ERC-ESICM multimodal algorithm: PRO

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  – European Society of Intensive Care Medicine (ESICM)

• Lead author, ERC-ESICM Advisory Statement on prognostication in comatose survivors of cardiac arrest (ASPAC)
Pros of ERC-ESICM Guidelines - 1

It overcomes the limitations of previous prognostication models:

- Based on evidence in non-TTM-treated patients
- Important biases were not addressed
- Inconsistent definition of important accuracy measures, as false positive rate
Pros of ERC-ESICM Guidelines - 2

ASPAC rates predictors based on:

1. The level of their accuracy and precision
2. The quality of supporting evidence, evaluated using the GRADE methodology
Accuracy of predictors

• Currently used indices predict poor outcome
• Ideally, false positive rate (FPR) should be 0% (=no patient is mistakenly predicted as having a poor outcome)
• We adopted FPR as the main measure of accuracy
Accuracy and precision

• Accuracy = how much the prediction is confirmed by study results
  – FPR, sensitivity, specificity

• Precision = how confident are we that the results of the predictive test are reproducible
  – Confidence interval (CI)
  – Upper bound of 95% confidence interval for FPR <5% to define good precision
Quality of evidence

• GRADE - Grading of Recommendations Assessment, Development and Evaluation
  – 2012-2014 version

• First-time use for prognostic accuracy studies
Quality of evidence (GRADE)

• Biases and flaws in literature
  – Self-fulfilling prophecy
  – Inconsistent definition of FPR
  – Inconsistent definition of poor neurological outcome
Quality of evidence (GRADE)

• Biases and flaws in literature
  – Self-fulfilling prophecy
  – Inconsistent definition of FPR
  – Inconsistent definition of poor neurological outcome
Bilaterally absent SSEP N20 wave ≤72 h

→ In 10/12 studies (551/577 pts) SSEP had been used as a criterion for withdrawal of life-sustaining treatments

<table>
<thead>
<tr>
<th>Nº studies</th>
<th>Nº patients</th>
<th>Sensitivity</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>577</td>
<td>49 [44-54]</td>
<td>0.5 [0-3]</td>
</tr>
</tbody>
</table>

Sandroni C et al., Resuscitation 2013;84:1324-38
Quality of evidence (GRADE)

• Biases and flaws in literature
  – Self-fulfilling prophecy
  – Inconsistent definition of FPR
  – Inconsistent definition of poor neurological outcome
Papers with a non-standard definition of false positive rate

• PROPAC Neurology 2006;66:62–68
  – Multicentre study, 407 patients

• PROPAC 2006 definition:
  \[
  \frac{\text{false positives}}{\text{patients with abnormal test result}}
  \]

• Standard definition:
  \[
  \frac{\text{false positives}}{\text{patients with favourable outcome}}
  \]
Absent or extensor motor response (M= 1-2) at 72h

- FPR (PROPAC 2006 definition)

\[
\frac{FP(7)}{FP(7) + TP(207)} = 3\%[1 \ 6]
\]

- FPR (standard definition)

\[
\frac{FP(7)}{FP(7) + TN(13)} = 35\%[12 - 58]
\]
Quality of evidence (GRADE)

- Biases and flaws in literature
  - Self-fulfilling prophecy
  - Inconsistent definition of FPR
  - Inconsistent definition of poor neurological outcome
Cerebral performance categories

<table>
<thead>
<tr>
<th>CPC</th>
<th>Neurological status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conscious, independent, no or minor neurological deficits</td>
</tr>
<tr>
<td>2</td>
<td>Conscious, independent, moderate neurological deficits</td>
</tr>
<tr>
<td>3</td>
<td>Conscious, dependent, major neurological deficits</td>
</tr>
<tr>
<td>4</td>
<td>Unconscious, dependent (vegetative)</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Poor neurological outcome = CPC 4, 5 or 5
CPC thresholds for poor neurological outcome

n = 87 prognostication studies

n. of studies


CPC 4-5

CPC 3-5

Pros of ERC-ESICM Guidelines - 3

• It includes predictive indices that were not considered in previous guidelines:
  – EEG
  – Imaging (brain CT, MRI)

• They are recommended as a standard for outcome assessment in patients who remain comatose after cardiac arrest

Consensus statement from the American Heart Association. Circulation 2011; 124: 2158-77
Techniques used for prognostication: a European Survey

<table>
<thead>
<tr>
<th>Technique</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG, intermittent</td>
<td>617 (63%)</td>
</tr>
<tr>
<td>Neuroimaging (CT-scan)</td>
<td>576 (58%)</td>
</tr>
<tr>
<td>Evoked potentials</td>
<td>351 (36%)</td>
</tr>
<tr>
<td>Neuroimaging (MRI)</td>
<td>390 (40%)</td>
</tr>
<tr>
<td>Biomarkers, NSE</td>
<td>187 (19%)</td>
</tr>
<tr>
<td>EEG, continuous</td>
<td>113 (11%)</td>
</tr>
<tr>
<td>Biomarkers, S-100B</td>
<td>48 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (4%)</td>
</tr>
</tbody>
</table>

