**C-GRApH**: A Validated Scoring System For The Early Risk Stratification Of Neurologic Outcomes After Out-of-hospital Cardiac Arrest Treated With Therapeutic Hypothermia

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University of Virginia, Charlottesville, VA, USA;1 Cleveland Clinic Foundation, Cleveland, OH, USA;2
• Estimated 326,000 out-of-hospital cardiac arrests (OHCA) in US in 2015
  – Survival to hospital discharge: 10%
  – Neurologic injury is the leading cause of death (67%) and results in significant disability in survivors

• Therapeutic hypothermia (TH)/targeted temperature management (TTM) improves neurologic outcomes after OHCA
  – Ventricular tachycardia/fibrillation (class I): 20% absolute risk reduction
  – Pulseless electrical activity/asystole (class IIb): 5% relative risk reduction
• Early prognosis after OHCA is problematic due to decreased specificity of prior gold-standard testing in the TH/TTM population.

• Current consensus recommendation: delay prognosis >72 hours
  – Given high morbidity/mortality even with TH/TTM, ethical (prolonged suffering for patients/families) and economic incentives exist for reliable early risk stratification.

• Multiple past scoring systems (e.g. OHCA, 5-R) developed to predict neurologic outcomes after OHCA at hospital presentation
  – Not validated in TH/TTM population
  – Heavily dependent on unreliable timing variables (e.g. time from arrest to return of spontaneous circulation).
Study Goals

To develop and validate a scoring system that effectively stratifies neurologic outcomes following out-of-hospital cardiac arrest in the TH/TTM population that:

1. Uses only objective data available at initial hospital presentation

2. Eliminates the use of unreliable timing variables

3. Is applicable to OHCA patients regardless of presenting rhythm

4. Can be easily calculated at the bedside by various sub-specialty providers that participate in post-OHCA care
Development Cohort

• Retrospective review of the prospectively-acquired, consecutive University of Virginia CCU OHCA database from 2008-2012 (n = 122)

• Inclusion criteria
  – Adult (age ≥ 18), resuscitated, non-traumatic OHCA
  – Intention to treat with TH/TTM at 32-34°C for 24 hours

• Primary outcome: favorable neurologic outcome at hospital discharge
  – Definition: Glasgow-Pittsburgh cerebral performance category (CPC) 1-2
    • CPC 1-2: Mild-moderate cerebral disability; able to perform ADLs independently
    • CPC 3: Severe cerebral disability; Dependent on others for ADLs
    • CPC 4: Vegetative state
    • CPC 5: Death
  – Retrospective assignment by consensus of blinded neurologists based on documented physical exam findings and consultation notes
Development Cohort

• Patient data at hospital presentation (demographics, pre-OHCA diagnoses, arrest characteristics, laboratory results) were compared between favorable (CPC 1-2) and poor (CPC 3-5) neurologic outcome groups

• Uni-variable logistic regression then performed with variables satisfying an *a priori* ρ<0.1 cutoff between outcome groups retained for multi-variable analysis (cut points identified for continuous variables)

• Stepwise multi-variable logistic regression then performed to eliminate variable co-dependence and create a composite scoring system with maximized c-statistic
Development Cohort Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CPC 1-2 (n = 33)</th>
<th>CPC 3-5 (n = 89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.6 ± 18.3</td>
<td>62.2 ± 15.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>73%</td>
<td>66%</td>
<td>0.57</td>
</tr>
<tr>
<td>Pre-OHCA coronary artery disease</td>
<td>21%</td>
<td>47%</td>
<td>0.023</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15%</td>
<td>31%</td>
<td>0.069</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18%</td>
<td>38%</td>
<td>0.021</td>
</tr>
<tr>
<td>COPD</td>
<td>3%</td>
<td>21%</td>
<td>0.052</td>
</tr>
<tr>
<td>≥ Stage III chronic kidney disease</td>
<td>6%</td>
<td>17%</td>
<td>0.271</td>
</tr>
<tr>
<td>Ventricular tachycardia/fibrillation</td>
<td>97%</td>
<td>56%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to CPR (min)</td>
<td>2.5 ± 3.8</td>
<td>4.1 ± 7.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Time to EMS (min)</td>
<td>7.7 ± 5.9</td>
<td>9.8 ± 9.5</td>
<td>0.31</td>
</tr>
<tr>
<td>Time to ROSC (min)</td>
<td>20.6 ± 11.9</td>
<td>34.8 ± 17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.20 ± 0.12</td>
<td>7.14 ± 0.16</td>
<td>0.021</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>5.6 ± 3.1</td>
<td>7.2 ± 3.6</td>
<td>0.045</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>0.71 ± 2.50</td>
<td>2.5 ± 7.95</td>
<td>0.227</td>
</tr>
<tr>
<td>Blood Glucose (mg/dL)</td>
<td>243 ± 86</td>
<td>308 ± 125</td>
<td>0.008</td>
</tr>
</tbody>
</table>
C-GRApH

