Biomarker Assessment For Neurotrauma Diagnosis and Improved Triage System (BANDITS):

2009 Interim Analysis

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Advanced Technology Applications for Combat Casualty Care (ATACCC)

BANYAN BIOMARKERS®

BANDITS Mission

BANDITS

Combines

- **state-of-the-art proteomic technology for biomarker discovery**
- **With comprehensive collection of clinical data including:**
  - **Continuous physiological monitoring of subjects**
  - **Neuroimaging**

Clinical validation of biomarkers will provide highly quantitative and objective diagnostic information *for triage and medical management* of *injured personnel in far-forward combat environments*

BANDITS
MILD, MODERATE, SEVERE TBI

RECRUITMENT

RECRUITMENT
Through July 31st, 2009

MULTI- CENTER SEVERE TBI FEASIBILITY STUDY (GCS 3-8):

All sites – 126 Patients } ***(GOAL 200)***

MILD (GCS 13-15) AND MODERATE (GCS 9-12) TBI PILOT STUDY

Total Patients studied

51 Mild TBI Patients
7 Moderate TBI Patients } ***(GOAL 50)***

- **Orlando Regional Medical Center**

13 Mild TBI Patients

2 Moderate TBI Patients

- **Washington Univ. St. Louis**

38 Mild TBI Patients

5 Moderate TBI Patients

*Pilot data from site selected for mild and moderate Feasibility Study

BANDITS
ASSAY DEVELOPMENT

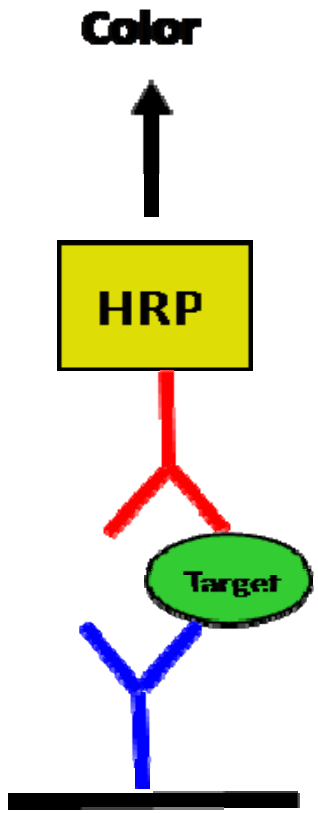
Summary of Assay Development Efforts

- **UCH-L1:** Assay works well in CSF and serum with sufficient sensitivity and precision – working on eliminating tertiary antibody.
- **GFAP:** Assay works well in CSF and serum with sufficient sensitivity and precision – working on eliminating streptavidin bridge.
- **SBDP145:** Assay works well in CSF but needs improvements in sensitivity for serum analyses; working on eliminating tyramide signal amplification

- **Current efforts** focused on:
  - Reducing assay complexity
  - Improving antibody affinities
  - Changing to simplified detection modes (colorimetric) to facilitate for easier transition into assay automation

Desired Assay Format

Simple, Robust, Automatable and Cost-effective



BANDITS
SEVERE TBI FEASIBILITY STUDY

Treatment and Control Groups

Severe TBI		
n	101	
Age, years Mean (SD)	48.78 ± 19.83	
Min-Max	19-88	
F/M, n	24/77	
F/M, %	23.8/ 76.2 %	
Ethnicity	Not Hispanic or Latino	99
	Hispanic or Latino	2
Race	Caucasian	89
	Asian	3
	Black or African American	8
	Other	1
GCS	3	30
	4	15
	5	15
	6	15
	7	16
	8	10
Mechanism of Injury:	Motor Vehicle Accident	34
	Moto Cycle Accident	4
	Gun Shot Wound	2
	Fall	43
	Sport Injury	4
	Assault	14
	Other	34

Control Groups

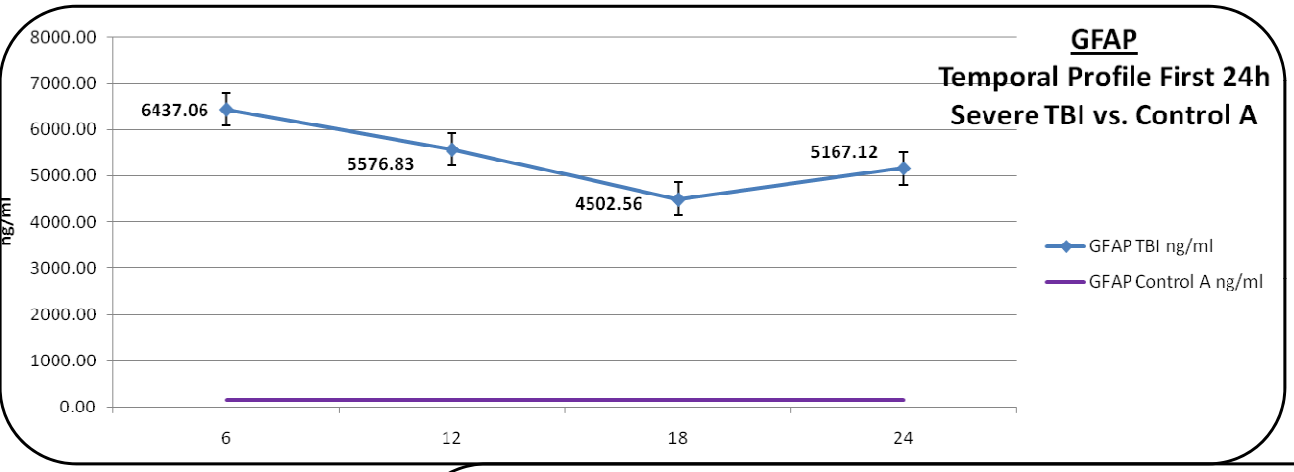
Control A (CSF)		
n	24	
Age, years Mean (SD)	57.12 ± 16.63	
Min-Max	23-83	
F/M, n	7/17	
F/M, %	29.2/ 70.3 %	
Ethnicity	Not Hispanic or Latino	24
	Hispanic or Latino	
Race	Caucasian	24
	Asian	
	Black or African American	
	Other	
GCS		
	15	24
Procedures:		
	Lumbar Puncture	11
	Intraventricular Placement	13
Causes:	Hydrocephalus	20
	Cyst (Colloid, Subarachnoidealis)	2
	SAH – a. comm. anterior aneurysm.	1
	Lumbalr liquor-drainage after ICH	1
	Other	

Normal Controls (Serum)		
n	167	
Age, years Mean (SD)	36.91 ± 14.06	
Min-Max	18-74	
F/M, n	72/95	
F/M, %	43.1/ 56.9 %	
Ethnicity	Not Hispanic or Latino	146
	Hispanic or Latino	13
	N/A	8
Race	Caucasian	53
	Asian	7
	Black or African American	4
	Middle Eastern	1
Alcohol (Y/N)	114/47	
	N/A 6	
Drug	19/ 147	
	N/A 1	
Smoke (Y/N)	54/112	
	N/A 1	
Health	Excellent	78
	Good	74
	Average	13
	N/A	2

