Noninvasive methods for steatosis assessment in MAFLD

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Noninvasive methods for steatosis assessment in MAFLD

- **Noninvasive methods for steatosis assessment rely on two different, but complementary, approaches:**

- **The biological approach based on serum biomarker levels**

  and

  The physical approach based on liver stiffness (measured mainly using Transient elastography)

Recent guidelines recognize the value of NITs

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

"*There has been significant interest in developing clinical prediction rules and noninvasive biomarkers for identifying SH [steatohepatitis]*"[1]

EASL
European Association for the Study of the Liver

"*There is increasing evidence for the prognostic value of non-invasive tests*"[2]

NITs have prognostic value in predicting both mortality and liver-related complications in patients with NAFLD/NASH and other chronic liver diseases[2]

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NIT, non-invasive test
1. Chalasani N et al. *Hepatology* 2018;67(1):328–357; 2. EASL-ALEH. *J Hepatol* 2015;63:237–264.

Non-invasive tests (NITs) offer alternative ways to determine the degree of fibrosis

NITs are reproducible, widely available and relatively low cost[1–4]

MONITOR	Safe and simple way to support disease monitoring over time[1]
COST EFFECTIVE	May be cost effective as opposed to biopsy[1]
ASSESS FIBROSIS	Assess the level – e.g. absence or presence – of fibrosis[2]
INCREASED IDENTIFICATION OF AF	Sequential use of NITs may increase the number of patients from identified with Advanced Fibrosis[3]

AF, advanced fibrosis; NIT, non-invasive test

1. Tapper EB et al. *Am J Gastroenterol* 2015; doi: 10.1038/ajg.2015.241; 2. Lucero C et al. *Gastroenterol Hepatol* (N Y). 2016;12(1):33–40; 3. Srivastava A et al. *J Hepatol* 2019;71(2):371–378; 4. Anstee QM et al. *Hepatology* 2019; doi: 10.1002/hep.30842.

- Due to the high prevalence of MAFLD and its progressive nature, there has been an urgent need to develop reliable noninvasive tests that can accurately predict the presence of advanced disease without the need for liver biopsy.
- These tests can be divided into those that predict the presence of NASH and those that predict the presence of fibrosis.

- With the development of new reliable methods to quantify liver steatosis and the rapid pace for drug discovery of new therapeutic agents to treat NASH and fibrosis ,
- it is anticipated that screening for MAFLD in high risk populations will become the standard of care in the near future.
- This will lead to the identification of a larger number of subjects with MAFLD to be targeted by intensive lifestyle modifications and new drugs.

- It is important for the clinician to realize that neither liver enzymes nor currently used imaging studies can accurately predict the presence of NASH

Biomarkers of MAFLD

- . Biomarkers of Hepatocyte Apoptosis
- Serum concentration of CK18 fragments as a noninvasive marker of the presence of NASH has been extensively validated in multiple studies [1]
- It has been recognized as the most promising single noninvasive test for this purpose by the AASLD guidelines for the diagnosis and management of NAFLD [2]

- 1- Musso G, et al Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver
- disease severity. Ann Med. 2011;43(8):617-49.

- 2. Chalasani N, et al. 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. Hepatology. 2012;55(6):2005-23.

- However, it should be noted that this assay is not commercially EASLLY
- and that there is no well-established CK18 fragment cutoff value for identifying NASH because each study utilized a study-specific cutoff value.

Predictive Models of NASH

- Predictive models that combine routinely assessed clinical variables with laboratory tests and different biomarkers have been developed to predict the presence of NASH.

Examples of predictive models

- That include the combination of clinical and laboratory data include ,

the HAIR score [Hypertension, Aspartate aminotransferase (ALT), Insulin Resistance] [1]

the NASH predictive index or NPI which includes age, female gender, body mass index (BMI), homeostatic model assessment (HOMA) of insulin resistance,and log [aspartate aminotransferase (AST) x ALT] [2].

1. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001;121(1):91-100. PubMed PMID: 11438497.

2. Zein CO, Edmison JM, Schluchter M, Feldstein AE, Zein NN, McCullough A. A NASH Predictive Index (NPI) for use in patients with nonalcoholic fatty liver disease [abstract]. Hepatology. 2007;46(4):747A.

- The accuracy of these models for predicting the presence of NASH is promising (AUROC of 0.87 to 0.90), but they lack external validation

Non-radiological tests

- Non-radiological tests can be divided into simple bedside models using combination of clinical variables [1] and more complex models that use serum markers of fibrosis such as the enhanced liver fibrosis (ELF) test [2].
- Imaging studies are based on the idea of measuring liver stiffness to assess for the presence of liver fibrosis.

