
BLOOD-BASED BIOMARKERS FOR PREDICTION OF INTRACRANIAL HEMORRHAGE AND OUTCOME IN PATIENTS WITH MODERATE OR SEVERE TRAUMATIC BRAIN INJURY

TAYLOR N. ANDERSON BS¹, JUN HWANG MS², MYRNA MUNAR PharmD³, LINDA PAPA MD⁴, HOLLY E. HINSON MD, MCR¹, ALLISON VAUGHAN MD⁵, SUSAN ROWELL MD, MCR^{1,5}



¹OREGON HEALTH & SCIENCE UNIVERSITY, PORTLAND, OR

²UNIVERSITY OF WASHINGTON, SEATTLE, WA

³OREGON STATE UNIVERSITY, CORVALLIS, OR

⁴ORLANDO REGIONAL MEDICAL CENTER, ORLANDO, FL

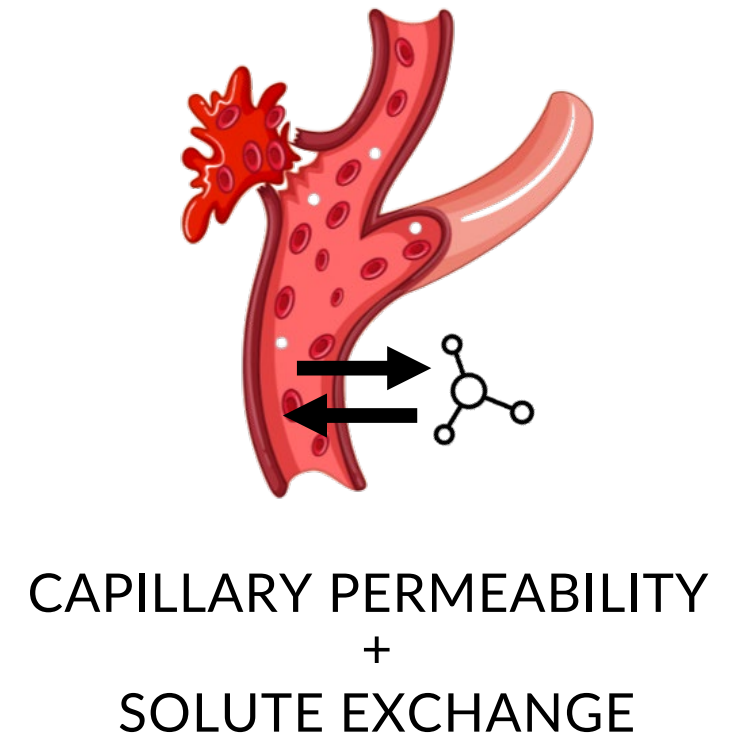
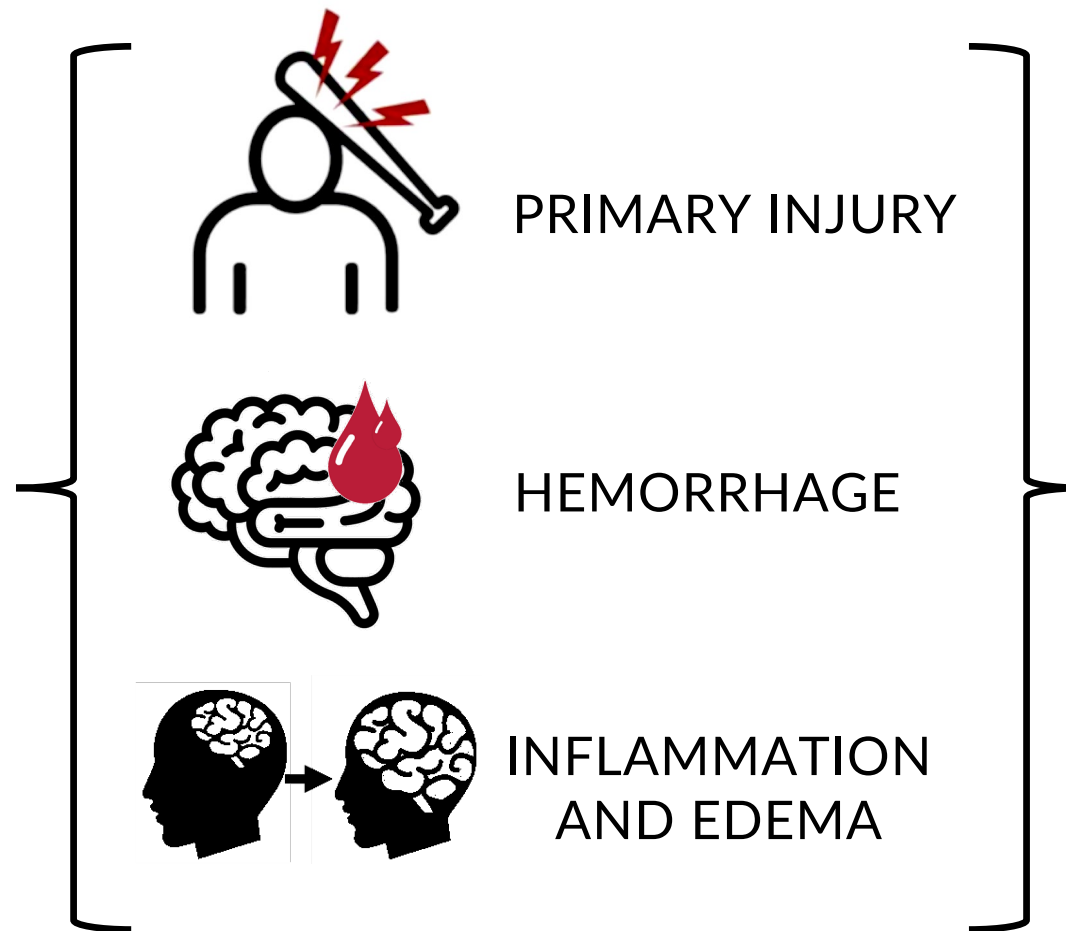
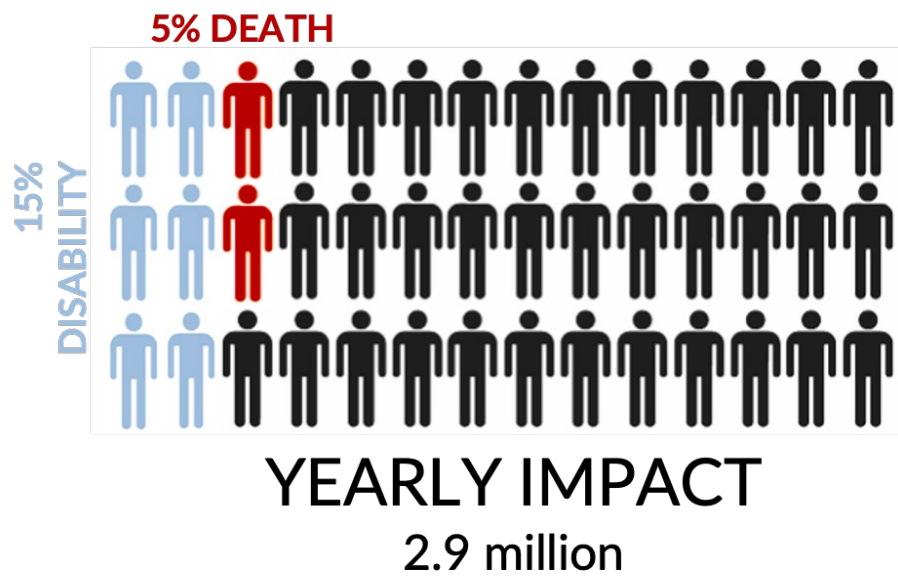
⁵DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC

