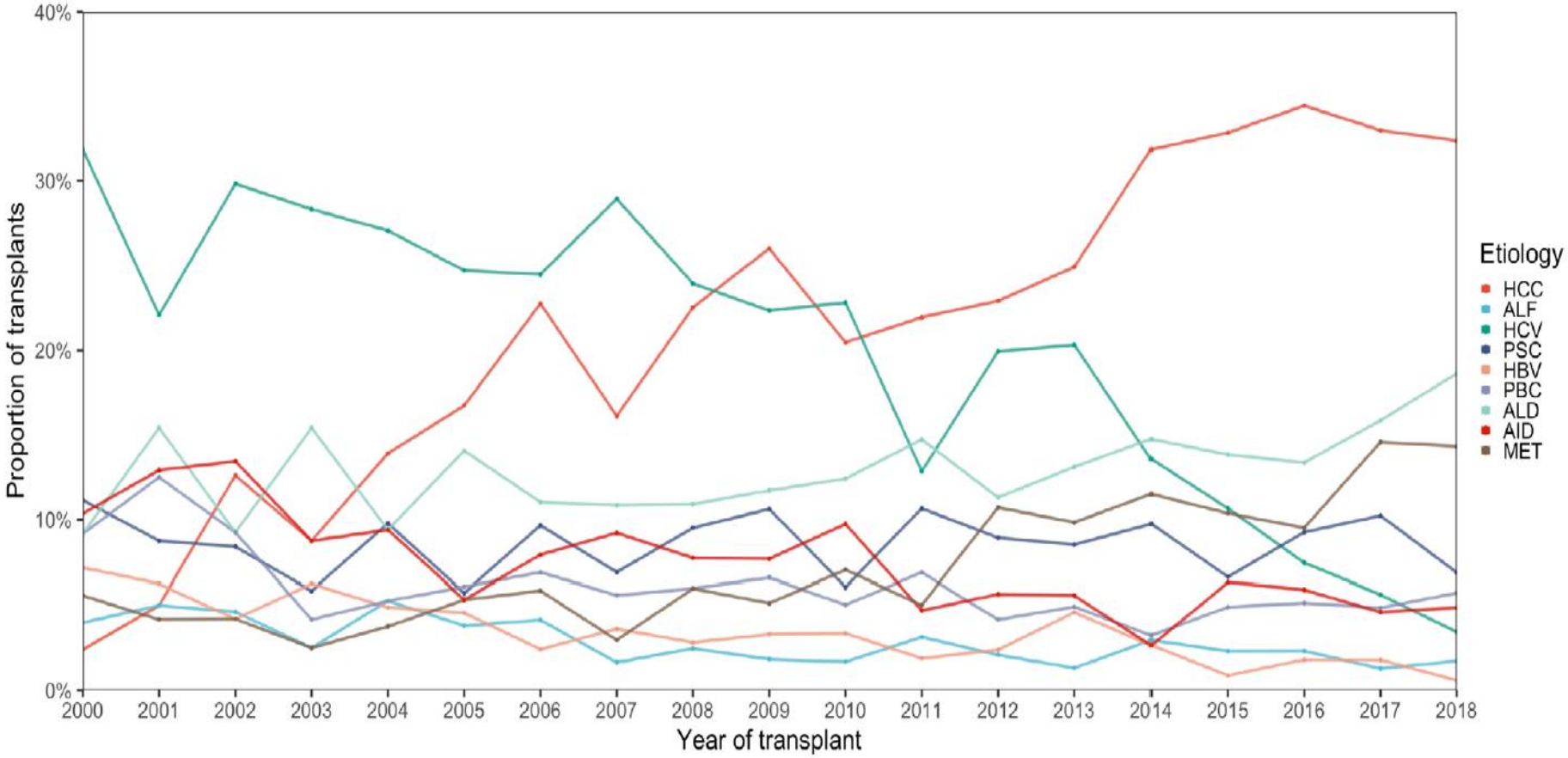


Figure 2: Model-estimated incident cases of hepatocellular carcinoma (A), decompensated cirrhosis (B) and incident liver-related death (C) related to nonalcoholic fatty liver disease for Canada, 2015–2030. Shaded areas represent 95% uncertainty interval.

Ivanics *et al.*



Ivanics, Tommy, et al. *Transplant International* (2021).

