NAFLD and NASH
The next *Tsunami* in liver disease
Are we ready?

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Case presentation

• 68 yo man with HTN, presents for evaluation of mass lesion in liver
  – discovered incidentally while undergoing CT chest
  ➔ Dedicated liver CT ordered
• 4 cm mass right lobe of the liver.
• Enlarged hypoechoic liver
• and normal spleen
CT Scan results

Arterial phase – hyper-enhancement

Portal Venous phase
“Wash out “

RED flags for HCC in appropriate clinical setting
• History
  – Retired office worker
  – **No known RF for HCV, HBV**
  – **ETOH socially < 1 drink daily**
    – No history of tobacco or other drugs
  No FH of cancer
• Medical problems included **HTN, HLP, pre -DM,**
  – *Voluntary weight loss 30 pounds – 12 months*
• Medications – Lisinopril and HCTZ
• PE: BP138/84, P 68, O2 sat 98%, 104.8 kg, BMI 28.5
  – No stigmata of liver disease
  – Heart –soft SEM and lungs – normal BS bilaterally
  – Abdomen: soft, obese, liver enlarged 2 cm down in RUQ--no appreciable spleen.
  – LE no edema
Laboratory work up

- **Basic**
  - ALT 50, AST 62,
  - Alk phos 158
  - Albumin 4.0,
  - INR 1.0
  - CBC normal -plt 181,000

Hepatitis serologies
- HBsAg -
- HBcAb –
- HBsAb+
- Anti HCV Ab –

- **Ferritin 501(elevated)**
- SI /TIBC = 24%
- ANA negative
- Ceruloplasmin -normal.
- Tumor markers all negative
  - CEA= 1.0,
  - AFP= 12.3,
  - CA19-9 = 6
Biopsy: of the lesion and the surrounding liver

- Biopsy of the mass lesion
  - HEPATOCELLULAR CARCINOMA, WELL TO MODERATELY DIFFERENTIATED

- Uninvolved Liver biopsy
  - LIVER, CT-GUIDED BIOPSY:
    - CIRRHOSIS WITH MILD CHRONIC HEPATITIS,
    - MACROVESICULAR STEATOSIS
      » Iron stains – negative
      » PAS diastase – negative
      » Copper - negative
Hepatocellular Carcinoma in NASH

NASH: Second leading cause of HCC in US

- 26% of HCC due to NASH
  - This number is increasing yearly.

“hidden cause of hepatocellular Carcinoma”

Many undiagnosed, can be seen without cirrhosis
  - 48% of 87 with NAFLD assoc HCC in NE UK were NOT cirrhotic

- HCC in cryptogenic cirrhosis
  - Many with RF for NASH, suspect “burnt out NASH”

* Younossi Z EASL 2015
** Christopher Paul Day EASL April 26, 2013
NAFLD and NASH
Objectives

• Discuss the prevalence of NAFLD in the world
• Discuss the natural history of the NAFLD and NASH
• Discuss the pathogenesis of the NAFLD and NASH.
• Discuss methods of differentiating NAFLD and NASH.
• Discuss clinical presentation of NAFLD
• Discuss current management and treatment options
Prevalence of NAFLD

• Most commonly diagnosed cause of chronic liver disease in Europe and US.

• Prevalence:
  – 30% in US*
    • 10% of children in US
  – 6-35% worldwide***
  – Even up to 35% in older populations****

* Younossi ZM Clin Gastro Hep 2011;9:524 -30
** NIDDK website
*** Vernon G et al Alim pHarmaco Ther 2011; 34: 274-85
**** Koehler EM J Hepatol 2012; 57; 1305-11
NASH Fastest growing cause of cirrhosis

• Number of transplants performed for NASH increasing

• At two major transplant centers
  – Mayo 1% in 2001 ->10% in 2009
  – UCLA 2% in 2002 ->25% currently
  – Slated to surpass HCV as leading cause for liver transplant in 2020

**UCLA and
*Mayo Clinic data
FATTY LIVER DISEASE: History

• Late 1800’s
  – Association between fatty liver and cirrhosis
    – First recognized - Pathologist’s observation

