EVALUATION OF THE NEW CRITERIA IN THE DIAGNOSIS OF CYSTIC FIBROSIS LIVER DISEASE

1Sophia Pouriki, 1Theodoros Alexopoulos, 1Alexandra Alexopoulou, 1Larisa Vasilieva, 2Filia Diamantea, 2Maria Gioka, 2Alexandra Nakou, 1Dimitrios Zampetas, 1Ilianna Mani, 1Spyros P Dourakis

12nd Department of Internal Medicine and Research Laboratory, Medical School, National and Kapodistrian University of Athens, “Hippokration” Hospital, Athens, Greece
2Third Respiratory Medicine Department, “Sismanogleio” General Hospital, Athens, Greece
CYSTIC FIBROSIS LIVER DISEASE (CFLD)-CHARACTERISTICS

- Nonspecific term without a consistent definition
- Several liver disorders
- Wide spectrum of severity and impact on outcome
  - Neonatal cholestasis
  - Elevated aminotransferases
  - Hepatic steatosis
  - Hepatic fibrosis
  - Focal biliary cirrhosis
  - Multilobular cirrhosis with or without portal hypertension

CYSTIC FIBROSIS LIVER DISEASE - EPIDEMIOLOGY

- Affects 30% of patients
- Third cause of death
  1) lung disease
  2) transplantation complications
- 2.5% of overall mortality
In other liver diseases with potential liver involvement, liver biopsy is considered as the gold standard for the diagnosis and staging.

However, liver biopsy has been considered as inconsistent in diagnosis of CFLD, due to patchy pattern of the disease.
DIAGNOSIS

• Hence, a combination of modalities additional to liver histology, including physical examination, biochemical and imaging were utilized in the conventional Debray criteria (DC).

• More recently, noninvasive biomarkers, liver function tests and radiologic imaging have been applied and were included in the New criteria (NC)
More CF patients were diagnosed with liver disease using NC and at earlier times compared to Debray Criteria (P=0.017)

Cystic Fibrosis Liver Disease (CFLD)
METHODS

• Observational prospective study
• Longitudinal data were collected from a cohort of genetically confirmed CF patients [35 ♂ (56.5%)]
• Follow-up 28-36 months
• CFLD was diagnosed by both Debray and New Criteria
## DEBRAY CRITERIA

### Diagnosis of CFLD if two or more categories are present

<table>
<thead>
<tr>
<th>• Physical Examination</th>
<th>Hepatomegaly: &gt;2 cm below the coastal margin on the mid-clavicular line, confirmed by ultrasonography and/or Splenomegaly, confirmed by US</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liver Function Tests</td>
<td>Increase of transaminases and GGT above upper limits at least three consecutive determinations over 12 months after excluding other causes</td>
</tr>
<tr>
<td>• Radiologic Testing</td>
<td>Ultrasonographic evidence of liver involvement or portal hypertension or biliary abnormalities</td>
</tr>
<tr>
<td>• Liver Biopsy</td>
<td>May be indicated</td>
</tr>
</tbody>
</table>

**NEW CRITERIA**

CFLD if there is histologic or radiologic evidence of cirrhosis or DLD or (+) in at least two of the following

<table>
<thead>
<tr>
<th><strong>• Liver Function Tests</strong></th>
<th>At least two persistently abnormal AST, ALT, GGT or ALP over a 2-year period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Radiologic Testing</strong></td>
<td>Evidence of hepatomegaly, splenomegaly, or portal hypertension by imaging</td>
</tr>
<tr>
<td><strong>• VCTE</strong></td>
<td>Abnormal Fibroscan at any time</td>
</tr>
<tr>
<td><strong>• Non Invasive fibrosis biomarker assessment</strong></td>
<td>Persistently abnormal APRI, FIB 4 or AAR</td>
</tr>
</tbody>
</table>

ULTRASOUND TRANSIENT ELASTOGRAPHY
(FIBROSCAN™)