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Natural History

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 65, NO. 5, 2017

Increased Risk of Mortality by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis

Parambir S. Dulai,[1,2] Siddharth Singh,[1,2] Janki Patel,[1] Meera Soni,[1] Larry J. Prokop,[3] Zobair Younossi,[4] Giada Sebastiani,[5] Mattias Ekstedt,[6] Hannes Hagstrom,[7] Patrik Nasr,[6] Per Stal,[7] Vincent Wai-Sun Wong,[8] Stergios Kechagias,[6] Rolf Hultcrantz,[7] and Rohit Loomba[1,2]

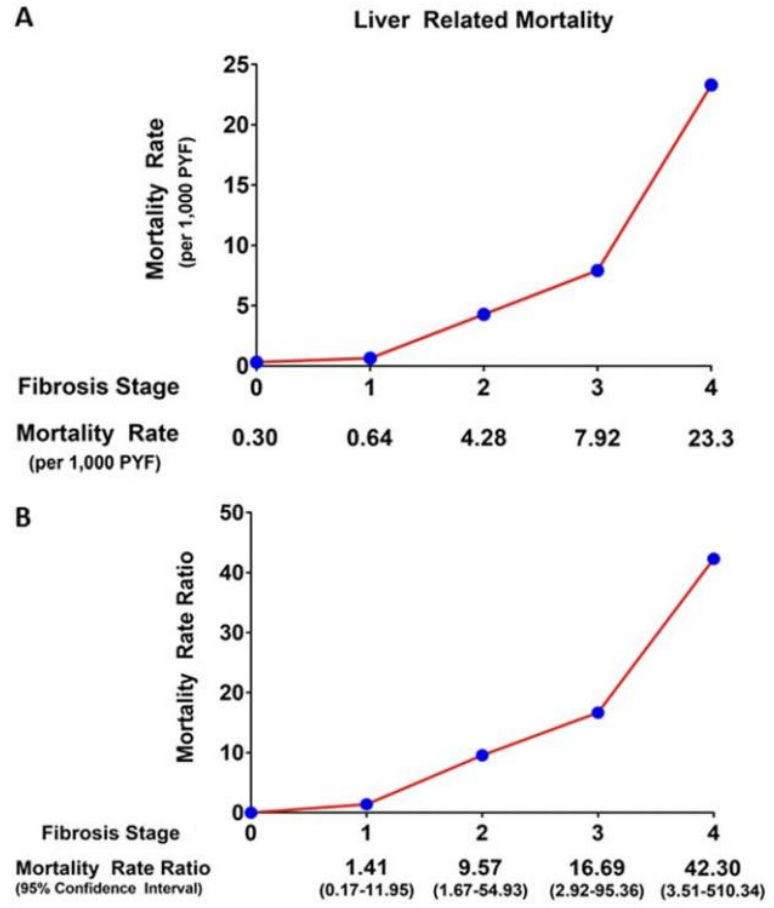

FIG. 4. Fibrosis stage–specific liver-related mortality rate and MRR. (A) Crude liver-related mortality rate by fibrosis stage. (B) Liver-related MRR with 95% CIs by fibrosis stage.