• 1970’s - Problem after Jejunoileal bypass

• 1980 - “NonAlcoholic SteatoHepatitis” Dr. J Ludwig
  • Steatohepatitis in the absence of significant alcohol consumption (currently thought to be):
    – 20 g/day in females
    – 30 g/day in males
  • And in the absence of known secondary clinical conditions
Steatosis and Steatohepatitis: known secondary causes

- **Drugs and Toxins**
  - Corticosteroids
  - Methotrexate
  - amiodarone
  - Tamoxifen
  - nifedipine

- **Viral Hepatitis**
  - HCV

- **Other**
  - Wilson’s disease,
  - bacterial overgrowth, cachexia,
  - sepsis, IBD

- **Nutritional Disorders**
  - Obesity
  - J-I bypass
  - TPN
  - Malnutrition

- **Metabolic disorders**
  - Galactosemia, tyrosenemia

- **Inherited disorders of lipoprotein metabolism**
  - Lypodystrophy
  - Abetalipoproteinemia

- **Genetic defects**
  - *PPARGC1a*
  - *PNPLA3*
**Spectrum of disease**

**NAFLD**

1. More than 5% fat in liver
2. No inflammation or fibrosis
3. Benign / usually not progressive
4. 10 – 20% of Americans

**NAFL**

- 1. More than 5% fat in liver
- 2. No inflammation or fibrosis
- 3. Benign / usually not progressive
- 4. 10 – 20% of Americans

**NASH**

1. Fatty liver with inflammation +/- fibrosis
2. At risk for progression to cirrhosis and Liver Cancer
3. 2-5% of Americans

The diagram illustrates the spectrum of disease, showing the relationship between NAFLD, NAFL, and NASH.
NAFLD

- Risk factors
  - Obesity*
  - Metabolic syndrome
  - Type II diabetes*
  - Triglycerides
  - HTN
  - Low HDL cholesterol
  - Age
  - ? gender
Association Between NASH, Type 2 Diabetes, and Hypertension in the Severely Obese

- Neither Diabetes nor HT (n = 57): 7%
- Hypertension Alone (n = 29): 31%
- Diabetes Alone (n = 8): 62%
- Both Diabetes and HT (n = 11): 75%

* BMI > 30
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Obesity trends in USA
60% of US adults are overweight
OVERWEIGHT & OBESITY IN CENTRAL AMERICA

Surveys from 1999-2009
Data from WHO global database
Copyright © 2012-2015 Obesity HQ
NAFLD: Prevalence in Children and Adolescents

- Australian study*
  - 1170 adolescents
    - Ultrasound diagnosis

- Prevalence of NAFLD = 12.8%

- Strong association with adiposity

- 36 children with NASH
  - (<12 yo)
  - “Abn LFTs” or “Abn US

- 30/36 obese”
  - 24 underwent biopsy
    - 17/24 fibrosis
    - 1/24 cirrhosis

*Koehler et al J Hepatology 2012

Childhood obesity on the rise

• Over 42 million obese children <5 years old

Close to 31 million of these are living in developing countries.
Overweight and obese children
  --likely to stay obese into adulthood
  --more likely to develop diabetes
and cardiovascular diseases
at a younger age

“One of the most serious global public health challenges of the 21st century.”

WHO Global database - 2013
The NAFLD Tsunami
NASH can rapidly progress to cirrhosis -- 15% over 5 years
NASH -> Increased Mortality

NASH is associated with

- Increased all cause mortality
- Increased mortality from liver disease (2.8% vs 0.2%) *
- Increased mortality from cardiovascular disease (15.5% vs 7.5% )*

“steatosis” – usually benign
- no difference in mortality
  – 129 NAFLD pts followed up 13.7 years

*P=0.04 for both

Ekstedt M et al HEPATOLOGY 2006;44:865-873.
What determines progression from NAFLD -> NASH?