DISCLOSURES

No relevant conflicts of interest

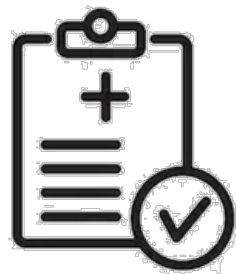
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TRAUMATIC BRAIN INJURY (TBI)



TBI CLASSIFICATION

- Standardized scoring systems
 - Clinical (labs, vitals, physical exam)
 - Radiographic (CT findings)
- Applications:



EVALUATION



PROGNOSIS



TRIAL INCLUSION

IMPACT

TABLE 1. Rotterdam Computed Tomography Classification^a

Predictor	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or subarachnoid hemorrhage	
Absent	0
Present	1
Sum score	+1

Marshall Scoring of TBI

	MLS	Cisterns	High or mixed-density lesion	Notes
I	None	Present	None	No visible pathology on CT scan
II	0-5mm	Present	None	
III	0-5mm	Compressed or absent	None	Swelling
IV	>5mm		None	
V	Any	Any	Any	Any lesion surgically evacuated
VI			>25cm ³	Not surgically evacuated

*MLS-midline shift

(Heustein Sy)

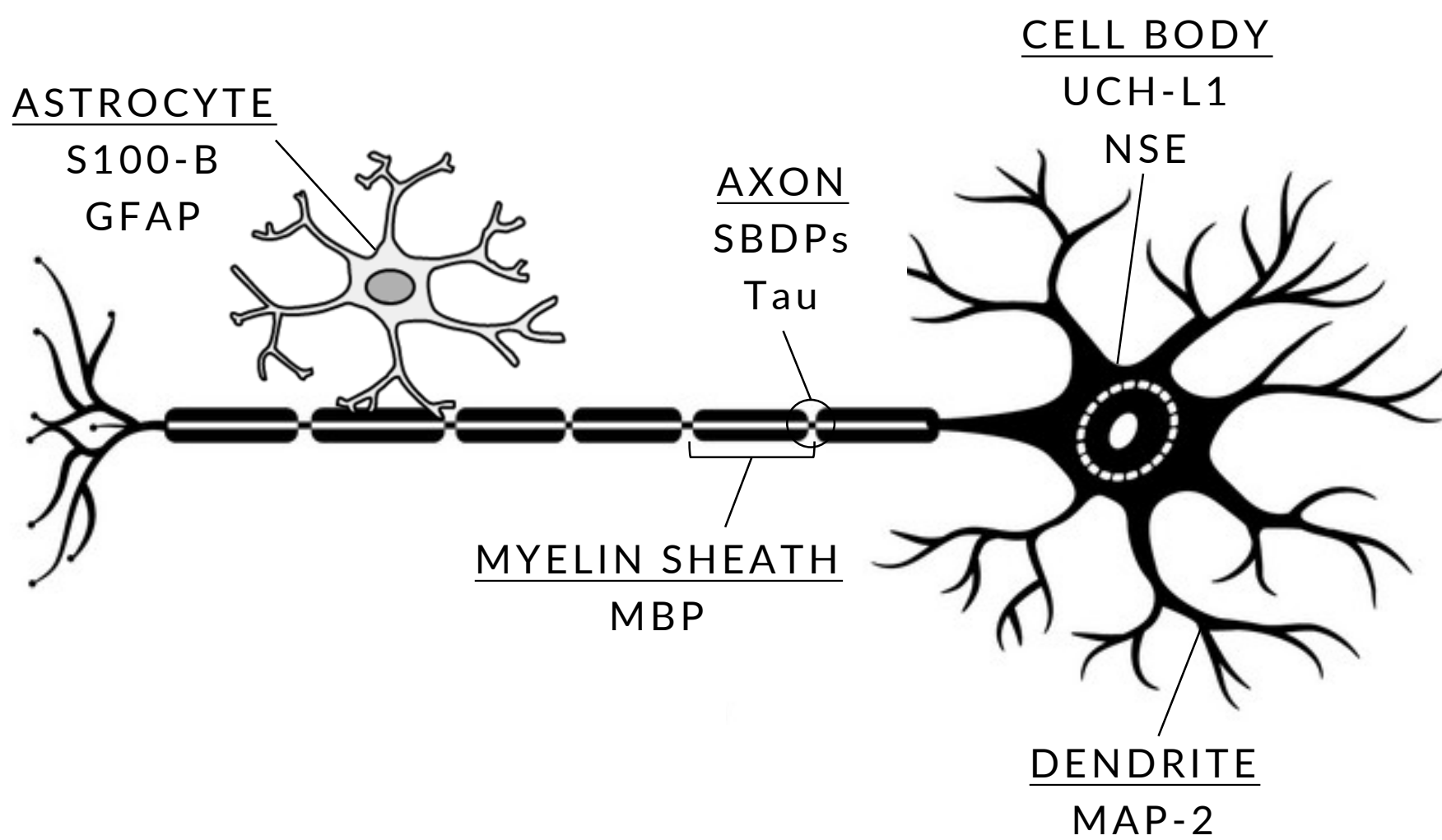
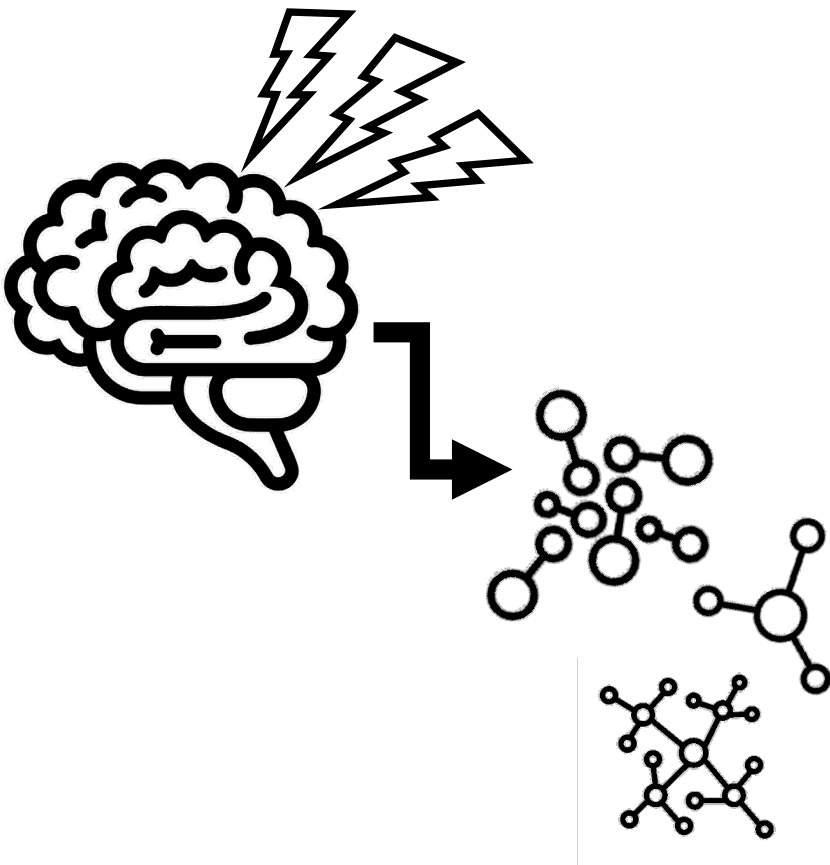
CLINICAL SCORING SYSTEMS