Probe positioning

Probes

50 Hz

2.5 cm

1 cm Ø

4 cm

Explored volume

transient elastography (>6.8 kPa)

Sandrin, Ultrasound Med Biol 2003
METHODS

Radiologic evidence of cirrhosis and diffuse liver disease

Lobulated contour

Diffuse heterogeneity

FIBROSI S-4 (FIB-4) CALCULATOR

$$Fib\ 4 = \frac{Age\ (years) \times AST\ level\ (\frac{U}{L})}{Platelet\ count\ \left(10^9\right) \times \sqrt{ALT\ \frac{U}{L}}}$$

- **Interpretation:**
  - FIB-4 score $< 1.45$ negative predictive value of 90% for advanced fibrosis
  - FIB-4 $> 3.25$ 97% specificity and a positive predictive value of 65% for advanced fibrosis

FIB 4 $> 3.25$
AST TO PLATELET RATIO INDEX (APRI) CALCULATOR

\[ APRI = \frac{\text{AST level (IU/L)}}{\text{AST (upper limit of normal) (IU/L)}} \times \frac{\text{Platelet count (10^9/L)}}{\text{Platelet count (10^9/L)}} \]

Interpretation

- APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis.
- APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.
METHODS- RESULTS

62 patients

33 months follow up

Debray Criteria

16 patients (25.8%) with CFLD

New Criteria

26 patients (41.9%) with CFLD
## PATIENT FEATURES- DEMOGRAPHICS- I

<table>
<thead>
<tr>
<th>Feature</th>
<th>Data by Criteria Debre</th>
<th>Data by New CFLD Criteria</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Subjects</td>
<td>CFLD</td>
<td>No CFLD</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>62</td>
<td>16 (25.8%)</td>
<td>46 (74.2%)</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>35 (56.5)</td>
<td>10 (62.5)</td>
<td>25 (54.3)</td>
</tr>
<tr>
<td>Alive/dead at end of follow-up</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Median age at CF diagnosis, Months (IQR)</td>
<td>6.00 (2.25-33.00)</td>
<td>6.00 (2.00-18.50)</td>
<td>6.00 (2.75-36.00)</td>
</tr>
<tr>
<td>Weight</td>
<td>60 (53-68)</td>
<td>65.5 (52.25-72.50)</td>
<td>60.00 (53.75-65.75)</td>
</tr>
<tr>
<td>Height</td>
<td>(1.63-1.75) 1.69</td>
<td>1.70 (1.65-1.75)</td>
<td>1.68 (1.61-1.75)</td>
</tr>
<tr>
<td>Median age at time of enrollment, years (IQR)</td>
<td>25 (22-31)</td>
<td>25.5 (21.0-29.0)</td>
<td>24.5 (22.00-31.25)</td>
</tr>
</tbody>
</table>
## CYSTIC FIBROSIS FEATURES

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Subjects</th>
<th>Data by Criteria Debre</th>
<th>Data by New CFLD Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CFLD</td>
<td>No CFLD</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>62</td>
<td>16 (25.8%)</td>
<td>46 (74.2%)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ΔF508/ΔF508</td>
<td>21 (33.9)</td>
<td>6 (37.5)</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>• ΔF508/Other</td>
<td>25 (40.3)</td>
<td>6 (37.5)</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>• Other</td>
<td>13 (21.0)</td>
<td>4 (25)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>• Unknown</td>
<td>3 (4.8)</td>
<td>0 (0)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Transplant lungs, n (%)</td>
<td>2 (3.2)</td>
<td>0 (0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Therapy, n (%)</td>
<td>11 (17.7)</td>
<td>5 (31.3)</td>
<td>6 (13)</td>
</tr>
</tbody>
</table>
## LABORATORY TEST RESULTS

