Pediatric Traumatic Brain Injury: Progress and Plans[‡]

JEFF GILL

Distinguished Professor, Department of Government
Professor, Department Mathematics & Statistics
Member, Center for Behavioral Neuroscience
American University

‡ Supported by Eunice Kennedy Shriver National Institute of Child Health & Human Development (NIH) Grant Number: 1R21HD086784-01A1.

Pediatric Traumatic Brain Injury

- Severe TBI remains a leading cause of pediatric death and disability.
- Motor vehicle accidents, falls, and abusive head trauma constitute the most common etiologies.
- Pharmacological neuroprotective therapies are *not* available for severe TBI, but guideline-based intensive care can improve outcomes.
- Guideline-based intensive care recommends avoidance of secondary insults that are consistently associated with abnormal brain metabolism and bad outcome, including intracranial hypertension, hyperventilation, hypoxia, and occasionally hypotension.
- ICP monitoring is a complex clinical issue: uneven application, nonlinear trajectory, poor predictive power.
- Today:
  - a brief discussion of a published paper showing the value of guideline based intensive care for PTBI.
  - prelimary results from ongoing (funded by NIH) research on biochemical-based analysis intended for evential clinical prescription.

General Measurement Issues for TBI

- Individual patient biological measures at discharge are often pseudo-interval (continuous) measures, but we also desire qualitative descriptive measures that summarize patient status.
- Clearly a standard categorical measure with many values would not be helpful here: for a $0-100$ scale what would it mean to be a 37 versus a 41?
- On the other end of the scale, dichotomous outcomes such as lived/died are too blunt to reflect the range of important potential outcomes.
- In both of the last cases, it is common for the for the data not to support modeling these outcomes in a regression context.

Implemented Measures

- Accordingly, the most useful scales for clinical outcomes have a modest number of informed categories.
- For example, the Extended Glasgow Outcome Scale (GOSE) is structured according to:

1	Death	D
2	Vegetative State	VS
3	Lower Severe Disability	SD-
4	Upper Severe Disability	SD+
5	Lower Moderate Disability	MD-
6	Upper Moderate Disability	MD+
7	Lower Good Recovery	GR-
8	Upper Good Recovery	GR+

(cf. Wilson JT, Slieker FJ, Legrand V, Murray G, Stocchetti N, Maas AI. Observer variation in the assessment of outcome in traumatic brain injury: experience from a multicenter, international randomized clinical trial. Neurosurgery. Jul;61(1):123-8; discussion 128-9. 2007.)

- Other similar categorized hospital discharge disposition scales also exist.

Unhelpful Measures For Statistical Outcomes Assessment

- Dichotomous survival, unless measured over time and uncensored.
- From "ASSESSING A PATIENT'S RISK AT DISCHARGE; USING A TOOL TO IDENTIFY APPROPRIATE POST DISCHARGE RESOURCES" (eq.Health study, `http://www.cfmc.org/integratingcare/files/AssessingRiskatDischargeRev4-11.pdf`):

Home With No Resources	45%
Home Health	23%
Hospice	1%
Skilled Care	11%
Long Term Acute Care/Rehab	9%
Other	11%

- Status codes, such as the Patient Discharge Status Codes on BCBS UB04 claim form, which are detailed nominal descriptors for billing and record-keeping purposes,

Recent Comparison, St. Louis Children's Hospital

- Often these ordinal measures track closely, but have observable differences, relative to the GOS (Observed Glasgow Outcome Scale: D, death; V, vegetative; SD, severe disabled; MD, moderate disabled; G, good recovery).

	GOS Code				
Discharge Disposition	1	2	3	4	5
Medical Examiner/Morgue	9	0	0	0	0
Different Acute Care Hospital	0	0	4	0	0
Inpatient Rehab Facility	0	1	19	16	4
Home With Healthcare	0	0	1	0	0
Home With Outpatient Rehab	0	0	6	9	2
Home With No Assistance	0	0	9	32	11

- Correlation:

```
library(polycor)
polychor(head.inj3$Destination, head.inj3$GOS_hospital_disharge) # NOTICE THE "h"
[1] 0.6705342
```

Ordered Outcomes Modeling

- The applied models are typically not ordered probit and ordered logit specifications, *despite the obvious ordered nature of the data.*
- Such models are standard tools for statisticians since Aitchison & Silvey (1957) and Bock and Jones (1968, Ch.8), and introduced to social science statistics by McKelvey and Zavoina (1975).
- However, you can find *no citations* to these models in clinical outcomes analysis until 1993.
- Now of course they are more common, but not fully appreciated by all medical outcomes researchers.