- Practitioner-dependent
- Subject to confounding
- Lack discrimination

TABLE 10-2 Glasgow Coma Scale

Eye Opening		Verbal Response		Motor Response	
	Points		Points		Points
Spontaneous	4	Oriented	5	Obeys commands	6
To voice	3	Confused	4	Localizes pain	5
To pain	2	Inappropriate words	3	Withdraws	4
None	1	Incomprehensible sounds	2	Abnormal flexion	3*
		Silent	1	Abnormal extension	2**
				No movement	1

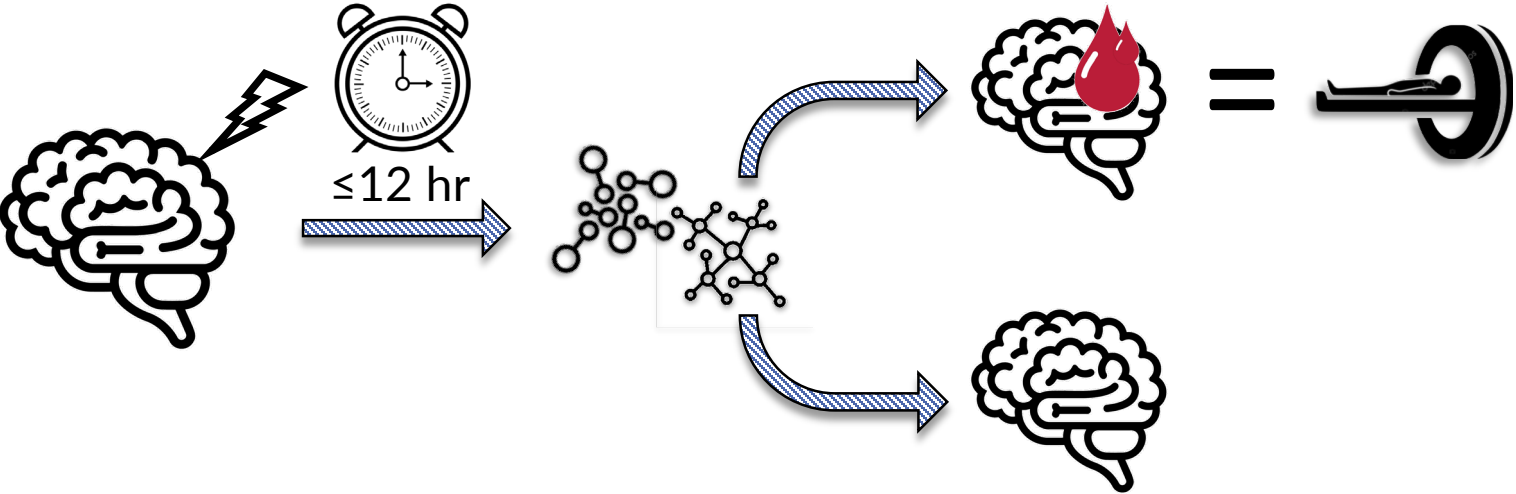
BIOMARKERS IN TBI



BIOMARKERS IN MILD TBI



2018 – FDA approves **Brain Trauma Indicator** for *mild TBI only*



BIOMARKERS IN MODERATE-SEVERE TBI

BIO-ProTECT (2019)

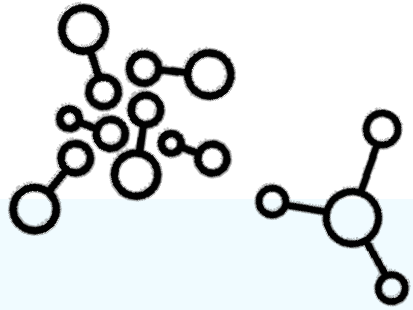
J Neurotrauma. 2019 Oct 15;36(20):2863-2871. doi: 10.1089/neu.2018.5809. Epub 2019 Jul 9.

Association of Very Early Serum Levels of S100B, Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and Spectrin Breakdown Product with Outcome in ProTECT III.

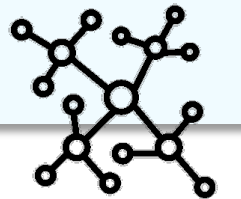
Frankel M¹, Fan L², Yeatts SD³, Jeromin A⁴, Vos PE⁵, Wagner AK⁶, Wolf BJ³, Pauls Q³, Lunney M⁷, Merck LH⁸, Hall CL¹, Palesch YY³, Silbergleit R⁹, Wright DW¹⁰.

- **S100B and GFAP improved prediction of 6-month outcome over prehospital variables**
- ***Did not evaluate radiographic endpoints***

STUDY HYPOTHESIS



In patients with moderate or severe TBI, serum levels of **GFAP, UCH-L1, and MAP-2** improve prediction of **CT findings, mortality, and 6-month neurologic outcome** over prehospital characteristics alone.