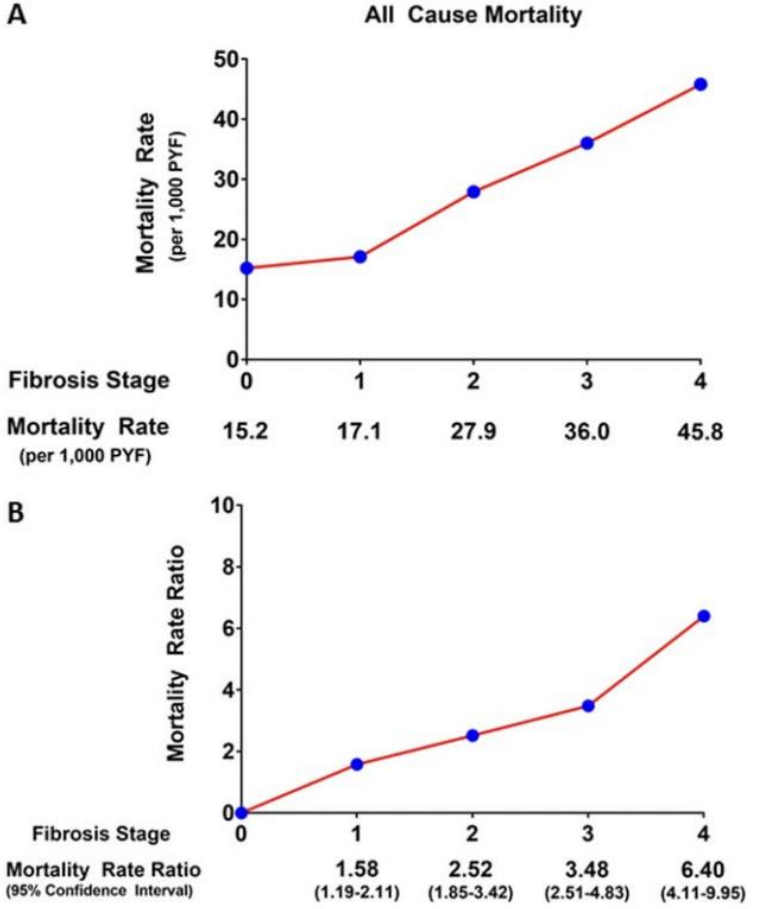

FIG. 2. Fibrosis stage–specific all-cause mortality rate and MRR. (A) Crude all-cause mortality rate by fibrosis stage. (B) All-cause MRR with 95% CIs by fibrosis stage.

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Comorbid Conditions associated with NAFLD

- Obesity.
- Type 2 DM.
- HTN.
- Dyslipidemia.
- OSA.
- CVD.
- CKD.

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T2DM

- Patients with T2DM have a higher prevalence of NAFLD (ranging from 30% to 75%).

  Stefan N, Cusi K. Lancet Diabetes Endocrinol. 2022;10:284–96.

- The most impactful risk factor for the development of NAFLD, fibrosis progression, and HCC.

  Bazick J, et al. CDiabetes Care. 2015;38: 1347–55.

- The probability of advanced fibrosis increases with the duration of T2DM.

- The relationship between NAFLD and T2DM is bidirectional. Even in the absence of overt diabetes. The presence of NAFLD is associated with a 2- to 5-fold risk of incident diabetes.

  Ballestri S, et al. J Gastroenterol Hepatol. 2016;31:936–44.

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Dyslipidemia

- Statins are safe in patients with NAFLD across the disease spectrum, including advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality.

Abdallah M,et al. Ann Hepatol. 2022;27:100738.

- Statins are often underused despite extensive data demonstrating safety, even among patients with cirrhosis.

- Statins are also considered safe in the context of compensated cirrhosis.

- In patients with decompensated cirrhosis and high CVD risk undergoing evaluation for liver transplantation, statin use can be considered with careful monitoring.

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Initial Evaluation

- Normal values provided by most laboratories are higher than what should be considered normal in NAFLD, in which a true normal alanine aminotransferase (ALT) ranges from 29 to 33 U/L in men and from 19 to 25 U/L in women.

TABLE 1 Initial evaluation of a patient with NAFLD

History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration
Physical examination	Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema)
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (Table 2). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype

Abbreviations: CBC, complete blood count; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus.

AASLD clinical guidelines

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Initial Evaluation

TABLE 3 Drugs with potential mechanistic links to macrovesicular steatosis or steatohepatitis

Drug	Mechanism	Histological pattern
Amiodarone	Promotion of DNL, impairment of β-oxidation	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis
5-FU	Accumulation of 5-FU catabolites reduce hepatic capacity to metabolize lipids	Hepatic steatosis
Irinotecan	Induces mitochondrial dysfunction, impaired autophagy	Steatohepatitis
Tamoxifen	Estrogen receptor modulator, promotion of DNL, impairment of β-oxidation. *May or may not be independent of concomitant metabolic risk factors	Steatosis and steatohepatitis
Methotrexate	Mitochondrial injury (inhibits mitochondrial electron transport chain), injury to canals of Hering	Steatosis, steatohepatitis, cirrhosis
Corticosteroids	Exacerbation of metabolic comorbidities, impairment of β-oxidation, impairment of hepatic triglyceride secretion, lipid peroxidation	Steatosis

Abbreviations: 5-FU, 5-fluorouracil; DNL, de novo lipogenesis.