Threshold Approach

- $\exists\ \mathbf{X}$, an $n \times k$ matrix of explanatory variables.
- Y observed on ordered/recorded on ordered categories: $Y_i \in [1, \ldots, k]$, for $i = 1, \ldots n$.
- Y assumed to be produced by an unobserved (latent) variable U.
- U is continuous on $\mathfrak{R}$ from $-\infty$ to ∞.
- The "response mechanism" for the r^{th} category:

$$Y = r \Longleftrightarrow \theta_{r-1} < U < \theta_r$$

- This requires there to be thresholds on $\mathfrak{R}$ (no intercept):

$$\mathbf{U}_i: \ \theta_0 \underset{c=1}{\longleftrightarrow} \theta_1 \underset{c=2}{\longleftrightarrow} \theta_2 \underset{c=3}{\longleftrightarrow} \theta_3 \ldots \theta_{C-1} \underset{c=C}{\longleftrightarrow} \theta_C$$

- The vector of (unseen) utilities across individuals in the sample, $\mathbf{U}$, is determined by a linear additive specification of explanatory variables: $\mathbf{U} = -\mathbf{X}\boldsymbol{\beta} + \mathbf{E}$, where $\boldsymbol{\beta} = [\beta_1, \beta_2, \ldots, \beta_p]$ does not depend on the θ_j, and $\mathbf{E} \sim F_{\mathbf{E}}$.

Threshold Approach

- For the observed vector $\mathbf{Y}$:

$$p(\mathbf{Y} \leq r|\mathbf{X}) = p(\mathbf{U} \leq \theta_r) = p(-\mathbf{X}\boldsymbol{\beta} + \mathbf{E} \leq \theta_r)$$
$$= p(\mathbf{E} \leq \theta_r + \mathbf{X}\boldsymbol{\beta}) = F_{\mathbf{E}}(\theta_r + \mathbf{X}\boldsymbol{\beta}).$$

- This is called the *cumulative model* because:

$$p(\mathbf{Y} \leq \theta_r|\mathbf{X}) = p(\mathbf{Y} = 1|\mathbf{X}) + p(\mathbf{Y} = 2|\mathbf{X}) + \ldots + p(\mathbf{Y} = r|\mathbf{X})$$

- A logistic distributional assumption on the errors produces the ordered logit specification:

$$F_{\mathbf{E}}(\theta_r - \mathbf{X}'\boldsymbol{\beta}) = P(\mathbf{Y} \leq r|\mathbf{X}) = [1 + \exp(-\theta_r - \mathbf{X}'\boldsymbol{\beta})]^{-1}$$

