Do Prognostic Models Matter in Neurocritical Care?
Disclosures
Objectives

• Discuss the importance of neuroprognostication and prognostic models in critically ill TBI patients

• Discuss some of the gaps in the current knowledge

• Present Canadian data on prognosis, withdrawal of life-sustaining therapies (WLST) and outcomes in critically ill TBI patients
What do you think this patient’s prognosis will be at one year?

- One week ago, you admitted a previously healthy 26 year-old man with severe TBI after a MVC. The patient was intubated at the scene and immediately transferred to the ED of your hospital. After adequate stabilization, his GCS is 6 (eye = 2, verbal = 1, motor = 3). Pupils are sluggish but equal and reactive. A head CT scan performed on arrival reveals diffuse edema. The patient has no other injuries. An intracranial monitor was installed and the ICP was 15 mmHg. The patient was not intoxicated and remained hemodynamically stable, as well as with an ICP below 20 mmHg during his ICU stay. A repeat CT scan showed diffuse edema with no sign of herniation.

- The family is very concerned about long-term neurological deficits and requests more information on prognosis from you.

- Based on the GOSe, what do you think his prognosis will be at one year?
Is TBI really a problem?

• 60% of all trauma cases are associated with a traumatic brain injury
  • Main cause of death
  • Main cause of permanent impairment
  • Most healthcare resource utilization

• Altered quality of life
Why are neuroprognostication and prognostic models so important?

- High incidence of withdrawal of life-sustaining therapies
  
  O’Callahan et al. Crit Care Med 1995

- Appropriate decisions?
  
  Mayer et al. Neurol 1999
  Becker et al. Neurol 2001

- New programs of organ donation following cardiocirculatory arrest
Public awareness

Michael Schumacher fate uncertain a month after ski fall

January 29, 2014

Michael Schumacher: Manager hopes driver will 'one day be back with us'

By Matias Grez

Michael Schumacher Health Updates: Is He Recovering?
Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study

Alexis F. Turgeon MD MSc, François Lauzier MD MSc, Jean-François Simard BSc, Damon C. Scales MD PhD, Karen E.A. Burns MD MSc, Lynne Moore PhD, David A. Zygun MD MSc, Francis Bernard MD, Maureen O. Meade MD MSc, Tran Cong Dung MD MSc, Mohana Ratnapalan HBSc, Stephanie Todd BSc MBT, John Harlock MD, Dean A. Fergusson PhD; for the Canadian Critical Care Trials Group.

CMAJ 2011
# Hospital mortality

## Table 2: Unadjusted and adjusted odds ratios by centre for mortality in hospital and after 28 days

<table>
<thead>
<tr>
<th>Centre</th>
<th>Hospital mortality</th>
<th>28-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR</td>
<td>Adjusted OR* (95% CI)</td>
</tr>
<tr>
<td>A</td>
<td>0.88 (0.62–1.25)</td>
<td>0.95 (0.65–1.41)</td>
</tr>
<tr>
<td>B</td>
<td>1.72 (1.25–2.39)</td>
<td>1.31 (0.90–1.92)</td>
</tr>
<tr>
<td>C</td>
<td>0.34 (0.22–0.53)</td>
<td><strong>0.61 (0.40–0.94)</strong></td>
</tr>
<tr>
<td>D</td>
<td>1.72 (1.25–2.39)</td>
<td><strong>1.57 (1.07–2.30)</strong></td>
</tr>
<tr>
<td>E</td>
<td>1.13 (0.81–1.58)</td>
<td>0.93 (0.62–1.38)</td>
</tr>
<tr>
<td>F</td>
<td>0.98 (0.70–1.38)</td>
<td>0.77 (0.42–1.39)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, OR = odds ratios.
*Adjusted for sex, age, pupillary reactivity and score on the Glasgow coma motor scale. The reference group was the average for all hospitals.
### Table 3: Unadjusted and adjusted odds ratios by centre for mortality in hospital and after 28 days following the withdrawal of life-sustaining therapy