- 1. Ratziu V, et al. Liver fibrosis in overweight patients. Gastroenterology. 2000;118(6):1117-23.
- 2. Guha IN, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology. 2008;47(2):455-60.

Simple Scores

- use information from standard liver tests and patient data…(1)

- **The AST-to-ALT ratio (AAR)**
- NFS (NAFLD fibrosis score)…(2)
- FIB-4 (Fibrosis-4)…(2)
- APRI (Aspartate aminotransferase/ platelet ratio index)…(3)

- 1. EASL. J Hepatol 2015;63:237–264; 2. Alkhouri N et al. Gastroenterol Hepatol (NY) 2012;8(10): 661–668; 3. Atay K et al. Biomedical Research 2017;28(2):565–570

The AST-to-ALT ratio (AAR)

- **The AST-to-ALT ratio (AAR) is the simplest predictive model for fibrosis.**

- **ALT is typically higher than AST in MAFLD; however, having an AAR > 1 is**
- **suggestive of the presence of advanced fibrosis.**

- **AAR has a good negative predictive value to rule out advanced fibrosis [1]**

- **1- McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265-9**.

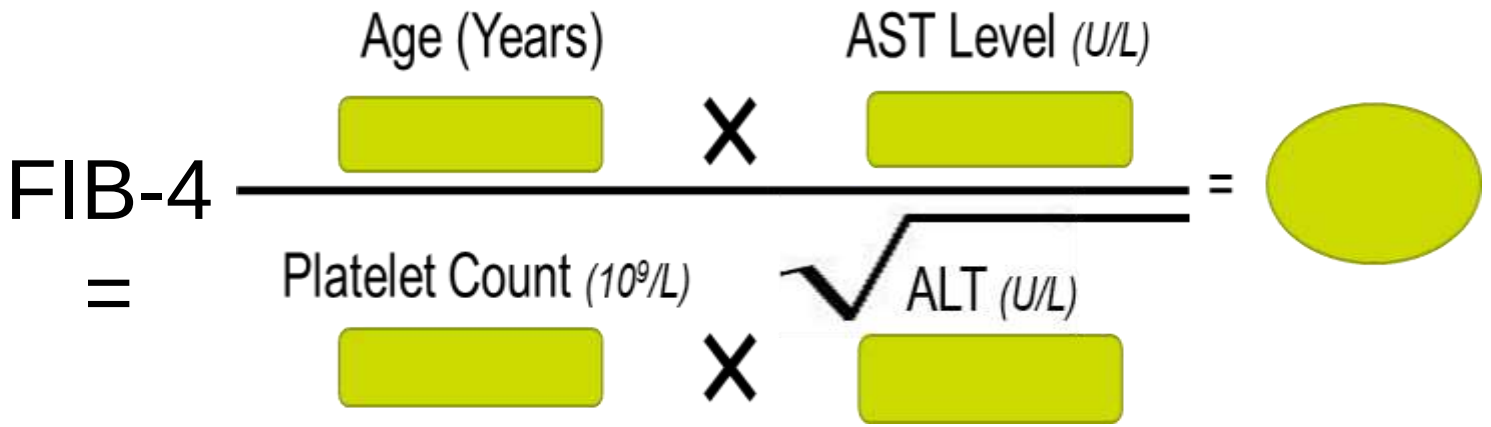
NAFLD fibrosis score

- **Perhaps the most validated score to date is the NAFLD fibrosis score (NFS) which was developed by Angulo et al in a large cohort of patients with NAFLD confirmed by biopsy to predict advanced fibrosis [1].**
- **NFS includes age, impaired fasting glucose/ diabetes, BMI, platelets, albumin and AST-to-ALT ratio with two cut-off values: < - 1.455 to predict the absence of advanced fibrosis (F0- F2) and > 0.675 to predict the presence of advanced fibrosis (F3-F4).**

- **1- Angulo P, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-54.**

Fibrosis 4 (FIB-4) can be easily calculated in office with a simple blood test and online calculators[1]

- Based on age, platelet count, alanine aminotransferase (ALT) level and aspartate aminotransferase (AST) level[2]
- Simple score that uses readily available patient data



