Maximizing Diagnostic Value & Efficiency for Abnormal LFTs in the Primary Care Setting

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Disclosures

No conflicts of interest to disclose
Learning Objectives

At the completion of today’s talk, physicians will:

1. Recognize high value practices in evaluating and referring patients with abnormal liver enzymes

2. Identify essential components of the diagnostic evaluation of abnormal liver enzymes

3. Apply high value principles to complex patients requiring co-management by liver specialists
ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD\textsuperscript{1}, Stanley M. Cohen, MD, FACG, FAASLD\textsuperscript{2} and Joseph K. Lim, MD, FACG, FAASLD\textsuperscript{3}
ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD¹, Stanley M. Cohen, MD, FACG, FAASLD² and Joseph K. Lim, MD, FACG, FAASLD³

Alcoholic liver disease
NAFLD/NASH
Autoimmune hepatitis
Hepatitis B virus
Hepatitis C virus
Hemochromatosis
Primary biliary cholangitis
Primary sclerosing cholangitis
Wilson’s disease

https://www.aasld.org/publications/practice-guidelines

"A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/l for males and 19 to 25 IU/l for females, and levels above this should be assessed by physicians"

"Clinicians may rely on local lab ULN ranges for alkaline phosphatase and bilirubin"
Critical to characterize pattern...

Abnormal LFT 101

Hepatocellular

AST/ALT

Mixed

Cholestatic

Alk Phos

Hyperbilirubinemia

Bilirubin

Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
Critical to characterize pattern...

Abnormal LFT 101

\[
R = \frac{\frac{\text{ALT}}{\text{ALT ULN}}}{\frac{\text{AP}}{\text{AP ULN}}}
\]

- **Hepatocellular**
  - \(\frac{\text{AST}}{\text{ALT}}\)
  - \(R > 5\)

- **Cholestatic**
  - \(\frac{\text{Alk Phos}}{\text{AP ULN}}\)
  - \(R < 2\)

- **Mixed**
  - \(R = 2 - 5\)

- **Hyperbilirubinemia**
  - Bilirubin

Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
HEPATOCELLULAR INJURY PATTERN
Case #1

A 45-year old woman presents to your clinic for her annual exam. Her PMH is notable for hypothyroidism and obesity (BMI 31). Her only medication is levothyroxine. Routine labs reveal the following:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgA1c</td>
<td>5.1</td>
</tr>
<tr>
<td>TSH</td>
<td>1.98</td>
</tr>
<tr>
<td>Ca</td>
<td>8.6</td>
</tr>
<tr>
<td>AST</td>
<td>79</td>
</tr>
<tr>
<td>ALT</td>
<td>67</td>
</tr>
<tr>
<td>TB</td>
<td>0.5</td>
</tr>
<tr>
<td>AP</td>
<td>116</td>
</tr>
<tr>
<td>Alb</td>
<td>4.2</td>
</tr>
<tr>
<td>TP</td>
<td>7.9</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>215</td>
</tr>
<tr>
<td>LDL</td>
<td>141</td>
</tr>
<tr>
<td>HDL</td>
<td>59</td>
</tr>
<tr>
<td>TG</td>
<td>132</td>
</tr>
</tbody>
</table>

Abnormal LFT 101

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca 8.6</td>
<td></td>
</tr>
<tr>
<td>AST 79</td>
<td></td>
</tr>
<tr>
<td>ALT 67</td>
<td></td>
</tr>
<tr>
<td>TB 0.5</td>
<td></td>
</tr>
<tr>
<td>AP 116</td>
<td></td>
</tr>
<tr>
<td>Alb 4.2</td>
<td></td>
</tr>
<tr>
<td>TP 7.9</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>215</td>
</tr>
<tr>
<td>LDL 141</td>
<td></td>
</tr>
<tr>
<td>HDL 59</td>
<td></td>
</tr>
<tr>
<td>TG 132</td>
<td></td>
</tr>
</tbody>
</table>
Case #1

What do you hypothesize is the most likely cause of this patient’s abnormal liver enzymes?