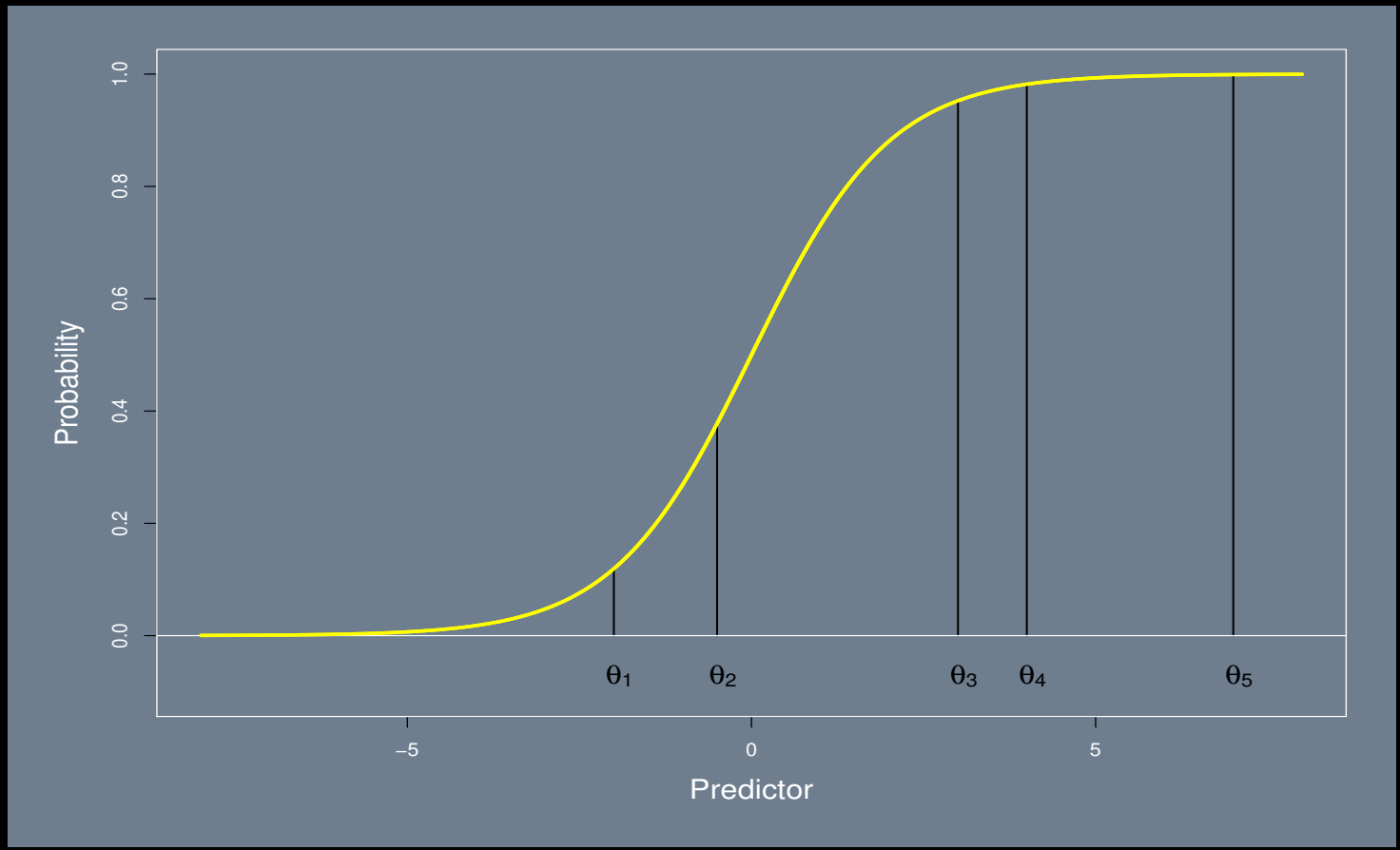
- The likelihood function is:

$$L(\boldsymbol{\beta}, \boldsymbol{\theta}|\mathbf{X}, \mathbf{Y}) = \prod_{i=1}^{n} \prod_{j=1}^{C-1} [\Lambda(\theta_j + \mathbf{X}_i'\boldsymbol{\beta}) - \Lambda(\theta_{j-1} + \mathbf{X}_i'\boldsymbol{\beta})]^{z_{ij}}$$

where $z_{ij} = 1$ if the ith case is in the jth category, and $z_{ij} = 0$ otherwise.

Interpretation

- Predicted probabilities use: $P(\mathbf{Y} \leq r|\mathbf{X}) = [1 + \exp(-\theta_r - \mathbf{X}'\boldsymbol{\beta})]^{-1}$ after estimation of $\boldsymbol{\beta}$.



