New York State
HCV Provider Webinar Series

Overview of Fibrosis Staging, Child’s Pugh, MELD Scores
Objectives

• Discuss the rationale to assess fibrosis in HCV infected patients
• Review prevalence of advanced fibrosis in US HCV infected patients
• Discuss techniques to assess fibrosis
  – Lab testing
  – Non-invasive imaging
  – Liver Biopsy
• Review Childs-Pugh Score and MELD related to predicting patient outcomes
• Analyze treatment response rates in HCV infected patients with cirrhosis
What is the Prevalence of Cirrhosis in US Patients Infected with HCV?

- An estimated 370,500 Americans with cirrhosis and 347,800 with advanced fibrosis (2007-2012)
  - Nearly one in five US adults with HCV infection have cirrhosis
- During 2007-2012
  - Cirrhosis was associated with
    - Increasing age (OR: 1.04)
    - Diabetes (OR: 2.33)
    - Obesity (OR: 2.96)
  - Advanced fibrosis was associated with
    - Increasing age (OR: 1.08)
    - Diabetes (OR: 3.37)

Rates of Fibrosis are Increasing as the Patient Population Ages

Prevalence of Cirrhosis or Advanced Fibrosis Among US Residents With HCV

Rationale to Assess Fibrosis in Patients with HCV

• Presence of cirrhosis:
  – Triggers routine cirrhosis care
    • Evaluation for esophageal and/or gastric varices
    • Surveillance for hepatocellular carcinoma
  – May effect rate of SVR
  – May affect treatment duration
  – May require use of ribavirin

• Does not require liver biopsy!
  – Non invasive tests
    – APRI/Fib-4/elastography/MRI/Fibroscan/Fibrosure

• All patients with liver disease should undergo an assessment of fibrosis
Compensated vs. Decompensated Cirrhosis

- Patients with **Decompensated Cirrhosis** have portal hypertension and/or one or more of the following complications
  - Ascites (Hepato-renal Syndrome, hepatic hydrothorax)
  - Hepatic Encephalopathy
  - Varices (esophageal, gastric)
  - Portal Hypertensive Gastropathy
  - Hepatocellular Carcinoma
Poor Survival Rates in Patients with Decompensated Cirrhosis

Patients with HCC at time zero were excluded

Tools to Assess: Fibrosis/Cirrhosis/Portal Hypertension

- **Physical Exam**
  - Nodular liver, splenomegaly
  - Presence of spider angiomata, palmar erythema, gynecomastia, caput medusa
    - Caveat: findings are specific for cirrhosis and/or portal HTN, but are not sensitive

- **Radiology**
  - Helpful if studies reveal:
    - Nodular liver
    - Enlarged caudate lobe
    - Enlarged Spleen
    - Reversal of flow in portal vein or the presence of portal vein collaterals
Lab Tests to Assess Fibrosis

• Liver Enzymes (AST/ALT) may be normal or elevated in patients with advanced fibrosis or cirrhosis
• Normal ALT does not mean “inactive HCV”
• Liver Tests including bilirubin, albumin, INR may be normal until patients have advanced cirrhosis
• Liver tests that suggest advanced fibrosis/cirrhosis include:
  – Platelet count < 150 K
  – AST:ALT ration > 1
  – Elevated globulins
Noninvasive Methods to Assess Hepatic Fibrosis

Serum Tests
- AST to platelet ratio (APRI)
- FIB4: Age, AST, ALT, platelets
- Fibrosure (Fibrotest in Europe)
- Other lab techniques:
  - ELF
  - Forns
  - Hepascore

Measurement of liver stiffness
- Transient elastography
- Acoustic radiation force impulse imaging
- Magnetic resonance elastography

## APRI and FIB-4 Calculation

**APRI** =

\[
\frac{\text{AST/ULN}}{\text{Platelets (10}^9/\text{L}) \times 100}
\]

- *If < 1.0*, correctly identifies patients **without** cirrhosis in 93% of cases (**high NPV**)
- *> 1.0* specificity 72% for F4 fibrosis