A. Alcohol-related liver disease
B. Non-alcoholic steatohepatitis
C. Chronic hepatitis C infection
D. Autoimmune hepatitis
Mild Elevation
2-5x ULN (50-150 IU/ml)

History & Physical Exam
Discontinue hepatotoxic meds & alcohol
Assess for risk factors for NAFLD and viral hepatitis

CBC, CMP, INR
HBsAg, HBcAb, HBsAb, HCV Ab (PCR if +), iron panel
Abdominal Ultrasound

If negative, consider observe and repeat LFT in 3 months
OR further investigation

If persistently elevated:
ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1-antitrypsin phenotype, and additional testing based on history (e.g., celiac disease, tick-borne illness)
If no diagnosis, consider liver biopsy

Adapted from Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
Mild Elevation
5-15x ULN (150-450 IU/ml)

History & Physical Exam
Discontinue hepatotoxic meds & alcohol
Assess for risk factors for NAFLD and viral hepatitis

CBC, CMP, INR
HBsAg, HBcAb, HBsAb, HCV Ab (PCR if +), iron panel
Abdominal Ultrasound

If negative, consider observe and repeat LFT in 3 months
OR further investigation

If persistently elevated:
ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1-antitrypsin phenotype,
HSV, CMV, EBV, and additional testing based on history (e.g., celiac disease, etc)
If no diagnosis, consider liver biopsy

Adapted from Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
Severe Elevation >15x ULN OR Massive Elevation >10,000 IU/ml

History & Physical Exam
Discontinue hepatotoxic meds & alcohol

Evaluate for signs of acute liver failure

CBC, CMP, INR, Liver US with dopplers
HAV IgM, HBsAg, HBcAb, HBsAb, HCV Ab, HSV, EBV, CMV
Ceruloplasmin, ANA, ASMA, Anti-LKM, IgG, serum/urine toxicology
Low threshold for N-acetylcysteine if any acetaminophen

If signs of acute liver failure → urgent liver consultation*
*DocLine 720-848-2828

If no diagnosis, consider liver biopsy
Performance metric of diagnostic tests
Non-alcoholic steatohepatitis (NASH) vs Alcohol-related SH (ASH)

NASH
• Prevalence = 1.5-6.5%
• ALT>AST (<10X ULN, 300 IU/ml)
• Metabolic risk factors
• No serologic testing

ASH
• Prevalence = 1.4%
• AST:ALT 2:1 (<10X ULN, 300 IU/ml)
• >40g alcohol/day (drink = 12g)
• Phosphatidylethanol (PETH)
  • Moderate-heavy use past 30d

Histologically indistinguishable!

Chalasani N et al. AASLD NAFLD Guidelines. Hepatology 2018
O’Shea R et al. AASLD ALD Guidelines. Hepatology 2010
Performance metric of diagnostic tests
Hepatitis B virus

• Prevalence (based on endemicity):
  • Low = <2%
  • Intermediate = 2-7%
  • High = >8%

• Progress to chronic infection
  • Vertical = >90%
  • Childhood = 5-25%
  • Adult = <5%

Terrault N et al. AASLD HBV Guidelines. Hepatology 2018
Performance metric of diagnostic tests
Hepatitis B virus

• Serologic testing:
  • HBsAg = acute or chronic infection
  • HBcAb = IgM window period, IgG prior exposure*
  • HBsAb = immune
  • HBeAg = replicating virus
  • HBV DNA = viremic

*Not all patients with detectable **HBV DNA** need antiviral therapy

Some patients with **HBcAb+ and negative DNA** need antiviral therapy

Terrault N et al. AASLD HBV Guidelines. Hepatology 2018
Performance metric of diagnostic tests
Hepatitis C virus

• US Prevalence (1.2% or 3.5 million w chronic HCV):
  • Birth cohort = 5%
  • Hemodialysis = 8%
  • PWID = >60%

• HCV antibody test:
  • 5-32% false-positive rate, associated with LVAD
  • 20% of patients will spontaneous clear virus
  • Takes up to 6 months to seroconvert

Always check HCV RNA PCR if antibody screen positive or concern for acute infection with negative antibody screen

Moorman AC et al. J Clin Vir 2017  
Performance metric of diagnostic tests
Epstein-Barr virus (EBV) and Cytomegalovirus (CMV)

• Prevalence:
  • EBV seroprevalence = 90-95%
  • CMV seroprevalence = 50.4%

• Serologic tests:
  • EBV – EBV DNA, EBV IgM
  • CMV – CMV DNA, CMV IgM, 4-fold increase in IgG

Always check CMV and EBV DNA if evaluating for acute viral hepatitis
Performance metric of diagnostic tests
Hereditary hemochromatosis

Ferritin is secreted by activated hepatic macrophages
Non-specific for hemochromatosis in the setting of liver inflammation
Performance metric of diagnostic tests
Hereditary hemochromatosis