Proportional-Odds Calculation for Ordered Logit

Rewrite According to:

$$p(\mathbf{Y} \leq \theta_r|\mathbf{X}) = \frac{\exp(\theta_r + \mathbf{X}\boldsymbol{\beta})}{1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})}$$

$$\begin{aligned} p(\mathbf{Y} > \theta_r|\mathbf{X}) &= \frac{1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})}{1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})} - \frac{\exp(\theta_r + \mathbf{X}\boldsymbol{\beta})}{1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})} \\ &= \frac{1}{1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})} \end{aligned}$$

so:

$$\frac{p(\mathbf{Y} \leq \theta_r|\mathbf{X})}{p(\mathbf{Y} > \theta_r|\mathbf{X})} = \frac{\exp(\theta_r + \mathbf{X}\boldsymbol{\beta})/(1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta}))}{1/(1 + \exp(\theta_r + \mathbf{X}\boldsymbol{\beta}))} = \exp(\theta_r + \mathbf{X}\boldsymbol{\beta})$$

which is nice. And:

$$\log\left[\frac{p(\mathbf{Y} \leq \theta_r|\mathbf{X})}{p(\mathbf{Y} > \theta_r|\mathbf{X})}\right] = \theta_r + \mathbf{X}\boldsymbol{\beta}$$

which is nicer.

Pediatric Neurocritical Care Program (Pineda *etal*, 2013)

- 10 years of PTBI STL Children's Hospital data with a change in the middle-point (September 2005).
- PNCP: a time-sensitive, severity-based approach to monitor and treat children with TBI that coordinated communication and activity amongst PICU staff and physician faculty and trainees, conforming with the 2003 Brain Trauma Foundation guidelines.
- This included a detailed training program, an explicit process for maintaining pathway fidelity, and continuous quality improvement.
- Groups: $n_{Pre-PNCP} = 63$, $n_{Post-PNCP} = 60$, treated as a fixed effect variable (treatment contrast).
- Tests for differences in demographics between the two periods failed to find statistically reliable differences.
- Outcomes: Medical Examiner/Morgue, Different Acute Care Hospital, Inpatient Rehab Facility, Home With Healthcare, Home With Outpatient Rehab, Home With No Assistance (better in the positive direction).

Results from the Ordered Probit Model

	Coefficient	Std.Err.	t-value
Post-PNCP	0.482477	0.216061	2.233
Age In Months	-0.004674	0.002127	-2.198
White	-0.318926	0.129315	-2.466
Length of Stay in PICU	-0.003776	0.007839	-0.482
Male	0.111984	0.107548	1.041
ICP Monitoring	0.997479	0.299579	3.330
Post-Resuscitation GCS	0.125677	0.060159	2.089
PRISM III	-0.065137	0.018125	-3.594
Injury Severity Scoreˆ2	-0.000315	0.000134	-2.345
Fall	0.291087	0.268258	1.085
Motor Vehicle Accident	0.197797	0.191271	1.034
Pedestrian Accident	0.147976	0.241442	0.613

NOTES:

- Reference category for the injury etiologies is "Other."
- Race (white) `-0.318926`, means that moving from 0=non-white to 1=white pushed the expected outcome down the scale of U towards more unfavorable outcomes.
- Coefficients such as ICP Monitoring `0.997479`, have the opposite effect.