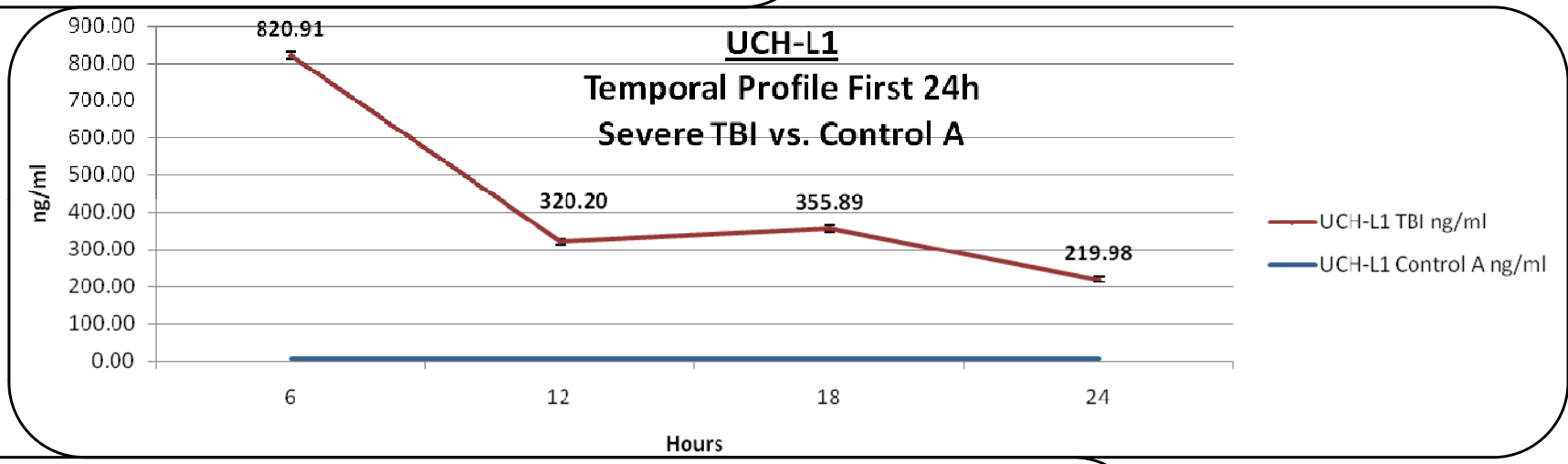
BANDITS
SEVERE TBI FEASIBILITY STUDY

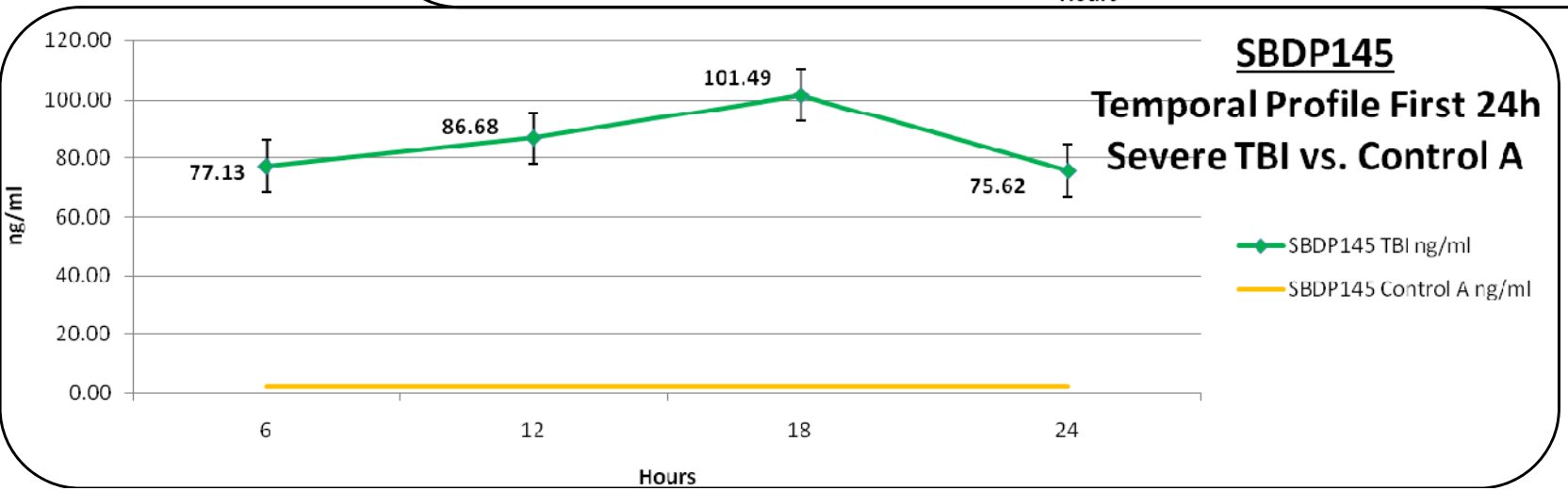
Biomarker Temporal Profile

Temporal Profile of CSF Levels of Biomarkers in the first 24 hours

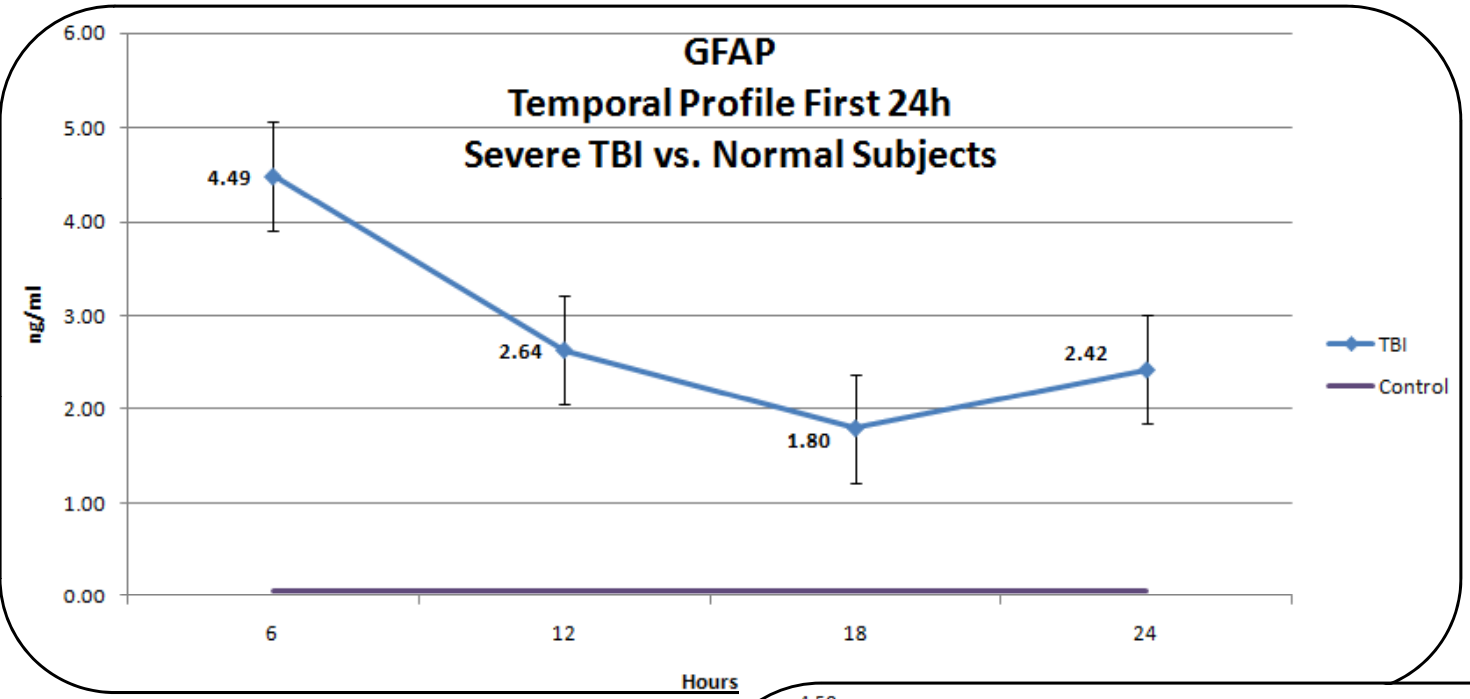


Sample Size – TBI	168	Sample Size – Control A	24

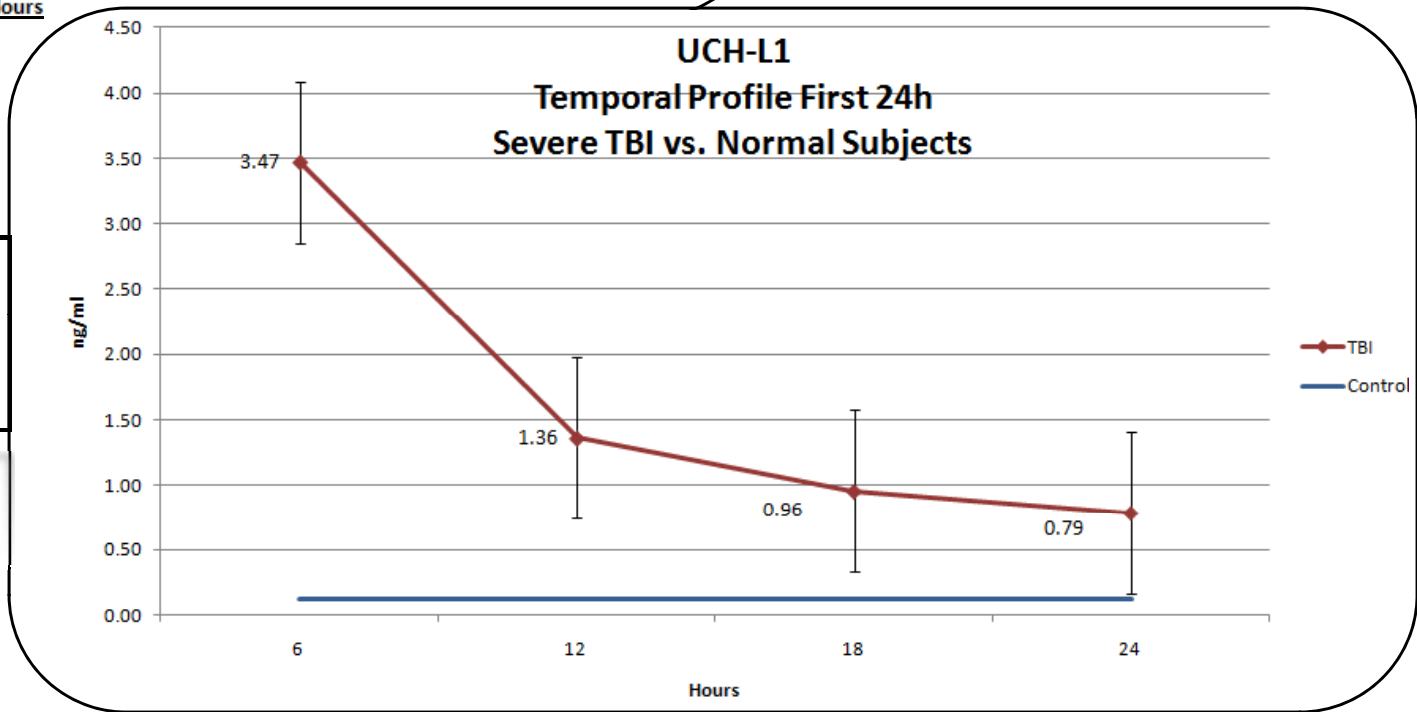




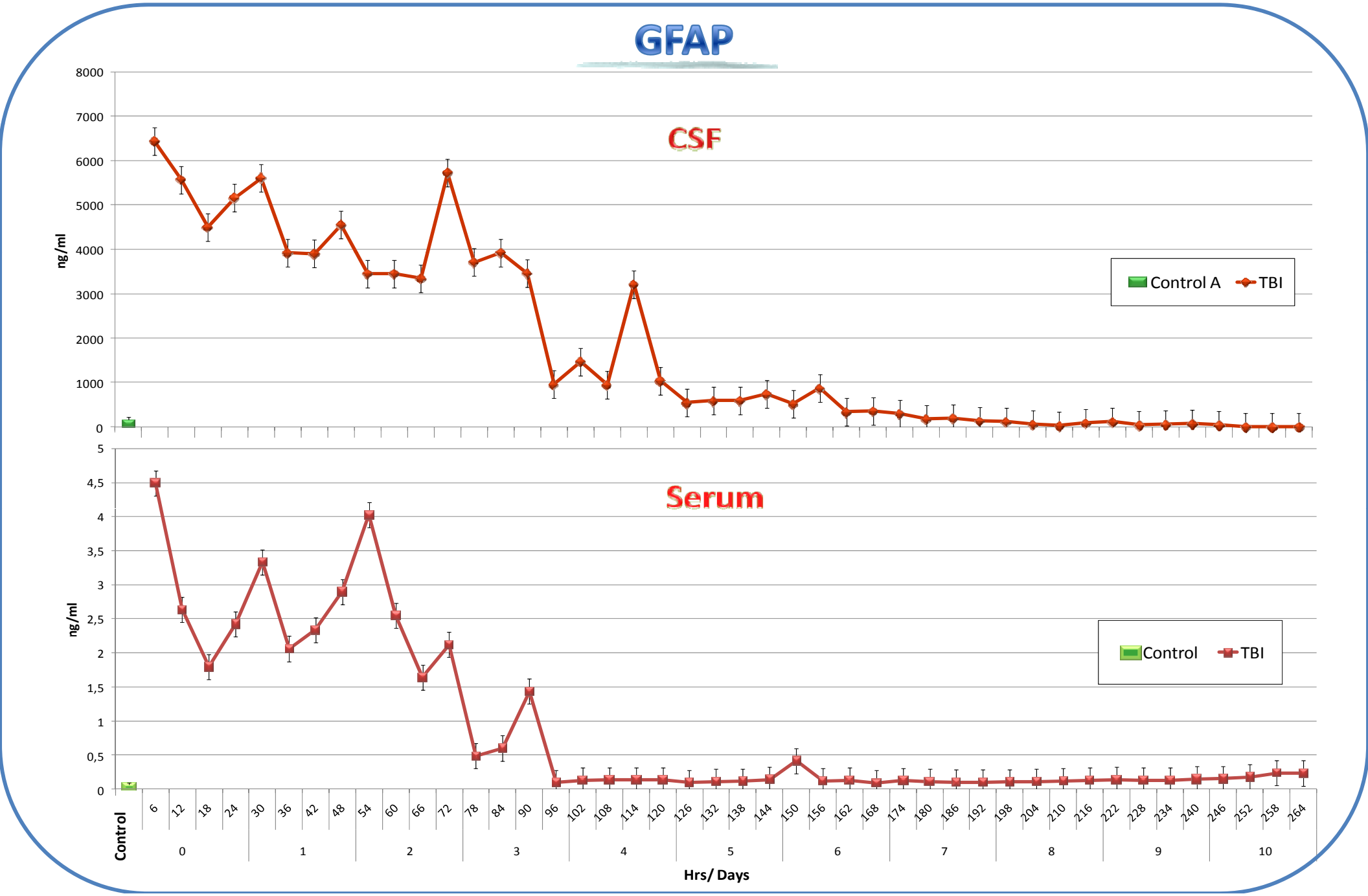
Temporal Profile of Serum Levels of Biomarkers in the first 24 hours