Calculator available at:
https://www.mdcalc.com

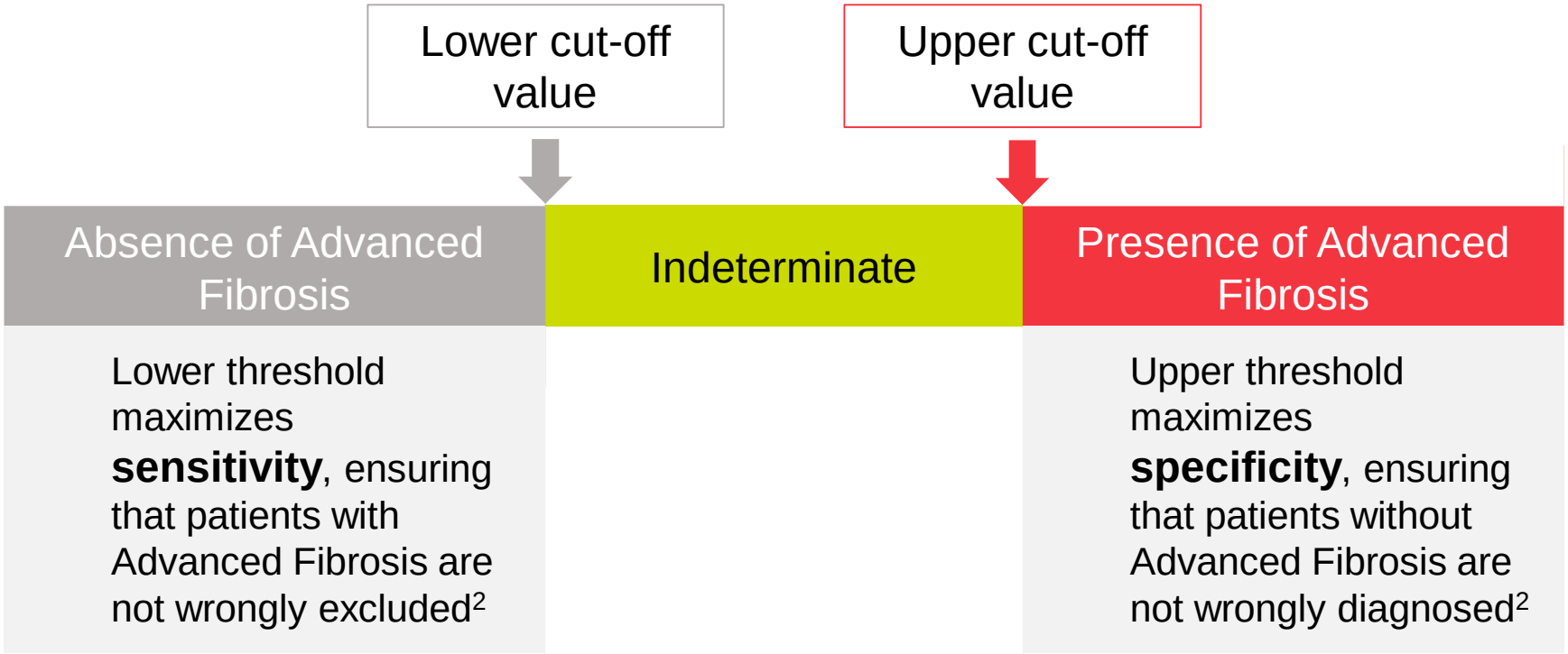
Permission to use MDCalc logo and FIB-4 URL has been kindly granted by Dr Graham Walker, Co-Creator of MDCalc

FIB-4, fibrosis-4; URL, Uniform Resource Locator

1. Fibrosis-4 calculator. Available at: https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. (Accessed September 2019); 2. Alkhouri N et al. *Gastroenterol Hepatol* (NY) 2012;8(10): 661–668.

What makes a good NIT?

- A good NIT is both **sensitive and specific** in determining the presence or absence of Advanced Fibrosis[1]



*The AUROC (Area Under the Receiver Operating Characteristic curve) gives an average performance of a model (NIT) along all sensitivity thresholds. The higher the AUROC (or the closer to 1.0 or similar) the better the model is at distinguishing between patients with disease and no disease[1]

AUROC, area under the receiver operating characteristic curve; NIT, non-invasive test