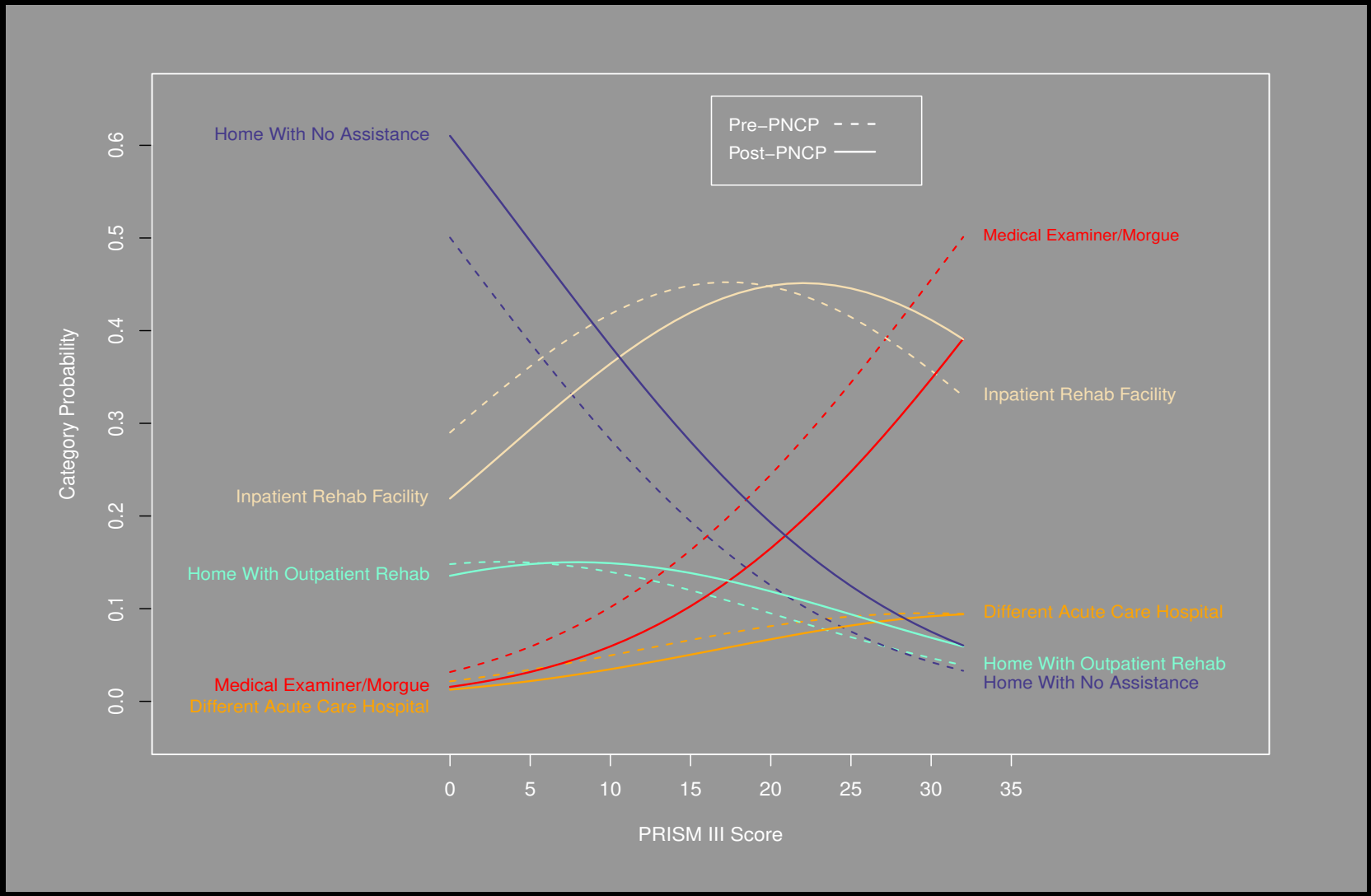
Ordered Probit Threshold Estimates

Threshold	Categories Separated	Coefficient	Std. Error	t-value
θ_1	Medical Examiner/Morgue *to* Different Acute Care Hospital	-0.647	0.188	-3.442
θ_2	Different Acute Care Hospital *to* Inpatient Rehab Facility	-0.377	0.226	-1.670
θ_3	Inpatient Rehab Facility *to* Home With Healthcare	0.979	0.262	3.733
θ_4	Home With Healthcare *to* Home With Outpatient Rehab	1.005	0.262	3.829
θ_5	Home With Outpatient Rehab *to* Home With No Assistance	1.433	0.266	5.391

NOTES:

- The literal value of these coefficients is unimportant.
- The statistical significance of these coefficients is unimportant.
- They are important only to "help" estimate the $\boldsymbol{\beta}$ coefficients.

