Serum Biomarker Panel Outperforms the Canadian CT Head Rule for Diagnosing Traumatic Intracranial Injury

Robert D. Welch, MD, MS
Department of Emergency Medicine
Wayne State University School of Medicine
Detroit, MI
# Co-Authors

- Linda Papa, MD, MSc
- Jeff Bazarian, MD, MPH*
- Rob Howard, BS
- James Chen, MD*
- Art Weber, BSΩ
- Syed Ayaz, MBBS
- Lawrence Lewis, MD*

<table>
<thead>
<tr>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlando Regional Medical Center</td>
</tr>
<tr>
<td>University of Rochester</td>
</tr>
<tr>
<td>Veridical Solutions</td>
</tr>
<tr>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>Banyan Biomarkers, Inc.</td>
</tr>
<tr>
<td>Wayne State University</td>
</tr>
<tr>
<td>Washington University</td>
</tr>
</tbody>
</table>

Welch and *authors above were part of the ALERT-TBI study and were contracted by Banyan Biomarkers, Inc. and the U.S. Army Medical Research and Materiel Command.

ΩWeber was employed by Banyan Biomarkers, Inc. at the time of the ALERT-TBI study.
Background

- **Serum Biomarker Panel** - predict absence of CT findings in patients with mild to moderate TBI
  - Glial Fibrillary Acidic Protein (GFAP)
  - Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1)
  - FDA approval February 2018

- **Canadian CT Head Rule** (CCTHR) – clinical decision tool
  - Published 2001
  - Primary outcome - to predict need for neurosurgical intervention
  - Secondary outcome – “clinically important” CT findings
  - Slow to implement in the U.S.
Objectives

• **Primary Objective**
  Evaluate and compare the test characteristics of the biomarker panel and the CCTHR for CT head findings among patients with mild TBI

• **Secondary Objective** (Not presented here due to time constraints)
  Minimal head injury (no LOC or amnesia)
  On “blood thinners”
Methods

• Secondary analysis of the prospective multi-center ALERT-TBI study
  • December 2012 to March 2014

• Inclusion
  • Suspected non-penetrating TBI patients ≥ 18 years
  • GCS 9-15
  • CT done per usual care at each of 15 US and 7 European study sites
  • CT and blood draw completed within 12 hours of injury

• Exclusion
  • Unable to determine time of injury or get valid consent
  • Stroke or neurosurgery within 30 days
  • Neurodegenerative disease, seizure, brain tumor
  • Pregnancy / breast feeding
  • Blood transfusion prior to blood sample obtained
Methods (cont.)

- CT images interpreted by 2 subspecialty board-certified study neuroradiologists blinded to clinical findings
- Adjudicated by a 3rd (subspecialty neuroradiologist)
- Serum concentrations GFAP and UCH-L1
  - Chemiluminescent enzyme-linked immunosorbent assays (ELISA)
  - Performed at 1 of 3 independent core labs by blinded personnel
- IRB approved at each study site

*Primary study results published in Lancet Neurology July 2018*
This Study

• Included only patients with GCS 14-15 (sub-analysis GCS 15 only)
• Conform to CCTHR inclusion criteria:
  • LOC, amnesia, and/or confusion
  • No “Blood Thinners”
  • No seizure post-injury
Biomarker Concentration Values

• GFAP
  Pre-specified cutoff: 22 pg/mL
  Reportable range: 10 – 320 pg/mL

• UCH-L1
  Pre-specified cutoff: 327 pg/mL
  Reportable range: 80 – 2560 pg/mL

*Biomarker panel “Negative” only if both were below cutoff*

*Biomarker panel “Positive” if either or both were above cutoff*
Panel 1: Canadian CT Head Rule

CT Head Rule is only required for patients with minor head injuries with any one of the following:

High risk (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (haemotympanum, ‘raccoon’ eyes, cerebrospinal fluid otorrhoea/rhinorrhoea, Battle’s sign)
- Vomiting ≥ two episodes
- Age ≥ 65 years

Medium risk (for brain injury on CT)
- Amnesia before impact > 30 min
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height > 3 feet or five stairs)

Minor head injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patients with a GCS score of 13–15.