<table>
<thead>
<tr>
<th>Centre</th>
<th>Hospital mortality following withdrawal</th>
<th>28-day mortality following withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR</td>
<td>Adjusted OR* (95% CI)</td>
</tr>
<tr>
<td>A</td>
<td>1.37 (0.74–2.55)</td>
<td>1.27 (0.65–2.45)</td>
</tr>
<tr>
<td>B</td>
<td>2.12 (1.19–3.79)</td>
<td><strong>2.42 (1.31–4.45)</strong></td>
</tr>
<tr>
<td>C</td>
<td>0.97 (0.45–2.10)</td>
<td>0.85 (0.37–1.96)</td>
</tr>
<tr>
<td>D</td>
<td>1.14 (0.67–1.93)</td>
<td>1.21 (0.70–2.09)</td>
</tr>
<tr>
<td>E</td>
<td>0.43 (0.25–0.72)</td>
<td><strong>0.42 (0.23–0.74)</strong></td>
</tr>
<tr>
<td>F</td>
<td>0.73 (0.42–1.27)</td>
<td>0.77 (0.42–1.39)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, OR = odds ratios.
*Adjusted for sex, age, pupillary reactivity and score on the Glasgow coma motor scale. The reference group was the average for all hospitals.
<table>
<thead>
<tr>
<th>Centre</th>
<th>No. of admissions</th>
<th>Deaths within first 3 d of care, no.</th>
<th>Among all deaths within the first 3 d of care, deaths following withdrawal of life-sustaining therapy</th>
<th>Among deaths following withdrawal of life-sustaining therapy, deaths occurring within the first 3 d of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>120</td>
<td>15</td>
<td>11/15, 73.3 (48.1–89.1)</td>
<td>11/26, 42.3 (25.5–61.1)</td>
</tr>
<tr>
<td>B</td>
<td>120</td>
<td>28</td>
<td>26/28, 92.9 (77.4–98.0)</td>
<td>26/46, 56.5 (42.3–69.8)</td>
</tr>
<tr>
<td>C</td>
<td>120</td>
<td>4</td>
<td>2/4, 50.0 (15.0–85.0)</td>
<td>2/9, 22.2 (6.3–54.7)</td>
</tr>
<tr>
<td>D</td>
<td>120</td>
<td>22</td>
<td>14/22, 63.6 (43.0–80.3)</td>
<td>14/39, 35.9 (22.7–51.6)</td>
</tr>
<tr>
<td>E</td>
<td>120</td>
<td>23</td>
<td>7/23, 30.4 (15.6–50.9)</td>
<td>7/18, 38.9 (20.3–61.4)</td>
</tr>
<tr>
<td>F</td>
<td>120</td>
<td>22</td>
<td>13/22, 59.1 (38.7–76.7)</td>
<td>13/22, 59.1 (38.7–76.7)</td>
</tr>
<tr>
<td>Total</td>
<td>720</td>
<td>114</td>
<td>73/114, 64.0 (54.9–72.3)</td>
<td>73/160, 45.6 (38.1–53.4)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.
Could differences in the management of patients be responsible for such results?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Reference</th>
<th>Topics (n)</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospital management</td>
<td>Brain Trauma Foundation, 2000</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Penetrating brain injury</td>
<td>Aarabi et al., 2001</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Pediatric guidelines</td>
<td>Adelson et al., 2003</td>
<td>17</td>
<td>0</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Field management of combat-related head trauma</td>
<td>Brain Trauma Foundation, 2005</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Surgical management of TBI</td>
<td>Bullock et al., 2006</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Revised guidelines for management of severe TBI</td>
<td>Brain Trauma Foundation, 2007</td>
<td>15</td>
<td>1</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>83</td>
<td>4</td>
<td>44</td>
<td>229</td>
</tr>
</tbody>
</table>

Maas et al. J Neurotrauma 2011
What can explain these variations in mortality?

- Differences in mortality between centres may be partly due to variation in physicians’ perceptions of long-term prognosis and physicians’ practice patterns for recommending WLST.
Clinical scenario

• One week ago, you admitted a previously healthy 26 year-old man with severe TBI after a MVC. The patient was intubated at the scene and immediately transferred to the ED of your hospital. After adequate stabilization, his GCS is 6 (eye = 2, verbal = 1, motor = 3). Pupils are sluggish but equal and reactive. A head CT scan performed on arrival reveals diffuse edema. The patient has no other injuries. An intracranial monitor was installed and the ICP was 15 mmHg. The patient was not intoxicated and remained hemodynamically stable, as well as with an ICP below 20 mmHg during his ICU stay. A repeat CT scan showed diffuse edema with no sign of herniation.