NORMAL LIVER

1st HIT
- Insulin resistance
- Fat accumulation in liver

STEATOSIS

2nd HIT
- Oxidative stress,
- Lipid peroxidation

Stellate cells activated

Environmental factors
- Genetic factors

INFLAMMATION & FIBROSIS
NAFLD -> NASH

• Suggested dietary factors that may contribute
  – Total saturated fats
    • Fructose
• The liver gut axis is important
  – role of microbiomes
• Genetic factors
  – PNPLA3
  – Other
• Obstructive Sleep apnea
  Night time hypoxemia

Zhu et al Hepatology 2013
NAFLD - Presentation

• NAFLD
  – Common diagnosis in patients with “incidental abnormal LFTs”
    • 26% of those presenting to primary care physicians*
      – 60 -70 % of those presenting to specialists

• However, most with NAFLD
  • Normal liver function tests.**

*Armstrong et al J Hepatology 2012
**Wong et al 2013
NAFLD -> Signs and symptoms

- Most are asymptomatic 50-100%
- Right upper quadrant pain 30%
- Fatigue, weakness, malaise 30%

- Physical examination
  - Normal 20 – 30%
  - Large liver up to 80%
  - Signs of portal hypertension <10%

- And some with NAFLD present with HCC
NAFLD -> Laboratory Abnormalities

• Liver enzymes
  – ALT > AST *
    • 2-3 x normal

• Alkaline Phosphatase
  – Normal or < 2x normal.

• Ferritin may be elevated
  • up to 5x normal

In patients with cirrhosis there may be reversal of the ALT/AST ratio
Optional

- US:
- Ultrasound “hyperechoic” liver
- diffuse fatty infiltration.
NAFLD -- diagnosis

Fatty infiltration results in a decrease in attenuation (Houndsfield units) <40 HU consistent with fatty infiltration

- sensitivity 75-80% (increases with increasing risk factors)
- IV contrast not needed for this determination
- allows evaluation of the contour of the liver (ie nodularity consistent with cirrhosis)
Who to evaluate?

- High index of suspicion
  - in obese patients with metabolic syndrome
  - Persistently unexplained abnormal AST, ALT or Alk phos
  - Persistently unexplained hepatomegaly
  - Abnormal hepatic imaging
    - suggestive of NAFLD
- Exclude other causes of liver disease
  - Especially viral hepatitis and alcohol
    - Women >20 gms /d
    - Men >30 gms /d
- Others………. 
NAFLD: what we need to know??

- Is it NAFL or NASH?
- If NASH,
  - *How much fibrosis?*
- Biopsy is still “gold standard”
  - Invasive
    - Up to 1% incidence of bleeding
    - Possibility of death
NASH HISTOLOGY

NASH: H and E stain, steatosis, swollen hepatocytes, inflammation, bridging fibrosis

NASH: Trichrome stain: pericellular fibrosis and bridging fibrosis

Cirrhosis: wide fibrous bands and nodularity
Stages of fibrosis
Non Invasive markers of fibrosis

• Clinical
  • signs of portal hypertension

• and laboratory data
  – ALT, AST, platelets
  – INR, albumin

• Serum tests
  – APRI
  – FIB-4
  – NAFLD fibrosis score

• Shear wave elastography
Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
FIB-4 = \frac{\text{Age (years)}}{\sqrt{\text{ALT (U/L)}}} \times \text{AST Level (U/L)} \times \text{Platelet Count (10^9/L)}
\]

< 1.45 => no advanced fibrosis
> 3.25 => cirrhosis

APRI: AST to Platelet Ratio

$$\text{APRI} = \frac{\text{AST level} \ (/ \ \text{ULN})}{\text{Platelet count} \ (10^9 / \text{L})} \times 100$$

Example

$$2.0 = \frac{60 \ / \ 40}{100} \times 100$$

- $1.5 - 2.0 \Rightarrow \text{cirrhosis}$
- $< 0.5 \text{ no adv fibrosis}$

Wai CT et al. Hepatology 2003; 38: 518 - 26
NAFLD Fibrosis Score

<table>
<thead>
<tr>
<th>NAFLD SCORE VALUE</th>
<th>High degree of accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; -1.455</td>
<td>No advanced fibrosis</td>
</tr>
<tr>
<td>&gt; 0.676</td>
<td>Advanced fibrosis</td>
</tr>
</tbody>
</table>

- The regression formula for prediction of severity of fibrosis:
  - -1.675
  - + 0.037 x age (yrs)
  - + 0.094 x BMI (kg/m²)
  - + 1.13 IFG / Diabetes (yes=1, no = 0)
  - + 0.99 x AST/ALT ratio
  - - 0.013 (x plt x10(9)/L)
  - - 0.66 x albumin (g/l)

http://www.nafldscore.com/

Angula et al Hepatology 2007; 45 : 846-53
Liver Fibrosis in NASH: Fibroscan with XL probe vs liver biopsy