• Prevalence: RARE – 0.2-0.5%
• Subtypes:
  • Type 1 – HFE gene mutation
  • Type 2 – HJV gene mutation
  • Type 3 – TFR2 gene mutation
  • Type 4 – SLC40A1 gene mutation
• Penetrance:
  • Only 10% of C282Y homozygotes develop iron overload

VanWagner L, Green R. Elevated Serum Ferritin. JAMA 2014
Bacon BR et al. AASLD Hemochromatosis Guidelines. Hepatology 2011
Crownover BK et al. Am Fam Physician 2013
Performance metric of diagnostic tests
Hereditary hemochromatosis

• Screening:
  • Transferrin Saturation >45% or Ferritin >ULN
    • NPV of TS <45%, Ferritin <200 = 97% (20% PPV)
    • Ferritin >1000 associated with advanced disease if HH

• Diagnostic test:
  • HFE gene mutation
    • C282Y/C282Y – Tissue iron overload
    • C282Y/H63D or C282Y/S65C – RARELY tissue iron overload
    • C282Y/WT or H63D/WT or S65C/WT – NO Tissue iron overload
    • H63D/H63D or S65C/WT – NO tissue iron overload
  • Hepatic iron quantification (MR or Liver biopsy)

VanWagner L, Green R. Elevated Serum Ferritin. JAMA 2014
Bacon BR et al. AASLD Hemochromatosis Guidelines. Hepatology 2011
Performance metric of diagnostic tests

Wilson’s Disease

• Prevalence: RARE – 0.003% (age <55)
• Screening:
  • Ceruloplasmin <20 mg/dL
  • AP:TB <4 (94% Sens, 96% Spec in acute WD)
• Diagnostic test:
  • Hepatic copper content
  • Serum free and 24h urine copper
  • Keyser-Fleischer rings
  • ATP7B mutation testing

Korman JD. Screening for WD in ALF. Hepatology 2008
Performance metric of diagnostic tests

Alpha-1-Antitrypsin Deficiency

• Prevalence: RARE – <0.003%

• Screening:
  • A1AT level
    • If low, proceed with gene testing
    • If undetectable (null mutation), NO liver disease

• Diagnostic test:
  • SERPINA1 mutation testing
    • PI*ZZ or PI*SZ = clinical liver disease
    • PI*MZ or PI*MM = NO clinical liver disease
  • Liver biopsy – PAS-D granules

Korman JD. Screening for WD in ALF. Hepatology 2008
Performance metric of diagnostic tests

Celiac Disease

• Prevalence = 9% of patients with abnormal LFT
  • 15-55% of patients with Celiac have abnormal LFT

• Diagnostic test:
  • Anti-Tissue Transglutaminase antibody
    • IgA (if IgA is normal)
    • IgG (if IgA is low)
  • Sensitivity 81-100%, Specificity 97-99%

• LFT should normalize on gluten-free diet

Performance metric of diagnostic tests
Structural or thrombotic etiologies

• Cross-sectional imaging has a low diagnostic yield for evaluating hepatocellular injury
  • 18% yield in mild elevations
  • 31% yield in moderate-severe elevations

• If Budd-Chiari is suspected, US should be performed by experienced provider or CT/MRI

Case #1

A 45-year old woman with hypothyroidism, obesity (BMI 31), and AST/ALT 2-5X ULN.

Initial work-up:

Liver US with dopplers – mild hepatic steatosis, otherwise normal

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV IgM</td>
<td>NR</td>
</tr>
<tr>
<td>HBsAg</td>
<td>NR</td>
</tr>
<tr>
<td>HBcAb</td>
<td>NR</td>
</tr>
<tr>
<td>HBsAb</td>
<td>27.1</td>
</tr>
<tr>
<td>HCV Ab</td>
<td>NR</td>
</tr>
<tr>
<td>Iron</td>
<td>45</td>
</tr>
<tr>
<td>% Saturation</td>
<td>32</td>
</tr>
<tr>
<td>Ferritin</td>
<td>55</td>
</tr>
<tr>
<td>AST</td>
<td>123</td>
</tr>
<tr>
<td>ALT</td>
<td>101</td>
</tr>
<tr>
<td>TB</td>
<td>0.8</td>
</tr>
<tr>
<td>AP</td>
<td>102</td>
</tr>
<tr>
<td>Alb</td>
<td>4.1</td>
</tr>
<tr>
<td>TP</td>
<td>8.3</td>
</tr>
</tbody>
</table>
Case #1

A 45-year old woman with hypothyroidism, obesity (BMI 31), and AST/ALT 2-5X ULN.