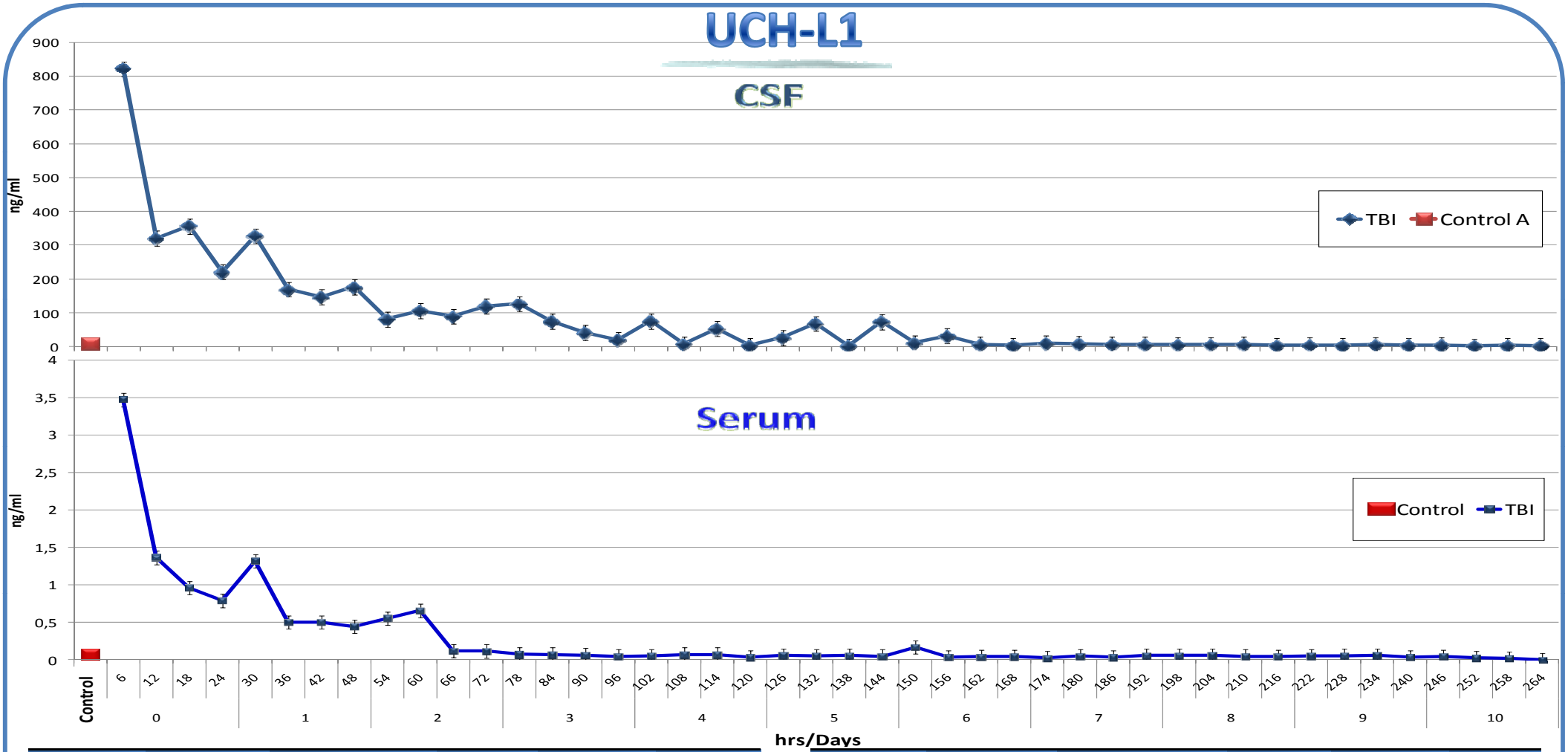
Sample Size – TBI	244	Sample Size – Controls	166



Temporal Profile of GFAP in CSF and Serum over study (10 Days)



Temporal Profile of UCH-L1 in CSF and Serum over study (10 Days) & Kinetics Analysis related



CSF UCH-L1	Cmax (ng/ml)	AUC (ng/ml*min)	Tmax hrs	T1/2term hrs	MRTsys hrs
count	19	19	19	18	19
mean	803.36	1066270.53	39.81	8.48	51.93
SD	2366.59	2492304.79	58.53	3.96	45.59
Median	**225.05**	**409776.60**	**24.05**	**8.93**	**39.41**
Min	0.15	263.60	2.30	1.41	5.84
Max	10529.12	10823220.76	266.38	17.24	215.53

SERUM UCH-L1	Cmax (ng/ml)	AUC (ng/ml*min)	Tmax hrs	T1/2term hrs	MRTsys hrs
count	20	20	18	12	18
mean	1.90	2709.86	41.65	11.43	51.80
SD	3.43	4797.48	57.88	4.71	37.72
Median	**0.57**	**1099.24**	**20.71**	**10.16**	**36.45**
Min	0.00	0.00	1.00	5.02	5.87
Max	11.76	18313.93	176.25	19.25	125.49

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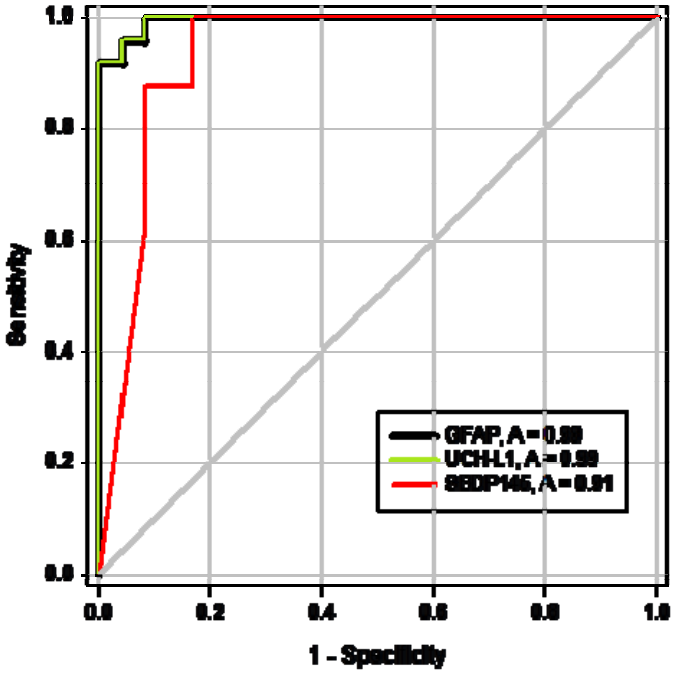
BANDITS
SEVERE TBI FEASIBILITY STUDY

ROC Curve Analysis of Diagnostic Utility

ROC analysis of **UCH-L1, GFAP and SBDP145** in human CSF (severe TBI vs. Control A) First 24 hours post-injury