Smooth Predictions From the Model

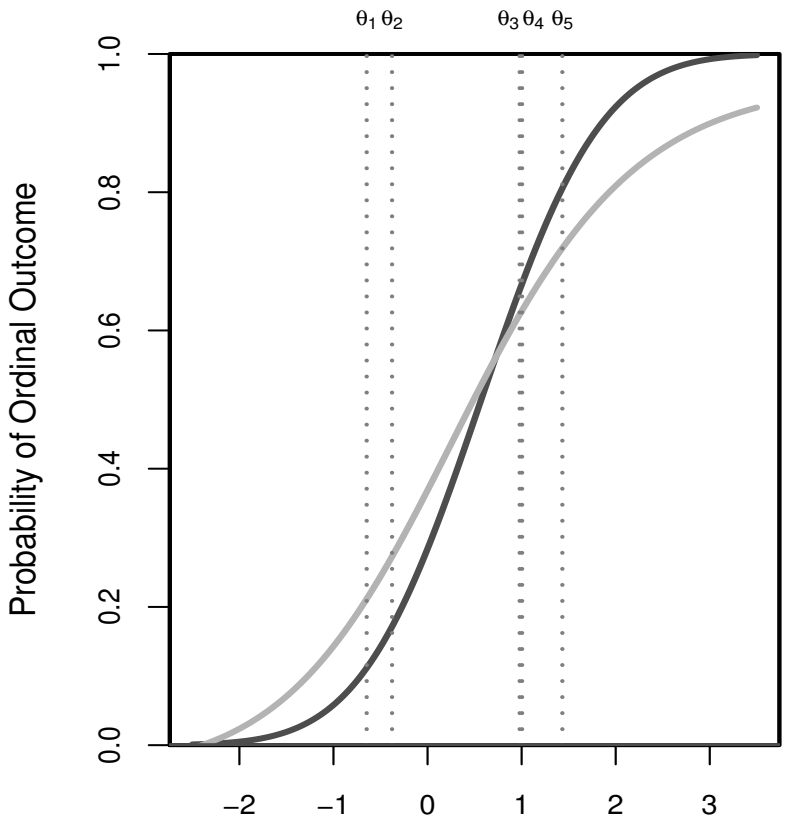


Making a Prediction Difference Using Race

- Suppose a predicted outcome on the U metric for a particular non-white patient was -0.4 (given values for all of the other $\mathbf{X}$ variables).
- Then the model would predict the category [Different Acute Care Hospital].
- If this was changed to a white patient, the coefficient β_{Race} would assign -0.318926 instead of 0 in the $\mathbf{X}_i\boldsymbol{\beta}$ calculation.
- This reduction gives the (hypothetical) patient a prediction of $U_i = -0.718926$, which corresponds to the categorical prediction of [Medical Examiner/Morgue].

Graphical Comparison

- The x-axis is the U metric and the y-axis is probability.
- The five θ cutpoints are given by the dotted vertical lines and labeled at the top.
- The slices give the probability for being in each of the categories for a white male following a motor vehicle accident, with all other explanatory variables set at the data mean.



Clinical Status of PTBI Patients

- *Secondary insults* continue to be reported in pediatric patients with severe TBI where intracranial hypertension (ICH) is the most common one.
- These can result in direct brain injury and even cerebral herniation and death, or contribute to low cerebral perfusion, worsening brain metabolism.
- Current recommendations for initiation of intracranial pressure (ICP) monitoring and management of ICH are based on clinical and radiological indicators of injury severity.
- Yet pediatric randomized trials lowering ICH have not demonstrated a benefit on outcomes.

Current Biomarker Theoretical Basis

- We propose a focus on neuropathological information from two serum based biomarkers of cellular injury:
  - ubiquitin carboxyl-terminal esterase L1 (UCH-L1)
  - glial fibrillary acidic protein breakdown products (GFAP-BDPs)

  that can improve our ability to characterize injury progression in pediatric severe TBI patients.
- These biomarkers may in the future also allow biological quantification of response to therapy, facilitating timely and individualized adjustments in patient care and consequently better outcomes.

UCH-L1

- A highly abundant neuronal protein thought to play a critical role in cellular protein degradation during both normal and pathological conditions.
- This soluble protein constitutes up to 10% of cytoplasmic protein in neurons, is elevated in cerebrospinal fluid (CSF) and serum following TBI, and is significantly associated with measures of injury severity and outcome in adults and children.
- Localized to neurons in the cerebral cortex, and has demonstrated anecdotal accuracy in stratifying adult patients with varying degrees of TBI within an hour of injury in addition to predicting outcomes.