Follow-up Testing:

- ANA 1:160
- ASMA 1:80
- AMA <1:40
- IgG 2321 (H)
- IgM 132

- IgA 187
- TTG-IgA <4
- Ceruloplasmin 32
- A1AT level 141
- A1AT Pheno MM

Referred to hepatologist, biopsy confirms AIH, started on azathioprine
CHOLESTATIC INJURY PATTERN
Case #2

A 67-year old woman presents to your clinic for evaluation of fatigue. The only other symptom she notes is itching, but attributes this to allergies. She is on vitamin D and calcium for osteopenia but has no other PMH. Her initial labs reveal:

```
6.1 14.1 119
  3.9 22 0.5 87

Ca 8.6
AST 39
ALT 47
TB 0.9
AP 436
Alb 3.4
TP 6.6

HgA1c 5.7
TSH 3.24
Total cholesterol 166
LDL 102, HD 53, TG 107
```
Case #2

What would be the next best diagnostic test to confirm the suspected diagnosis?

A. Anti-nuclear antibody
B. Anti-mitochondrial antibody
C. MRCP
D. Liver biopsy
Elevated Alkaline Phosphatase + Normal total bilirubin and serum transaminases

History & Physical Exam
Check GGT (or AP isoenzymes)

- Elevated
  - Check RUQ US
  - AMA, ANA, ASMA
  - Evaluate hepatotoxic meds

- Normal
  - Evaluate for non-hepatobiliary etiologies

If AP elevated >6 months, liver biopsy

- Abnl US
- +AMA

Liver biopsy if >2X ULN
Observation if 1-2X ULN

MRCP or ERCP if duct dilation on RUQ US

Diagnostic for PBC, Rx ursodiol and assess response

Adapted from Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
Elevated Alkaline Phosphatase + Elevated total bilirubin and/or serum transaminases

History & Physical Exam
Check RUQ Ultrasound

- Normal
- Duct dilation

Check AMA, ANA, ASMA
Evaluate hepatotoxic meds

- Negative
- +AMA

Liver biopsy if >2X ULN
Observation if 1-2X ULN
Diagnostic for PBC, Rx ursodiol and assess response

If AP elevated >6 months, liver biopsy or MRCP

Adapted from Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017
Performance metric of diagnostic tests
Primary Biliary CHOLANGITIS (PBC)

• Prevalence = RARE – 0.03%

• Screening:
  • Elevated alkaline phosphatase on LFT +/- AST/ALT
  • ANA
  • IgM

• Diagnostic test:
  • Anti-mitochondrial antibody (AMA) – Sens 87.3%, Spec 98.7%
  • Liver biopsy
    • Only in AMA Neg, AST/ALT >5X ULN, or ursodiol refractory

Lindor KD et al. AASLD PBC Guidelines. Hepatology 2009
Leung PS et al. Hepatology 1992
Performance metric of diagnostic tests
Primary Sclerosing Cholangitis (PSC)

• Prevalence: RARE – 0.006% (5% of IBD patients)
• Screening test:
  • Liver ultrasound
• Diagnostic test:
  • MRCP
    • Sensitivity 86%, Specificity 94%
  • ERCP (Only for assessment of dominant stricture or intervention)
  • Liver biopsy (Only if small duct PSC suspected)

Chapman R et al. AASLD PSC Guidelines. Hepatology 2010
Dave M et al. Radiology 2010
Case #2

A 67-year old woman with fatigue and pruritus, labs notable for cholestatic predominant pattern of liver injury and thrombocytopenia.

Initial work-up:
Liver US with dopplers w normal bile ducts, nodular liver, splenomegaly

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Test</th>
<th>Result</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV Total Ab</td>
<td>Reactive</td>
<td>ANA</td>
<td>&lt;1:40</td>
<td>AST</td>
<td>32</td>
</tr>
<tr>
<td>HBsAg</td>
<td>NR</td>
<td>ASMA</td>
<td>&lt;1:40</td>
<td>ALT</td>
<td>51</td>
</tr>
<tr>
<td>HBcAb</td>
<td>NR</td>
<td>AMA</td>
<td>1:320</td>
<td>TB</td>
<td>0.8</td>
</tr>
<tr>
<td>HBsAb</td>
<td>&lt;3.1</td>
<td>IgG</td>
<td>1221</td>
<td>AP</td>
<td>298</td>
</tr>
<tr>
<td>HCV Ab</td>
<td>NR</td>
<td>IgM</td>
<td>342 (H)</td>
<td>Alb</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TP</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Diagnosed with PBC, started on ursodiol, transient elastography confirms cirrhosis
HYPERBILIRUBINEMIA PATTERN
Elevated total bilirubin

