1. **DIAGNOSTIC PERFORMANCE OF THE HEPQUANT SHUNT TEST IN PREDICTION OF LARGE ESOPHAGEAL VARICES IN WELL-COMPENSATED FIBROSIS OR CIRRHOSIS DUE TO CHRONIC HEPATITIS C**

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2. **Background**

Methods to select patients for EGD should not miss those with risk for large varices (Miss Rate should be ≤5%) and should effectively rule out those at low risk. Invasive biopsy and HVPG are risky, costly, and poorly tolerated; and noninvasive blood tests together with elastography lack sensitivity (meta-analysis of Expanded Baveno VI found Miss Rate ~10%, Staflidou, et al, 2019).

HepQuant SHUNT, a dual cholate clearance test, was developed as a global liver function test capable of monitoring hepato-cellular function, total hepatic perfusion, portal inflow to the liver, and portal-systemic shunting. The diagnostic performance of four SHUNT test parameters were compared for assessing the risk for large varices.

3. **Subjects**

217 well-compensated subjects with chronic hepatitis C enrolled in the QLFT ancillary study of the HALT-C Trial had the SHUNT test and subsequent EGD. Of the 217 subjects, 74 had varices, of which 22 had large varices (17 with cirrhosis, 5 with only fibrosis). SHUNT Test cutoffs (●) were selected to have a Miss Rate (FNR) ≤ 5% for large varices by ROC analysis.

DSI was highly reproducible and had the best diagnostic performance with lowest NLR.

4. **Methods**

**SHUNT Test Administration:**
- IV [24-13C]-cholic acid, 20mg, mixed with human albumin
- Oral [2,2,4,4-d₄]-cholic acid, 40mg, mixed with juice

**SHUNT Test Blood Sampling:**
- Baseline, 5, 20, 45, 60, and 90 minutes after dosing

**SHUNT Test Analysis:**
- LC-MS/MS of serum to calculate:
  - Portal-systemic Shunting (SHUNT, %)
  - d4-CA concentration at 60 min normalized to 75 kg body weight (STAT, µM)
  - Portal Hepatic Filtration Rate (Portal HFR, mL/min/kg)
  - Disease Severity Index (DSI, score)

5. **Results:**

**SHUNT Test Outputs’ Reproducibility**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PLR</th>
<th>NLR</th>
<th>FNR</th>
<th>FOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHUNT</td>
<td>95.5%</td>
<td>39.5%</td>
<td>15.1%</td>
<td>98.7%</td>
<td>1.577</td>
<td>0.115</td>
<td>4.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>STAT</td>
<td>95.5%</td>
<td>50.3%</td>
<td>17.8%</td>
<td>99.0%</td>
<td>1.919</td>
<td>0.090</td>
<td>4.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Portal HFR</td>
<td>95.5%</td>
<td>50.8%</td>
<td>17.9%</td>
<td>99.0%</td>
<td>1.939</td>
<td>0.090</td>
<td>4.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>DSI</td>
<td>95.5%</td>
<td>53.8%</td>
<td>18.9%</td>
<td>99.1%</td>
<td>2.068</td>
<td>0.084</td>
<td>4.5%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

**ICC**
- SHUNT: 0.74
- STAT: 0.90
- Portal HFR: 0.84
- DSI: 0.94

6. **Results:**

**SHUNT Test Outputs’ Diagnostic Performance**

7. **Conclusion**

The HepQuant SHUNT test, in particular DSI, has diagnostic performance characteristics that favor its potential use to “Rule Out” large esophageal varices. A pivotal trial to validate the DSI cutoff of 18.3 is underway.