DUAL CHOLATE TEST AND PREDICTION OF DECOMPENSATION, LIVER TRANSPLANTATION, DEATH AND HOSPITALIZATION IN CIRRHOSIS: A PROSPECTIVE STUDY

Mohammad Amin Fallahzadeh MD, MPH¹
Daniel Hansen MD¹; James F. Trotter MD¹; Gregory T. Everson MD²; Giovanna Saracino PhD¹; Robert S. Rahimi MD¹; Steve Helmke PhD²; Jodi Boutte¹; Sumeet K. Asrani MD MSc¹

¹Baylor University Medical Center, Dallas, TX, USA
²University of Colorado Denver School of Medicine, Aurora, Colorado, United States; and, HepQuant LLC, Greenwood Village, CO, USA
Mohammad Amin Fallahzadeh

Internal Medicine Resident
Baylor University Medical Center
Dallas, TX, USA
Disclosures

Mohammad Amin Fallahzadeh

• I disclose NO personal or financial conflict of interest

− Dr. Gregory Everson and Dr. Steve Helmke are employees at HepQuant and equity members of HepQuant LLC.

− Dr. James Trotter received funding from HepQuant for his contribution to this study.
Outline

• Background
• Dual Chololate Test and Disease Severity Index (DSI)
• Methods/Results
• Key Points
Background
Non-invasive markers to predict hepatic decompensation are lacking

Compensated 112 million
Decompensated 11 million
Cirrhosis deaths 1 million

CTP and MELD/MELD-Na are suboptimal predictors of decompensation, especially in early disease

Asrani SK, et al J Hepatol 2019
Murray C, et al JAMA 2013
Sepanlou S, et al Lancet Gastroenterol hepatol 2020
Gaps In Knowledge

• **Functional impairment** precedes clinical manifestations, symptoms, and complications.

• Hepatologists are in need of sensitive tests of global **hepatic function** and physiology, that can also be linked to clinical outcomes.
Dual Cholate Test and DSI
Dual Cholate Test Administration

Simultaneous PO and IV Administration of Cholate Compounds

- 40 mg d4-Cholate mixed with juice
- 20 mg 13C-Cholate mixed with human albumin

Peripheral Blood Sampling at 5, 20, 45, 60, 90 min.

- Indwelling intravenous catheter for timed blood draws
- Serum samples shipped to HQ lab for LC-MS/MS

Investigational/research use
The Dual Cholate Clearance Test Assesses Hepatocyte Function (Cholate Uptake), Systemic Inflow, Portal Inflow, and Quantifies Portal-Systemic Spillover

Spillover (HQ SHUNT) ~ 20%

Healthy Liver

Liver Disease

Viral,
NASH,
EtOH,
Biliary,
Auto-
immune

Diseased Liver

Clearance of IV CA  Clearance of PO CA

Clearance of IV CA  Clearance of PO CA

Viral, NASH, EtOH, Biliary, Autoimmune
Hepatic Filtration Rates, Portal-Systemic SHUNT and DSI

SHUNT
- IV / Oral clearance

DSI range
- 0 (Healthy)
- 50 (Severe end-stage disease)
Hypothesis

• **DSI** as calculated by Dual cholate test could potentially predict future adverse outcomes of **decompensation**, **liver transplant (LT)**, or **liver-related death**.
Methods/Results
Methods

• Single-center, prospective, cohort study

• Patient population: age >18, cirrhosis, 2011-2018
  – Convenience sampling of cirrhotic clinic patients.
  – Excluded grade 3 or 4 hepatic encephalopathy, pregnancy, life expectancy <1 year

• Primary outcome:
  – Compensated patients: decompensation, LT, death
    • Decompensation defined as acute deterioration in liver function characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, variceal hemorrhage or spontaneous bacterial peritonitis.
  – Whole cohort: LT, death

• Secondary outcome
  – Total number of hospitalizations
Results

• 70 patients
  – Mean age 56.5 years (IQR:10.5), 71% men, 34% HCV
  – 50% compensated at baseline
  – No significant difference in demographics between compensated and decompensated groups