History & Physical Exam
Review Medications
Assess liver transaminases and alkaline phosphatase

Evaluate for hemolysis
Evaluate for Gilbert’s syndrome

Persistent unexplained elevation

UGT1A1 genotype (Gilbert’s)
Consider Liver biopsy if neg

Conjugated

RUQ US
Evaluate for overt etiologies (e.g., sepsis, TPN, cirrhosis)

Dilated ducts
ERCP or MRCP

Normal ducts
AMA, ANA, ASMA

Unconjugated

If TB remains elevated and unexplained, has upward trend, or is associated with elevated transaminases, consider liver biopsy

Adapted from Kwo PY et al. AJG 2017
Case #3

A 37-year old man presents to your clinic for evaluation of jaundice for 2 weeks. He has no PMH and received a 7 day course of amoxicillin/clavulanic acid 6 weeks ago after being diagnosed with a sinus infection at an urgent care clinic. His initial labs reveal:

\[
\begin{array}{cccc}
8.1 & 17.2 & 391 \\
3.9 & 22 & 0.5 & 87 \\
\end{array}
\]

Ca 8.6

AST  67
ALT  51
TB  23.9
DB  13.2
AP  167
Alb  3.2
TP  6.6

INR 1.0
Case #3

What is the next best step in managing this patient?

A. AMA
B. ERCP
C. Liver biopsy
D. Observation
Drug-induced Liver Injury (DILI) incidence = 0.001-0.0001%
Case #3

Labs normalize over 2 months without need for biopsy
ROLE OF LIVER BIOPSY
Case #4

A 55-year old man with PMH notable for hyperlipidemia, hypertension, and OSA presents to your clinic for follow-up of abnormal liver enzymes. He has had mild elevation in transaminases (2-3x ULN) for the past 2 years. Serologic work-up has been negative. Labs this visit reveal:

\[
\begin{array}{cccc}
8.1 & 17.2 & 391 \\
3.9 & 22 & 0.5 & 87 \\
\end{array}
\]

\[
\begin{array}{cccc}
139 & 99 & 11 & Ca 8.6 \\
\end{array}
\]

\[
\begin{array}{cccc}
AST & 56 \\
ALT & 49 \\
TB & 0.4 \\
AP & 78 \\
Alb & 3.9 \\
TP & 6.6 \\
\end{array}
\]

INR 1.0
Case #4

Which of the following tests is diagnostic of NASH?

A. Elevated transaminases
B. Hepatic steatosis on cross-section imaging
C. Transient elastography
D. Liver biopsy
Value of liver biopsy is diminishing...

• Diagnosis
  • Multiple diseases
  • Unknown etiology
  • Suspected NASH

• Prognosis
  • Fibrosis staging
  • Percent necrosis

• Management
  • Ongoing inflammation
Value of liver biopsy is diminishing...

- **Diagnosis**
  - Multiple diseases
  - Unknown etiology
  - Suspected NASH

- **Prognosis**
  - Fibrosis staging
  - Percent necrosis

- **Management**
  - Ongoing inflammation

Effectively therapy for concurrent diseases that may preclude the need for biopsy

**EXAMPLE:** HCV + suspected NASH; treat HCV and biopsy only if LFT fail to normalize

Value of liver biopsy is diminishing...

• Diagnosis
  • Multiple diseases
  • Unknown etiology
  • Suspected NASH

• Prognosis
  • Fibrosis staging
  • Percent necrosis

• Management
  • Ongoing inflammation

No NASH-specific therapies and have ability to stage fibrosis non-invasively

Only utility of biopsy is enrollment in clinical trials

Value of liver biopsy is diminishing...

- Diagnosis
  - Multiple diseases
  - Unknown etiology
  - Suspected NASH
- Prognosis
  - Fibrosis staging
  - Percent necrosis
- Management
  - Ongoing inflammation


Transient Elastography or Well Validated Biomarkers
Value of liver biopsy is diminishing...