METHODS - PROCEDURES

Placebo arm of “Prehospital Tranexamic Acid Use for TBI”
- 20 trauma centers, USA and Canada



250 mL SALINE

- Bolus + 8hr infusion



HEAD CT

- ED arrival + repeat <24hr



BLOOD SAMPLES

- ED arrival



BIOMARKERS

- GFAP, UCH-L1, MAP-2

METHODS - STATISTICS

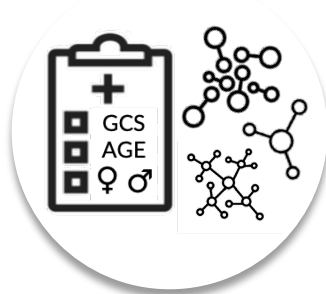
PREDICTORS



**PREHOSPITAL
VARIABLES (PH)**
(age, GCS, gender)



**PH + SINGLE
BIOMARKERS**



**PH + ALL 3
BIOMARKERS**

OUTCOMES

CLINICAL



MORTALITY



**6-MONTH
GOS-E + DRS**

RADIOGRAPHIC



**INTRACRANIAL
HEMORRHAGE**



**MARSHALL
SCORE 5+6**

POPULATION

Characteristic	(N = 243)
Median age (IQR)	35 [24, 53]
Male sex	78%
Median Prehospital Glasgow Coma Score (IQR)	8 [5, 10]
ICH on initial CT scan	55%
Mass lesion (Marshall 5+6)	12%
ICH progression	21%
Mortality within 48 hours	7%
Mortality within 28 days	13%
Extended Glasgow Outcome Score (GOS-E) ≤ 4	34%
Disability Rating Scale (DRS) ≥ 7	24%
Median time from injury to blood sample (min)	84

RESULTS:

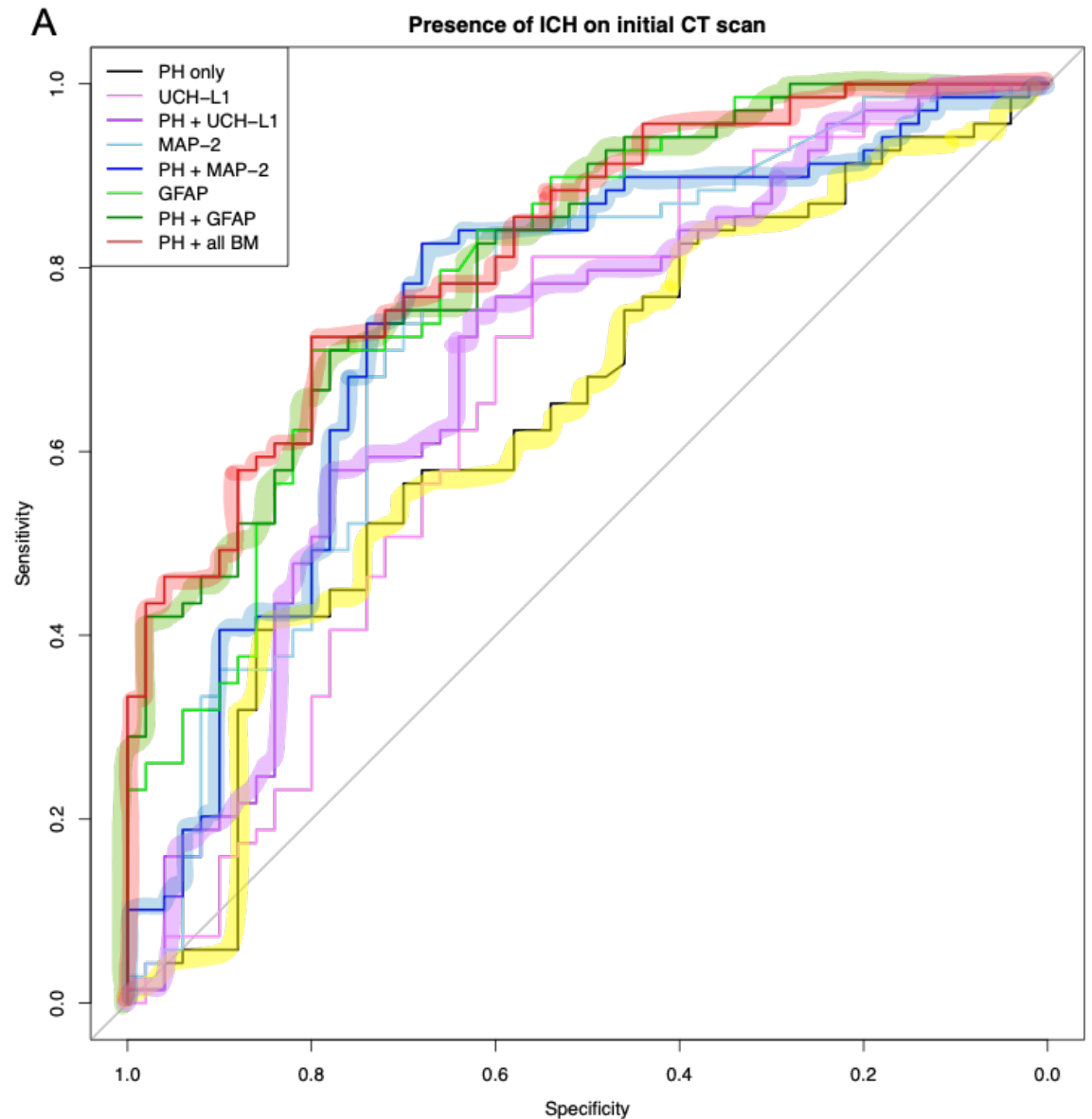
RADIOGRAPHIC ENDPOINTS

INTRACRANIAL HEMORRHAGE

Addition of individual biomarkers to PH improved prediction over PH alone (AUC = 0.639)

- GFAP (0.816)**
- MAP-2 (0.752)**
- UCH-L1 (0.699)*
- Combined biomarkers (0.824)**

(*p<0.01, **p<0.001)