Fig. 1. Box plots showing the interquartile range (box), median (thick line), range (thin lines) and outliers (circles) of the liver stiffness. A steady stepwise increase of the elasticity was observed with increasing severity of hepatic fibrosis ($p<0.0001$ by Kruskal–Wallis test).
Non invasive markers of Fibrosis in NASH

Table 4. AUC, accuracy, sensitivity, specificity, predictive values, likelihood ratios of baseline liver histology, HVPG and non-invasive fibrosis biomarkers to predict clinical outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Fibrosis stage</th>
<th>HVPG</th>
<th>APRI</th>
<th>FIB-4</th>
<th>NAFLD fibrosis score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC±SE (95% CI)</strong></td>
<td>0.85±0.04 (0.76–0.93)</td>
<td>0.81±0.06 (0.70–0.91)</td>
<td>0.89±0.03 (0.82–0.96)</td>
<td>0.89±0.03 (0.83–0.95)</td>
<td>0.79±0.06 (0.69–0.91)</td>
</tr>
<tr>
<td><strong>Accuracy (%)</strong></td>
<td>75.9</td>
<td>86.1</td>
<td>86</td>
<td>86</td>
<td>84.1</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>81.3</td>
<td>62.5</td>
<td>50</td>
<td>56.3</td>
<td>50</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>75</td>
<td>90.2</td>
<td>92.3</td>
<td>91.2</td>
<td>90.1</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>36.1</td>
<td>52.6</td>
<td>50</td>
<td>52.9</td>
<td>47</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>95.8</td>
<td>93.3</td>
<td>92.3</td>
<td>92.2</td>
<td>91.1</td>
</tr>
<tr>
<td><strong>LR+</strong></td>
<td>3.25</td>
<td>6.4</td>
<td>6.5</td>
<td>6.4</td>
<td>5.06</td>
</tr>
<tr>
<td><strong>LR-</strong></td>
<td>0.25</td>
<td>0.42</td>
<td>0.54</td>
<td>0.48</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Legend: HVPG, hepatic venous pressure gradient; APRI, AST-to-Platelet Ratio; NAFLD, nonalcoholic fatty liver; AUC, area under the curve; SE, standard error; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio. Accuracy, sensitivity, specificity, PPV, NPV and LR are computed based on the cut-off values adopted in the multivariate analysis: histologic fibrosis F3-F4, HVPG>10, APRI≥1.5, FIB-4>3.25, NAFLD fibrosis score>0.676.

doi:10.1371/journal.pone.0128774.t004

We still need clinically useful validated NASH fibrosis markers with PPV >90% so we know

- who to screen for HCC
- Who needs treatment
Treatment
NASH Treatment:

• Therapies directed at obesity / metabolic syndrome

• #1--Life style changes
  – Weight loss and exercise
    • Improves steatosis and inflammation
      – Weight loss 7-9%* necessary
      – Life style intervention >> education alone
    • ongoing motivation
      – Diet, exercise and behavioral modification

PromratK, et al Hepatology 2010;51(1) 121
NASH Treatment

- Bariatric surgery*

- 21 studies
  - 18 improved steatosis
  - 11 decreased inflammation
  - 6 improved fibrosis
  - 4 worse fibrosis

*AASLD “Insufficient evidence to recommend as primary treatment for NASH”

Chavez-Tapia NC et al Cochrane Database systemic review 2010
Treatment: Insulin sensitizers / GLP-1 agonists

– Metformin
  – No evidence for benefit in NASH
  • But emerging evidence of anti – cancer effect
    – 62% decrease in HCC in diabetics on metformin*

– GLP1 agonists – liraglutide**
  • Decreased ALT and steatosis
    – associated with weight loss

*Chen HP et al. Gut 2013 ; 62; 606-615
**Yuiciero E et al Hepatology 2015; 45: 269-78
Treatment - statins

- Statins
  - Definitely safe
  - Dramatic decrease in HCC in pts with DM II on statins
    - OR 0.63 (0.5 – 0.8)*
  - Less severe NASH in dyslipidemics on statins
  - Even improved LFTs in some cases

* El Serag et al Gastro 2009; 136: 1601-8
** Basaranoglu M J Hepatol 1999; 31(2)384
What about coffee?