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Subjects</th>
<th>Data by Criteria Debre</th>
<th>Data by New CFLD Criteria</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>CFLD</td>
<td></td>
<td>No CFLD</td>
</tr>
<tr>
<td>AST</td>
<td>24.0 (16.5-31.0)</td>
<td>29.50 (23.00-52.25)</td>
<td>22.00 (16.00-27)</td>
<td>0.012</td>
<td>28.5 (21.25-35.75)</td>
</tr>
<tr>
<td>ALT</td>
<td>28.0 (15.5-37.0)</td>
<td>36.5 (18.5-47.0)</td>
<td>26.0 (15.0-32.5)</td>
<td>0.045</td>
<td>26.00 (15.75-44.50)</td>
</tr>
<tr>
<td>g-GT</td>
<td>19 (11-31)</td>
<td>21.50 (19.00-58.50)</td>
<td>16.00 (10.25-26.50)</td>
<td>0.026</td>
<td>27.5 (17.5-51.5)</td>
</tr>
<tr>
<td>ALP</td>
<td>107.5 (81.25-133.75)</td>
<td>131.5 (98.25-175.75)</td>
<td>99.00 (79.25-120.75)</td>
<td>0.022</td>
<td>131.50 (96.75-159.25)</td>
</tr>
<tr>
<td>Total Bil</td>
<td>0.46 (0.30-0.64)</td>
<td>0.48 (0.28-0.63)</td>
<td>0.45 (0.31-0.65)</td>
<td>0.643</td>
<td>0.50 (0.36-0.64)</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.35 (3.90-4.60)</td>
<td>4.40 (3.95-4.60)</td>
<td>4.30 (3.875-4.525)</td>
<td>0.412</td>
<td>4.40 (3.90-4.62)</td>
</tr>
<tr>
<td>INR</td>
<td>1.09 (1.01-1.16)</td>
<td>1.105 (1.032-1.165)</td>
<td>1.09 (1.01-1.115)</td>
<td>0.411</td>
<td>1.115 (1.07-1.17)</td>
</tr>
<tr>
<td>PLT</td>
<td>318 (230.5-398.5)</td>
<td>305.0 (205.0-392.7)</td>
<td>318.0 (234.0-398.5)</td>
<td>0.670</td>
<td>282 (197-376)</td>
</tr>
</tbody>
</table>
## NONINVASIVE MARKERS OF FIBROSIS

<table>
<thead>
<tr>
<th>Feature</th>
<th>All Subjects</th>
<th>Data by Criteria Debre</th>
<th></th>
<th>Data by New CFLD Criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CFLD</td>
<td>No CFLD</td>
<td>CFLD</td>
<td>No CFLD</td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>62</td>
<td>16 (25.8%)</td>
<td>46 (74.2%)</td>
<td>26 (43.5%)</td>
<td>36 (56.5%)</td>
</tr>
<tr>
<td>Median Stiffness (IQR)</td>
<td>5.30 (4.35-6.65)</td>
<td>6.75 (4.50-8.88)</td>
<td>5.10 (4.00-6.13)</td>
<td>0.03</td>
<td>7.4 (5.2-8.8)</td>
</tr>
<tr>
<td>IQR (median IQR)</td>
<td>1.1 (0.7-1.5)</td>
<td>1.00 (0.80-1.80)</td>
<td>0.95 (0.60-1.35)</td>
<td>0.232</td>
<td>1.00 (0.88-1.80)</td>
</tr>
<tr>
<td>AAR</td>
<td>0.84 (0.73-1.18)</td>
<td>0.86 (0.71-1.34)</td>
<td>0.82 (0.74-1.17)</td>
<td>0.885</td>
<td>1.11 (0.72-1.46)</td>
</tr>
<tr>
<td>APRI</td>
<td>0.20 (0.12-0.32)</td>
<td>0.29 (0.16-0.72)</td>
<td>0.18 (0.12-0.28)</td>
<td>0.038</td>
<td>0.27 (0.19-0.43)</td>
</tr>
<tr>
<td>FIB4</td>
<td>0.39 (0.29-0.55)</td>
<td>0.44 (0.34-1.02)</td>
<td>0.37 (0.28-0.50)</td>
<td>0.072</td>
<td>0.54 (0.39-0.87)</td>
</tr>
<tr>
<td>FIBRO (&gt;6.8) N%</td>
<td>14 (22.6%)</td>
<td>8 (50%)</td>
<td>6 (13%)</td>
<td>0.002</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>APRI(&gt;0.50) N%</td>
<td>5 (8.1%)</td>
<td>5 (31.3%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>FIB-4 (&gt;3.25) N%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AAR (&gt;1) N%</td>
<td>23 (37.1%)</td>
<td>7 (43.8%)</td>
<td>16 (34.8%)</td>
<td>0.603</td>
<td>15 (55.6)</td>
</tr>
</tbody>
</table>
NEW CRITERIA

