The role of Fibroscan: pre and post SVR

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Hospital Universitario de Valme. Sevilla.

HEPAVIR-Cirrhosis Study Group
What’s the current role of Fibroscan?

Outline

• **Before treatment.**
  – Non-invasive assessment of liver fibrosis (including rule in/out cirrhosis).
  – Predictor of response to DAA?
  – Management of liver cirrhosis.
    • Prediction of liver-related events and mortality.
    • Implications for esophageal varices surveillance policies.

• **After treatment.**
  – Non-invasive assessment of liver fibrosis. Clinical meaning?
  – Management of liver cirrhosis.
    • Non-invasive assessment of portal hypertension.
    • Role for the prediction of events (including HCC) post-SVR?

• **Conclusions.**
The begin of the Fibroscan:
An non-invasive alternative to biopsy

Shear Wave Speed Measurement

Measure
Shear Wave Speed \( V_s \) (m/s)

Calculate
Equivalent Stiffness \( E \) (kPa)

\[ E = 3\rho V_s^2 \]

- Elasticity (Stiffness)
- Liver Tissue Density
- Velocity of Shear Wave

Range: 2.5 to 75 kPa

Slow
Fast
The begin of the Fibroscan:
An non-invasive alternative to biopsy

- Non invasive and painless.
- Rapid (5-10 minutes).
- More representative of the liver.
- Well accepted: Can be frequently repeated.
- High intra/inter-observer concordance.
- Validity criteria:\footnote{1}{
  - IQR of measures < 30% median value.
  - Success rate of acquisitions > 60%.
  - LS values range from 2.5 to 75 kPa.
  - 95\textsuperscript{th} percentile healthy population: 6.8 kPa\footnote{2}{Conti F. Dig Liver Dis 2011.}}
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• **Conclusions.**
Non-invasive assessment of liver fibrosis before therapy
Still needed in the era of DAA?

• Cirrhosis is still a key factor for treatment decisions:
  – Sub-optimal rates of SVR for some regimens in the presence of cirrhosis.
  – Extended duration or use of RBV in some circumstances.
  – Some options of shortened durations only if cirrhosis is excluded.
  – Role of LS in the prediction of SVR in cirrhotics?

• Cirrhosis must be ruled in/out before therapy.
  – Need for long-term follow-up after SVR (including US surveillance for HCC).

• Baseline liver fibrosis and the need of follow-up visits after SVR.
  – No need of monitoring if F0-F1 prior to DAA and no on-going risk practices.
  – F2 patients should be monitored until regression/no progression to F3/F4.
## TE as non-invasive tool for assessing liver fibrosis

### Diagnostic performance of TE in patients with HCV

<table>
<thead>
<tr>
<th>Fibrosis score (Metavir)</th>
<th>Significant fibrosis $F \geq 2$</th>
<th>Severe fibrosis $F \geq 3$</th>
<th>Cirrhosis $F = 4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors [17,18]</td>
<td>Ziol</td>
<td>Castera</td>
<td>Ziol</td>
</tr>
<tr>
<td>Number of patients</td>
<td>163/251</td>
<td>136/183</td>
<td>76/251</td>
</tr>
<tr>
<td>(%)</td>
<td>65</td>
<td>74</td>
<td>30</td>
</tr>
<tr>
<td>Cut-off (kPa)</td>
<td>8.8</td>
<td>7.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>56</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>56</td>
<td>48</td>
<td>93</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>88</td>
<td>95</td>
<td>71</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>6.63</td>
<td>6.09</td>
<td>5.76</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.48</td>
<td>0.37</td>
<td>0.16</td>
</tr>
<tr>
<td>Area under the ROC curve</td>
<td>0.79</td>
<td>0.83</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Castera L.  
J Hepatol 2008.
TE as non-invasive tool for assessing liver fibrosis
Performance of TE in HIV/HCV-coinfected patients

- n=169\(^1\) and n=197\(^2\) HIV/HCV-coinfected patients with liver biopsy and TE.

<table>
<thead>
<tr>
<th></th>
<th>No/Minimal fibrosis (F(\leq 1))</th>
<th>Significant fibrosis ((\geq F2))</th>
<th>Cirrhosis (F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off value (kPa)</td>
<td>≤ 6</td>
<td>7.2</td>
<td>≥ 9</td>
</tr>
<tr>
<td>AUROC</td>
<td>0.86</td>
<td>0.87</td>
<td>0.86</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>68</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>Specificity</td>
<td>84</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>NPV (%)</td>
<td><strong>90</strong></td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>54</td>
<td><strong>88</strong></td>
<td><strong>85</strong></td>
</tr>
<tr>
<td>Missclassified patients (%)</td>
<td>16</td>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

1\(^{\text{Vergara S. Clin Infect Dis 2007.}}\) 2\(^{\text{Macías J. J Hepatol 2008.}}\)
Clinical interpretation of LS values in HIV/HCV

• High accuracy for the diagnosis of cirrhosis.
  – $\text{LS} \geq 14.6 \text{ kPa}$: Assume cirrhosis.
  – $\text{LS} < 10 \text{ kPa}$: Rule-out cirrhosis (according to Baveno VI\textsuperscript{1}).