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Initial Evaluation

TABLE 2 When to consider testing for less common causes of hepatic steatosis and steatohepatitis

Condition	Clinical scenario	Diagnostic test	Treatment
Hypobetalipoproteinemia	Low LDL, low triglycerides, fat malabsorption	ApoB level, genetic testing (MTTP, PCSK-9)	Low-fat diet, fat-soluble vitamin supplementation
LAL deficiency	Markedly elevated LDL-C and low HDL-C, elevated triglycerides, xanthelasma, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis on liver biopsy	Enzyme assay, genetic testing	LAL replacement
Nutrient deficiency (eg, carnitine, choline)	Anorexia, short bowel, bypass surgeries	Nutrient levels	Supplementation
Wilson disease	Younger age, neuropsychiatric symptoms, low alkaline phosphatase, low ceruloplasmin	24-h urine copper; quantitative copper on liver biopsy	Chelation
Celiac disease	Iron deficiency, abdominal pain, bloating, vitamin D deficiency, bone loss, diarrhea, dermatitis herpetiformis	Tissue transglutaminase IgA, duodenal biopsy	Gluten-free diet

Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IgA, immunoglobulin A; LAL, lysosomal acid lipase; LDL-C, LDL cholesterol.

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Role of Alcohol Consumption

- Patients with clinically significant hepatic fibrosis (≥ F2) should abstain from alcohol use completely.
- Abstinence, particularly for those patients with moderate-to-heavy alcohol intake, may lower the risks of fibrosis progression and hepatic and extrahepatic malignancies in patients with NAFLD.

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Associated Endocrine Disorders

- ✓ Hypothyroidism.
- ✓ GH deficiency.
- ✓ Hypogonadism.
- ✓ PCOS.

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NAFLD in Lean Individuals

- The prevalence of NAFLD in lean individuals varies from 4.1% in the United States to as high as 19% in Asia.

Younossi ZM, et al. Medicine (Baltimore). 2012;91:319–27.
YeQ, etal. Lancet Gastroenterol Hepatol. 2020;5:739–52.

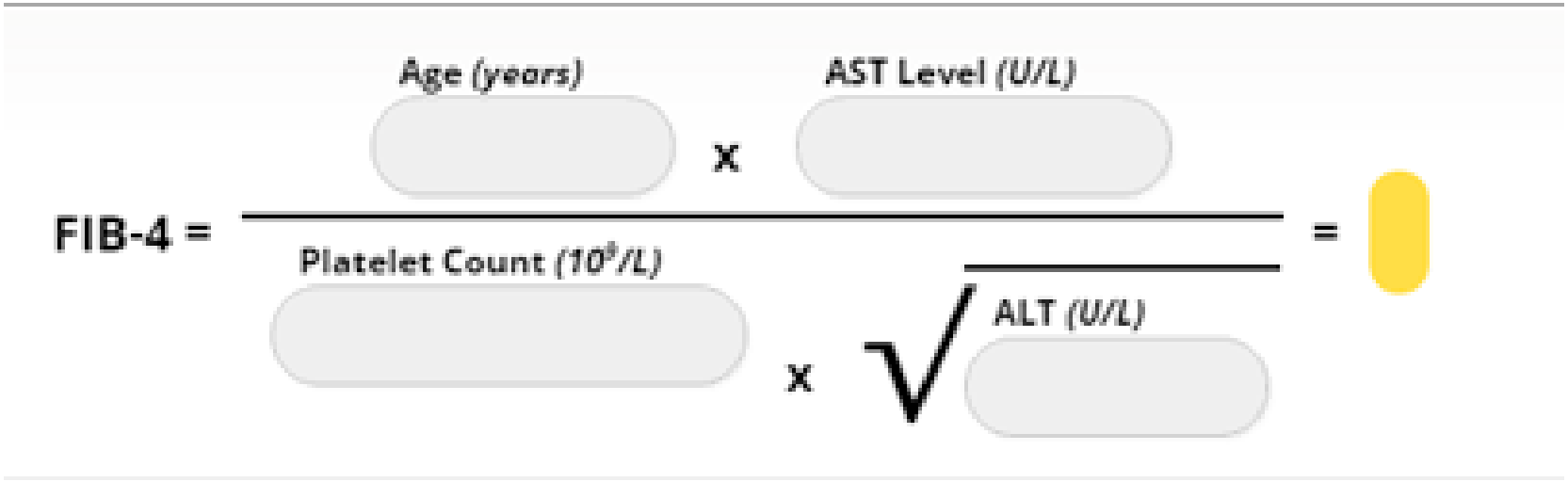
- Management of NAFLD in patients without obesity can be clinically challenging. Recommending weight loss may not be appropriate for lean patients with NAFLD, but dietary modifications and exercise in this group may be beneficial.