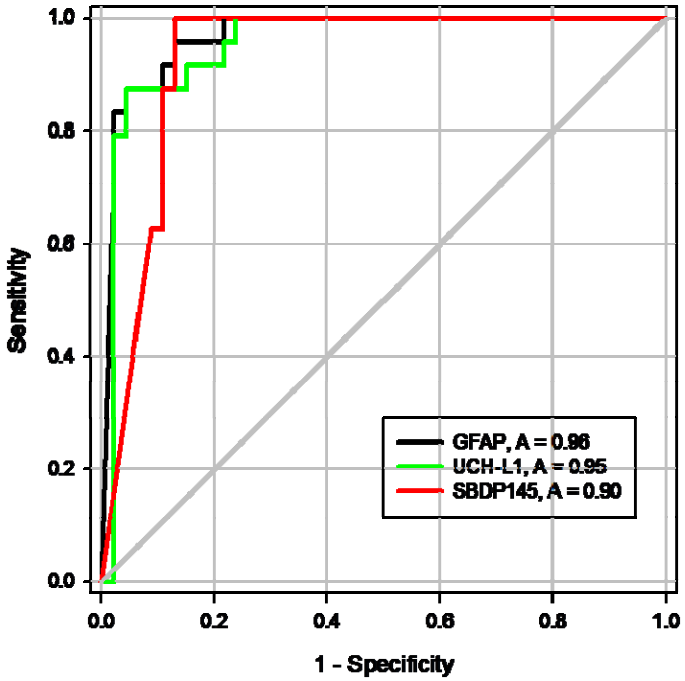
First 6h Post-Injury

Sample Size - TBI	24
Sample Size - Control A	24



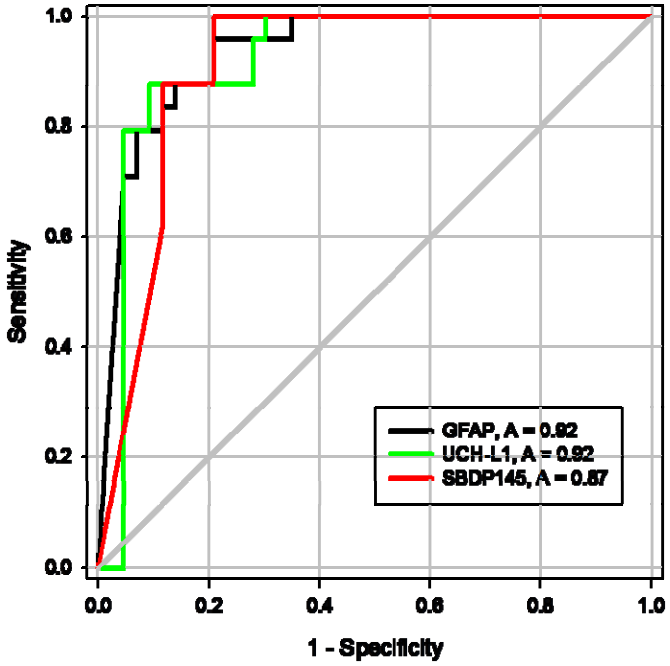
7- 12 h Post-Injury

Sample Size - TBI	46
Sample Size - Control A	24



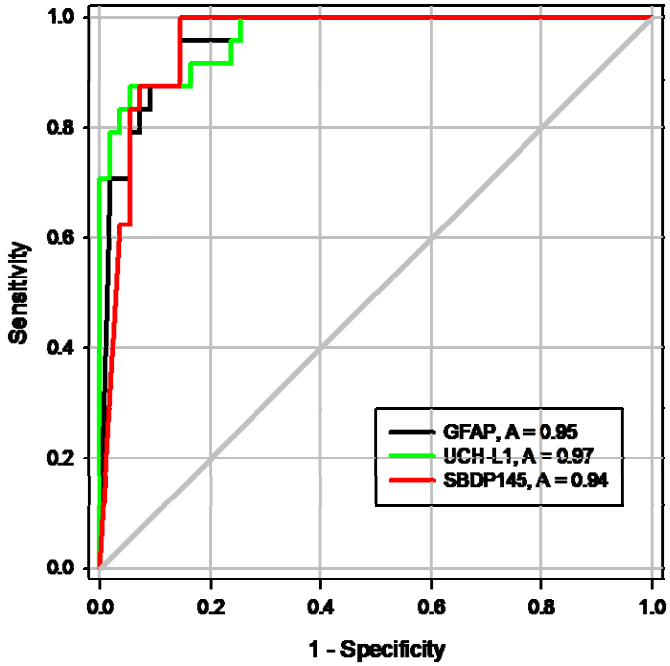
13-18 h Post-Injury

Sample Size - TBI	43
Sample Size - Control A	24



19-24h Post-Injury

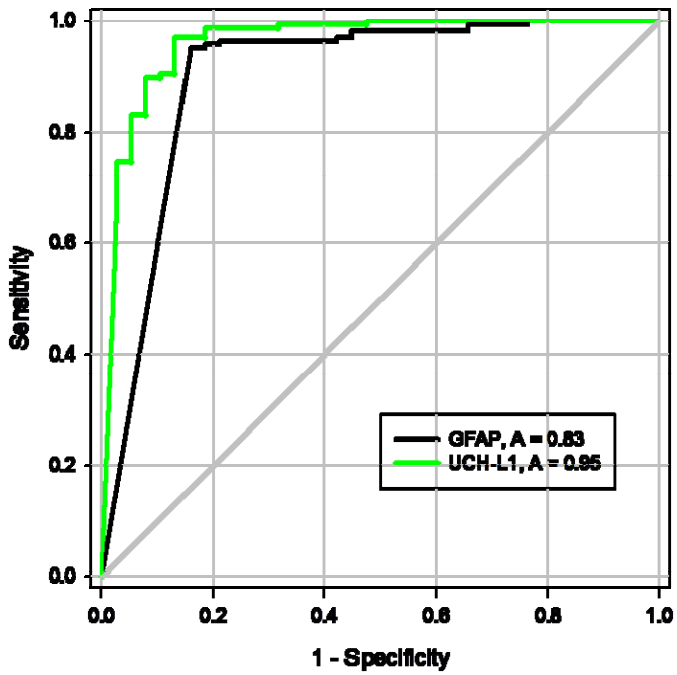
Sample Size - TBI	55
Sample Size - Control A	24



ROC analysis of **UCH-L1 and GFAP** in human serum (severe TBI vs. Normal Controls) First 24 hours post-injury

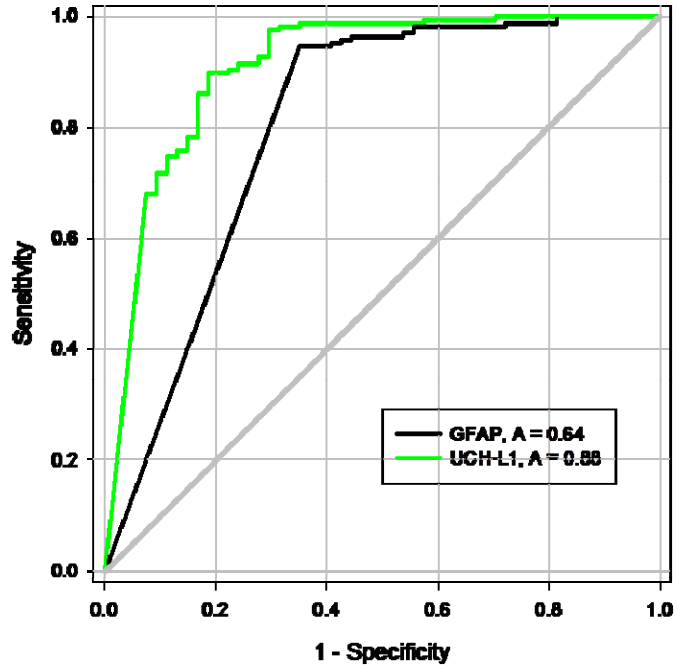
First 6h Post-Injury

Sample Size - TBI	38
Sample Size – Control	166



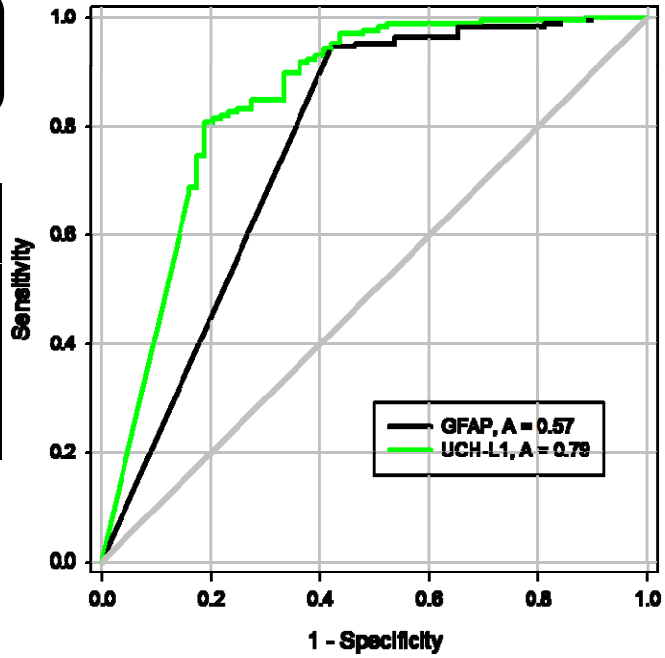
7- 12 h Post-Injury

Sample Size - TBI	54
Sample Size – Control	166



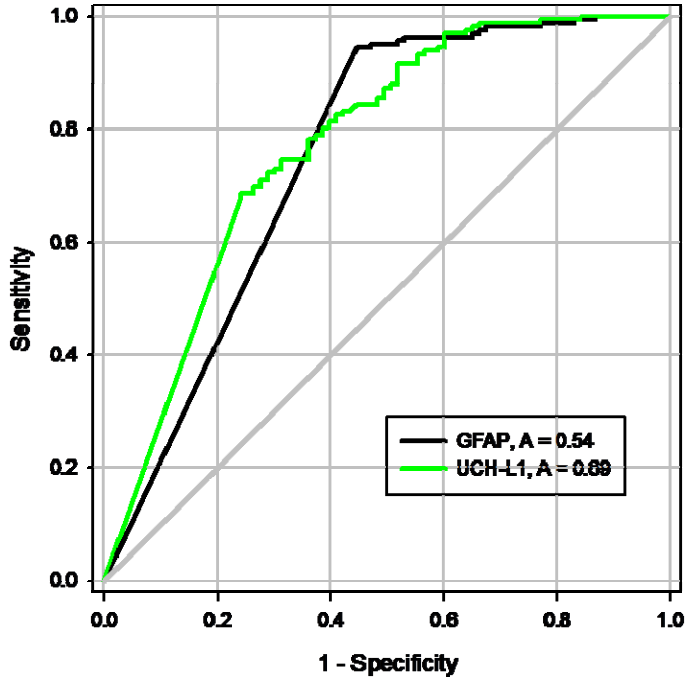
13-18 h Post-Injury

Sample Size - TBI	69
Sample Size - Control	166



19-24h Post-Injury

Sample Size - TBI	83
Sample Size – Control	166



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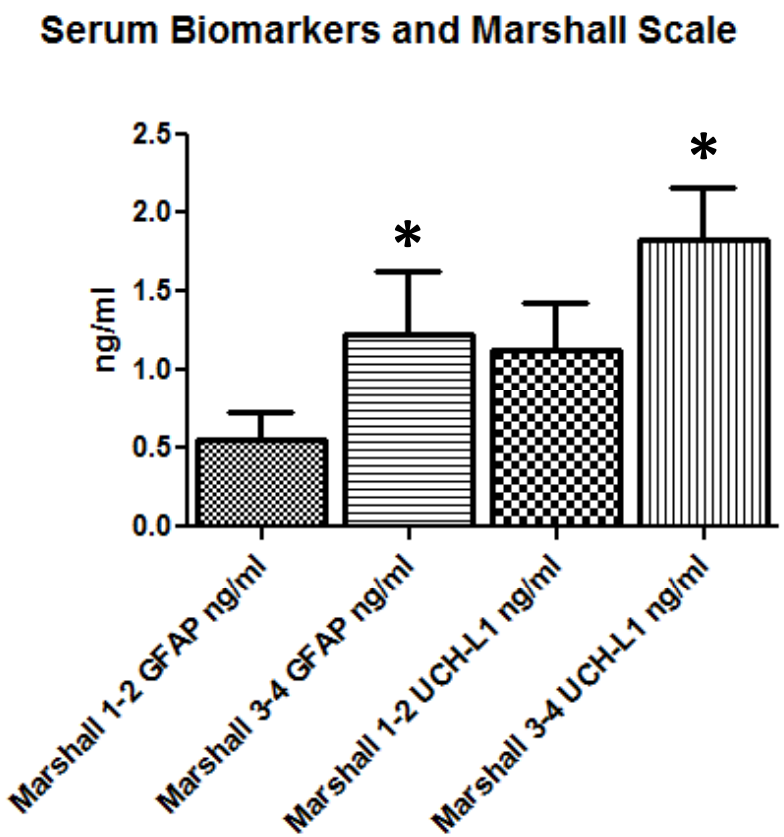
SEVERE TBI FEASIBILITY STUDY

Biomarkers vs. CT Scan

MARSHALL COMPUTERIZED TOMOGRAPHY (CT) CLASSIFICATION

Category	Definition
Diffuse injury I *(no visible pathology)*	No visible intracranial pathology seen on CT scan.
Diffuse injury II	Cisterns are present with midline shift 0–5 mm and/or lesions densities present; no high or mixed density lesion >25 cc; may include bone fragments and foreign bodies.
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm; no high or mixed density lesion 25 mm.
Diffuse injury IV (shift)	Midline shift 5 mm; no high or mixed density lesion 25 cc
Evacuated mass lesion	Any lesion surgically evacuated.
Nonevacuated mass lesion	High or mixed density lesion 25 cc; not surgically evacuated