• Optimal accuracy for differentiate moderate fibrosis.
  – $\text{LS} \leq 6 \text{ kPa}$: Assume F0-F1.
  – $\text{LS} \geq 9 \text{ kPa}$: Assume F2-F4.
  – $\text{LS} 6-9 \text{ kPa}$: Grey area.
  • If $\text{LS} > 7.2 \text{ kPa}$: probably $\geq F2$, specially if APRI $\geq 1.5$ and/or Forns $\geq 6.9$\textsuperscript{2}.

• Drawbacks:
  – Suboptimal performance to discriminate F2-F3.
  – Lower validity if ALT flares / inflammation\textsuperscript{3}.
  – Unreliable results if obesity or ascites.

\textsuperscript{1}Baveno VI Consensus. J Hepatol 2015.
\textsuperscript{2}Macias J. J Hepatol 2008.
\textsuperscript{3}Vispo E. Antivir Ther 2009.
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• **After treatment.**
  – Non-invasive assessment of liver fibrosis. Clinical meaning?
  – Management of liver cirrhosis.
    • Non-invasive assessment of portal hypertension.
    • Role for the prediction of events (including HCC) post-SVR?

• **Conclusions.**
Liver stiffness predicts the response to DAA in HCV-infected patients (with or without HIV coinfection) with cirrhosis GEHEP-MONO and HEPAVIR-DAA cohorts

- n=344 HCV-infected patients with cirrhosis (LS ≥ 12.5 kPa) treated with DAA-based Rx.
  - 207 (60%) coinfected by HIV.
  - PR plus DAA: n= 198 (58%); DAA IFN-free: n= 146 (42%).

Impact of baseline LS on treatment outcomes

Relapse

<table>
<thead>
<tr>
<th>Group</th>
<th>12.5-20.9 kPa</th>
<th>&gt;=21 kPa</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-PI Group</td>
<td>5</td>
<td>18</td>
<td>0.024</td>
</tr>
<tr>
<td>IFN-free Group</td>
<td>2</td>
<td>8</td>
<td>0.278</td>
</tr>
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</table>

SVR12

<table>
<thead>
<tr>
<th>Group</th>
<th>12.5-20.9 kPa</th>
<th>&gt;=21 kPa</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-PI Group</td>
<td>60</td>
<td>47</td>
<td>0.064</td>
</tr>
<tr>
<td>IFN-free Group</td>
<td>95</td>
<td>87</td>
<td>0.232</td>
</tr>
</tbody>
</table>

Impact of LS on SVR12 rate to DAA in HIV/HCV-coinfected patients

COINFECOVA-2 cohort

- n=515 HIV/HCV-coinfected patients treated with DAA IFN-free regimens.
- Cirrhosis: 54%. Treatment experienced 46%. G1a 47%; G1b 14%; G3 13%; G4 20%.

SVR12 rates according to baseline LS (n=489)

Treatment regimens (%)

- SOF/LDV: 56%
- SOF + SMV: 15%
- SOF + DCV: 20%
- 3D / 2D: 8%
- Other: 1%

Mínguez C. AIDS 2018.
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• Conclusions.
Liver stiffness correlates with portal hypertension in HIV/HCV-coinfected patients

- **n=38 HIV/HCV-coinfected patients** undergoing TE and invasive HVPG assessment.
- Correlation LS-HVPG: $r^2 0.46; p < 0.001$.
- AUROC (95% CI) of LS for clinically significant PH: 0.80 (0.64-0.97).

### Table 2

Transient elastography values (median and IQR) according to HVPG

<table>
<thead>
<tr>
<th>mmHg</th>
<th>N</th>
<th>Median transient elastography value, kPa</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVPG &lt;10</td>
<td>10</td>
<td>13.7</td>
<td>7.6–27.7</td>
</tr>
<tr>
<td>HVPG &lt;12</td>
<td>15</td>
<td>21.1</td>
<td>12–23.9</td>
</tr>
<tr>
<td>HVPG ≥10</td>
<td>28</td>
<td>36.6</td>
<td>21.8–65.4</td>
</tr>
<tr>
<td>HVPG ≥12</td>
<td>23</td>
<td>39.1</td>
<td>30–68</td>
</tr>
</tbody>
</table>
Portal hypertension: a key step in cirrhosis

Figure 1: Pathophysiology of portal hypertension in cirrhosis

Tsochatzis EA. Lancet 2014.