Management of NAFLD in Primary Care Setting

- General population-based screening for NAFLD is not advised.

- High-risk individuals:
  - T2DM.
  - Medically complicated obesity.
  - Family history of cirrhosis.
  - More than mild alcohol consumption.

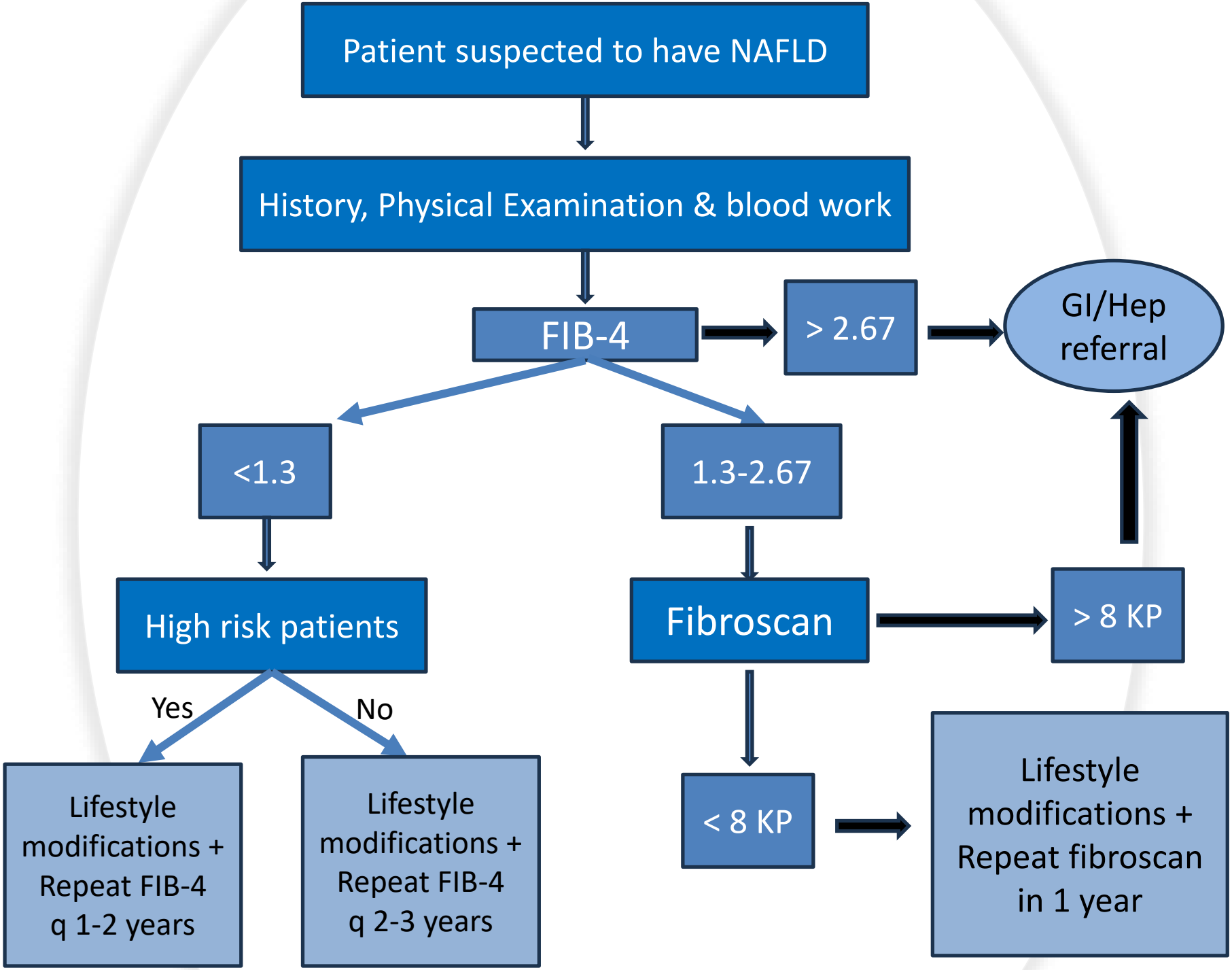
Management of NAFLD in Primary Care Setting