- Coffee
  - Less fibrosis associated with increased coffee caffeine consumption
    - Less fibrosis associated with >7 cups of coffee per week

Molloy JW et al Hepatology 2012; 55: 429-36
PIVENS Trial

Pioglitazone, Vitamin E or placebo for NASH?

– Largest trial so far
  • 247 adults with NASH
– RCT for 96 weeks
  • Vitamin E 800 u daily vs
  • Pioglitazone 30 mg daily vs
  • Placebo
– Liver biopsy at entry and exit
– Primary outcome was improvement in histology

Sanyal AJ et al. NEJM 2010, 362: 1675-85
### PIVENS Trial

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E</th>
<th>Pioglitazone *</th>
<th>placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement Steatohepatitis</td>
<td>43%</td>
<td></td>
<td>19%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>34%</td>
<td></td>
<td>19%</td>
<td>0.04</td>
</tr>
<tr>
<td>Improvement Histology</td>
<td>52%</td>
<td></td>
<td>23%</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>47%</td>
<td></td>
<td>23%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**No difference in fibrosis score**

*Pioglitazone associated with weight gain 4.7 kg over course of study

Sanyal AJ et al. NEJM 2010, 362: 1675-85
What about empiric treatment with vitamin E?

• Some will recommend it, but ....
  – 50% will not respond to vitamin E
    • LFTs not reliable way to assess response
  – Vita E associated with
    • Increased all cause CV death
    • Increased risk Hemorrhagic Stroke
    • ?? Effect on Prostate cancer
  – Long term safety needs to be determined
Obeticholic acid

- Semi synthetic bile acid analog
  - (6 alpha – chenodeoxycholic acid)
- Potent activator of Farnesoid X receptor
  - Reduces liver fat
    - Decreases Hepatic TG
  - Increases insulin sensitivity
  - Decreases markers of inflammation
FLINT trial*

• Obeticholic Acid
  – 25 mg OCA daily vs placebo
    – RCT multicenter, phase IIb
  – 72 weeks of treatment
  – 283 adults
  – Liver biopsy at beginning and end of trial
    • NAFLD Activity score ≥4
  – Primary endpoint – histologic improvement
    • No worsening in fibrosis and improved NAS ≥2

* Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Neuschwander-Teri et al Lancet 2015 march 14-20 pg 956-65
### FLINT trial: Effects of Obeticholic acid on histology

<table>
<thead>
<tr>
<th></th>
<th>OCA 25 mg daily</th>
<th>placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>46%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis improvement</td>
<td>35%</td>
<td>19%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hepatocellular ballooning</td>
<td>46%</td>
<td>31%</td>
<td>0.03</td>
</tr>
<tr>
<td>Lobular steatosis</td>
<td>61</td>
<td>38</td>
<td>0.001</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td>53</td>
<td>35</td>
<td>0.007</td>
</tr>
<tr>
<td>NASH resolution</td>
<td>22%</td>
<td>13%</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Improved histology, NAS decrease ≥ 2, No increase in fibrosis

Neuschwander-Teri et al Lancet 2015 March 14-20 pg 956-65
FLINT TRIAL
safety and tolerability

• Adverse events
  – *Pruritis*
    • higher in treatment group
      – 23% vs 6%
    • Moderate
    • Only one persons discontinued the medication because of pruritis
  – No difference in other AEs

Neuschwander-Teri et al Lancet 2015 march 14-20 pg 956-65
Other possibilities …..

- Lipid-lowering medications
  - Clofibrate
    - Known to decrease TG in alcohol-fed rats
    - Trial -- no change in steatosis or fibrosis
  - Gemfibrozil
    - Short trial of 600 mg/d - Decrease in transaminases; no histology reported--Independent of entry TG level

- Ursodeoxycholic acid
  - One randomized placebo-controlled trial – 126 pt - No difference in fibrosis, or inflammation

- ? LOXL2 Inhibitor
  - Anti fibrotic- inhibits cross-linking collagen--Clinical trial ongoing
Management Algorithm for NAFLD

Persistently elevated LFTs

- Yes
  - Proceed with work up and rx

- No
  - Rule out other causes of liver disease
    - Yes
      - Consider biopsy
        - cirrhosis
        - Surveillance for HCC
    - No
      - Consider alternate diagnosis
        - Diet, exercise, no ETOH, rx
        - HTN, DM, HLP.
        - Follow labs – AST, ALT, AP, Bili, plt, INR, NAFLD score
          - NAFLD score < -1.455, APRI < 0.5, Fib-4 < 1.45
            - Reassure
            - Continue diet, exercise