**FIB-4** =

\[
\frac{\text{Age (years) \times AST U/L}}{\text{Platelets (10}^9/\text{L}) \times \text{ALT U/L}}
\]

- *If < 1.9*, correctly identifies patients **without** cirrhosis in 92% of cases (**high NPV**)
- *< 1.45* = F0-F1 fibrosis
- *> 3.25* = F3-F4 fibrosis

Fibrosure

- Fibrosure (available in US)
- Fibrotest (available in Europe)
- Components of these tests:
  - Age
  - Gender
  - serum y-glutamyl transferase (GGT)
  - total bilirubin (TB)
  - a-2 macroglobulin
  - Haptoglobin
  - apolipoprotein A1
  - alanine aminotransferase (ALT) if also assessing inflammation

<table>
<thead>
<tr>
<th>Result</th>
<th>METAVIR</th>
</tr>
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<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>
Benefits of Non-Invasive Fibrosis Testing

- Good for mild vs advanced fibrosis
- Cheap, noninvasive
- Best validated in hepatitis C

- Significant overlap across stages
- May be influenced by other factors
- Caveat: may not be so sensitive for F2-F3

Leroy, J Hepatol. 2007;775-82.
How Accurate are Non-Invasive Tests of Fibrosis?

Systematic Review of 172 Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet &lt; 140</td>
<td>0.56</td>
<td>0.91</td>
<td>0.71</td>
</tr>
<tr>
<td>APRI &gt; 0.5</td>
<td>0.81</td>
<td>0.55</td>
<td>0.71</td>
</tr>
<tr>
<td>APRI &gt; 1.5</td>
<td>0.37</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>AST/ALT &gt; 1</td>
<td>0.35</td>
<td>0.77</td>
<td>0.59</td>
</tr>
<tr>
<td>ELF &gt; 8.75</td>
<td>0.85</td>
<td>0.70</td>
<td>0.81</td>
</tr>
<tr>
<td>FIB-4 &gt; 1.45</td>
<td>0.64</td>
<td>0.68</td>
<td>0.74</td>
</tr>
<tr>
<td>FIB-4 &gt; 3.25</td>
<td>0.50</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Fibrotest &gt; 0.1</td>
<td>0.92</td>
<td>0.38</td>
<td>0.79</td>
</tr>
<tr>
<td>Fibrotest &gt; 0.7</td>
<td>0.22</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Forns &gt; 4.2</td>
<td>0.88</td>
<td>0.52</td>
<td>0.76</td>
</tr>
<tr>
<td>Forns &gt; 6.9</td>
<td>0.36</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Hepascore &gt; 0.46</td>
<td>0.60</td>
<td>0.79</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Liver Stiffness by Transient Elastography

- Ultrasound-based technique
- Determines liver “stiffness”
- Correlates well with fibrosis
- No ceiling, ie, increases with worsening cirrhosis → predicts complications (eg, varices)
- Simple to use – minimal training
- Other methods in development
  - Shear wave elastography

Caveats: Fails in up to 20% (especially in obese patients) – improved with XL probe.
Influenced by inflammation – it falsely elevates measurements
Liver Stiffness by Transient Elastography

- Very good for minimal fibrosis (F0-2) vs cirrhosis (F4)
- Lots of overlap in the middle
- Becoming more widely available

Correlation Between Liver Stiffness (kPA) & Fibrosis Stage

F1: Patient with F1 liver fibrosis, exhibiting mean elasticity values of 6.8 kPa. Standard deviation of 0.7 kPa demonstrate tissue homogeneity.
Liver biopsy was required to assess fibrosis infrequently and only when Fibroscan and Fibrotest results did not concur.
Fibroscan and Fibrosure Results Predict Overall 5 Year Patient Survival in HCV Infection

- Measures stiffness of liver by introducing shear waves via MRI.
- Older MRI units can be "upgraded" to perform MRE.
- Software Upgrade allows assessment of Liver Stiffness.
Liver Biopsy

Pros
- Gold standard for intermediate fibrosis stages
- Assess activity (inflammation)
- Other diagnoses
  - Fatty liver
  - Autoimmune