• Based on the GOSe, what do you think his prognosis will be at one year?
  • 1) favourable (GOSe 5-8) – lower moderate disability, upper moderate disability, lower good recovery, upper good recovery
  • 2) neutral on the matter
  • 3) unfavourable (GOSe 1-4) – death, vegetative state, lower severe disability, upper severe disability
Determination of Neurological Prognosis and Clinical Decision Making in Adult Patients With Severe Traumatic Brain Injury: A Survey of Canadian Intensivists, Neurosurgeons, and Neurologists

Turgeon et al. Crit Care Med 2013
How can we better assess prognosis?

• Many known/potential predictive factors of prognosis
  • Event-related characteristics
  • Patients’ characteristics
  • Clinical exam
  • Radiological imaging
  • Electrophysiological tests
  • Tissue biomarkers
When evaluating neurological PROGNOSIS in patients with SEVERE TRAUMATIC BRAIN INJURY, HOW USEFUL do you consider the followings and HOW FREQUENTLY do you use them?
What factors may be associated with prognosis?

- **Event-related characteristics**
  - Transfer time
  - Cardiorespiratory arrest

- **Patients’ characteristics**
  - Age
  - Co-morbidities

- **Clinical exam**
  - Level of consciousness following stabilization – GCS
    - Motor score
  - Pupillary reactivity
  - Episodes of hypotension
  - Episodes of hypoxemia

- **Clinical measures**
  - Increased ICP
  - Decreased brain tissue oxygenation
What factors may be associated with prognosis?

- Radiological imaging
  - CT scan
  - MRI
- Electrophysiological tests
  - EEG
  - SSEP
- Tissue biomarkers
  - Serum
  - CSF
Brain oxygen monitoring

• PbtO$_2$
  • Value < 15 mmHg associated with unfavourable outcome

Valadka et al. 1998
Nangunoori et al. *Neuro Crit Care* 2011

• Brain oxygen saturation
  • NIRS
  • Limited data available and reliability/validity
Neuroimaging-CT

• CT scan
  • Type of lesion
    • intra-parenchymal hematoma > sub-dural > epidural
  • Basal cistern
    • Compression or absence (OR 2.45 [1.9-3.2])
  • Medial shift
    • > 5 mm (OR 2.2 [1.6-2.9])
  • Sub-arachnoid hemorrhage
    • Extended t-SAH (OR 2.64 [2.4-2.9])
  • Marshall score
    • Score III and IV (OR 2.5, OR 3.0)
• Unfavourable prognosis at 6 months (GOS 1-3)

Rovlias et al. J Neurotrauma 2004
Mass et al. (IMPACT)J Neurotrauma 2007
Neuroimaging-MRI

- Magnetic Resonance Imaging
  - SWI – susceptibility weighted imaging
  - Lesions
    - Corpus callosum
    - Mesencephalon
    - Basal ganglia

- ≈40 studies (the largest with ~100 patients)
  - Mainly 1.5 Tesla MRI
  - Variable periods following admission
    - 7 to 21 days

Wedekind et al. J Trauma 1999
Mannion et al. J Neurotrauma 2007
Weiss et al. J Neurol 2008
**Neuroimaging-MRI**

- Diffusion Tensor Imaging (DTI) MRI
- MRI-spectroscopy
- Functional MRI (fMRI)

- Limited access and few data to support its clinical use

Tollard et al. Crit Care Med 2009
Electrophysiological tests-SSEP

- SomatoSensory Evoked Potentials
- Systematic review
  - Observational studies
  - SSEP - coma - prognosis
  - Median nerve, N20
  - > 4 patients/study

- 41 studies
  - 14 studies only on TBI (adults/teenagers)

Robinson et al. Crit Care Med 2003
Electrophysiological tests-SSEP

Robinson et al. Crit Care Med 2003

% Awakening

Adult & Teen Trauma (n=838)
61% Awakened

SEP Absent (n=232)
5% Awaken
CI = 2.7%

SEP Present (n=606)
82% Awaken
CI = 79-85%

SEP Abnormal (n=236)
70% Awaken
CI = 64-75%

SEP Normal (n=284)
89% Awaken
CI = 85-92%

TBI
Child

Present Normal
Absent Abnormal

Robinson et al. Crit Care Med 2003

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Early somatosensory evoked potential grades in comatose traumatic brain injury patients predict cognitive and functional outcome*

David A. Houlden, PhD; Amanda B. Taylor, MD; Anthony Feinstein, MD; Rajiv Midha, MD; Allison J. Bethune, BSc; Craig P. Stewart, MA; Michael L. Schwartz, MD

- Single center prospective study (n=81)
- Median nerve SSEP day 1, 3 and 7
- 6-point scoring system