PALS = parenchymal extinction lesions, NO = nitric oxide, CO = carbon monoxide, VEGF = vascular endothelial growth factor, RES = reticuloendothelial system.
Liver stiffness predicts clinical outcome in HIV/HCV-coinfected patients with compensated cirrhosis

**HEPAVIR-cirrhosis cohort**

- n=239 HIV/HCV coinfected patients with compensated cirrhosis (LS ≥ 14 kPa).
- Median (Q1-Q3) follow-up: 20.7 (9.5-34.5) months.
- Liver decompensation (LD): 31 (13%; 95% IC: 9%-17%).

**Probability of LD at 1 year:**
- LS < 40 kPa: 3%.
- LS ≥ 40 kPa: 20%.

**Ability of LS < 40 kPa to predict a LD:**
NPV: 92%; PPV 30%
Progression of liver stiffness predicts clinical outcome in HIV/HCV-coinfected pts with compensated cirrhosis and LS < 40 kPa

HEPAVIR-cirrhosis cohort

- n=247 HIV/HCV coinfecteds with compensated cirrhosis (LS ≥ 14 kPa) and LS < 40 kPa.
- Significant progression of LS was defined as an increased ≥ 30% over the baseline value.
The combination of LS and CTP stage in a new predictive index improves the ability of CTP to predict clinical outcome in HIV/HCV-coinfected patients with compensated cirrhosis.
Liver stiffness and the risk of esophageal varices (and bleeding!)
Liver stiffness and the presence of esophageal varices in HIV-HCV coinfected patients with cirrhosis

- n=100 HIV/HCV coinfected patients with compensated cirrhosis (LS ≥ 14 kPa).
- Undergoing upper endoscopy for esophageal varices (EV) surveillance.
- 19% showed EV at risk of bleeding (F1 plus red signs or CTP C stage, F2 or F3).
- A LS < 21 kPa had a 100% NPV for the presence of EV at risk of bleeding.
Expanding consensus in portal hypertension
Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension

Roberto de Franchis*, on behalf of the Baveno VI Faculty†

Identification of patients with cACLD who can safely avoid screening endoscopy (new)

- Patients with a liver stiffness < 20 kPa and with a platelet count > 150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy (1b; A).
- These patients can be followed up by yearly repetition of TE and platelet count (5; D).
- If liver stiffness increases or platelet count declines, these patients should undergo screening esophagogastrroduodenoscopy (5; D).
Upper endoscopy is not necessary in ALL cirrhotics!!
Liver stiffness and risk of variceal bleeding

HEPAVIR-Cirrhosis Cohort

Study population
\( (n=446) \)

2006-2009
\( (n=195) \)
- LS < 21 kPa
  \( (n=66) \)
  - Refused UGE
    \( (n=19) \)
  - UGE
    \( (n=47) \)
- LS ≥ 21 kPa
  \( (n=129) \)
  - Refused UGE
    \( (n=4) \)
  - UGE
    \( (n=125) \)

2010-2014
\( (n=251) \)
- LS < 21 kPa
  \( (n=131) \)
  - Refused UGE
    \( (n=28) \)
  - UGE
    \( (n=92) \)
- LS ≥ 21 kPa
  \( (n=120) \)

LS < 21 kPa during the entire follow-up
\( (n=117) \)
- UGE
  \( (n=17) \)
- No UGE
  \( (n=90) \)

Progression to LS > 21 kPa during follow-up
\( (n=24) \)
- UGE
  \( (n=24) \)

Liver stiffness and risk of variceal bleeding
A LS < 21 kPa has a 100% NPV for portal hypertensive GI bleeding

- Median (RIQ) follow-up: 4.1 (2.1-5.6) years.
- Fifteen (3.4%; 95% CI: 1.7-5) patients developed a first variceal bleeding.
- Density of incidence: 0.8 per 100 person-years (95% CI: 0.5-1.4).

