Non-invasive Monitoring of Liver Disease

Hin Hin Ko
Giada Sebastiani
Feb 29, 2016

This program was co-developed with CAG/Merck and was planned to achieve scientific integrity, objectivity, and balance.
Accreditation

This event is an accredited (Section 1) group learning activity as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada (RCPSC). The program was produced under the RCPSC guidelines for the development of co-developed educational activities between the Canadian Association of Gastroenterology (CAG) and Merck Canada Inc.
Dr. Sebastiani: speaker for Merck, Abbvie, Gilead, ViiV; advisory board member for Merck, BMS; she received unrestricted research funding from Merck, ViiV
Learning Objectives

At the end of this session, participants will be able to:

• Recognize the clinical importance of staging fibrosis for management and prognosis in chronic liver diseases

• Identify and describe the different non-invasive modalities to diagnose and monitor liver disease

• Compare and contrast the benefits and limitations of the non-invasive monitoring modalities, such as Fibroscan, Fibrotest, Fib-4 and APRI
### Non-invasive monitoring of liver disease

#### CanMEDS Roles Covered:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>(as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>(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.)</td>
</tr>
</tbody>
</table>
WHY IS IT IMPORTANT TO STAGE LIVER FIBROSIS?
End-Points in Fibrogenic CLDs

- S0
- K/F0

- S1
- K/F1

- S2
- K/F2

- S3-S4
- K/F3

- S5-S6
- K/F4

Indication for Treatment

F: METAVIR
S: ISHAK’s
K: KLEINER

Screening for Oesophageal Varices
Screening for HCC
WHY FIBROSIS STAGE is PIVOTAL in CHRONIC LIVER DISEASES?

• Management
  – definitive indication to antiviral therapy in HCV and HBV and to interventions on metabolic risk factors/vitamin E therapy in NAFLD/NASH when >F2 by METAVIR/Kleiner
  – Screening for HCC and esophageal varices when F4

• Prognosis
  – The more the liver disease is advanced, the less time it takes to develop cirrhosis and end-stage complications
STAGING of FIBROSIS: HOW?

- Liver biopsy (gold standard)
  - Advantages: direct information on fibrosis, inflammation, steatosis, comorbidities
  - Limits: semiquantitative, invasive, costly, prone to sampling errors

- Blood tests (biomarkers)
- Fibroscan (transient elastography)
LIVER BIOPSY IS AN INVASIVE PROCEDURE!

- PAIN
- BLEEDING
- COST
- HOSPITALIZATION
Complications

- HALT-C reported complications of liver biopsy in HCV patients with advanced liver disease
  - 1.1% serious adverse events
  - 0.6% due to bleeding (most common)
    - More common if platelet < 60,000
    - INR > 1.3

- The mean cost in Canada for a complicates liver biopsy requiring hospitalization is $4,579

Interobserver variability –

THE SMALLER THE SAMPLE, 
THE MILDERTHE DISEASE

REFERENCE
SAMPLE

cm 1  

cm 1

Colloredo et al, J Hepatol 2003
THE LENGTH OF THE SAMPLE

High Stage

$p < .001$

Colloredo et al, J Hepatol 2003
## CONSENSUS AMONG PATHOLOGISTS?

<table>
<thead>
<tr>
<th>Author</th>
<th>Length (mm)</th>
<th>Portal tracts (n°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedossa, Hepatology 2003</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>Scheuer, Hepatology 2003</td>
<td>Bigger is better</td>
<td>NA</td>
</tr>
<tr>
<td>Guido, Sem Liv Dis 2004</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>AASLD, position paper on liver biopsy 2008</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>APASL, consensus conference on fibrosis 2009</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>
NON-INVASIVE METHODS
SERUM NON-INVASIVE MARKERS for LIVER FIBROSIS

DIRECT MARKERS
Matrix Components and Enzymes regulating Fibrogenesis / Fibrolysis

INDIRECT MARKERS
Markers of Liver Inflammation / Function

Combination of Direct / Indirect Tests

Procollagen III, Type IV collagen, Hyaluronic acid, YKL-40, Metalloproteinases and their Inhibitors