Cons
- Invasive
- Complications*
- Sampling error
- Expensive
- Requires experts
  - Biopsy
  - Pathology

*Complications include:
Pain, bleeding, hollow viscus perforation – mortality in 0.005%
Indications for Liver Biopsy

Documented HCV infection (HCV RNA positive) plus:

- Inconclusive, unreliable, or unavailable non-invasive tests
- Diagnostic uncertainty
  - Concern about concomitant condition
    - Fatty liver
    - Alcohol
    - Autoimmune hepatitis
    - Drug-induced liver injury
    - Other i.e., unexplained lab results (AMA, ANA, Ceruloplasmin, Alpha 1 AT, Ferritin)
Options for Liver Biopsy in Patients Unable to Undergo Transcutaneous Liver Biopsy

- In patients who are coagulopathic and/or have significant ascites, transcutaneous liver biopsy may not be possible.
- Transjugular liver biopsy with hepatic and portal pressure measurements can provide liver tissue and assess if the patient has portal HTN.
  - Portal pressure – free hepatic vein pressure > 10 mmHg = clinically significant portal HTN, when ascites, varices, encephalopathy may occur.
# Liver Biopsy Appearance and Categories of Fibrosis

<table>
<thead>
<tr>
<th>General Appearance</th>
<th>Categorical Assignment</th>
<th>Categorical description (Ishak Stage)</th>
<th>Fibrosis Measurement (Ishak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishak²</td>
<td>Knodell¹,³</td>
<td>METAVIR⁴</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>F0</td>
<td>No fibrosis (normal)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>F1</td>
<td>Fibrous expansion of some portal areas ± short fibrous septa</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>F1</td>
<td>Fibrous expansion of most portal areas ± short fibrous septa</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>F2</td>
<td>Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>F3</td>
<td>Fibrous expansion of portal areas with marked bridging (P-P) as well as portal-to-central (P-C)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>F3</td>
<td>Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>F4</td>
<td>Cirrhosis, probable or definite</td>
</tr>
</tbody>
</table>

Methods to Predict Outcomes in Patients with Liver Disease
Child-Turcotte-Pugh (CTP) Calculator

This calculator is used for the classification of the severity of cirrhosis

<table>
<thead>
<tr>
<th>Points*</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1-2 (or precipitant-induced)</td>
<td>Grade 3-4 (or chronic)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild/Moderate (diuretic-responsive)</td>
<td>Severe (diuretic-refractory)</td>
</tr>
<tr>
<td>Billirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT (sec prolonged) or INR</td>
<td>&lt;4 &lt;1.7</td>
<td>4-6 1.7-2.3</td>
<td>&gt;6 &gt;2.3</td>
</tr>
</tbody>
</table>

*CTP score is obtained by adding the score for each parameter.

CTP class:
A= 5-6 points
B= 7-9 points
C= 10-15 points

https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality

CTP has better prognostic utility in predicting outcomes after Surgical Procedures
**Surgical Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=64)</th>
<th>Morbidity (n=28)</th>
<th>Mortality at 3 mo (n=7)</th>
<th>Mortality at 1 y (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP class A</td>
<td>23</td>
<td>7 (30)</td>
<td>0 (0)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>CTP class B</td>
<td>31</td>
<td>13 (42)</td>
<td>3 (10)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>CTP class C</td>
<td>10</td>
<td>8 (80)</td>
<td>4 (40)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Emergent</td>
<td>10</td>
<td>9 (90)</td>
<td>2 (20)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Ascites</td>
<td>34</td>
<td>21 (62)</td>
<td>6 (18)</td>
<td>14 (41)</td>
</tr>
</tbody>
</table>

Number of patients (percentages) shown.
Ascites=ascites present on physical examination and/or imaging studies; emergent=emergency surgery performed; morbidity=postoperative complications or death within 30 days.

MELD and MELD Sodium are useful to predict survival in patients with cirrhosis.

MELD Score

<table>
<thead>
<tr>
<th>INR</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>2.2</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.8</td>
</tr>
</tbody>
</table>

☐ Dialysis two or more times in the past week?