- **Diagnosis**
  - Multiple diseases
  - Unknown etiology
  - Suspected NASH

- **Prognosis**
  - Fibrosis staging
  - Percent necrosis

- **Management**
  - Ongoing inflammation

If no/minimal fibrosis and low likelihood of treatable etiology, utility of biopsy may be limited unless progressive fibrosis.

# Serum Biomarker Performance

* = to detect significant fibrosis, ≥F2 (or F4)

<table>
<thead>
<tr>
<th>Test</th>
<th>AUROC*</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotest®</td>
<td>0.87</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>Fibrospect II®</td>
<td>0.83</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>Enhanced Liver Fibrosis score®</td>
<td>0.78 (0.89)</td>
<td>87</td>
<td>51</td>
</tr>
<tr>
<td>Hepascore®</td>
<td>0.82 (0.89)</td>
<td>63</td>
<td>89</td>
</tr>
<tr>
<td>Fibrometer®</td>
<td>0.89</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>APRI (AST-to-Plt Ratio)</td>
<td>0.80 (0.89)</td>
<td>41-91</td>
<td>47-95</td>
</tr>
<tr>
<td>Fibrosis Probability Index (FPI)</td>
<td>0.77</td>
<td>42-85</td>
<td>48-98</td>
</tr>
<tr>
<td>HALT-C model</td>
<td>0.81</td>
<td>47-88</td>
<td>45-92</td>
</tr>
<tr>
<td>ViraHep-C</td>
<td>0.83</td>
<td>51-90</td>
<td>54-90</td>
</tr>
<tr>
<td><strong>FIB-4</strong></td>
<td><strong>0.85</strong></td>
<td><strong>38-74</strong></td>
<td><strong>81-98</strong></td>
</tr>
<tr>
<td>NAFLD Fibrosis Score (NFS)</td>
<td>0.82</td>
<td>43-77</td>
<td>97</td>
</tr>
</tbody>
</table>

Adapted from EASL-ALEH Clinical Practice Guidelines. J Hep 2015
Serum Biomarker Performance
Equivalent performance to Transient Elastography

* = to detect significant fibrosis, ≥F2 (or F4)

<table>
<thead>
<tr>
<th>Disease/Study</th>
<th>AUROC*</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>0.82 (0.93)</td>
<td>97 (77)</td>
<td>35 (90)</td>
</tr>
<tr>
<td>HBV</td>
<td>0.87 (0.93)</td>
<td>74 (75)</td>
<td>88 (90)</td>
</tr>
<tr>
<td>PBC</td>
<td>0.91 (0.99)</td>
<td>67 (93)</td>
<td>100 (99)</td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>0.91 (0.92)</td>
<td>80 (86)</td>
<td>91 (84)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>0.80 (0.94)</td>
<td>76 (78)</td>
<td>80 (96)</td>
</tr>
</tbody>
</table>

Adapted from EASL-ALEH Clinical Practice Guidelines. J Hep 2015
FIB-4 Score

https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10^9/L)} \times \sqrt{\text{ALT (U/L)}}} = 1.24
\]

<1.45 has 90% NPV to exclude advanced fibrosis (≥F3)
>3.25 is 97% specific for advanced fibrosis
NAFLD Fibrosis Score

http://gihep.com/calculators/hepatology/nafld-fibrosis-score/

\[-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (x109/l)} - 0.66 \times \text{albumin (g/dl)}\]

\[-1.455 = F0-F2\]

\[>0.675 = \text{advanced fibrosis}\]
Case #4

A 55-year old man with PMH notable for hyperlipidemia, hypertension, and OSA, with suspected NASH. A FIB-4 score and NAFLD Fibrosis Score are calculated:

\[
\text{FIB-4} = 1.24 \ (F0-F2) \\
\text{NFS} = -2.88 \ (F0-F2)
\]

Monitor labs q6 months, repeat biomarker scores in 2 years, biopsy if labs rise or fibrosis progression.
Conclusions

• Pattern recognition of LFT abnormalities allows you to focus work-up to highest yield testing

• Guidelines support a step-wise approach for mild elevation in transaminases focusing on highest prevalence diseases (ASH, NASH, viral hepatitis)

• Knowledge of prevalence and screening vs diagnostic tests is critical for high value diagnosis of less common causes of abnormal LFT

• Value of liver biopsy is diminishing with advent of non-invasive tools for fibrosis staging

• Biomarker scores are useful to stage fibrosis and can be helpful tools to triage patients to the appropriate level of care
Thank You!

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