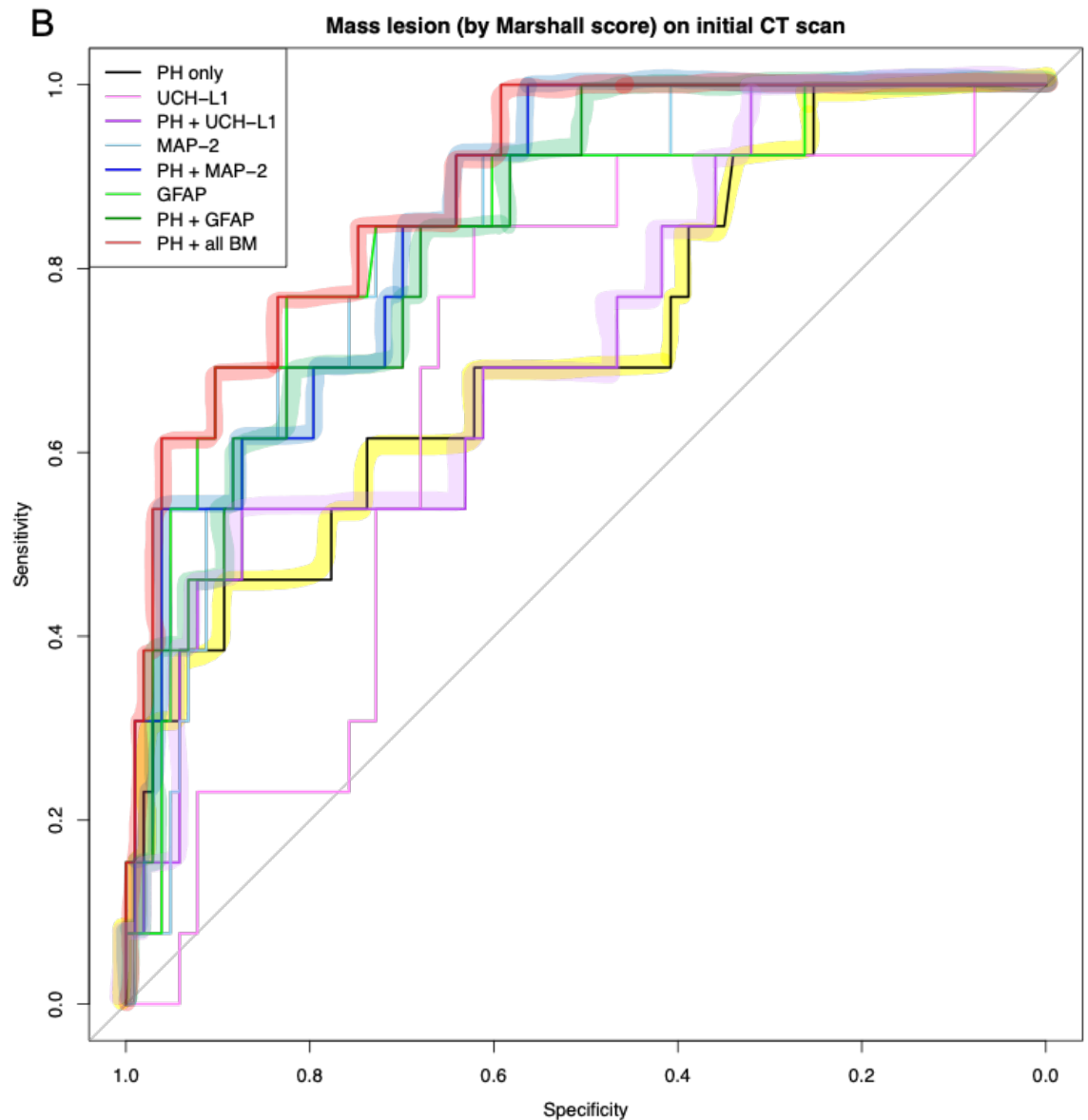


MARSHALL SCORE 5 OR 6

Addition of GFAP and MAP-2 to PH (not UCH-L1) improved prediction over PH alone (AUC = 0.715)

- **GFAP (0.839)***
- **MAP-2 (0.857)***
- **UCH-L1 (0.686)**
- **Combined biomarkers (0.891)***

(*p<0.01, **p<0.001)



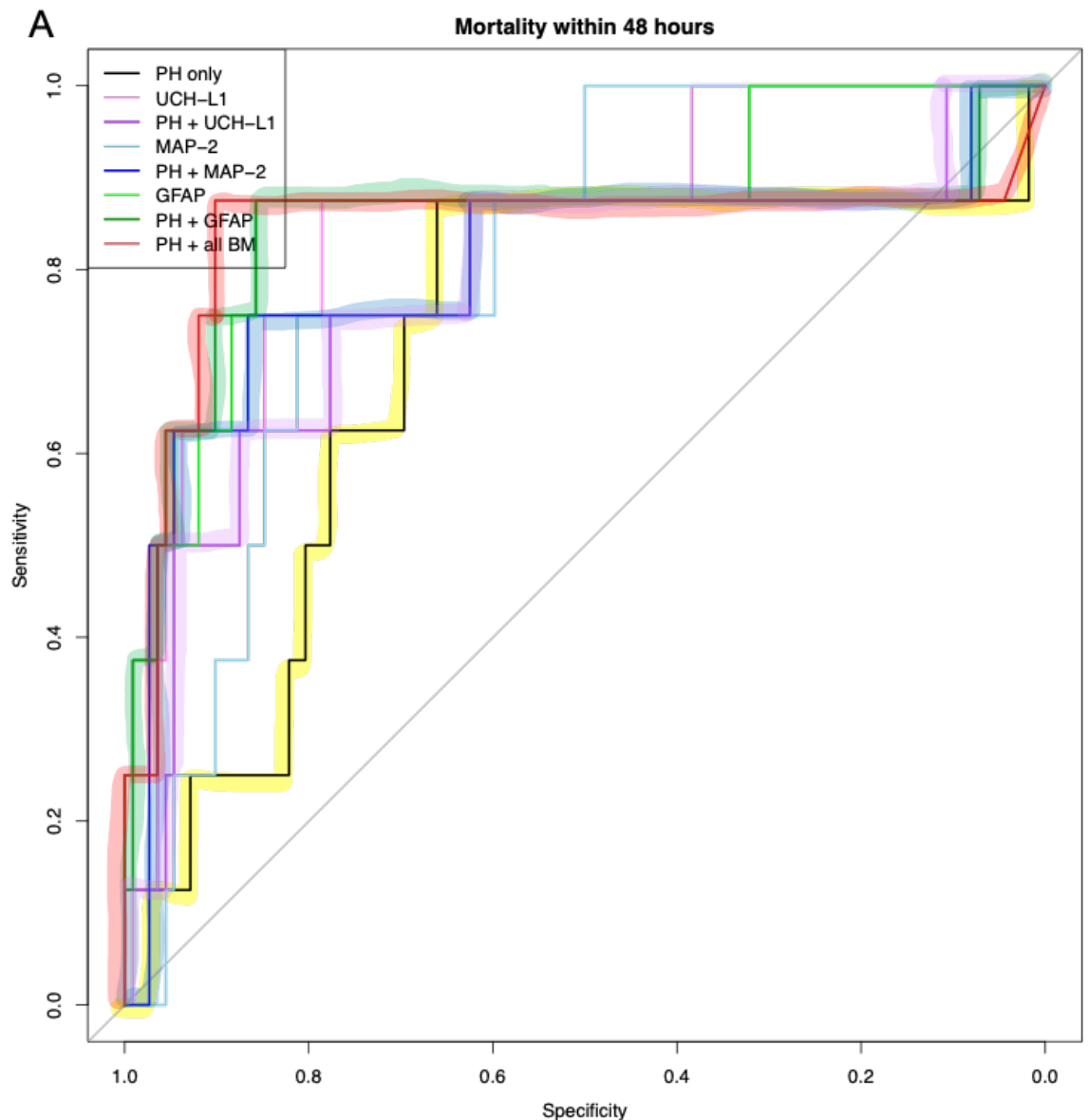
RESULTS: CLINICAL ENDPOINTS

48-HOUR MORTALITY

Addition of GFAP and MAP-2 to PH (not UCH-L1) improved prediction over PH alone (AUC = 0.713)