**Without Diffuse Disease**
- No CFLD: 40.8%
- CFLD: 10.2%
- New criteria: 8.1%

**With Diffuse Disease**
- No CFLD: 23%
- CFLD: 30.7%
- New criteria: 23%
The New criteria are able to identify 16.1% more CFLD patients compared to historical ones.
The multiple non invasive biomarkers incorporated in New Criteria may enhance the ability to detect CFLD.
THANK YOU
CRITERIA DEBRAY AND AAR -II

- AAR ≤ 1
- AAR > 1

<table>
<thead>
<tr>
<th>No CFLD by Criteria Debre</th>
<th>CFLD by Criteria Debre</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.0%</td>
<td>37.0%</td>
</tr>
<tr>
<td>29</td>
<td>17</td>
</tr>
</tbody>
</table>

$P = 0.631$
NS

AAR ≤ 1
AAR > 1
CRITERIA DEBRAY AND APRI - I

\[ P = 0.038 \]

\begin{align*}
\text{No CFLD by Criteria Debre} & : 0.18 (0.12-0.28) \\
\text{CFLD by Criteria Debre} & : 0.29 (0.16-0.72)
\end{align*}
CRITERIA DEBRAY AND APRI -II

- APRI ≤ 0.50
- APRI > 0.50

31.3%

68.7%

100%

P < 0.001

46

11

5

No CFLD by Criteria Debre

CFLD by Criteria Debre
NEW CRITERIA AND APRI -II

APRI ≤ 0.50
100%

APRI > 0.50
80.8%
P = 0.006

Count (N, %)

No CFLD by New Criteria
36
19.2%

CFLD by New Criteria
21
5

NEW CRITERIA AND APRI -II

P = 0.006
NEW CRITERIA AND APRI -I

P = 0.002

No CFLD by New Criteria: 0.16 (0.09-0.26)
CFLD by New Criteria: 0.27 (0.19-0.43)
CRITERIA DEBRAY AND AAR -I

P = 0.885

0.82 (0.74-1.17)

0.86 (0.71-1.34)
NEW CRITERIA AND AAR -I

\[ P = 0.037 \]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CFLD by New Criteria</td>
<td>0.80 (0.723-1.00)</td>
</tr>
<tr>
<td>CFLD by New Criteria</td>
<td>1.11 (0.72-1.46)</td>
</tr>
</tbody>
</table>
NEW CRITERIA AND AAR -II

- AAR ≤ 1
- AAR > 1

P = 0.009

Count (N, %)

No CFLD by New Criteria

CFLD by New Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CFLD by New Criteria</td>
<td>27</td>
<td>75%</td>
</tr>
<tr>
<td>CFLD by New Criteria</td>
<td>15</td>
<td>57.7%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>42.3%</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>25%</td>
</tr>
</tbody>
</table>
PATIENTS WITH CFLD ACCORDING TO NEW CRITERIA

New criteria

N = 13
50%

N = 13
50%