Definition CT Positive (Intracranial Injury)

- Acute epidural hematoma
- Acute subdural hematoma
- Indeterminate extra-axial lesions
- Parenchymal hematoma
- Intraventricular hemorrhage
- Subarachnoid hemorrhage
- Petechial hemorrhagic or bland sheer injury
- Ventricular compression
- Ventricular trapping
- Non-hemorrhagic contusion
- Brain herniation
- Global or focal brain edema
- Post-traumatic ischemia

**Does not include isolated skull fractures**
CCTHR - Clinically Unimportant CT Findings

Neurologically intact patient with only one of the following:

• Solitary contusion < 5mm
• SAH < 1mm thick
• Subdural hematoma < 4mm thick
• Isolated pneumocephaly
• Closed depressed skull fracture not through inner table

• Neuroradiologist re-reviewed positive CTs to confirm “clinically important” vs non-important
Data Analysis

- Biomarker panel and CCTHR compared to the gold-standard CT
  - All study-defined positive intracranial CT findings
  - Clinically important CT findings vs non-important or negative

- Sensitivity
- Specificity
- Negative predictive value (NPV)
- Exact 95% Clopper-Pearson confidence limits
1959 Subjects (GCS 9-15)

39 Subjects (GCS 9-13)

1920 Subjects (GCS 14-15)

330 Subjects on anti-coagulant meds

1590 Subjects not on anti-coagulant meds

671 Subjects with no LOC, PTA or Confusion

919 Subjects Evaluated

67 Subjects CT Positive

852 Subjects CT Negative
RESULTS

• 919 patients met our main study inclusion criteria
  67 (7.3%) CT positive
  852 (92.7%) CT negative

• 563 (61.3%) Male

• 123 (13.4%) ≥ 65 years of age
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (N=919)</th>
<th>CT Positive (N=67)</th>
<th>CT Negative (N=852)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>43.0 (18.09)</td>
<td>50.2 (16.34)</td>
<td>42.4 (18.11)</td>
</tr>
<tr>
<td>[Range]</td>
<td>[18 - 97]</td>
<td>[20 - 85]</td>
<td>[18 - 97]</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>563 (61.3%)</td>
<td>44 (65.7%)</td>
<td>519 (60.9%)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>592 (64.4%)</td>
<td>50 (74.6%)</td>
<td>542 (63.6%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>288 (31.3%)</td>
<td>12 (17.9%)</td>
<td>276 (32.4%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>55 (6.0%)</td>
<td>1 (1.5%)</td>
<td>54 (6.3%)</td>
</tr>
<tr>
<td>Other/Unknown race</td>
<td>46 (5.0%)</td>
<td>6 (9.0%)</td>
<td>40 (4.7%)</td>
</tr>
<tr>
<td><strong>Mechanism of Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceleration</td>
<td>212 (23.1%)</td>
<td>18 (26.9%)</td>
<td>194 (22.8%)</td>
</tr>
<tr>
<td>MVC</td>
<td>309 (33.6%)</td>
<td>21 (31.3%)</td>
<td>288 (33.8%)</td>
</tr>
<tr>
<td>Pedestrian MVC</td>
<td>43 (4.7%)</td>
<td>5 (7.5%)</td>
<td>38 (4.5%)</td>
</tr>
<tr>
<td>MVC Unknown</td>
<td>1 (0.1%)</td>
<td>-</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Fall</td>
<td>437 (47.6%)</td>
<td>33 (49.3%)</td>
<td>404 (47.4%)</td>
</tr>
<tr>
<td>Assault</td>
<td>102 (11.1%)</td>
<td>7 (10.4%)</td>
<td>95 (11.2%)</td>
</tr>
<tr>
<td>Sports Injury</td>
<td>29 (3.2%)</td>
<td>3 (4.5%)</td>
<td>26 (3.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (2.6%)</td>
<td>3 (4.5%)</td>
<td>21 (2.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>49 (5.3%)</td>
<td>2 (3.0%)</td>
<td>47 (5.5%)</td>
</tr>
</tbody>
</table>