- **GFAP (0.842)****
- **MAP-2 (0.801)***
- **UCH-L1 (0.779)**
- **Combined biomarkers (0.841)****

(* $p < 0.01$, ** $p < 0.001$)

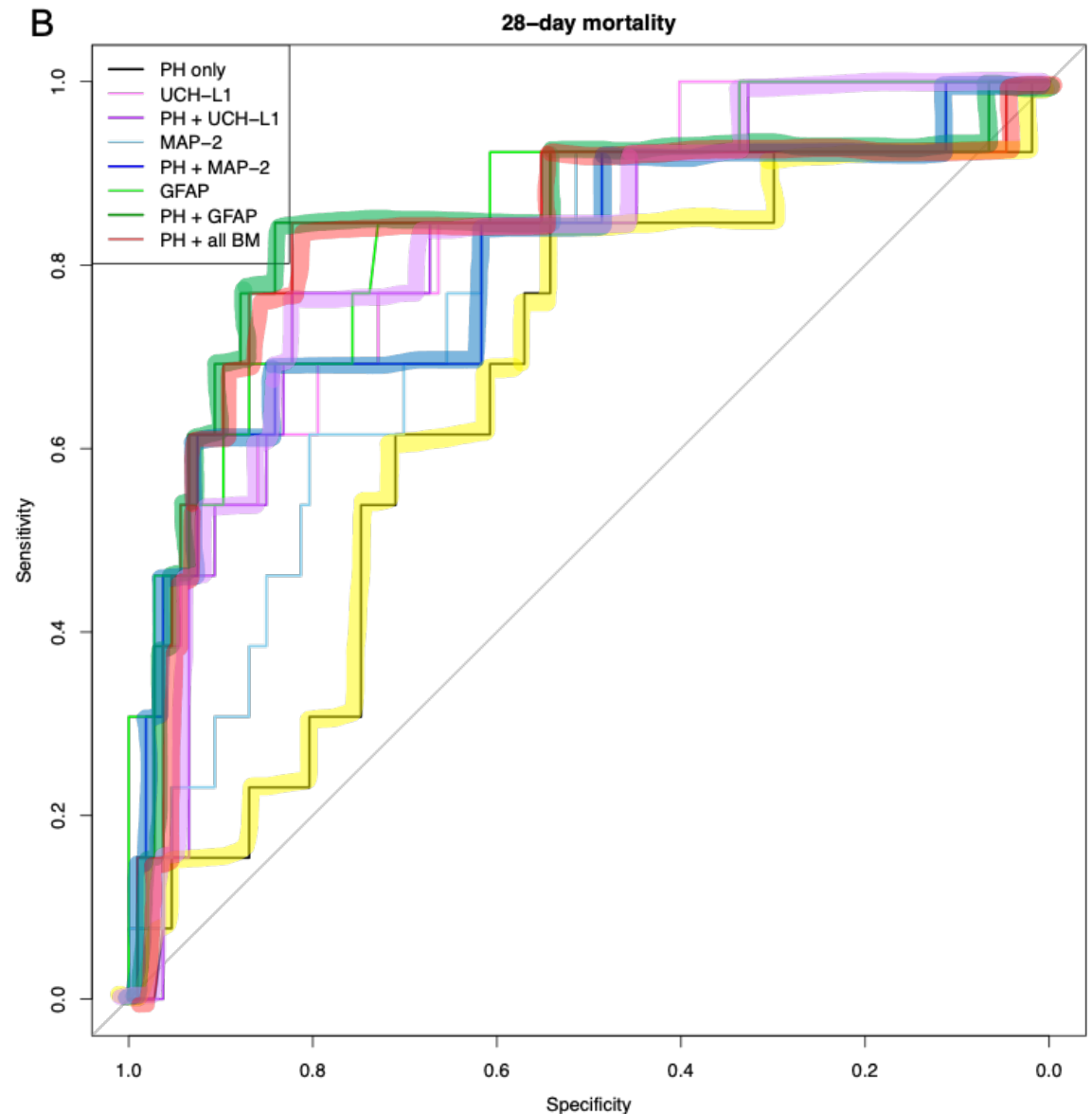


28-DAY MORTALITY

Addition of individual biomarkers to PH improved prediction over PH alone (AUC = 0.660)

- GFAP (0.843)**
- MAP-2 (0.799)*
- UCH-L1 (0.809)*
- Combined biomarkers (0.838)**

(* $p < 0.01$, ** $p < 0.001$)