![Graph showing the probability of variceal bleeding over years for patients with LS < 21 kPa and LS ≥ 21 kPa.](image)

- Patients at risk
  - LS < 21 kPa: 197, 170, 141, 117, 88, 50, 30
  - LS ≥ 21 kPa: 249, 216, 198, 171, 147, 94, 55

- Probability
  - LS < 21 kPa
  - LS ≥ 21 kPa

- Years
  - p=0.001

Liver stiffness and risk of variceal bleeding
A LS < 21 kPa has a 100% NPV for portal hypertensive GI bleeding

Baseline LS and LS at the bleeding episode (n=15)

- Baseline LS
- LS at the bleeding episode

HEPAVIR-CIRRHOSIS recommendations for EV surveillance and follow-up endoscopies

• Endoscopy for EV surveillance in patients with cirrhosis only if LS ≥ 21 kPa.
  – LS assessment every year in those not undergoing endoscopy.

• Follow-up endoscopy in those with LS ≥ 21 kPa:
  – Compensated cirrhosis, no EV and ongoing liver injury (active alcohol, lack of SVR): Repeat every 2 years.
  – Compensated cirrhosis, small EV, no beta-blocker therapy and ongoing liver injury (active alcohol, lack of SVR): Repeat every year.
  – Compensated cirrhosis, no EV and etiological factor removed (long-lasting abstinence, SVR): Repeat every 3 years.
    • If LS decreases to < 21 kPa endoscopy can be safely avoid.
  – Compensated cirrhosis, small EV and etiological factor removed (long-lasting abstinence, SVR): Repeat every 2 years.
    • If no EV in follow-up endoscopy and LS < 21 KPa avoid endoscopy.
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• Conclusions.
LS after SVR to DAA...
What is expected to happen?
Changes in liver stiffness in HCV-infected patients with or without HIV treated with Peg-IFN plus RBV

- n=143 HCV-infected patients treated with Peg-IFN plus RBV.
  - 97 (68%) also infected by HIV.
- SVR and baseline LS were independent predictors of LS decrease.
  - No impact of HIV.

**Figure 1.** Median LSM at baseline and at the pre-planned date of SVR evaluation.

**Figure 2.** Changes in baseline LSM at the pre-planned date of SVR evaluation.
Long-term changes of LS after the use of all-oral DAA GEHEP-MONO and HEPAVIR-DAA cohorts (n=255)

* Baseline vs EOT: p < 0.0001
** Baseline vs 1 year: p < 0.0001
*** EOT vs 1 year: p < 0.0001
Long-term changes of LS after the use of all-oral DAA GEHEP-MONO and HEPAVIR-DAA cohorts (n=255)

Proportion of patients with improvement of LS 48 weeks after EOT according to baseline values

- Baseline LS > 7.2 kPa: 30.3%, n=238
- Baseline LS > 12.5 kPa: 35.8%, n=148
- Baseline LS > 21 kPa: 42.5%, n=87

But.. what do these reductions of LS after SVR mean?
Lower correlation between LS and biopsy after SVR?

Data from peg-IFN-RBV studies

- n=37 patients achieving SVR to Peg-IFN plus RBV
- Undergoing liver biopsy and LS assessment after SVR (median 61 months).

Impact of SVR to all-oral DAA on portal hypertension

Is there a point of no return?

- n=100 cirrhotics achieving SVR to DAA with baseline HVPG ≥ 6 mm Hg.
- HVPG and LS measurement after SVR (mean 16 weeks after SVR).
- Changes of HVPG after SVR: 80% decrease; 10% no change; 10% increase.

Baseline HVPG 10-15 mm Hg  
n=21

Baseline HVPG 16 mmHg  
n=20

After SVR:
43% decreased (14% to normal)  
No progression

After SVR:
40% decreased (0% to normal)  
20% progression.
Impact of SVR to all-oral DAA on portal hypertension

Correlation between PH and post-SVR liver stiffness

AUROC of post-SVR liver stiffness to predict HVPG ≥ 10 mm Hg:
0.93 (95% IC: 0.89-0.99)

Post-SVR LS < 12.5 kPa:
100% NPV to rule out HVPG ≥ 10 mm Hg

Post-SVR LS > 25.3 kPa:
94% PPV to predict HVPG ≥ 10 mm Hg

Mandorfer M. J Hepatol 2016.
Impact of all oral DAA regimens on portal hypertension in HIV/HCV-coinfected patients: Role of post-SVR LS

- n=22 HIV/HCV-coinfected patients with SVR to DAA undergoing HVPG and LS assessment before and after treatment.
- All patients with post-SVR LS > 20 kPa had clinically significant PH (CSPH).
- None of the patients with post-SVR < 10 kPa had CSPH.