Obese and Metabolic syndrome

- No
  - Probably NAFLD
    - Diet, exercise, no ETOH, rx
    - HTN, DM, HLP.
    - Follow labs – AST, ALT, AP, Bili, plt, INR, NAFLD score
      - NAFLD score < -1.455, APRI < 0.5, Fib-4 < 1.45
        - Reassure
        - Continue diet, exercise
Summary:

1. NAFLD is increasing in prevalence all over the world
   - This is true in children and adolescents and elderly
2. Obese patients with DM and metabolic syndrome are high risk for NASH
3. The incidence of liver failure and hepatocellular carcinoma in patients with NASH is increasing
   - HCC can occur in cirrhosis and non-cirrhotic NASH
   - Patients with cirrhosis and advanced fibrosis need to be screened for HCC
4. NASH contributes directly to cardiovascular and liver related morbidity and mortality
5. Current non invasive methods of disease staging can help identify those patients at each end of the spectrum.
Summary treatment:
1. Weight loss and exercise are first line treatment
   – Lifestyle advice should be emphasized for all
   – Motivation will be key
2. In patients with NASH and Diabetes
   – Suggest Metformin and TZD
     • Metformin especially for its anti cancer effects
3. Low threshold for statin
   • Decreased incidence of cancer also
4. For those with NASH only
   – vitamin E is an option for therapy
   – Obeticholic acid may be option in near future
   – *Newer treatments are in evolution or in clinical trials*
Dessert for the person with cirrhosis

• **Potent anti-oxidants**
  – Vitamin C
    • Increased NO which has been associated with improved liver function
  – Dark chocolate
    • Decreased post prandial elevation of portal pressure
  – Coffee
    • Decreased progression of fibrosis