*Categories not mutually exclusive*
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (N=919)</th>
<th>CT Positive (N=67)</th>
<th>CT Negative (N=852)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of Consciousness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>715 (77.8%)</td>
<td>57 (85.1%)</td>
<td>658 (77.2%)</td>
</tr>
<tr>
<td>No</td>
<td>157 (17.1%)</td>
<td>6 (9.0%)</td>
<td>151 (17.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>47 (5.1%)</td>
<td>4 (6.0%)</td>
<td>43 (5.0%)</td>
</tr>
<tr>
<td>Post-Traumatic Amnesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>545 (59.3%)</td>
<td>57 (85.1%)</td>
<td>488 (57.3%)</td>
</tr>
<tr>
<td>No</td>
<td>361 (39.3%)</td>
<td>9 (13.4%)</td>
<td>352 (41.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (1.4%)</td>
<td>1 (1.5%)</td>
<td>12 (1.4%)</td>
</tr>
<tr>
<td>Drug or Alcohol Intoxication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>259 (28.2%)</td>
<td>19 (28.4%)</td>
<td>240 (28.2%)</td>
</tr>
<tr>
<td>No</td>
<td>651 (70.8%)</td>
<td>45 (67.2%)</td>
<td>606 (71.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (1.0%)</td>
<td>3 (4.5%)</td>
<td>6 (0.7%)</td>
</tr>
<tr>
<td>GCS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>55 (6.0%)</td>
<td>12 (17.9%)</td>
<td>43 (5.0%)</td>
</tr>
<tr>
<td>15</td>
<td>864 (94.0%)</td>
<td>55 (82.1%)</td>
<td>809 (95.0%)</td>
</tr>
</tbody>
</table>
Main Study Population (GCS 14 and 15)
(All study-defined CT findings)

CCTHR

Sensitivity: 70.1% (57.7% - 80.7%)
Specificity: 55.5% (52.1% - 58.9%)
NPV: 95.5% (93.8% - 97.5%)

Biomarker Assay

Sensitivity: 95.5% (87.5% - 99.1%)
Specificity: 38.8% (35.6% - 42.2%)
NPV: 99.1% (97.4% - 99.8%)

Table of CCTHR by CT

<table>
<thead>
<tr>
<th>CCTHR</th>
<th>CT positive</th>
<th>CT negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>47</td>
<td>379</td>
<td>426</td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>473</td>
<td>493</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>852</td>
<td>919</td>
</tr>
</tbody>
</table>

Table of Assay by CT

<table>
<thead>
<tr>
<th>Assay</th>
<th>CT positive</th>
<th>CT negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>64</td>
<td>521</td>
<td>585</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>331</td>
<td>334</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>852</td>
<td>919</td>
</tr>
</tbody>
</table>
Main Study Population – GCS 15 only
(All study-defined CT findings)

CCTHR (GCS=15)

Sensitivity: 63.6% (49.6% - 76.2%)
Specificity: 58.5% (55.0% - 61.9%)
NPV: 95.9% (93.8% - 97.5%)

Biomarker Assay (GCS=15)

Sensitivity: 94.5% (87.5% - 99.1%)
Specificity: 39.7% (36.3% - 43.1%)
NPV: 99.1% (97.3% - 99.8%)
Main Study Population (GCS 14 and 15)
(Significant CT findings only)

**CCTHR**

Sensitivity: 71.2% (56.9% - 82.9%)
Specificity: 55.1% (51.8% - 58.5%)
NPV: 97.0% (95.0% - 98.3%)

**Biomarker Assay**

Sensitivity: 96.2% (86.8% - 99.5%)
Specificity: 38.8% (35.0% - 41.6%)
NPV: 99.4% (97.9% - 99.9%)
Potential Change in CT Positive Proportion

**Main analysis (GCS 14 and 15)**
- 7.3% of 919 patients CT positive
- 10.9% of 585 patients if applied biomarker panel (missed 3 positive cases)

**Clinically important CT findings**
- 5.7% of 919 patients clinically important CT findings
- 8.5% of 585 patients if applied biomarker panel (missed 2 patients)

**Adding those without LOC, amnesia, etc.**
- 5.2% of 1590 patients CT positive
- 8.1% of 984 patients if applied biomarker panel
Limitations