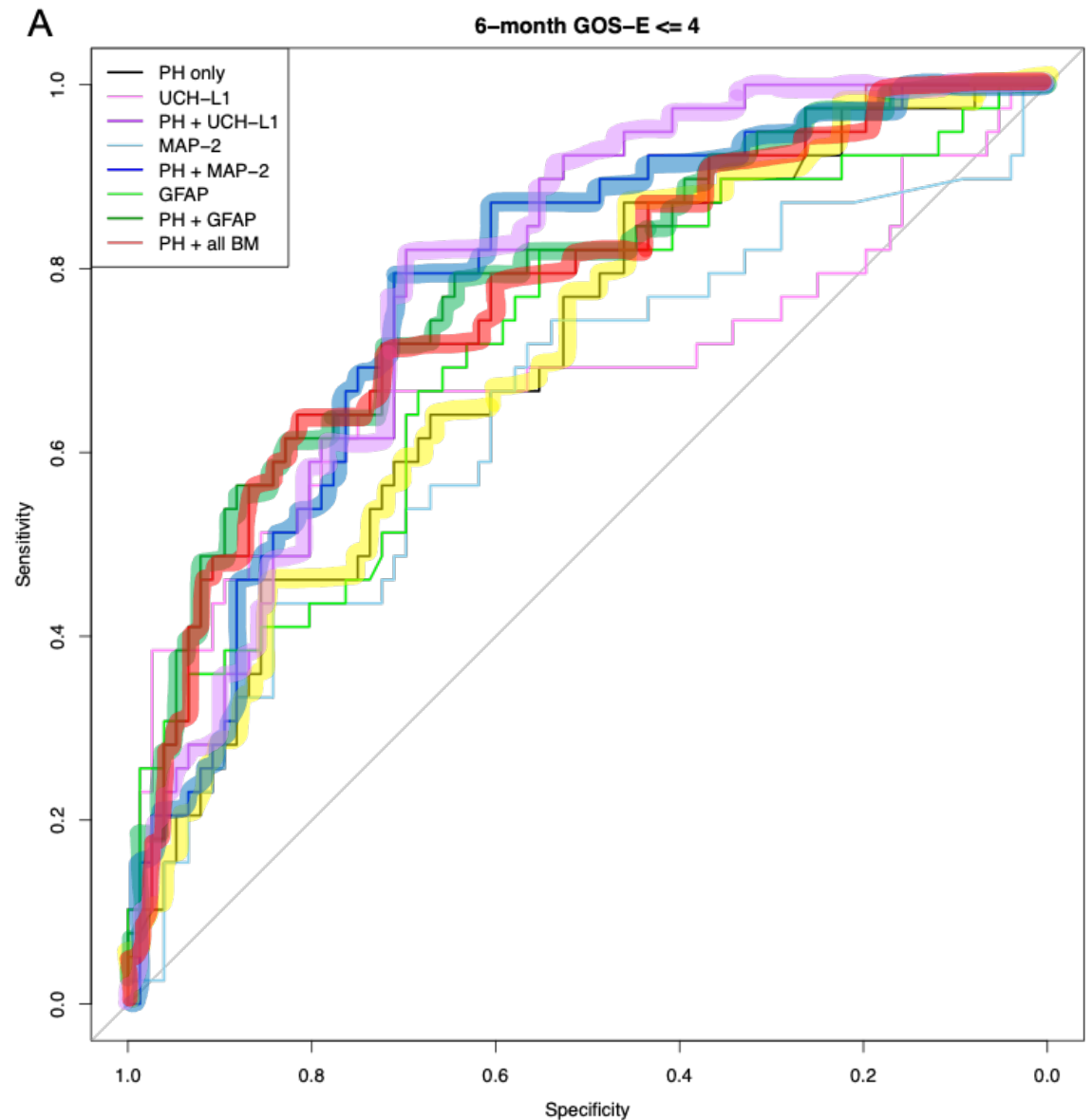


6-MONTH GOSE

Addition of individual biomarkers to PH improved prediction over PH alone (AUC = 0.700)

- GFAP (0.780)**
- MAP-2 (0.777)*
- UCH-L1 (0.788)*
- Combined biomarkers (0.771)**

(*p<0.01, **p<0.001)

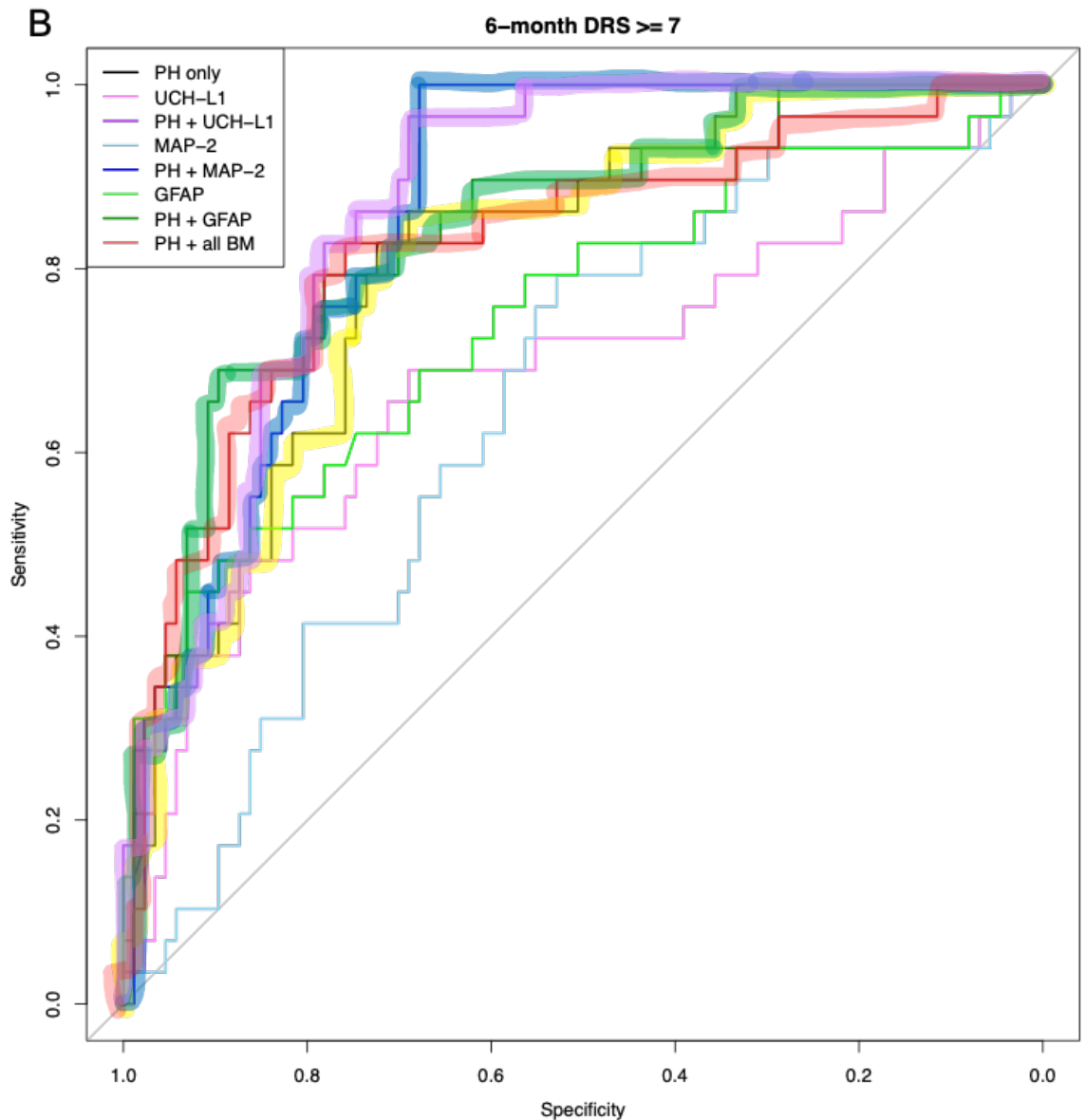


6-MONTH DRS

Addition of GFAP and MAP-2 to PH (not UCH-L1) improved prediction over PH alone (AUC = 0.811)

- **GFAP (0.841)****
- **MAP-2 (0.862)***
- **UCH-L1 (0.865)**
- **Combined biomarkers (0.822)****

(*p<0.01, **p<0.001)



CONCLUSIONS

Serum biomarker levels improved prediction of radiographic findings, mortality, and long-term outcome in moderate-to-severe TBI.