< 1.3	Low risk
1.3-2.67	Moderate risk
>2.67	High risk

Useful Tips

- In patients older than age 65, a FIB-4 cutoff of > 2.0 should be used.
- FIB-4 has low accuracy in those under age 35; thus, secondary assessment should be considered in those <35 with increased metabolic risk or elevated liver chemistries.
- FIB-4 should not be used in acutely ill patients.


Patient suspected to have NAFLD
History, Physical Examination & blood work
FIB-4
> 2.67
GI/Hep referral
<1.3
1.3-2.67
High risk patients
Fibroscan
> 8 KP
Yes
No
Lifestyle modifications + Repeat FIB-4 q 1-2 years
Lifestyle modifications + Repeat FIB-4 q 2-3 years
< 8 KP
Lifestyle modifications + Repeat fibroscan in 1 year

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Indications of GI/Hepatology Referral

- FIB-4 score>2.67.
- High risk patients with FIB-4=1.3-2.67.
- Persistent elevations in transaminases (>6-12 months).
- Abnormal work up (positive AILP).

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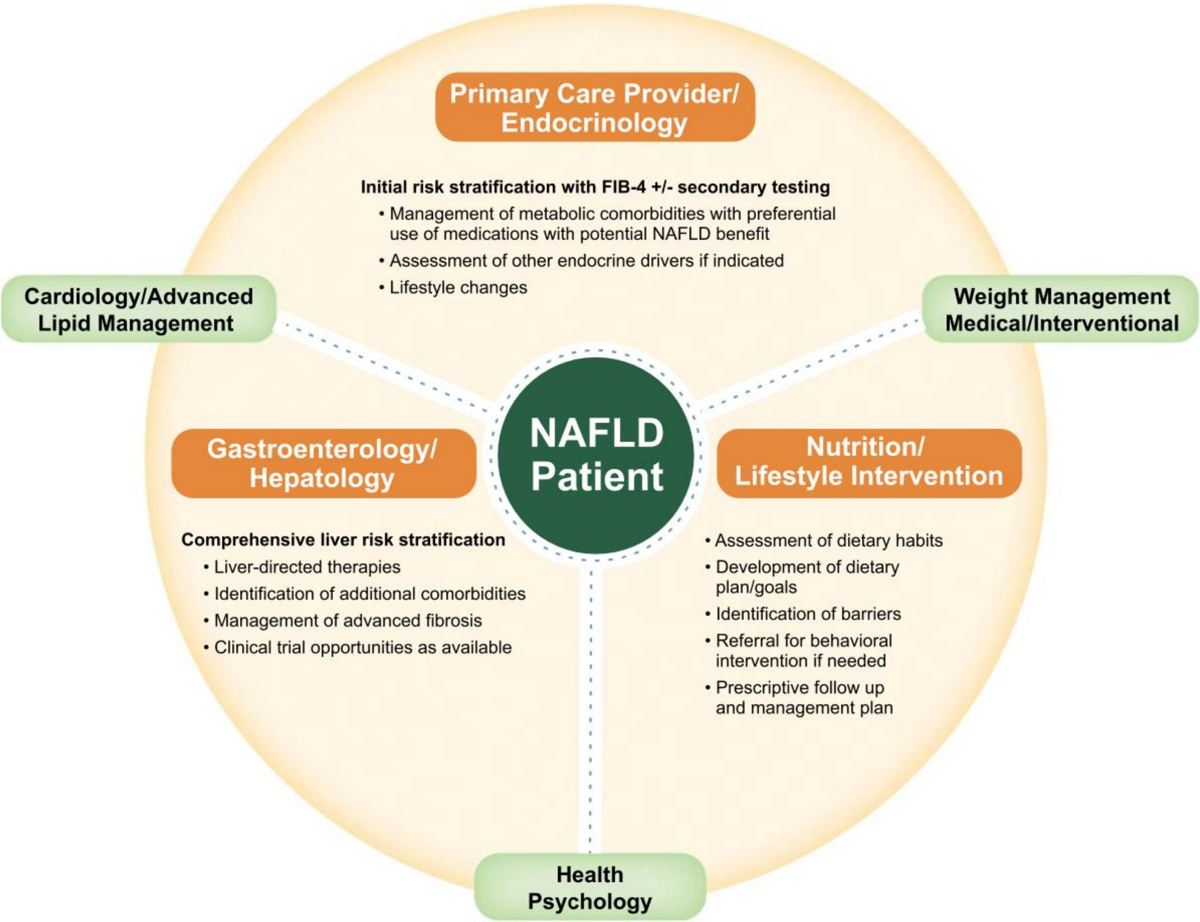
Treatment