GFAP

- A type III intermediate filament that forms part of the cytoskeleton of mature astrocytes and other glial cells.
- GFAP is only found in the central nervous system, and it presence in the blood is a marker of astrogial injury.
- Central nervous system (CNS) injury (only) causes gliosis and subsequently up-regulates blood GFAP, making it a potential marker of TBI as opposed to other trauma.
- Specifically, GFAP is a product of astrocyte cytoskeleton degradation by calpain protease (calcium-dependent, non-lysosomal) activation and therefore considered specific to the CNS.
- Elevated concentrations of GFAP two days post injury portend a poor prognosis and are thought to reflect the presence of a secondary insults (i.e. ICH and low brain tissue oxygen tension)

The Data

- A prospective case-control cohort study, $n = 67$ pediatric patients (17 years old and younger) admitted to the Intensive Care Unit at Saint Louis Children's Hospital with severe TBI (post-resuscitation GCS) score 8 or less (12).
- In the case of suspected non-accidental trauma, children with computerized tomography evidence of old intracranial hemorrhage were excluded.
- Dr. Rachel Berger and colleagues at the University of Pittsburgh provided control samples from a cohort of 30 normal children either as part of a 1-year wellness check-up or during the workup of an acute injury for which TBI was ruled out.
- Blood plasma was collected from these control patients admitted to the Pediatric Intensive Care Unit with normal mental status and no history of TBI (GCS = 15).
- Blood was sampled at regular time points following injury (6, 24, 48, 72 hours) and centrifuged for 10 minutes at 5,000 revolutions per minute and erum from these samples was stored at -80C until the time of assay.

ROC Curves

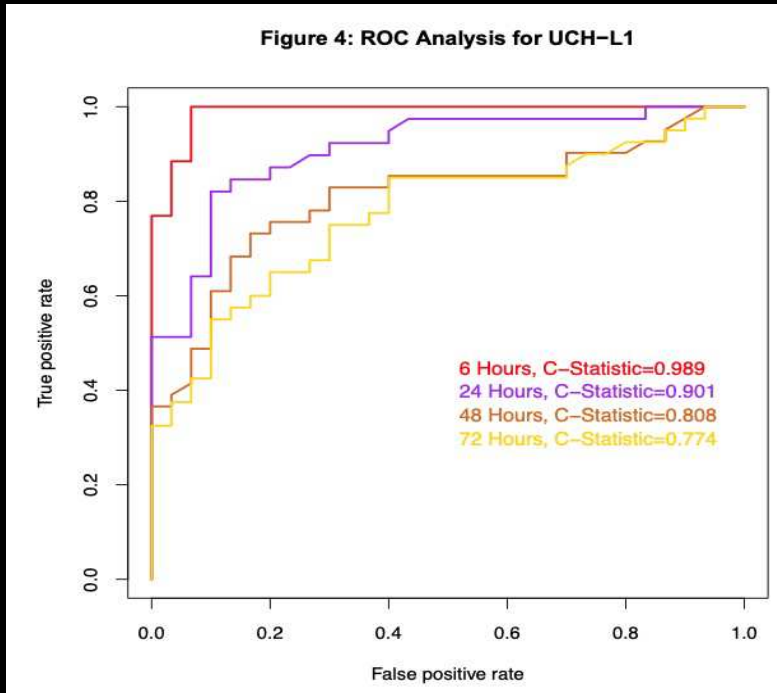


Figure 4: ROC Analysis for UCH−L1
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
6 Hours, C−Statistic=0.989
24 Hours, C−Statistic=0.901
48 Hours, C−Statistic=0.808
72 Hours, C−Statistic=0.774