• Mean Follow-up period: 4.2 years
### Results of Dual Cholate Study

<table>
<thead>
<tr>
<th></th>
<th>Whole group</th>
<th>Compensated</th>
<th>Decompensated</th>
<th>P</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=70)</td>
<td>(N=35)</td>
<td>(N=35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal HFR, ml/min/kg</td>
<td>6.5 (1.5-30.9)</td>
<td>9.7 (3.9-30.9)</td>
<td>3.5 (1.5-15.0)</td>
<td>&lt;0.001</td>
<td>29.1 ± 9.0</td>
</tr>
<tr>
<td>Systemic HFR, ml/min/kg</td>
<td>3.5 (1.1-9.9)</td>
<td>4.1 (1.5-9.9)</td>
<td>2.4 (1.1-6.2)</td>
<td>&lt;0.001</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>SHUNT, %</td>
<td>57.1 (12.0-103.1)</td>
<td>37.4 (12.0-103.1)</td>
<td>69.3 (29.6-92.2)</td>
<td>&lt;0.001</td>
<td>24.1 ± 7.5</td>
</tr>
<tr>
<td>DSI</td>
<td>26.8 ± 9.5</td>
<td>20.9 ± 6.8</td>
<td>32.6 ± 8.0</td>
<td>&lt;0.001</td>
<td>9.2 ± 3.4</td>
</tr>
</tbody>
</table>
DSI cutoff to predict outcomes

![ROC Curve with DSI=24]

Sensitivity vs. 1 - Specificity graph with the DSI cutoff highlighted at 24.
Comparison of DSI with MELD-Na

Baseline Clinical Characterization

Outcome in Follow-Up

* MELD-Na driven by renal failure: bilirubin 1.0 mg/dL, INR 1.3, Alb 4.4 g/dL, creatinine 6.3 mg/dL. The Dashed Red Line is the Cutoff DSI 24.
DSI associated with Decompensation, LT or Death

<table>
<thead>
<tr>
<th>Composite outcome for whole cohort</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.01 (0.97-1.06)</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.93 (0.65-5.74)</td>
<td>0.24</td>
</tr>
<tr>
<td>MELD-Na score</td>
<td>1.12 (1.06-1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DSI (≥24 / &lt;24)</td>
<td>4.28 (1.43-12.80)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Similar results for compensated patients only: HR: 4.92 (95% CI: 1.42-17.06)
DSI associated with number of Hospitalizations

- DSI $\geq 24$ was an independent predictor of total number of hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>IRR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.98 (0.95-1.01)</td>
<td>0.22</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.42 (0.18-0.98)</td>
<td>0.044</td>
</tr>
<tr>
<td>Cirrhosis stage,</td>
<td>2.85 (1.43-5.66)</td>
<td>0.003</td>
</tr>
<tr>
<td>decompensated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD-Na score</td>
<td>1.13 (1.06-1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DSI ($\geq 24 / &lt;24$)</td>
<td>5.42 (2.53-11.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Baseline DSI and future outcome of LT or death

![Graph showing cumulative incidence over time for DSI ≥ 24 and DSI < 24 patients at risk.]

- Patients at risk:

<table>
<thead>
<tr>
<th>DSI ≥ 24</th>
<th>39</th>
<th>26</th>
<th>20</th>
<th>15</th>
<th>12</th>
<th>5</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI &lt; 24</td>
<td>29</td>
<td>24</td>
<td>22</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
Key Takeaways

• Dual Cholate Test may help accurately identify patients at risk of decompensation, LT, or death.

• DSI is an independent predictor of the composite outcome, particularly in low or intermediate MELD-Na.

• Dual Cholate test may be useful in prioritizing patients for liver transplantation and aid the allocation process for low or intermediate risk.

Limitations

• Small sample size
• Male predominance
• No comparators such as liver biopsy or elastography to assess correlation with DSI
Thank you!