Long-term impact of SVR to all-oral DAA in patients with clinically significant portal hypertension

- Multicentre prospective study of patients with HCV-related cirrhosis and CSPH (HVPG $\geq$10 mmHg) achieving SVR after all-oral antiviral therapy.
- $n=77$ patients with CSPH 24 weeks after therapy (SVR 24) underwent a new haemodynamic assessment 96 weeks after EOT (SVR 96).
- At baseline: 31% previous DC; 86% varices, 21% CTP stage B; 67% LS $>21$ kPa.

Significant decrease (> 20% from baseline):
43% at SVR24 and 67% at SVR 96.
Long-term impact of SVR after DAA in patients with CSPH
Are current LS cut-offs not reliable to discard CSPH after DAA?

Changes of liver stiffness after DAA

Long-term impact of SVR after DAA in patients with CSPH
Are current LS cut-offs not reliable to discard CSPH after DAA?

Changes of liver stiffness after DAA

-8.5±2 kPa (-32±4%); p<.01

-6.3±1.7 (-25±5%); p<.01 -1±1 (-5±3%); p<.01

Performance of LS cut-offs to predict CSPH

<table>
<thead>
<tr>
<th>Test</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.6 kPa</td>
<td>72%</td>
<td>50%</td>
<td>83%</td>
<td>33%</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>21 kPa</td>
<td>58%</td>
<td>93%</td>
<td>97%</td>
<td>38%</td>
<td>8.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>
LS as a surrogate marker of fibrosis and portal hypertension after SVR: **Summary**

- **LS improves significantly and rapid after SVR to DAA.**
  - Is it fibrosis or inflammation? Biopsy studies very unlikely to be performed.
  - A significant proportion of patients showing “normalizations” at 1 year.

- **LS probably also correlates with PH after SVR but...**
  - Correlation might be weaker than in the pre-SVR period.
  - Cut-off values for rule in/out CSPH still to be determined (if possible...)
  - A LS > 21-25 kPa after SVR probably reflects persistence of CSPH.

- **¿Clinical implications of long-term changes of LS after DAA?**
  - If post-SVR LS correlates with post-SVR PH... will it predict clinical events?
  - Does “normalization of LS” mean “reversal of cirrhosis”?
  - Can we use post-SVR evolution of LS to stop at any time HCC surveillance?
LS at SVR with peg-IFN plus RBV predicts clinical events

LS < 7 kPa at SVR has a high NPV for future events

- n=190 patients achieving SVR to Peg-IFN plus RBV.
- Mean (SD) LS at SVR: 7.1 (5.4) kPa.
- 10 (5.3%) developed a liver-related event. Median follow-up of 43 months.

Probability of liver-related events according to LS at SVR

Follow-up after SVR to DAA
Infectious Diseases Unit H.U. Valme protocol

Baseline LS > 14 kPa
Clinical visits every 6 mo (every 3 if decompensated) including HCC US screening
LS assessment every year

Baseline LS 9.5-14 kPa
Clinical visits every year
LS assessment every year

Baseline LS < 9.5 kPa
LS assessment 1 year after EOT

* Confirm in a second TE 6 months apart
What’s the current role of Fibroscan?

Take-home messages

• More than non-invasive assessment of fibrosis before DAA...
  – Rule in/out cirrhosis and planification of future clinical visits after SVR.
  – Prediction of SVR to DAA among those with cirrhosis.

• Key in the management of cirrhosis, especially to..
  – Determine the risk of portal hypertension and/or clinical events.
  – Stratify the need for surveillance endoscopy: do not perform if LS < 21 kPa.
  – Patients with cirrhosis should undergo a LS examination at least every year.

• Probably useful for monitoring disease progression after SVR...
  – Prediction of clinically significant portal hypertension and events after SVR?
  – If so, potential role for stratifying patients at risk for clinical events after SVR.
## Acknowledgments

HEPAVIR-Cirrhosis Study Group

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital de Valme, Sevilla</td>
<td>Pilar Rincón, María Iglesias, Juan Macías, Juan A. Pineda</td>
</tr>
<tr>
<td>Hospital Reina Sofía, Córdoba</td>
<td>Antonio Rivero Juárez, Ángela Camacho, Teresa Brieva, Antonio Rivero</td>
</tr>
<tr>
<td>Hospital de La Línea, Cádiz</td>
<td>Monserrat Pérez-Pérez</td>
</tr>
<tr>
<td>Hospital de Puerto Real, Cádiz</td>
<td>Francisco Téllez</td>
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<td>Marina Villalobos, Guillermo Ojeda, Manuel Márquez Solero, Rosario Palacios</td>
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<td>Hospital Virgen Macarena, Sevilla</td>
<td>María J. Ríos, Inmaculada López Montesinos</td>
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<tr>
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<td>Mohamed Omar, Maria A. Gómez Vidal</td>
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