LEVELS OF BIOMARKERS IN THE FIRST 24HRS AND 1ST CT



UCH-L1

Mann Whitney test	
P value (two-tailed)	*0.0291

GFAP

T- test	
P value (one-tailed)	*0.0485

Sample Size – TBI Marshall 1-2	21	**Sample Size – TBI Marshall 3-4**	15

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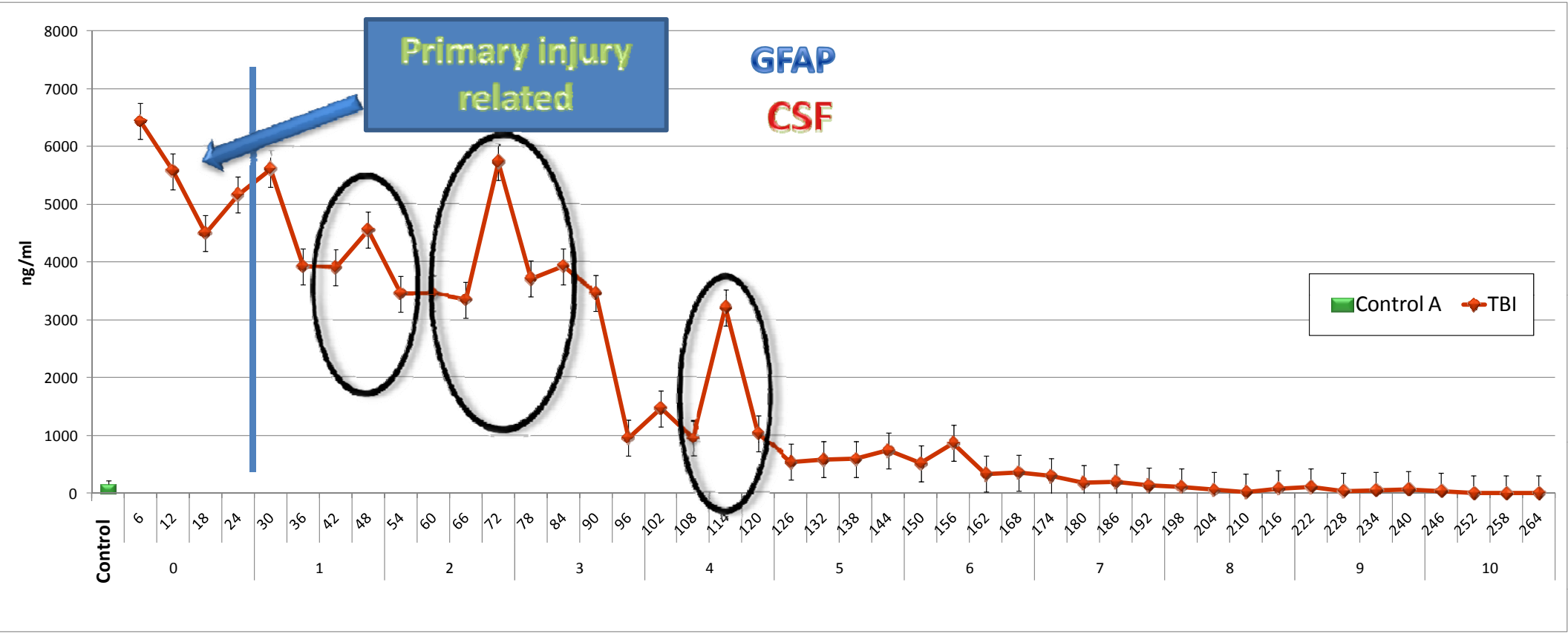
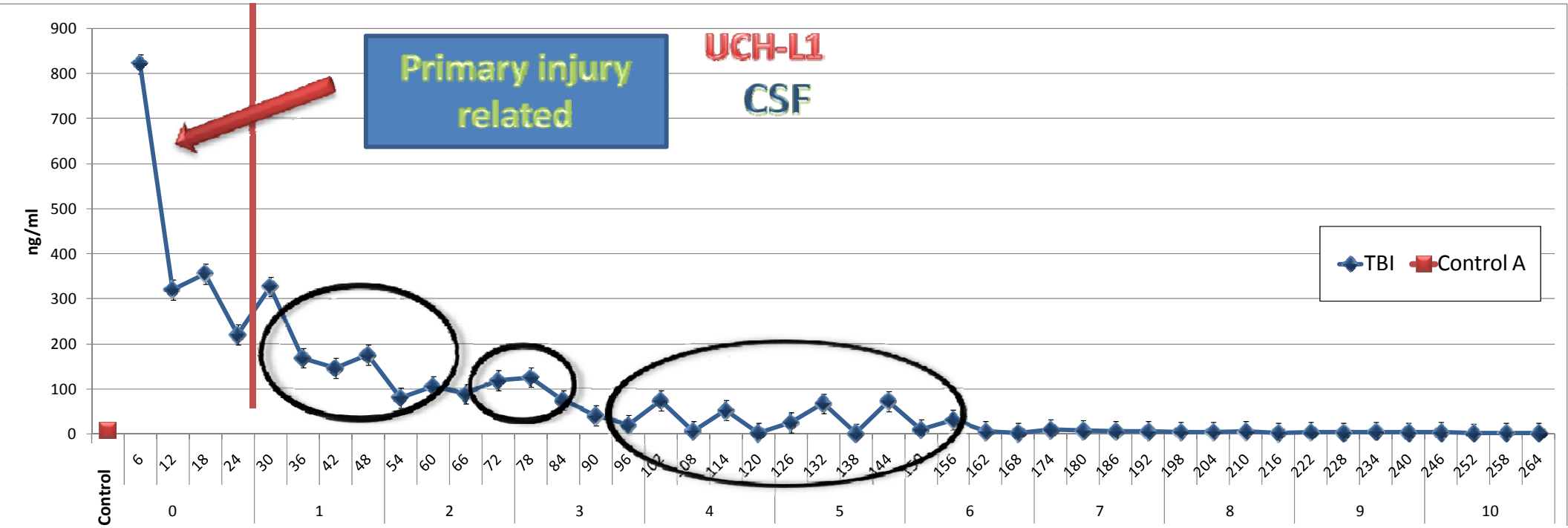
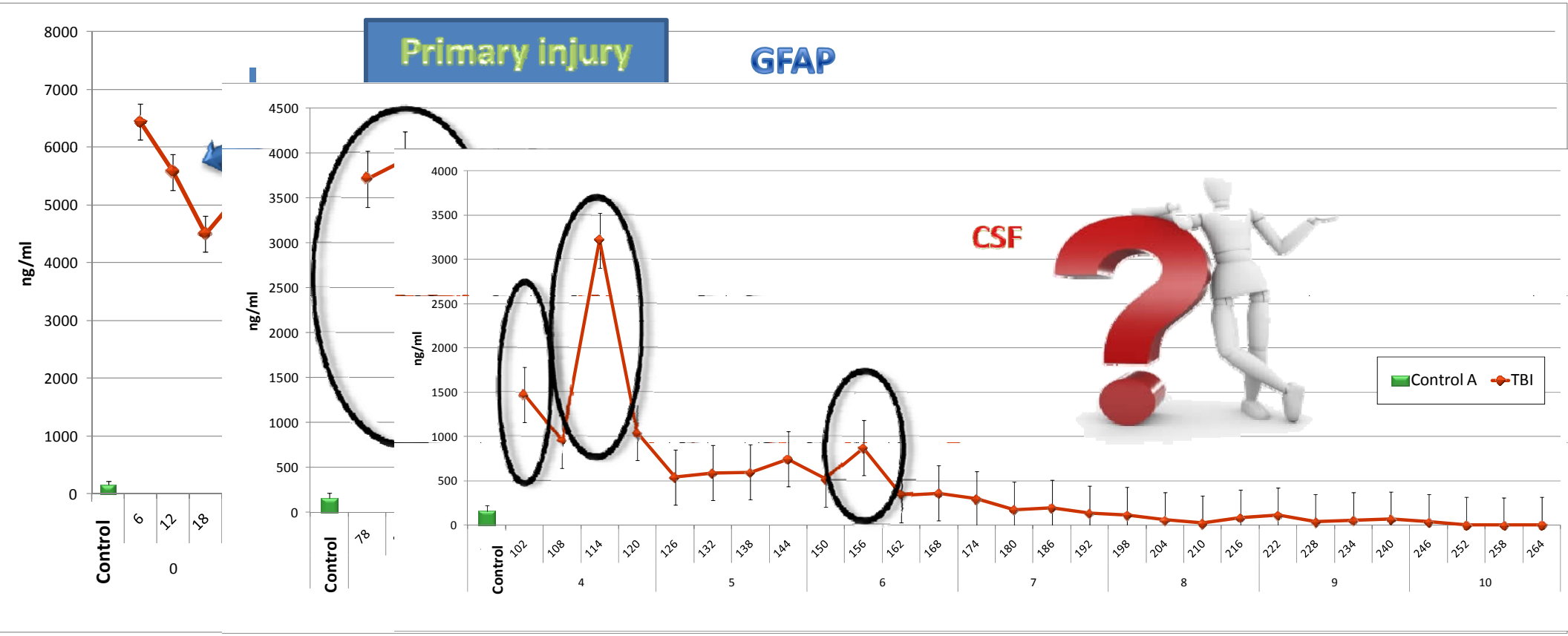
SEVERE TBI FEASIBILITY STUDY

Biomarkers vs. Secondary Insults

Continuous Physiological Monitoring


Primary injury related
GFAP
CSF
ng/ml
Control A
TBI
Control


Primary injury related
UCH-L1
CSF
ng/ml
TBI
Control A
Control


Primary injury
GFAP
CSF
ng/ml
Control A
TBI
Control
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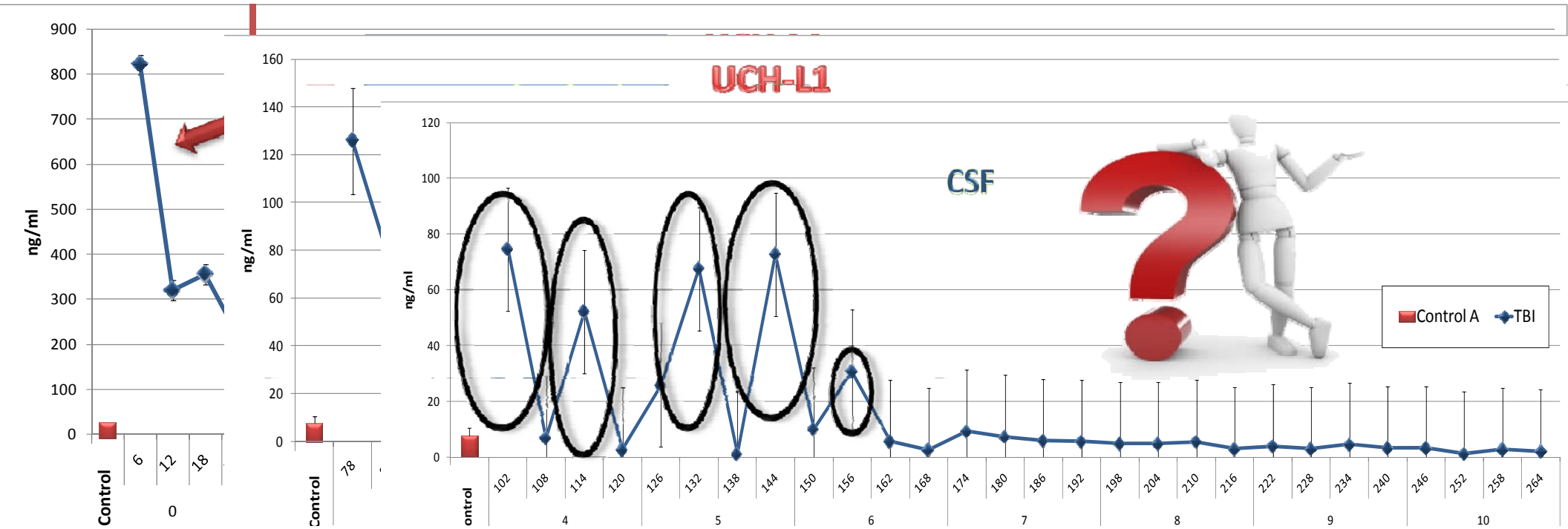
UCH-L1
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Influence of data resolution and interpolation method on assessment of secondary brain insults in neurocritical care