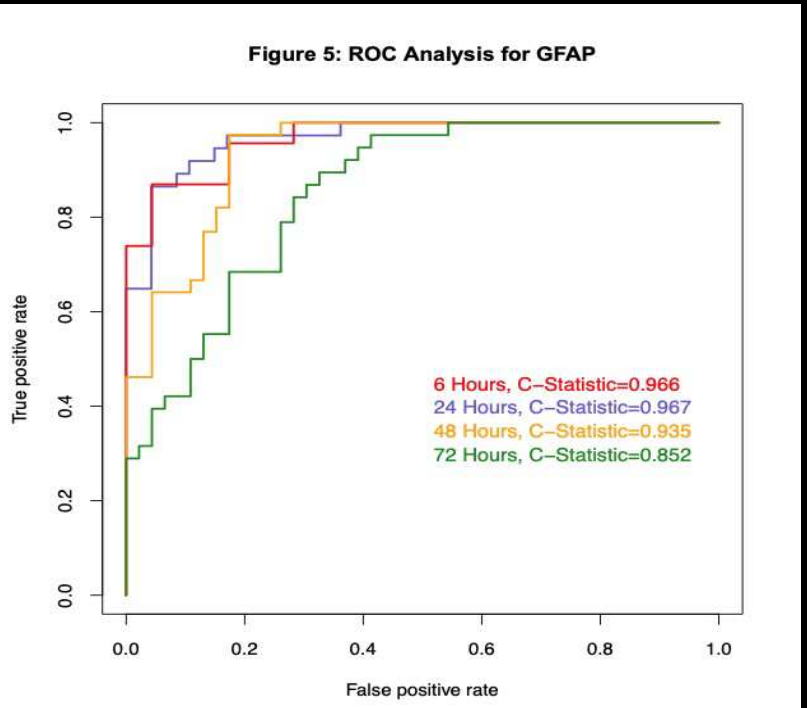


Figure 5: ROC Analysis for GFAP
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
6 Hours, C−Statistic=0.966
24 Hours, C−Statistic=0.967
48 Hours, C−Statistic=0.935
72 Hours, C−Statistic=0.852

Discharge Model, Biomarkers at 24 Hours

```
biom1 <- polr(as.factor(GOSE.hospital.D.C) ~ (UCHL1.ng.ml.24hrSerum)
                                           + (GFAP.ng.ml.24.hr.Serum)
    + Age.mo + Post.Res.GCS + NAT
    , data=biomarkers.stl[1:67,])

Coefficients:
                           Value Std. Error t value
UCHL1.ng.ml.24hrSerum  -0.3802111  0.2991090 -1.2711
GFAP.ng.ml.24.hr.Serum -0.0542211  0.0249381 -2.1742
Age.mo                 -0.0091644  0.0064066 -1.4305
Post.Res.GCS            0.3433188  0.1921960  1.7863
NAT                    -3.0600989  1.1653334 -2.6259
```

Discharge Model, Biomarkers at 48 Hours

```
biom2 <- polr(as.factor(GOSE.hospital.D.C) ~ (UCHL1.ng.ml.48hrSerum)
                                           + (GFAP.ng.ml.48hrSerum)
    + Age.mo + Post.Res.GCS + NAT
    , data=biomarkers.stl[1:67,])

Coefficients:
                         Value Std. Error  t value
UCHL1.ng.ml.48hrSerum -0.489430  0.2426552 -2.01698
GFAP.ng.ml.48hrSerum  -0.097880  0.0272559 -3.59115
Age.mo                -0.007701  0.0059658 -1.29085
Post.Res.GCS           0.070040  0.1796915  0.38978
NAT                   -0.296157  1.3070076 -0.22659
```

Discharge Model, Biomarkers at 72 Hours

```
biom3 <- polr(as.factor(GOSE.hospital.D.C) ~ (UCHL1.ng.ml.72hrSerum)
                                           + (GFAP.ng.ml.72hrSerum)
    + Age.mo + Post.Res.GCS + NAT
    , data=biomarkers.stl[1:67,])

Coefficients:
                         Value Std. Error  t value
UCHL1.ng.ml.72hrSerum -1.448308  0.6202287 -2.33512
GFAP.ng.ml.72hrSerum  -0.188987  0.0586528 -3.22212
Age.mo                -0.018231  0.0091357 -1.99555
Post.Res.GCS          -0.203829  0.3367397 -0.60530
NAT                   -0.384292  1.6886275 -0.22758
```