AST, ALT, γGT, Platelets, Bilirubin, Albumin, Cholesterol, ApoA1, a2-Macroglobulin, Haptoglobin
## Indirect Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Cut-off</th>
<th>AUROC</th>
<th>Classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>0.5 / 1.5</td>
<td>0.69-0.88</td>
<td>51%</td>
</tr>
<tr>
<td>Forns’ index</td>
<td>4.2 / 6.9</td>
<td>0.60-0.86</td>
<td>49%</td>
</tr>
<tr>
<td>Fib-4</td>
<td>1.45 / 3.25</td>
<td>0.82-0.89</td>
<td>72.8%</td>
</tr>
<tr>
<td>AST-to-ALT ratio</td>
<td>1</td>
<td>0.51-0.83</td>
<td>100%</td>
</tr>
</tbody>
</table>

APRI = AST, platelets

Forns’ index = GGT, cholesterol, platelets, age

Fib-4 = platelets, AST, ALT, age

APRI: THE PROTOTYPE OF THE SIMPLE BIOMARKERS FOR LIVER FIBROSIS

APRI=[AST (/ULN) x 100] / Platelet (10⁹/L)

1

Absence of cirrhosis

2

Presence of cirrhosis

50% of Pts

Wai et al, Hepatology 2003
Performance of the Aspartate Aminotransferase-to-Platelet Ratio Index for the Staging of Hepatitis C-Related Fibrosis: An Updated Meta-Analysis

Zhong-Hua Lin, Yong-Ning Xin, Quan-Jiang Dong, Qing Wang, Xiang-Jun Jiang, Shu-Hui Zhan, Ying Sun and Shi-Ying Xuan

- 40 studies included, n=8,739
- APRI can be used in clinical practice as a good tool for the confirmation of severe fibrosis/cirrhosis when other clinical signs and examinations are nondecisive
- It is cheap and simple → reference test to be compared with the others

Although APRI shows less diagnostic accuracy than some other noninvasive methods, it is still the first choice for HCV patients to identify fibrosis in regions with limited healthcare resources
### Direct Biomarkers and Combination Panels

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC for &gt;F2</th>
<th>AUC for F4</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotest® γGT, bilirubin, haptoglobin, ApoA1, α2M</td>
<td>0.74-0.87</td>
<td>0.71-0.87</td>
<td>![Green Light]</td>
</tr>
<tr>
<td>Fibrospect® Hyaluronan, TIMP1, α2M</td>
<td>0.82-0.87</td>
<td>-</td>
<td>![Yellow Light]</td>
</tr>
<tr>
<td>ELF® Hyaluronan, PIIINP, TIMP1</td>
<td>0.80</td>
<td>0.95</td>
<td>![Red Light]</td>
</tr>
<tr>
<td>Fibrometer® Platelets, PT, AST, α2M, hyaluronan, BUN</td>
<td>0.85-0.89</td>
<td>0.91</td>
<td>![Red Light]</td>
</tr>
<tr>
<td>Hepascore® Hyaluronan, bilirubin, γGT, α2M</td>
<td>0.79-0.85</td>
<td>0.95-0.94</td>
<td>![Red Light]</td>
</tr>
</tbody>
</table>

Sebastiani et al, CCLM 2011
In Situ

Liver Injury

Fibrotic Matrix
Activated Stellate Cells

In Serum: FibroTest

Alpha2Macroglobulin
Total Bilirubin
Gamma GT
Apolipoprotein A1
Haptoglobin

Imbert-Bismut et al, Lancet 2001
FIBROTEST IN HEPATITIS C

FibroTest Estimate of fibrosis stage

<table>
<thead>
<tr>
<th>FibroTest</th>
<th>Estimate of fibrosis stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75-1.00</td>
<td>F4</td>
</tr>
<tr>
<td>0.73-0.74</td>
<td>F3-F4</td>
</tr>
<tr>
<td>0.59-0.72</td>
<td>F3</td>
</tr>
<tr>
<td>0.49-0.58</td>
<td>F2</td>
</tr>
<tr>
<td>0.32-0.48</td>
<td>F1-F2</td>
</tr>
<tr>
<td>0.28-0.31</td>
<td>F1</td>
</tr>
<tr>
<td>0.22-0.27</td>
<td>F0-F1</td>
</tr>
<tr>
<td>0.00-0.21</td>
<td>F0</td>
</tr>
</tbody>
</table>