- One-year outcome (GOS, Barthel, Rivermead, General health questionnaire, attention)
Electrophysiological tests-EEG

- Electroencephalogram
  - Continuous EEG

- Absence of variability (alpha)
  - Mean 3 day PAV
  - GOS 1-3 at 6 months

<table>
<thead>
<tr>
<th>PAV cutpoint</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>100</td>
<td>20</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>0.15</td>
<td>74</td>
<td>66</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>0.20</td>
<td>39</td>
<td>87</td>
<td>48</td>
<td>82</td>
</tr>
<tr>
<td>0.25</td>
<td>17</td>
<td>93</td>
<td>42</td>
<td>80</td>
</tr>
</tbody>
</table>

Gutling et al. Neurol 1995
Vespa et al. J Neurosurg 2002
Hebb et al. J Neurotrauma 2007
Nenadovic et al. J Neurotrauma 2008
Tissue biomarkers

- Many serum proteins identified
  - S100-ß
  - Neuron Specific Enolase (NSE)
  - GFAP
  - UCH-L1
  - ...
  - > 100 small cohort studies

- Association observed
- Unknown thresholds for clinical significance

Mussack et al. Crit Care Med 2002
Woertgen et al. Brain Inj 2002
Stalnacke et al. J Rehab Med 2005
Haqqani et al. J Neurotrauma 2007
Korfias et al. Int Care Med 2007
Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients by Glasgow outcome score</th>
<th>Mean (SE) difference in ln concentration (µg/L)</th>
<th>Geometric mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raabe et al 1998</td>
<td>≤3: 6, &gt;3: 9</td>
<td>1.45 (0.47)</td>
<td></td>
</tr>
<tr>
<td>Raabe et al 1998</td>
<td>≤3: 20, &gt;3: 24</td>
<td>1.30 (0.75)</td>
<td></td>
</tr>
<tr>
<td>Jackson et al 2000</td>
<td>≤3: 25, &gt;3: 5</td>
<td>0.65 (0.54)</td>
<td></td>
</tr>
<tr>
<td>Chatfield et al 2002</td>
<td>≤3: 8, &gt;3: 12</td>
<td>1.42 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Woertgen et al 2002</td>
<td>≤3: 24, &gt;3: 30</td>
<td>1.38 (0.24)</td>
<td></td>
</tr>
<tr>
<td>Li et al 2004</td>
<td>≤3: 18, &gt;3: 22</td>
<td>0.55 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Ucar et al 2004</td>
<td>≤3: 34, &gt;3: 14</td>
<td>0.41 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Vos et al 2004</td>
<td>≤3: 40, &gt;3: 44</td>
<td>0.69 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Sawasachi et al 2005</td>
<td>≤3: 12, &gt;3: 29</td>
<td>2.66 (0.34)</td>
<td></td>
</tr>
<tr>
<td>Wang et al 2006</td>
<td>≤3: 15, &gt;3: 19</td>
<td>0.97 (0.45)</td>
<td></td>
</tr>
<tr>
<td>Ghor et al 2007</td>
<td>≤3: 13, &gt;3: 15</td>
<td>0.64 (0.24)</td>
<td></td>
</tr>
<tr>
<td>Lavicka et al 2007</td>
<td>≤3: 41, &gt;3: 57</td>
<td>1.08 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Olivecrona et al 2009</td>
<td>≤3: 23, &gt;3: 25</td>
<td>0.13 (0.27)</td>
<td></td>
</tr>
<tr>
<td>Rainey et al 2009</td>
<td>≤3: 50, &gt;3: 50</td>
<td>1.04 (0.19)</td>
<td></td>
</tr>
<tr>
<td>Wiesmann et al 2010</td>
<td>≤3: 38, &gt;3: 22</td>
<td>1.17 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Murillo-Cabezas et al 2010</td>
<td>≤3: 32, &gt;3: 55</td>
<td>0.19 (0.16)</td>
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</tr>
<tr>
<td>Vos et al 2010</td>
<td>≤3: 36, &gt;3: 43</td>
<td>0.75 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Stein et al 2012</td>
<td>≤3: 7, &gt;3: 16</td>
<td>1.70 (0.59)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>≤3: 442, &gt;3: 491</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $t^2=0.24, \chi^2=80.54, \text{df}=17, P<0.001, t^2=79%$

Test for overall effect: $z=7.06, P<0.001$

**Fig 4** Association between S-100β protein (shown as mean (SE) ln transformed concentration) and Glasgow outcome score ≤3 in patients with moderate and severe traumatic brain injury.
Other tissue biomarkers

- Brain microdialysis
  - Lactate/pyruvate ratio > 25
  - Glucose, glycerol, glutamate
  - pH
  - Unfavourable prognosis at 6 months (GOS 1-3)

- Few data from small cohort studies

  Clauen et al. J Neurosurg 2005
  Karathanou et al. Crit Care 2006
  Karathanou et al. J Neurosurg Sc 2011
  Timofeev et al. J Cerebral Blood flow met 2013
Which factors are the most important ones for prognostic evaluation?