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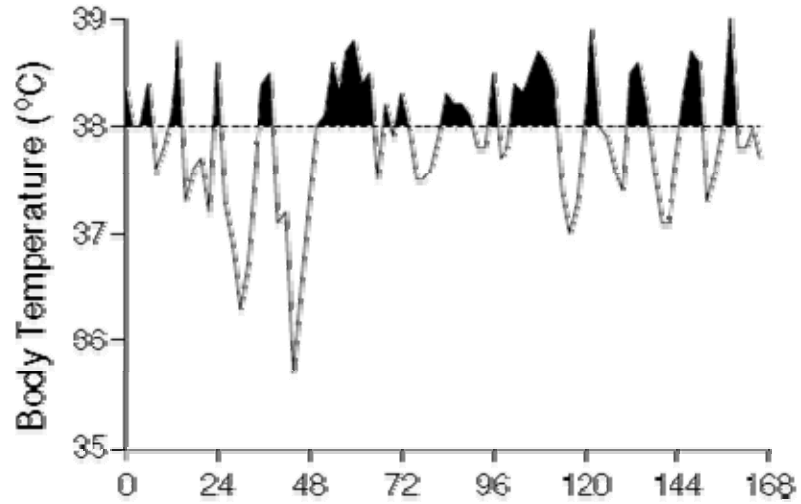
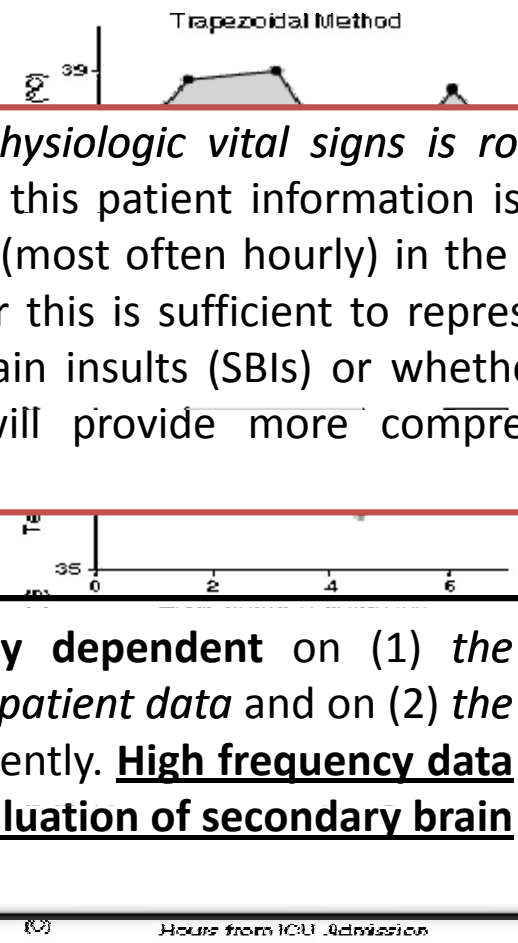
Abstract
Continuous monitoring of physiologic vital signs is routine in neu
However, this patient information is usually only recorded interm
often hourly) in the medical record. It is unclear whether this i
represent the occurrence of secondary brain insults (SBIs) or
frequent data collection will provide more comprehensive in
patient care. In 16 patients, physiologic data were acquired
via two methods: per clinical routine, usually hourly, in the m
(MR) and every minute via a custom data acquisition system (DA). SBIs were
defined as a mean arterial pressure <90 mmHg, an intracranial pressure >
20 mmHg or a temperature >37.5 °C. Number of events, cumulative duration
of events and area un
methods and 95% lim
MR data interpolation
data frequently differe
events and AUC. MR
95% limits of agreeme
data, but even these li
insults is highly depen
to acquire patient data
intermittently. High f
precise evaluation of secondary brain injury in neurocritical care.



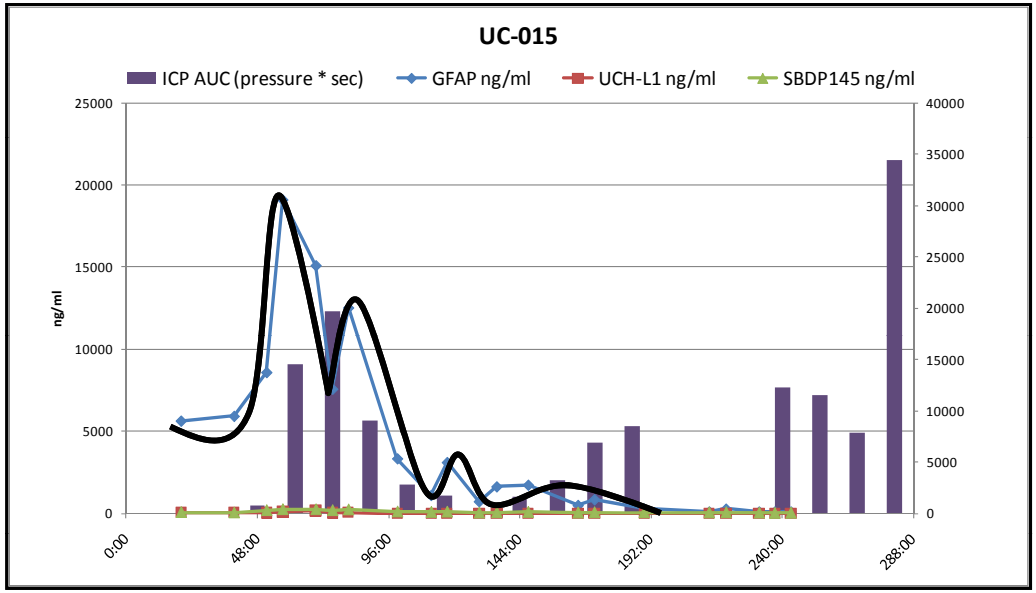


Continuous monitoring of physiologic vital signs is routine in neurocritical care. However, this patient information is usually *only recorded intermittently* (most often hourly) in the medical record. It is unclear whether this is sufficient to represent the occurrence of secondary brain insults (SBIs) or whether more frequent data collection will provide more comprehensive information for patient care.

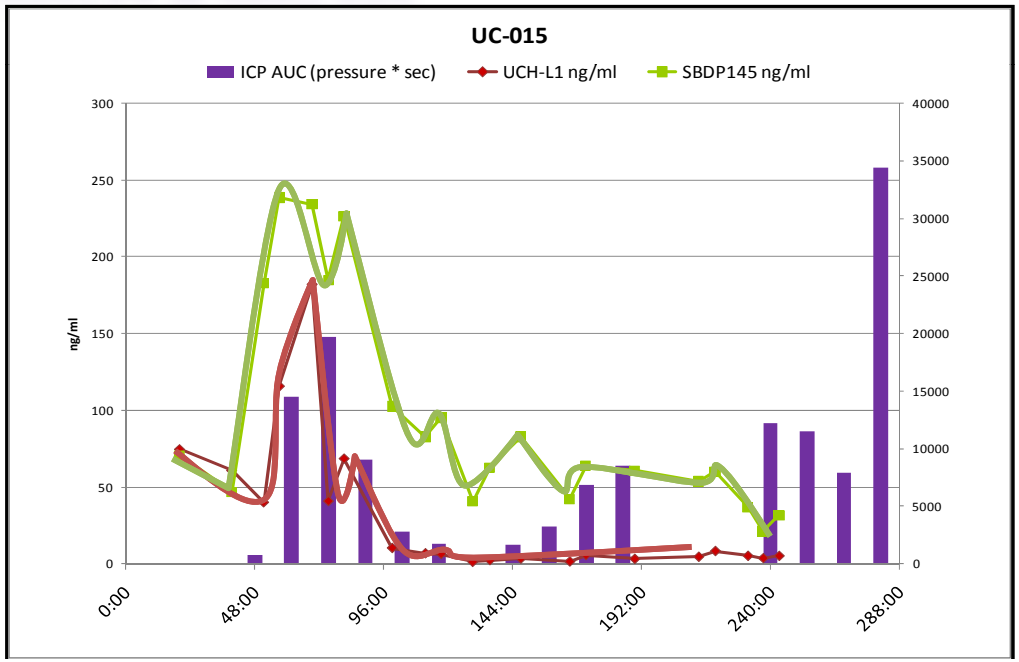
Assessment of secondary brain insults is **highly dependent** on (1) *the temporal resolution of the method used to acquire patient data* and on (2) *the interpolation method* if data are acquired intermittently. **High frequency data acquisition may be necessary for more precise evaluation of secondary brain injury** in neurocritical care.