Blood Donors

Imbert-Bismut et al, Lancet 2001
Risk factors for biomarkers
- hemolysis (Fibrotest)
- Gilbert (Fibrotest)
- systemic inflammation (Fibrotest)
- extra-hepatic cholestasis (Fibrotest)
- thrombocytopenia not liver-related (APRI)
Liver stiffness

- Assessed by US (FibroScan®) & more recently by MRI
- Evaluates velocity of propagation of a shock wave within liver tissue (examines a physical parameter of liver tissue which is related to its elasticity)
- Rationale
  - Normal liver is viscous
  - Not favorable to wave propagation
  - Fibrosis increases hardness of tissue
  - Favors more rapid propagation

FibroScan

- Painless
- Rapid (5 min)
- Bedside/Outpatient
- Immediate results (3 - 75 kPa)
- >1500 peer-reviewed studies
Position of probe & explored volume

« The stiffer the liver, the faster the shear wave propagates »

Cylinder of 1 cm wide & 4 cm long
From 25 mm to 65 mm below skin surface
This volume is at least 100 times bigger than a biopsy sample
Results

Stiffness (kPa)
Median value of 10 shots

At least 10 shots
Success rate ≥60%

IQR * (kPa)
Interval around median
Contains 50% of valid shots
≤ 30% of median value
# Accuracy in Hepatitis C

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cut-off for ≥F2</th>
<th>AUC for ≥F2</th>
<th>Cut-off for F4</th>
<th>AUC for F4</th>
<th>N of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degos 2010</td>
<td>5.2</td>
<td>0.75</td>
<td>12.9</td>
<td>0.90</td>
<td>913</td>
</tr>
<tr>
<td>Kettaneh 2007</td>
<td>6.8</td>
<td>0.79</td>
<td>17.6</td>
<td>0.91</td>
<td>935</td>
</tr>
<tr>
<td>Castera 2005</td>
<td>7.1</td>
<td>0.83</td>
<td>12.5</td>
<td>0.95</td>
<td>183</td>
</tr>
<tr>
<td>Sandrin 2003</td>
<td>7.6</td>
<td>0.88</td>
<td>14.4</td>
<td>0.99</td>
<td>106</td>
</tr>
<tr>
<td>Arena 2008</td>
<td>7.8</td>
<td>0.91</td>
<td>14.8</td>
<td>0.98</td>
<td>150</td>
</tr>
<tr>
<td>Ziol 2005</td>
<td>8.7</td>
<td>0.79</td>
<td>14.5</td>
<td>0.97</td>
<td>327</td>
</tr>
<tr>
<td>Cross 2010</td>
<td>8.9</td>
<td>0.89</td>
<td>10.1</td>
<td>0.97</td>
<td>187</td>
</tr>
</tbody>
</table>

Sebastiani & Alberti J Vir Hepat 2012
Correlation between LSM & fibrosis stage?

THE CLINICAL USE OF CUT-OFF

**HEPATITIS B**

7.2 / 8.7

F2

12.5 / 14.5

F4

NASH 10.2 - 17.5 kPa

9.0-11.0

HEPATITIS C

**Fibrosis Stage**

- Chan HLY et al., *J Viral Hepat.* 2009; 16 (1), 36-44.
- Castera et al, *Gastroenterology* 2005
APPLICABILITY of FIBROSCAN in CLINICAL PRACTICE

• RISK FACTORS OF FAILURE → Obesity, Ascites, narrow intercostal spaces

• RISK FACTORS OF POOR QUALITY → N measurements, IQR

• RISK FACTORS OF FALSE POSITIVITY → ALT flares, extra-hepatic cholestasis, hepatic congestion, meal effect
CONTRAINDICATIONS TO FIBROSCAN (as per manufacturer recommendations)

- Pregnancy
- Pacemaker
FIBROSCAN FAILURE

n=2114

Wong et al: 25.5% if BMI > 30,
2.6% if BMI < 30

Reliable results with the XL probe were obtained in 61% of patients in whom the M probe was unreliable

FALSE POSITIVE : ALT FLARES

![Graph: IU/L vs kPa over time (M2, M4, M8, M12)]

FALSE-positive : Cholestasis

- Liver stiffness significantly correlated with bilirubin levels in patients with extra-hepatic cholestasis (r=0.67, p<0.05)