• Secondary semi-planned analysis
• Determination of CCTHR often by non-physician
• Included GCS 14 and 15 for main analysis
• Time-related limitations:
  • Unable to always determine if GCS was really 15 at 2 hours post-injury
  • Study related delayed blood sampling
  • 12 hours for biomarker study vs. 24 hours for CCTHR
• Implication of positive vs. clinically important CT scans beyond scope
CCTHR

• Sensitivity for any injury (70.1%) lower than the original study (92.0%)
  • LOC and disorientation was not always “witnessed”
  • Improved CT imaging (technology) and interpretations by neuroradiologists
  • CT done in only 67% of patients (2078 of 3121) in the CCTHR study
• Other studies have described lower sensitivity of CCTHR
Implementation of the CCTHR

• 2004 Britain
  • CT use often determined by presence of skull fracture
  • CCTHR increased CT use

• 2010 Canada
  • 6 intervention sites / 6 control sites
  • Both intervention and control sites had an INCREASE in imaging (13.3% and 6.7% respectively)
  • Difference in increase 6.7% (p=0.16)
Kaiser Study - 2018

- Pre and post-implementation of CCTHR
- 13 non-trauma EDs
- GCS < 15 in over 10% in both pre and post-periods

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Head Bleed</th>
<th>Skull Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Implementation</td>
<td>3.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Post-Implementation</td>
<td>4.8%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
Cost-Effectiveness

• Journal Neurotrauma (March 2019)
• ALERT-TBI data but independent of our group and study sponsor
  • *Mild TBI with a probability of intracranial bleed of 0.104, the biomarker screen is cost-effective at $308.96 or less per test.*
  • Moderate TBI with probability of 0.663, screening is cost-effective at $73.41 or less per test
Fig. 1 Timeline of the development of cardiac biomarkers for the diagnosis of acute myocardial infarction

Implications

• CCTHR published 2001 and still trying to implement
• Biomarker assay panel
  • Objectively able to decrease head CT utilization with high sensitivity
  • Cost-effective
• Exploratory in nature
• *We need to start somewhere!*
Thank You!
References


Next Steps

• Abbott Laboratories¹
  • I-Stat® Device
  • Results expected in 15 minutes or less
  • Expected to be available in 2019
• Biomerieux²
  • VIDAS® Family Instrumentation
  • Commercial launch date has not been disclosed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (N=919)</th>
<th>CT Positive (N=67)</th>
<th>CT Negative (N=852)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury to blood draw</td>
<td>3.23 (2.4, 4.0)</td>
<td>3.43 (2.4, 4.6)</td>
<td>3.22 (2.4, 4.0)</td>
</tr>
<tr>
<td>Median (25%, 75%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFAP pg/mL</td>
<td>24.5 (10.0, 72.9)</td>
<td>175.5 (78.6, 320.0)</td>
<td>20.8 (10.0, 61.3)</td>
</tr>
<tr>
<td>Median (25%, 75%) n=855</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCH-L1 pg/mL</td>
<td>255.6 (147.7, 554.1)</td>
<td>666.2 (352.6, 1274.4)</td>
<td>239.7 (141.9, 489.6)</td>
</tr>
<tr>
<td>Median (25%, 75%) n=897</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Includes those without LOC (GCS 14 and 15)  
(All study-defined CT findings)

### CCTHR

<table>
<thead>
<tr>
<th>CCTHR</th>
<th>CT positive</th>
<th>CT negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>59</td>
<td>654</td>
<td>713</td>
</tr>
<tr>
<td>N</td>
<td>24</td>
<td>853</td>
<td>877</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>1507</td>
<td>1590</td>
</tr>
</tbody>
</table>

**Sensitivity:** 71.1% (60.1% - 80.5%)  
**Specificity:** 56.6% (54.1% - 59.1%)  
**NPV:** 97.3% (96.0% - 98.2%)

### Biomarker Assay

<table>
<thead>
<tr>
<th>Assay</th>
<th>CT positive</th>
<th>CT negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>80</td>
<td>904</td>
<td>984</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>603</td>
<td>606</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>1507</td>
<td>1590</td>
</tr>
</tbody>
</table>

**Sensitivity:** 96.4% (89.8% - 99.2%)  
**Specificity:** 40.0% (37.5% - 42.5%)  
**NPV:** 99.5% (98.6% - 99.9%)