- **Variables** (1 point each, equally weighted)
  - **C**: Coronary artery disease (CAD), pre-arrest
    - Definition: history of prior MI, CABG, PCI, or obstructive lesion >50% on cardiac catheterization (not chart diagnosis alone)
    - **NOT** included if CAD diagnosed during OHCA hospitalization
  - **G**: Glucose (blood) > 200 mg/dL
    - Fingerstick, blood gas, or metabolic panel
  - **R**: Rhythm of arrest **NOT** ventricular tachycardia (VT) or fibrillation (VF)
    - If AED only rhythm discriminator, shockable = VT/VF
  - **A**: Age > 45 years
  - **pH**: pH (arterial) < 7.0

- Scoring system ranging from 0 to 5 with higher score predictive of worse neurologic outcome
  - C-statistic: .818 (95% CI .74-.90, p<0.001)
Validation Cohort

• Combination of internal and external cohorts (n = 344)
  – Internal (n= 72)
    • Consecutive new, prospective cohort from University of Virginia OHCA database from 2013-4
  – External (n = 272)
    • Consecutive retrospective review of prospectively-acquired Cleveland Clinic Foundation OHCA database from 2012-4
      – CCU, MICU, NNICU, SICU settings
      – Main academic center and satellite “community” hospitals
      – CPC scores assigned prospectively

- Other ICU 42%
- CCU 58%
- Community 39%
- Academic 61%
Characteristics of Development vs. Validation Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Development Cohort (n = 122)</th>
<th>Validation Cohort (n = 344)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>42 (34%)</td>
<td>110 (32%)</td>
<td>0.625</td>
</tr>
<tr>
<td>CPC</td>
<td>3.8 (1.7)</td>
<td>4 (1.5)</td>
<td>0.115</td>
</tr>
<tr>
<td>C-GRAPh Score</td>
<td>2.4 (1.0)</td>
<td>2.8 (1.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death/Withdrawal &lt;72 hrs</td>
<td>43 (35%)</td>
<td>85 (25%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Witnessed Arrest</td>
<td>104 (85%)</td>
<td>265 (77%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>70 (57%)</td>
<td>162 (47%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Time to ROSC (min)</td>
<td>30.3 (17.2)</td>
<td>26.7 (17.3)</td>
<td>0.083</td>
</tr>
<tr>
<td>Male Gender</td>
<td>83 (68%)</td>
<td>194 (56%)</td>
<td>0.025</td>
</tr>
<tr>
<td>CAD</td>
<td>49 (40%)</td>
<td>117 (34%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>290 (119)</td>
<td>268 (127)</td>
<td>0.089</td>
</tr>
<tr>
<td>VT/VF</td>
<td>82 (67%)</td>
<td>129 (38%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>59.7 (15.5)</td>
<td>62.3 (15.2)</td>
<td>0.110</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.17 (0.15)</td>
<td>7.15 (0.19)</td>
<td>0.165</td>
</tr>
</tbody>
</table>
Receiver Operating Characteristic

ROC Curve

- Development Cohort n=122
  AUC 0.818 (95% CI 0.737 – 0.899)
  P-value <0.001

- Validation Cohort n=344
  AUC 0.814 (95% CI 0.759 – 0.869)
  P-value <0.001
Neurologic Outcomes
Stratified by C-GRAPH Score
Neurologic Outcomes by C-GRAPh Score in Development, Validation, and Composite Cohorts

Favorable Neurologic Outcome by C-GRAPh Score

- Development (n = 122)
- Validation (n = 344)
- Composite (n = 466)
Study Limitations & Future Directions

**Study Limitations**
- Partially retrospective
- Small sample sizes at score extremes

**Future Directions**
- Fully prospective, multi-site validation
- Long-term follow-up of neurologic outcomes and quality of life assessment
Conclusions

• C-GRApH provides excellent stratification of neurologic outcomes following OHCA in patients treated with TH/TTM using objective data available at hospital presentation
  – Nearly identical ROC (c-statistic 0.82, p<0.001) and stratification by score in both the development and validation cohorts

• Applicable to varied ICU and hospital settings

• Simple pneumonic that is easy to use

• Provides early objective outcome data to aid in family discussions

• Identifies a patient cohort (score ≥ 4) that derives little to no benefit from TH/TTM, aggressive intervention, and ICU care following OHCA
Questions?