Calc

MELD Score 22.7

\[
MELD_i = \text{round}^{1}[ 0.378 \times \log_e(\text{bilirubin}) + (1.120 \times \log_e(\text{INR})) + (0.957 \times \log_e(\text{creatinine})) + 0.643 ] \times 10
\]

\(^1\) rounded to the tenth decimal place.

http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model
MELD and Prognosis

As MELD rises, survival decreases

MELD and Prognosis

As MELD rises, survival decreases

MELD and Prognosis

As MELD rises, survival decreases

P<0.0001

As MELD rises, survival decreases.

As MELD rises, survival decreases.

MELD and Prognosis

As MELD rises, survival decreases.

MELD PREDICTS PRE- & POST-TRANSPLANT OUTCOMES

Any MELD > 15 predicted better outcomes if patient was transplanted vs remaining on waiting list.
MELD PREDICTS PRE- & POST-TRANSPLANT OUTCOMES

<table>
<thead>
<tr>
<th>MELD</th>
<th>6-11</th>
<th>12-14</th>
<th>15-17</th>
<th>18-20</th>
<th>21-23</th>
<th>24-26</th>
<th>27-29</th>
<th>30-39</th>
<th>≥40</th>
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<tbody>
<tr>
<td>Hazard Ratio</td>
<td>3.64</td>
<td>2.35</td>
<td>1.21</td>
<td>0.62</td>
<td>0.38</td>
<td>0.22</td>
<td>0.18</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td>p-values</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.41</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Mortality risk transplanted vs waitlist

Any MELD > 15 predicted better outcomes
IF PATIENT WAS TRANSPLANTED vs
Remaining on waiting list
At any MELD score > 10, patients with serum Na+ < 136 had higher death rates when compared to patients with normal serum Na+.

As of January 2016, MELD-Na is used by UNOS for organ allocation.
What is the One Year Survival in Patients With and Without Various Manifestations of Portal HTN?
Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities

Patients without portal HTN have low death rates and low rates of developing manifestations of portal HTN. However, as pts develop varices and/or ascites, death rates increase.

Summary

Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)

APRI
Fib-4
Fibrosure
Plat < 150K

Imaging: US, CT, MRI

Elastography (FibroScan, MRE, ARFI, Supersonic etc.)

HVPG

Consider hepatic vein catheterization with Hepatic Vein and Portal Vein Pressure Measurements with Transjugular liver biopsy to Assess for Portal Hypertension

Liver Biopsy: 1:50,000 of liver tissue
Algorithm to Assess Severity of Liver Disease

Complications of cirrhosis (variceal hemorrhage, ascites, encephalopathy)

**OR**

- Plt < 100,000/µl + AST > ALT
- Cirrhotic liver on imaging

Patient has cirrhosis

Screen for Liver Cancer
Assess for Liver Transplantation

HCV-RNA positive

History + physical exam

- CBC
- Liver profile
- Ultrasound

Fibrosis assessment with transient elastography and/or fibrosis serum panel

Reliable/Agree

Disagree, unreliable, unavailable, or diagnostic uncertainty

Manage HCV according to fibrosis stage

Liver Biopsy
Baseline factors significantly associated with all-cause mortality:

- Older age
- GT 3 (2-fold increase in mortality and HCC)
- Higher Ishak fibrosis score
- Diabetes
- Severe alcohol use

530 patients followed for a median of 8.4 years

- SVR patients
- Non-SVR patients

Regression of Advanced Fibrosis or Cirrhosis by FibroScan Post SVR

- Retrospective chart review of SVR12 and prospective FibroScan, biopsy, and/or clinical assessment after SVR12 (n=100)
  - Cirrhosis/F3-F4 (65%/35%)
- Regimens
  - Sofosbuvir-based (45%), telaprevir + PR (29%), PR (16%), clinical trial/other (10%)
- Overall median time to improvement: 2.5 years after SVR
  - Cirrhosis versus F3-F4: 3.0 versus 2.5 years
- Predictor of regression in F3-F4 at baseline: APRI (P<0.05)
- Surrogate marker of improvement of baseline cirrhosis: decrease in ALT (P=0.03)