Total 1025 responses (80% Europe)
Pros of ERC-ESICM Guidelines - 4

• It accounts for interference from sedation and TTM on clinical examination
• Predictors are applied according to a time line based on the timing of TTM and subsequent recovery
<table>
<thead>
<tr>
<th>Days</th>
<th>Cardiac arrest</th>
<th>Controlled temperature</th>
<th>Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>Exclude confounders, particularly residual sedation</td>
<td>Unconscious patient, M=1-2 at ≥72h after ROSC</td>
<td>Prognostication</td>
</tr>
</tbody>
</table>
Pros of ERC-ESICM Guidelines - 4

• It accounts for interference from sedation and TTM on clinical examination
• Predictors are applied according to a time line based on the timing of TTM and subsequent recovery
• Predictors are stratified according to their robustness
Strength of predictors

• Most robust
  – Ocular reflexes
  – SSEPs

• Characteristics:
  – FPR <5%, 95% CIs <5% in TTM-treated patients
  – documented in ≥5 studies
  – at least 3 different groups of investigators
Prognostication

Cardiac arrest

Days 1-2

Controlled temperature

Days 3-5

Rewarming

Exclude confounders, particularly residual sedation

Unconscious patient, M=1-2 at ≥72h after ROSC

One or both of the following:
- No pupillary and corneal reflexes
- Bilaterally absent N20 SSEP wave

Yes

Poor outcome very likely (FPR <5%, narrow 95%CIs)

No

Wait at least 24h
Recommendation on level-of-care in 313/939 (33%) prognosticated patients
Less robust predictors

• Include:
  – Status myoclonus
  – EEG
  – Biomarkers
  – Neuroimaging

• Characteristics:
  – FPR <5% but wider 95% CIs
  – and/or inconsistent definition/threshold
Prognostication

Days 1-2

Cardiac arrest

Controlled temperature

Rewarming

Exclude confounders, particularly residual sedation

Unconscious patient, M=1-2 at ≥72h after ROSC

One or both of the following:
- No pupillary and corneal reflexes
- Bilaterally absent N20 SSEP wave

Wait at least 24h

Two or more of the following:
- Status myoclonus ≤48h after ROSC
- High NSE levels
- Unreactive burst-suppression or status epilepticus on EEG
- Diffuse anoxic injury on brain CT/MRI

Indeterminate outcome
Observe and re-evaluate

Poor outcome likely

Poor outcome very likely
(FPR <5%, narrow 95% CIs)

Days 3-5

Magnetic Resonance Imaging (MRI)

EEG - NSE

SSEP

Use multimodal prognostication whenever possible
Pros of ERC-ESICM Guidelines - 5

• Multimodal approach
• Even the most robust predictors do not ensure 100% specificity
  – Important when WLST is considered
AAN 2006
Prognostication algorithm

Coma

Exclude major confounders

No brain stem reflexes at any time (pupil, cornea, oculocephalic, cough)

Yes

Brain Death testing

Or

Day 1
Myoclonus Status Epilepticus

Yes

Poor outcome

Or

Day 1-3
SSEP absent N20 responses*

Yes

Poor outcome

Or

Day 1-3
Serum NSE >33 μg/L*

Yes

Poor outcome

Or

Day 3
Absent pupil or corneal reflexes; extensor or absent motor response

Yes

Poor outcome

Indeterminate outcome

5 - Pros of multimodality

• Predictors of good neurological outcome can be considered to counterbalance false-negative predictions

• Parisian OHCA registry (2016)
  – 4/194 patients with an eventually good outcome had an apparent bilaterally absent pupillary reflex (FPR 2%).
  – All of these patients had a reactive EEG

Pros of ERC-ESICM Guidelines - 6

- Flexible design
- Continuous evidence evaluation
- Planned update every 5 years
  - ILCOR evidence review for resuscitation guidelines
  - Interim statements allowed
ERC-ESICM algorithm: limitations

1. Combinations of predictors need to be validated prospectively

2. Predictors need an unbiased confirmation in populations with no or late WLST
   – Studies ongoing

3. Other EEG predictors need to be included
   – Using consistent definitions (ACNS)
   – Timing of EEG will need revision
Causes of death

• CPC and mRS only report death regardless of underlying cause
• Death from direct “neurological” mechanism uncommon
• CPC5b, CPC5w, CPC5c....

Future developments

1. Evaluation of multiple prediction models
   – Using appropriate evidence evaluation measures

2. Inclusion of predictors of good neurological outcome
Thank you for your attention!

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