BIOMARKERS vs. ICP

GFAP

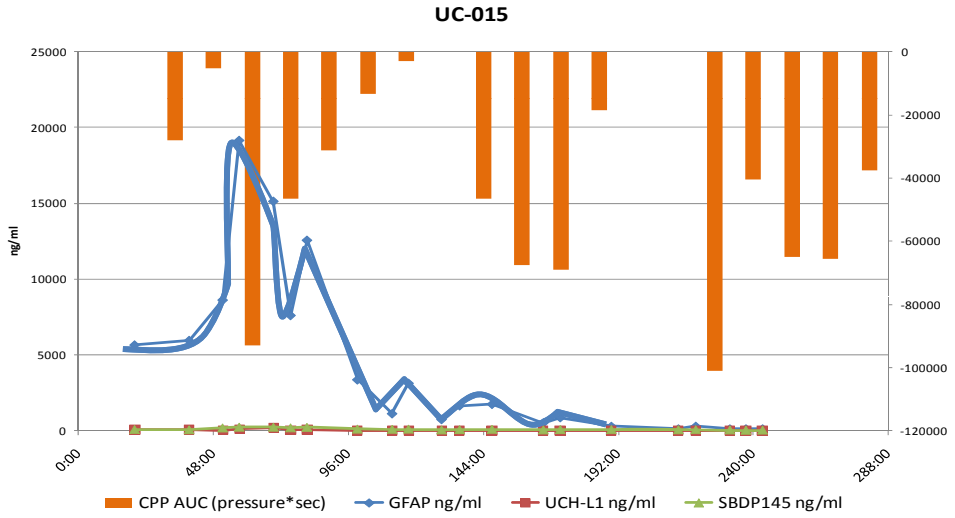


UCH-L1 & SBDP145

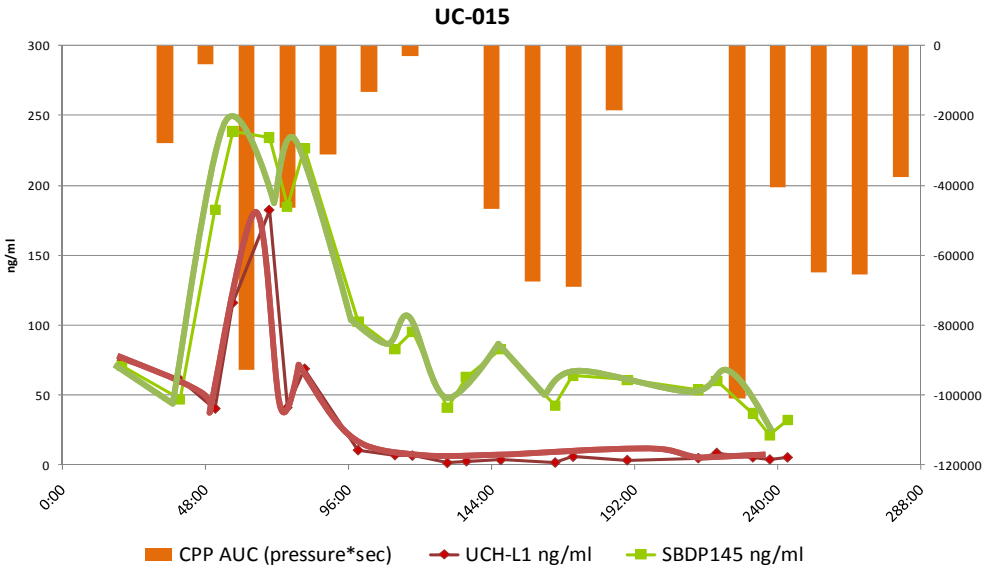


Biomarkers vs. CPP

GFAP



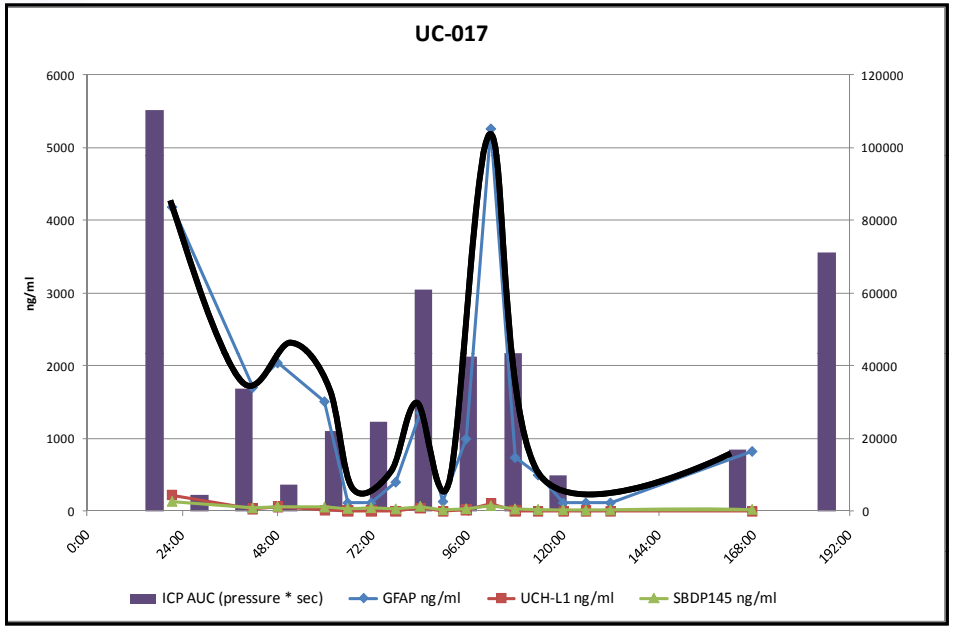
UCH-L1 & SBDP145



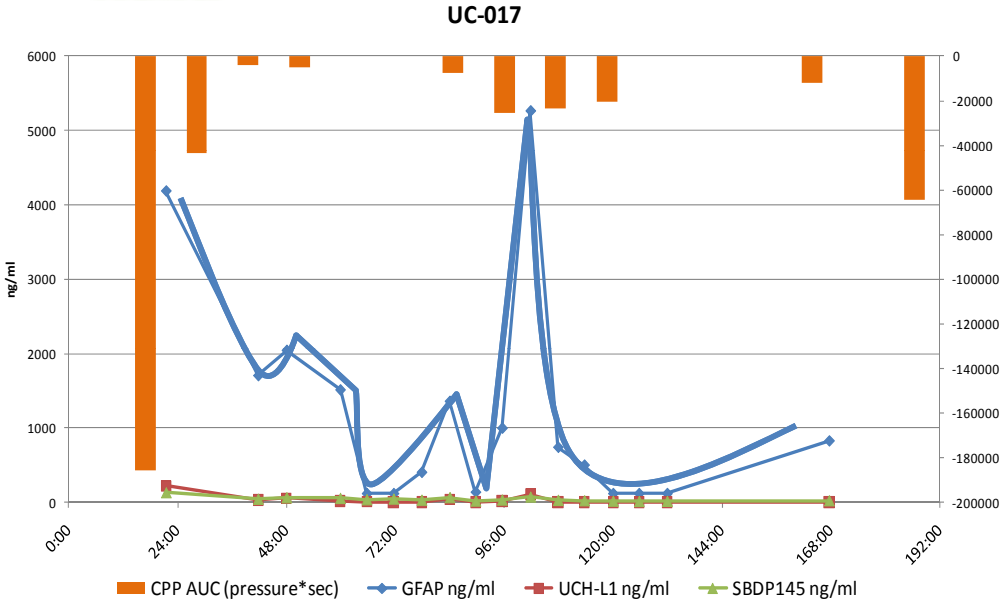
BIOMARKERS vs. ICP

Biomarkers vs. CPP

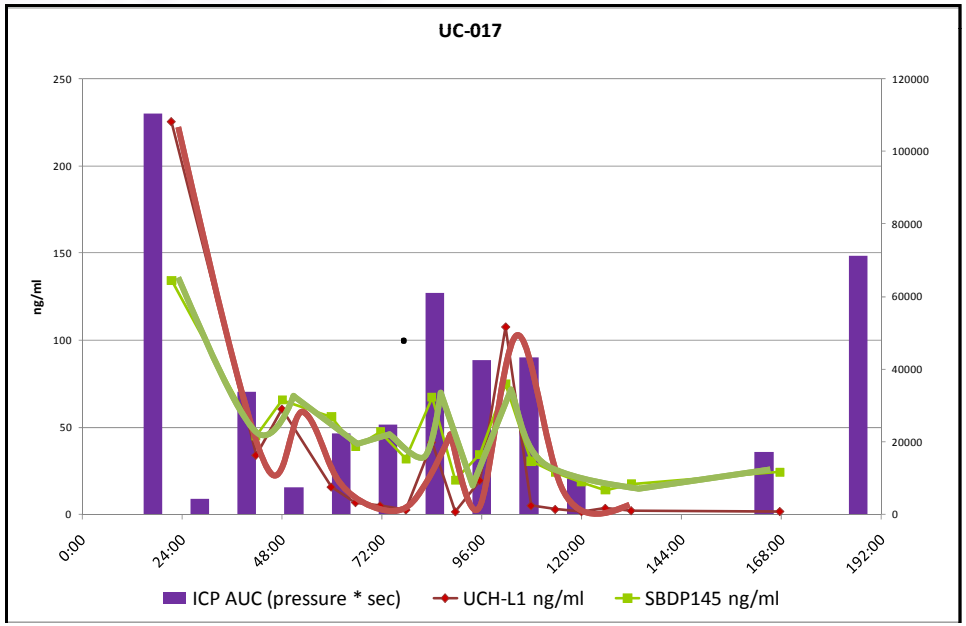
GFAP



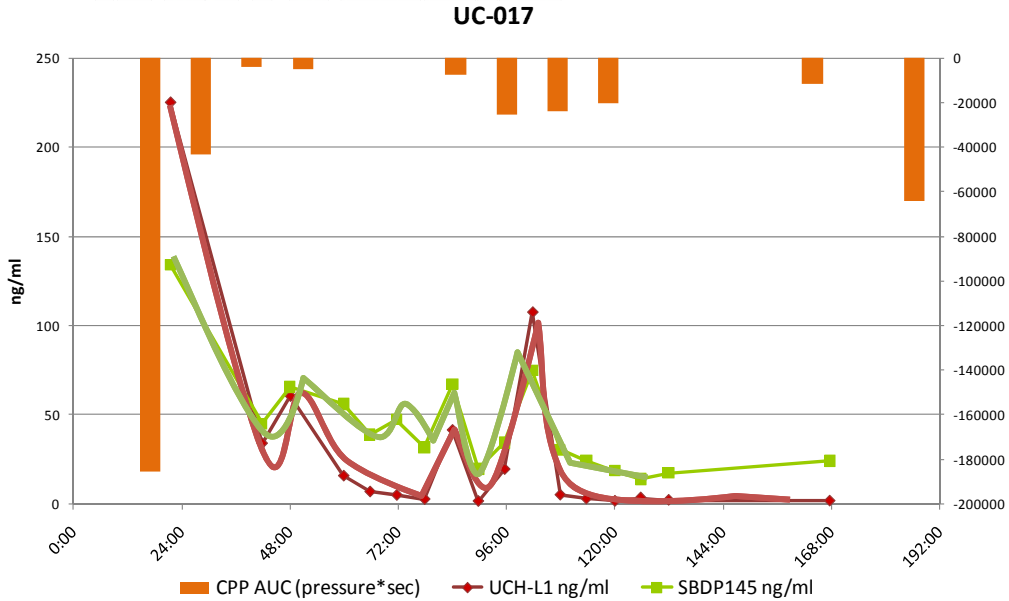
GFAP



UCH-L1 & SBDP145



UCH-L1 & SBDP145



BANDITS
SEVERE TBI FEASIBILITY STUDY

Biomarkers vs. Secondary Insults

Tissue Oxygenation

LICOX Data

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X. Brain Oxygen Monitoring and Thresholds

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Brain Tissue Oxygen Monit

Several studies investigated
outcome and brain tissue oxy
1998, Valadka et al. reported a
34 patients with severe TBI and
of death increased with increasing duration of time of
$P_{br}O_2$ less that 15 mm Hg.[12] Additionally, their data suggest that the occurrence of any $P_{br}O_2$ less than or equal to 6 mm Hg, regardless of its duration, is associated with an increased chance of death. Bardt et al. also reported in 1998 a prospective case series of 35 patients with severe TBI and found that $P_{br}O_2$ values less than 10 mm Hg for more than 30 min had considerably higher rates of mortality (56% vs. 9%).1 Likewise, rates of favorable outcome (GOS 4–5) were lower (22% vs. 73%) in this group. In 2000, van den Brink et al. reported a prospective case series of 101 patien
values less than 10 mm Hg
were associated with increas
comes.[13] In this study both depth and duration of low
$P_{br}O_2$ correlated with mortality. A 50% risk of death was associated with $P_{br}O_2$ values less than 15 mm Hg lasting 4 h or longer.