1. Bewick V et al. *Crit Care* 2004;8(6):508–512; 2. Anstee QM et al. *Hepatology* 2019; doi: 10.1002/hep.30842.

Complex Predictive Models for Fibrosis

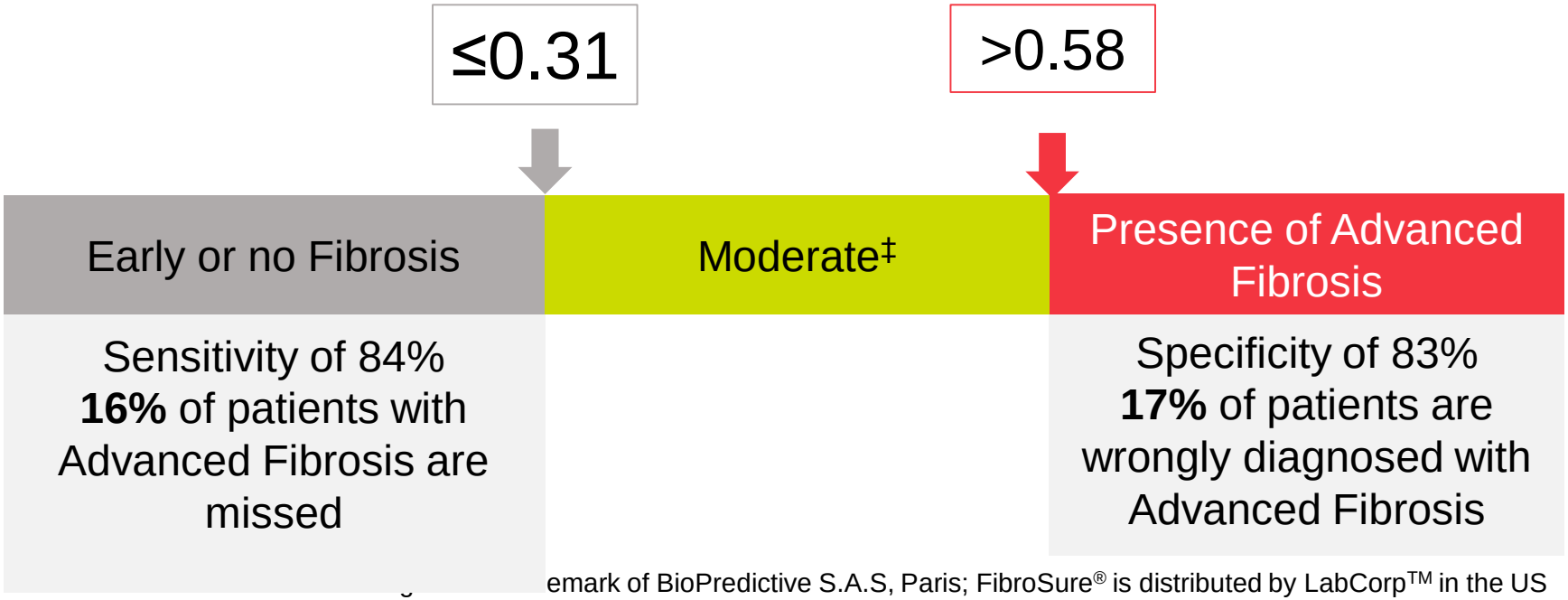
- The European Liver Fibrosis (ELF)

- The FibroTest

(FibroTest®) can determine the presence of Advanced Fibrosis

- Proprietary serum test that combines five biomarkers: haptoglobin, α2-macroglobulin, apolipoprotein A1, total bilirubin and gamma glutamyl-transferase*[1]

FibroTest® cut-off scores and accuracy for measuring Advanced Fibrosis†[2,3]



emark of BioPredictive S.A.S, Paris; FibroSure® is distributed by LabCorp™ in the US

*False positives can arise from haemolysis, Gilbert syndrome, cholestasis and inflammation due to increased levels of α2-macroglobulin and haptoglobin[4]
†In patients with hepatitis C
‡Moderate, F1–F2 and F2–bridging fibrosis with few septa[3]
AUROC, area under the receiver operating curve; SE, standard error

1. Alkhouri N et al. *Gastroenterol Hepatol* (NY) 2012;8(10): 661–668; 2. Poynard T et al. *Comp Hepatol* 2004;3:8; 3. LabCorp NASH FibroSure sample report. Available at: https://files.labcorp.com/testmenu/550140.pdf (Accessed October 2019); 4. Lucero C and Brown RS. *Gastroenterol Hepatol* 2016;12(1):33–40.

Imaging for steatosis

Imaging for steatosis

Includes many E.g. Ultrasound,Fibroscan,CAP, MRI,extra .

Summary

- Accurate noninvasive diagnosis of NASH and advanced fibrosis within the spectrum of NAFLD is of utmost importance .
- Recent advances in serology-based predictive models and imaging studies now allow clinicians to diagnose the stage of steatosis and fibrosis in patients with MAFLD.

Summary

- We envision a future where liver biopsy becomes obsolete for the purpose of determining the severity of MAFLD and clinicians can rely solely on noninvasive tests to determine disease progression and response to novel therapeutic options.

THANK YOU