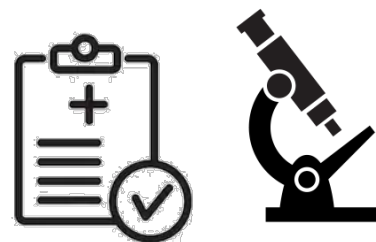
- Earliest time to biomarker collection in a TBI trial (84 min).

LIMITATIONS

- Included patients with **polytrauma**
- **7%** of patients lost to 6-month follow-up

FUTURE DIRECTIONS

- Compare predictive value to **IMPACT score** (current gold standard)
- Define standard biomarker **cutoff ranges** for clinical use





THANK YOU FOR YOUR ATTENDANCE

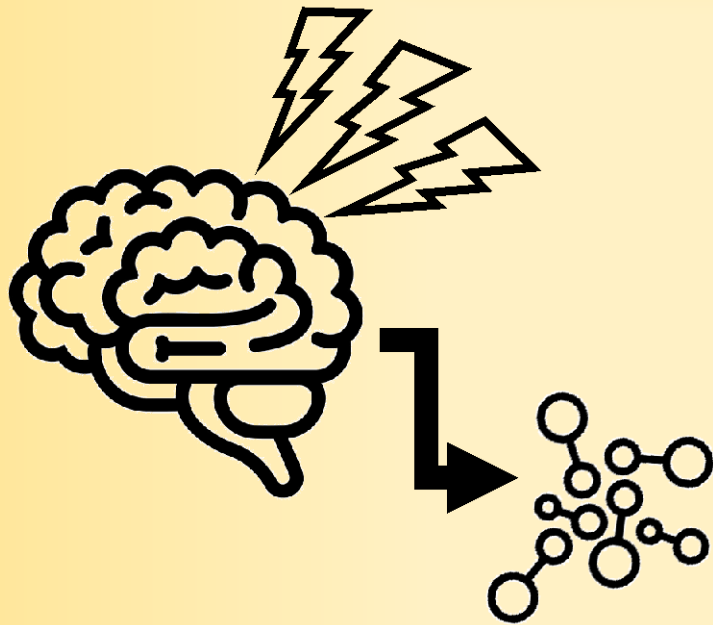


Special thanks to the patients, families, EMS personnel, and research coordinators who made this study possible.



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METHODS



Moderate-severe TBI
(n=243)

Serum GFAP, UCH-L1, MAP-2

RESULTS



Biomarkers improved prediction of radiologic findings, mortality, and 6-month clinical outcome.
($p < 0.05$)

CONCLUSIONS



Biomarkers may have utility for triage and outcome prediction in moderate-severe TBI.

GOS-E AND DRS

GOS-E	Definition
Vegetative State	Unable to obey commands
Lower severe disability	Dependent on others for care
Upper severe disability	Independent at home
Lower moderate disability	Independent at home and outside the home but with some physical or mental disability
Upper moderate disability	Independent at home and outside the home but with some physical or mental disability, with less disruption than the lower moderate disability
Lower good recovery	Able to resume normal activities with some injury-related problems
Upper good recovery	No problem

Patient Name _____
 Rater _____
 Date Completed _____

Disability Rating Scale (DRS)

Arousability, Awareness, & Responsivity

- | | | |
|--|---|--|
| Eye Opening | Communication Ability | Motor Response |
| <input type="checkbox"/> 0 Spontaneous | <input type="checkbox"/> 0 Oriented | <input type="checkbox"/> 0 Obeying |
| <input type="checkbox"/> 1 To Speech | <input type="checkbox"/> 1 Confused | <input type="checkbox"/> 1 Localizing |
| <input type="checkbox"/> 2 To Pain | <input type="checkbox"/> 2 Inappropriate | <input type="checkbox"/> 2 Withdrawing |
| <input type="checkbox"/> 3 None | <input type="checkbox"/> 3 Incomprehensible | <input type="checkbox"/> 3 Flexing |
| | <input type="checkbox"/> 4 None | <input type="checkbox"/> 4 Extending |
| | | <input type="checkbox"/> 5 None |

Cognitive Ability for Self Care Activities

Knows how and when to feed, toilet or groom self

- | | | |
|---------------------------------------|---------------------------------------|---------------------------------------|
| Feeding | Toileting | Grooming |
| <input type="checkbox"/> 0.0 Complete | <input type="checkbox"/> 0.0 Complete | <input type="checkbox"/> 0.0 Complete |
| <input type="checkbox"/> 0.5 | <input type="checkbox"/> 0.5 | <input type="checkbox"/> 0.5 |
| <input type="checkbox"/> 1.0 Partial | <input type="checkbox"/> 1.0 Partial | <input type="checkbox"/> 1.0 Partial |
| <input type="checkbox"/> 1.5 | <input type="checkbox"/> 1.5 | <input type="checkbox"/> 1.5 |
| <input type="checkbox"/> 2.0 Minimal | <input type="checkbox"/> 2.0 Minimal | <input type="checkbox"/> 2.0 Minimal |
| <input type="checkbox"/> 2.5 | <input type="checkbox"/> 2.5 | <input type="checkbox"/> 2.5 |
| <input type="checkbox"/> 3.0 None | <input type="checkbox"/> 3.0 None | <input type="checkbox"/> 3.0 None |

Dependence on Others

Level of Functioning

Physical & cognitive disability

- | | |
|------------------------------|---|
| <input type="checkbox"/> 0.0 | Completely Independent |
| <input type="checkbox"/> 0.5 | |
| <input type="checkbox"/> 1.0 | Independent in special environment |
| <input type="checkbox"/> 1.5 | |
| <input type="checkbox"/> 2.0 | Mildly Dependent-Limited assistance
Non-resident helper |
| <input type="checkbox"/> 2.5 | |
| <input type="checkbox"/> 3.0 | Moderately Dependent-moderate assist
Person in home |
| <input type="checkbox"/> 3.5 | |
| <input type="checkbox"/> 4.0 | Markedly Dependent
Assistance with all major activities, all times |
| <input type="checkbox"/> 4.5 | |
| <input type="checkbox"/> 5.0 | Totally Dependent
24-hour nursing care |

Psychosocial Adaptability

Employability

As full time worker, housemaker, student

- | | |
|------------------------------|--------------------------------|
| <input type="checkbox"/> 0.0 | Not Restricted |
| <input type="checkbox"/> 0.5 | |
| <input type="checkbox"/> 1.0 | Selected jobs, competitive |
| <input type="checkbox"/> 1.5 | |
| <input type="checkbox"/> 2.0 | Sheltered workshop, Noncompet. |
| <input type="checkbox"/> 2.5 | |
| <input type="checkbox"/> 3.0 | Not Employable |

Total Score (sum all scores) _____

Revised 2009 Santa Clara Valley Medical Center