Freedman ND et al Hepatology 2009
Hernandez-Guerra M et al Hepatology 2006
Gottardi et al EASL April 15 2010
<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoff for Sensitivity and Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
<th>Positive Likelihood Ratio (Range)</th>
<th>Negative Likelihood Ratio (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Range)†</td>
<td>Samples, n§</td>
<td>Median (Range)†</td>
<td>Samples, n§</td>
<td>Median (Range)†</td>
<td>Samples, n§</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt;140 to &lt;155 × 10^9 cells/L</td>
<td>0.78 (0.41 to 0.93)</td>
<td>9</td>
<td>0.87 (0.84 to 0.94)</td>
<td>9</td>
<td>0.89 (0.64 to 0.99)</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Varied</td>
<td>Not calculated</td>
<td>–</td>
<td>Not calculated</td>
<td>–</td>
<td>0.90 (0.80 to 0.97)</td>
</tr>
<tr>
<td>Age-platelet index</td>
<td>≥6.0</td>
<td>0.67 (0.43 to 0.80)</td>
<td>5</td>
<td>0.87 (0.81 to 0.93)</td>
<td>3</td>
<td>0.86 (0.64 to 0.91)</td>
</tr>
<tr>
<td>APRI</td>
<td>&gt;1.0 or ≥1.0</td>
<td>0.77 (0.33 to 1.0)</td>
<td>19</td>
<td>0.75 (0.30 to 0.87)</td>
<td>19</td>
<td>0.84 (0.54 to 0.97)</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 or ≥2.0</td>
<td>0.48 (0.17 to 0.76)</td>
<td>18</td>
<td>0.94 (0.65 to 0.99)</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>AST–ALT ratio</td>
<td>&gt;1.0</td>
<td>0.36 (0.12 to 0.78)</td>
<td>17</td>
<td>0.92 (0.59 to 1.0)</td>
<td>17</td>
<td>0.72 (0.52 to 0.91)</td>
</tr>
<tr>
<td>Cirrhosis discrimin score (Bonacini index)</td>
<td>&gt;2.0 or &gt;3.0</td>
<td>0.85 and 1.0</td>
<td>2</td>
<td>0.58 and 0.22</td>
<td>2</td>
<td>0.74 (0.61 to 0.91)</td>
</tr>
<tr>
<td></td>
<td>&gt;7.0</td>
<td>0.17 (0.15 to 0.34)</td>
<td>3</td>
<td>1.0 (0.75 to 1.0)</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>ELF or simplified ELF index</td>
<td>Varied</td>
<td>Not calculated</td>
<td>–</td>
<td>Not calculated</td>
<td>–</td>
<td>0.88 (0.78 to 0.91)</td>
</tr>
<tr>
<td>FIB-4</td>
<td>&gt;1.45</td>
<td>0.90</td>
<td>1</td>
<td>0.58</td>
<td>1</td>
<td>0.87 (0.83 to 0.92)</td>
</tr>
<tr>
<td></td>
<td>&gt;3.25</td>
<td>0.55</td>
<td>1</td>
<td>0.92</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>FibroIndex</td>
<td>&gt;1.82 or &gt;1.90</td>
<td>0.70 and 0.91</td>
<td>2</td>
<td>0.91 and 0.78</td>
<td>2</td>
<td>0.86 (0.78 to 0.92)</td>
</tr>
<tr>
<td>Fibrometer</td>
<td>Varied</td>
<td>Not calculated</td>
<td>–</td>
<td>Not calculated</td>
<td>–</td>
<td>0.91 (0.89 to 0.94)</td>
</tr>
<tr>
<td>FibroTest</td>
<td>&gt;0.56 or &gt;0.66</td>
<td>0.85 and 0.82</td>
<td>2</td>
<td>0.74 and 0.77</td>
<td>2</td>
<td>0.86 (0.71 to 0.92)</td>
</tr>
<tr>
<td></td>
<td>&gt;0.73, &gt;0.75, or &gt;0.862</td>
<td>0.56 (0.30 to 1.0)</td>
<td>7</td>
<td>0.81 (0.24 to 0.96)</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Forns index</td>
<td>&gt;4.2</td>
<td>0.98</td>
<td>1</td>
<td>0.27</td>
<td>1</td>
<td>0.87 (0.85 to 0.91)</td>
</tr>
<tr>
<td></td>
<td>&gt;6.9</td>
<td>0.67</td>
<td>1</td>
<td>0.91</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>GUCCI</td>
<td>&gt;1.0 to &gt;1.56</td>
<td>0.67 (0.54 to 0.80)</td>
<td>5</td>
<td>0.86 (0.78 to 0.89)</td>
<td>5</td>
<td>0.82 (0.78 to 0.86)</td>
</tr>
<tr>
<td>Hepascore</td>
<td>&gt;0.801 to ≥0.84</td>
<td>0.72 (0.71 to 1.0)</td>
<td>6</td>
<td>0.86 (0.81 to 0.97)</td>
<td>6</td>
<td>0.89 (0.88 to 0.94)</td>
</tr>
<tr>
<td>Lok index</td>
<td>≥0.2 or &gt;0.26</td>
<td>0.90 (0.67 to 1.0)</td>
<td>6</td>
<td>0.50 (0.30 to 0.82)</td>
<td>6</td>
<td>0.80 (0.61 to 0.91)</td>
</tr>
<tr>
<td></td>
<td>≥0.5 or &gt;0.6</td>
<td>0.53 (0.40 to 0.79)</td>
<td>7</td>
<td>0.88 (0.60 to 0.95)</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Pohl index</td>
<td>Positive</td>
<td>0.30 (0.26 to 0.40)</td>
<td>4</td>
<td>0.98 (0.90 to 0.99)</td>
<td>4</td>
<td>0.65 (0.64 to 0.66)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; APRI = AST–platelet ratio index; AST = aspartate aminotransferase; AUROC = area under the receiver-operating characteristic curve; ELF = enhanced liver fibrosis; GUCCI = Göteborg University Cirrhosis Index; METAVIR = Meta-analysis of Histologic Data in Viral Hepatitis.

* Defined as METAVIR stage F4, Ishak stages 3 to 6, or equivalent.
† Ratios based on median sensitivity and specificity at the specified cutoff; ranges based on values from individual studies.
‡ Not calculated for groups of <3 studies (results from individual studies provided).
§ Some studies reported results for >1 population sample.
‖ Excludes 1 study with positive likelihood ratio of infinity due to specificity of 1.
¶ Positive likelihood ratio of infinity in 2 studies due to specificity of 1.