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Weight Loss

- Weight loss of 3%–5% improves steatosis, but greater weight loss (> 10%) is generally required to improve NASH and fibrosis.

Koutoukidis DA, et ala systematic review and meta-analysis. JAMA Intern Med. 2019; 179:1262–71.

- ≤ 10% of patients achieve effective weight loss despite structured interventions at 1 year, and fewer than half of these maintain the weight lost 5 years after intervention, highlighting the need for ongoing nutrition support through multidisciplinary care .

Malespin MHet al. Clin Gastroenterol Hepatol. 2022;20:2393–5.

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Diet

- Excessive fructose consumption in particular increases the risk of NAFLD, NASH, and advanced fibrosis independent of calorie intake.

Abdelmalek MF, et al. Hepatology. 2010

- The Mediterranean diet is often recommended to patients with NAFLD based on its associated improvement in cardiovascular health and reduction in liver fat.

Haigh L, Ket al. a systematic review and meta-analysis. Clin Nutr. 2022;41:1913–31.

- Coffee consumption (caffeinated or not) of at least 3 cups daily is associated with less advanced liver disease.

ChenYP, et al. Clin Nutr. 2019;38: 2552–7.

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Exercise

- Has hepatic and cardiometabolic benefit, independent of weight loss.
- Regular moderate exercise can prevent or improve NAFLD.
- Patients should be encouraged to exercise as much as possible.

Sung KC, et al. J Hepatol. 2016;65:791–7.

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Bariatric Surgery

- Can resolve NASH, improve hepatic fibrosis, induce sustained weight loss of up to 30%, cure diabetes, and decrease all-cause morbidity and mortality.

Fakhry TK, et al. Systematic review and meta-analysis. Surg Obes Relat Dis. 2019;15:502–11.

- Resolution of NASH without worsening of fibrosis occurred in 80% of patients 1 year following bariatric surgery, which was maintained at 5 years.

Lassailly G, et al. Gastroenterology. 2020;159:1290–301.

- Should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery.

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Available Medications

- No FDA-approved drugs for the treatment of NASH at any disease stage.
- There are medications approved for other indications that have shown benefits for NASH in clinical trials and should be considered under specific circumstances.

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Vitamin E

- Improves serum aminotransferases in addition to steatosis, inflammation, and cellular ballooning on biopsy.
- Concern about the risks of vitamin E on bleeding and specifically hemorrhagic stroke has been raised.
- The relationship between vitamin E and prostate cancer are conflicting.
- Vitamin E can be considered in select individuals as it improves NASH in some patients without diabetes. However, potential risks should be discussed with patients before initiation of long-term high- dose (eg, 800 IU daily) vitamin E therapy.

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Thiazolidinediones (Pioglitazone)

- The studies are contradicting.
- Potential side effects associated with pioglitazone include weight gain, osteoporosis in post- menopausal women, a debated risk of bladder cancer, and potential risk for worsening heart failure in those with pre-existing cardiac dysfunction.
- Its use in clinical practice has been overtaken by the increasing use of newer antidiabetic agents (GLP-1RA and SGLT-2) with pleiotropic metabolic benefits, most notably weight loss and reduction in cardiovascular mortality.

GLP-1RAs (Semaglutide)

- The biological effects of GLP-1RAs on lipids, glucose metabolism, weight loss, and cardiovascular outcomes make them attractive agents for treatment of NASH.

- Approved for treatment of T2DM and 2 of them for obesity, but not for NASH without DM.