SVR to HCV Therapy Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

*Ascites, variceal bleeding.
SVR to HCV Therapy Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

Therapy: Interferon and Ribavirin: SVR 33%

*C: Ascites, variceal bleeding.
SVR to HCV Therapy Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

Therapy: Interferon and Ribavirin: SVR 33%

*Ascites, variceal bleeding.
LDV/SOF ± RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-naïve Patients

Non-Cirrhotic

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
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</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>179/180</td>
<td>179/181</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>178/184</td>
<td>181/184</td>
</tr>
<tr>
<td>SVR12 (%)</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

Cirrhotic

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>32/34</td>
<td>31/33</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>34/34</td>
<td>36/36</td>
</tr>
<tr>
<td>SVR12 (%)</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

LDV/SOF ± RBV for 12 vs 24 Weeks: SVR12 in GT 1 Treatment-experienced Patients

Effect of Tx Duration and RBV in Cirrhotic, PI-Experienced, GT1 Pts (LDV/SOF)


Pts with previous IFN, riba, boceprevir, telaprevir, simeprevir, or faldaprevir failure
SVR12 in GT 1b Cirrhotic Patients Treated with PTV/RTV/OMV + DSV + RBV for 12 vs 24 Weeks

- Pooled analysis of Phase 3 trials
- All treated with RBV

Ombitasvir/Paritaprevir/r + Dasabuvir in HCV Genotype 1b With Cirrhosis

- Phase 3, open-label study (n=60)
  - Treatment-naïve (n=27) or pegIFN-experienced (n=33), genotype 1b
  - HCV RNA >1000 IU/mL
  - Compensated cirrhosis (Child-Pugh A), no history of decompensation
  - Creatinine clearance >30 mL/min
- Ombitasvir/paritaprevir/r + dasabuvir for 12 weeks
- All patients achieved SVR12
- Safety
  - No discontinuations due to adverse events
  - No grade 3/4 hemoglobin declines

Ombitasvir/Paritaprevir/r + Dasabuvir in HCV Genotype 1b With Cirrhosis

- Phase 3, open-label study (n=60)
  - Treatment-naïve (n=27) or pegIFN-experienced (n=33), genotype 1b
  - HCV RNA >1000 IU/mL
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- All patients achieved SVR12
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SVR12

Elbasvir and grazoprevir: Efficacy in Treatment-Naive HCV GT1-Infected

SVR Rates for GT1 Subjects Receiving 12 Weeks of Therapy

Overall SVR

- Overall SVR: 95%
- Without Cirrhosis: 94%
- With Compensated Cirrhosis: 97%

SVR by GT1 Subtype

- GT1a: 92%
- GT1b: 98%

SVR by Cirrhosis Status

- Without Cirrhosis: 144/157 (92%)
- With Compensated Cirrhosis: 129/131 (98%)

- Without Cirrhosis: 207/220 (94%)
- With Compensated Cirrhosis: 66/68 (97%)

- <1% (1/288) of subjects experienced on-treatment virologic failure
- 3% (10/288) of subjects relapsed after treatment

Sofosbuvir/Velpatasvir for 12 Weeks in GT 1, 2, 4, 5, 6 HCV-Infected Patients

SVR12 (%)

Total: 99% (618/624)
Non-Cirrhotic: 99% (496/501)
Cirrhotic: 99% (120/121)
Treatment-Naïve: 99% (418/423)
Treatment-Experienced: 99% (200/201)

Summary

• Prevalence of cirrhosis in patients with HCV is increasing
• Assessment of fibrosis is critical in all patients with HCV
  – May affect therapy choice
  – Requires surveillance for varices and liver cancer
• Non-invasive assessment of fibrosis is possible
  – Plat count < 150
  – APRI, Fib-4, Fibrosure
  – Fibroscan, MRE
• Despite the presence of cirrhosis, SVR rates are high in patients who undergo therapy