- Liver stiffness reduction following successful bilirubin drainage

\[ \text{Bilirubin (mg/dL) or Liver stiffness (kPa)} \]

\[ \text{Bilirubin (mg/dL)} \quad \text{Liver Stiffness (kPa)} \]

\[ \text{Before intervention} \]

\[ \text{After intervention} \]

False positive TE measurements
cardiac insufficiency: A case study

• Liver biopsy showed:
  – Major sinusoidal dilation, perisinusoidal fibrosis and nodular hepatic regeneration, compatible with cardiac hepatopathy – no cirrhosis
  – Mild necrotic and inflammatory activity (A1F2)

• Upon correction of cardiovascular dysfunction, liver biopsy showed:
  – No visible sinusoidal dilation and nodular hepatic regeneration
  – Mild necrotic and inflammatory activity (A1F1)

Effect of ingestion of a meal on the elasticity of the liver in patients with cirrhosis and portal hypertension

4 hours fasting required!!

Berzigotti et al, PLoSONE 2013
## Serum biomarkers vs TE

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Serum Biomarkers        | • Good reproducibility  
                         | • High applicability (90%)  
                         | • Well validated  
                         | • Can be performed in the outpatient clinic               | • Non-specific of liver liver  
                         | • Unable to discriminate between intermediate stages of fibrosis  
                         | • Cost and limit availability                                      |
| Transient elastography  | • User-friendly  
                         | • Good reproducibility  
                         | • High performed for cirrhosis (AUROC>0.90)  
                         | • Most widely used and validated technique                 | • requires a dedicated machine  
                         | • Applicability lower than serum markes (obesity, ascites)  
                         | • Falsely elevated results in setting of acute hepatitis, liver congestion, food intake |
EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

Hepatitis C (HIV coinfection) Treatment-naive

Combine Two non-invasive tests: TE + serum biomarker

Discordance
- Repeat exams and search for explanations
- Discordance
  - Liver biopsy if results influence management

Concordance
- No severe fibrosis-cirrhosis
- Severe fibrosis-cirrhosis
  - No liver biopsy antiviral treatment screening for varices screening for HCC
  - No liver biopsy follow-up or antiviral treatment (if extra-hepatic manifestations)

Terms and Conditions
Liver fibrosis stage is the single most important factor impacting on the prognosis of patients with liver disease.
Monitoring of disease progression complications of cirrhosis

711 patients with liver diseases
F3F4 144

OV grade II / III
Ascites
HCC
Bleeding
Noninvasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients With Chronic Hepatitis C

JULIEN VERGNIOL,* JULIETTE FOUCHER,*‡ ERIC TERREBONNE,* PIERRE-HENRI BERNARD,‡ BRIGITTE LE BAIL§,‖ WASSIL MERROUCHE,* PATRICE COUZIGOU,* and VICTOR DE LEDINGHEN*‖

1457 patients with chronic hepatitis C
Outcomes defined as death
Or need for liver transplantation

Simple Noninvasive Systems Predict Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

PAUL ANGULO,¹ ELISABETTA BUGIANESI,² EINAR S. BJÖRNSSON,³ PHUNCHAI CHARATCHAROENWITTHAYA,⁴ PETER R. MILLS,⁵ FRANCISCO BARRERA,⁶ SVANHILDUR HAFLIDADOTTIR,³ CHRISTOPHER P. DAY,⁷,§ and JACOB GEORGE⁶,§

320 with biopsy-proven NAFLD

Canadian Digestive Diseases Week 2016

GASTROENTEROLOGY 2013; ■:1-8
SUMMARY AND CLINICAL DIRECTIONS

- Liver fibrosis staging is pivotal for management of patients with chronic liver diseases
- Non-invasive tools for liver fibrosis diagnosis have high diagnostic and prognostic accuracy
- They can be used for risk stratification, prioritization for interventions such as antiviral/metabolic therapy, surveillance for HCC/varices and liver transplantation
- An optimal way to stage liver fibrosis in clinical practice is to combine two non-invasive tests and reserve liver biopsy to discordant cases or where an overlapping etiology is suspected
Thank you
Evaluation and Certificate of Attendance

Please visit the CAG website at http://www.cag-acg.org/ to complete the session evaluation and to receive your certificate of attendance.

Or better yet, download the CDDW™ App from the CAG website!