Semaglutide

The NEW ENGLAND JOURNAL of MEDICINE

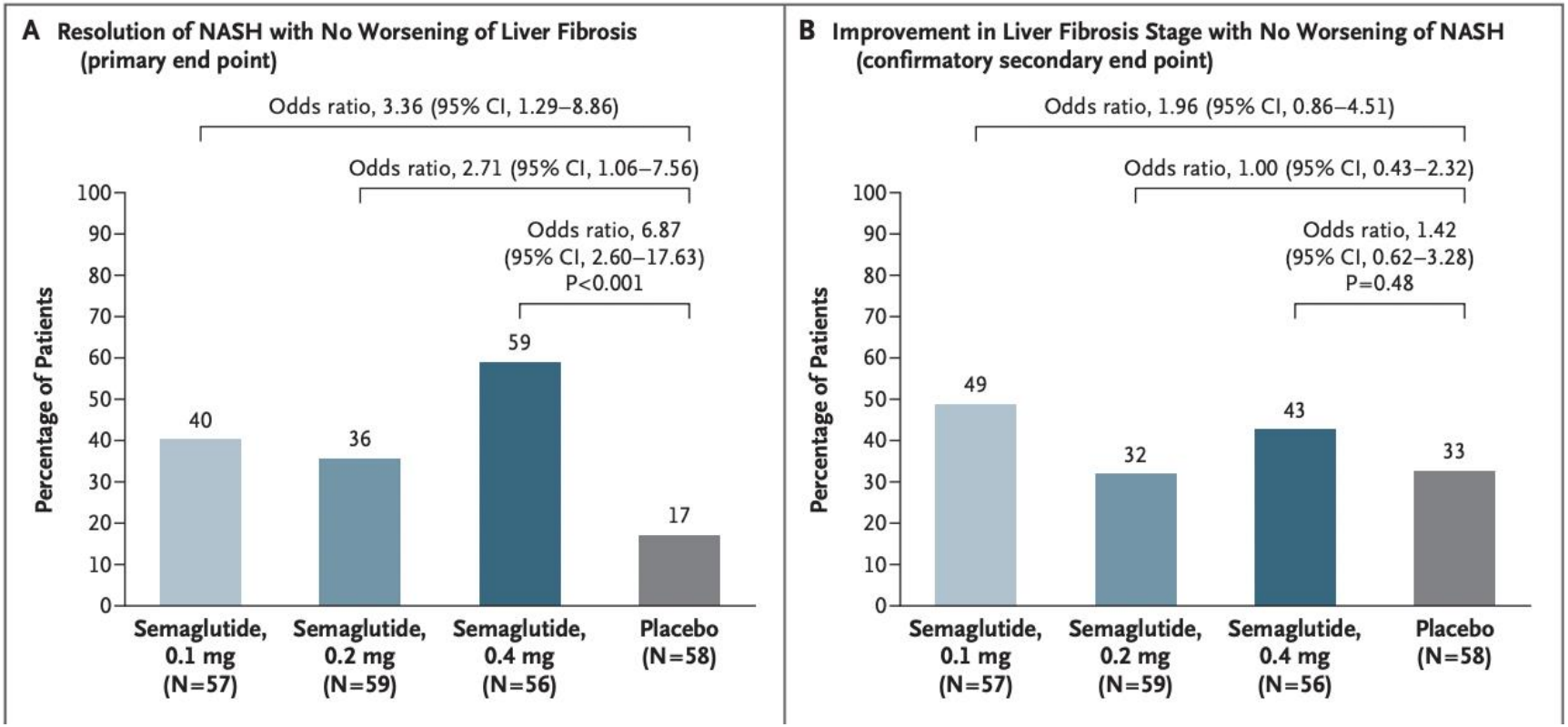
ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

ABSTRACT

Semaglutide



Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH, as it confers a cardiovascular benefit and improves NASH

Available Agents Without Evidence of Histological Benefits in NASH

- Metformin.
- Ursodeoxycholic acid.
- Ezetimibe.
- Silymarin (milk thistle).

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Take Home Message

- NAFLD may represent a growing burden on the Canadian health care system over the next decade.
- Prevention efforts should be aimed at reducing the incidence of NAFLD and slowing fibrosis progression among those already affected.
- General population-based screening for NAFLD is not advised.
- FIB-4 has good NPV as a screening tool for high-risk patients.
- The management of NAFLD requires sustained, multidisciplinary efforts.

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