1. Age
2. GCS motor score
3. Pupillary response to light

4. Lesion compatible with ‘DAI’
   - Lesions in the white matter
     - Brain stem
     - Hemisphere
     - Corpus callosum

How can we determine prognosis?

• Many known/potential predictive factors of prognosis
  
  • Event-related characteristics
  • Patients’ characteristics
  • Clinical exam
  • Radiological imaging
  • Electrophysiological tests
  • Biological markers

• None of these predictive factors contains sufficient prognostic information for clinical decision making
Systematic reviews of prognostic models

• Three systematic reviews
  • Multiple methodological flaws
    • Single center studies
    • Retrospective
    • Limited number of predictors
    • Bias by indication (tests)

• None of the models can be used in clinical practice

Two recent prognostic models using large databases

• CRASH database
  • Data from the CRASH RCT on steroids in moderate and severe TBI
  • N=1008 patients
  • Validation in IMPACT database
    Perel et al. BMJ 2008

• IMPACT database
  • Database from Phase III neuroprotection trials
  • N=9205 patients
  • Validation in CRASH database
    Steyerberg et al. Plos 2008
Most recent models

Steyenberg et al. PlosMed 2008
CRASH study investigators. BMJ 2008
Most recent models

- Excellent for baseline risk assessment
  - Improve trial design and risk adjustment
  - Clinical audit

- Certainly not optimal for clinical decision-making
  - Mainly derived from admission data
  - Do not consider secondary cerebral injury
  - Do not consider most prognostic tests used

- Limited ability for accurate prognostic assessment
TBI-Prognosis Program of Research

Survey of Canadian physicians
Beliefs toward the determination of prognosis
1. Intensivists
2. Neurosurgeons
3. Neurologists

Systematic reviews
1. Prognostic models
2. Biomarkers
3. Outcome measures

Multicenter retrospective cohort study
1. Variation in withdrawal of life-sustaining therapy and mortality
2. Practice variation
3. Factors associated with the decision to withdraw life-sustaining therapy

Canadian multicenter preliminary study cohort (TBI-Prognosis pilot study)

Early Determination of long-term Prognosis in critically ill patients with Severe TBI
(TBI-Prognosis multicenter prospective study)

TBI-QualE study

Shared Decision-Making project
TBI-Prognosis Study schematic

- Admission
- Day 1: CT scan, Blood samples
- Day 3: Blood samples
- Day 7: MRI, EEG and SSEP, CT scan
- Hospital discharge
- 6 months: Blood samples
- 12 months: eGOS, EQ-5D-5L

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What can we say about prognosis then?

• No perfect test, no perfect model
• Major improvement over the last decade
• Multimodal approach required

• Perfect determination of long-term prognosis is not possible

• However, better prognostic information through prognostic models is required for both clinicians and families in order to give the most appropriate cares in a predominantly young healthy population
We must go beyond opinion-based medicine

• One week ago, you admitted a previously healthy 26 year-old man with severe TBI after a MVC. The patient was intubated at the scene and immediately transferred to the ED of your hospital. After adequate stabilization, his GCS is 6 (eye = 2, verbal = 1, motor = 3). Pupils are sluggish but equal and reactive. A head CT scan performed on arrival reveals diffuse edema. The patient has no other injuries. An intracranial monitor was installed and the ICP was 15 mmHg. The patient was not intoxicated and remained hemodynamically stable, as well as with an ICP below 20 mmHg during his ICU stay. A repeat CT scan showed diffuse edema with no sign of herniation.

• The family is very concerned about long-term neurological deficits and requests more information on prognosis from you.

• Based on the GOSe, what do you think his prognosis will be at one year?
What is the role of prognostic models then?

• Provide prognostic information as objective as possible

• Balance *prognosis* and *patient’s wishes*

• Obtain informed consent for care
  • Decision for aggressive care require the same consent as for the limitation of care
  • Concept often mistaken