Several studies investigated the *relationship between outcome and brain tissue oxygen tension* (PbrO2). In 1998, Valadka et al. reported a prospective case series of 34 patients with severe TBI and found that *the likelihood of death increased with increasing duration of time of PbrO2 less that 15 mm Hg*.

Acta Neurochir (Wien) (2005) 147: 51–56
DOI 10.1007/s00701-004-0408-z

Acta Neurochirurgica
Printed in Austria

Clinical Article

Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen

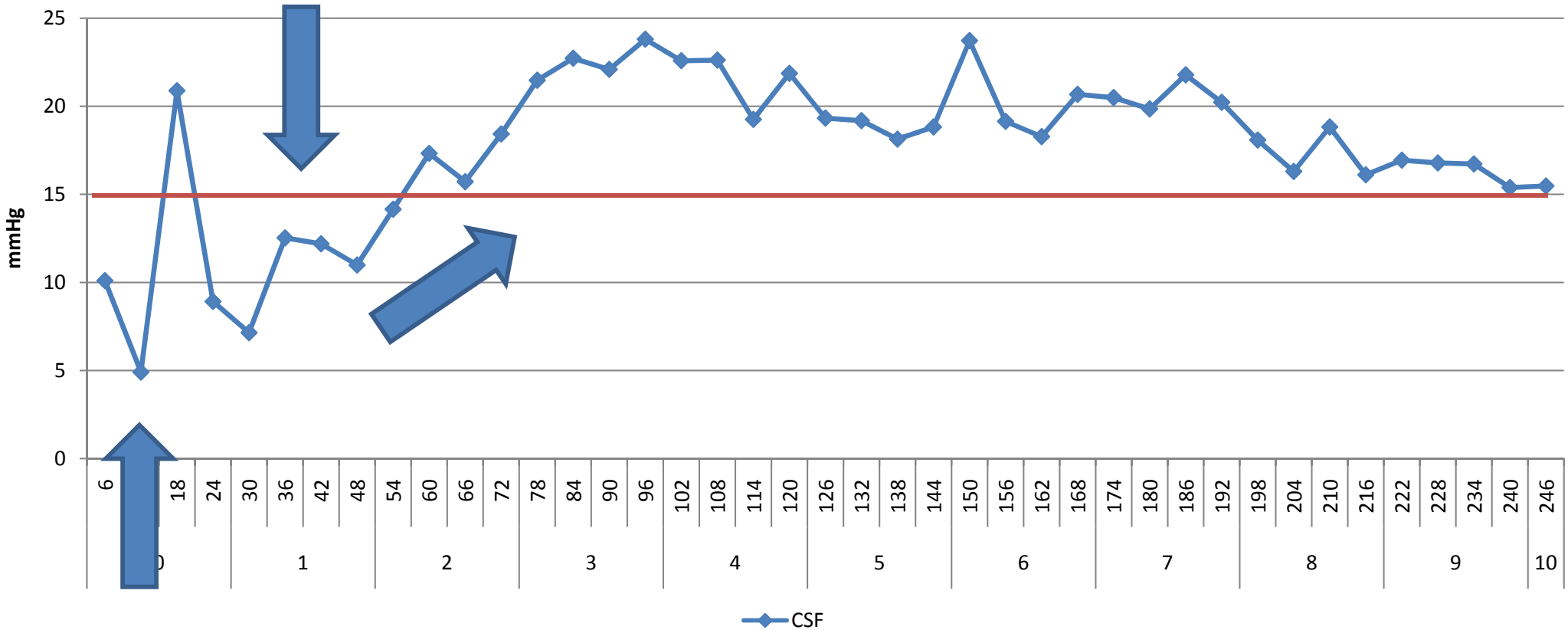
M. Jaeger[1], M. Soehle[2], M. U. Schuhmann[1], D. Winkler[1], and J. Meixensberger[1]

Cerebral hypoxia has been shown as an ***independent predictor of outcome after traumatic brain injury*** (TBI) in several clinical studies

Bratton SL, et al J Neurotrauma. 2007;24 Suppl 1:S65-70.
Valadka AB, et al Crit Care Med 1998;26:1576–1581.

N= 6 Patients

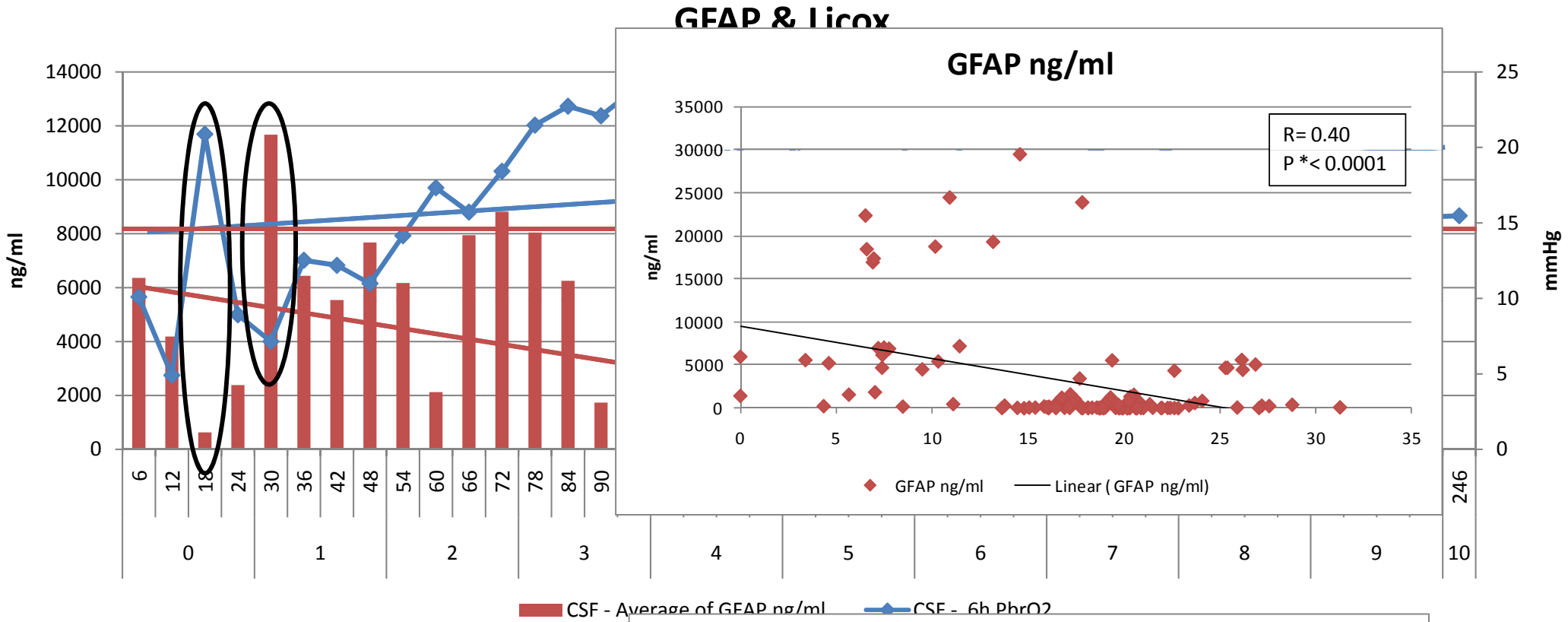
LICOX Data

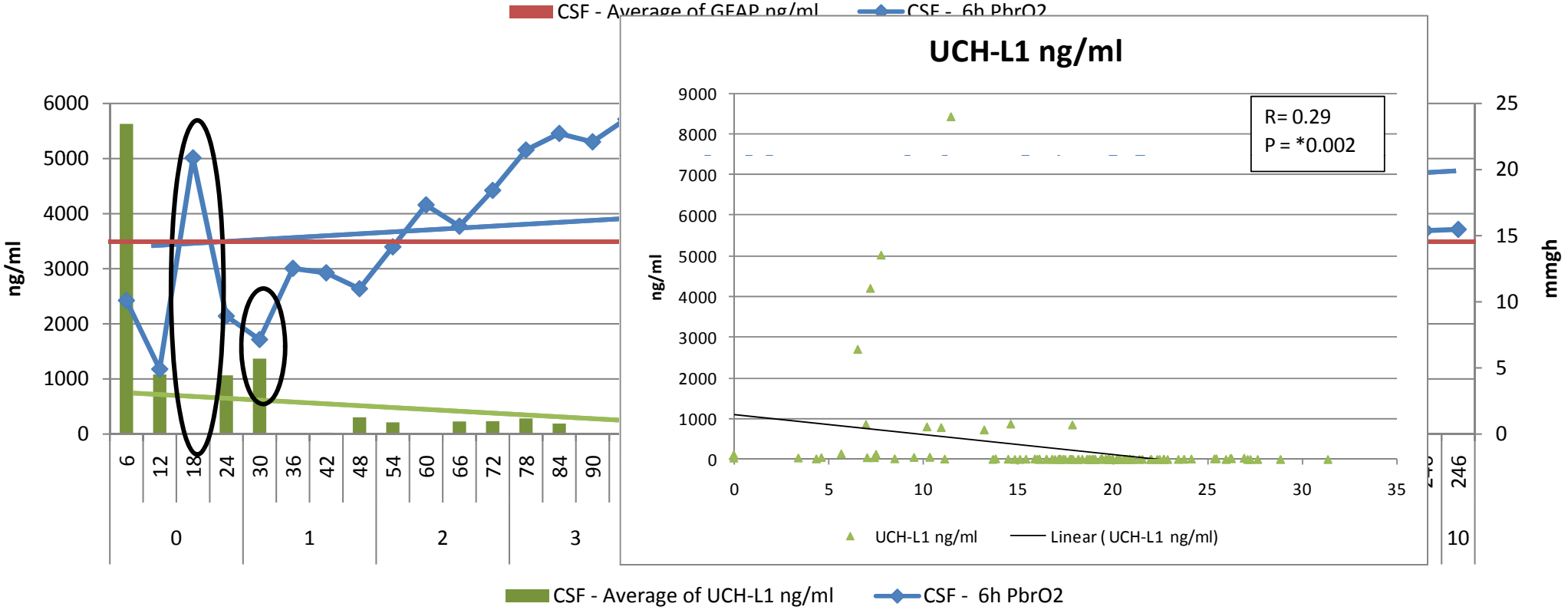


CBF is typically ***very low during the first 24 hours*** following severe TBI, and may be reduced by more than 50% of normal. It may be further reduced in regions of contusion and subdural hematoma. CBF *increases over the next few days* provided there is no increase in ICP.

Licox	Mean (mmHg)	SEM
PBO_2 first 24hrs	11.11	2.30
PBO_2 over study	17.51	0.59

Marion, D. W., et al(1991). J Neurosurg 74,407-414
Jaggi, J. L., et al (1990). J Neurosurg 72, 176-182


GFAP & Licox
GFAP ng/ml
R= 0.40
P *< 0.0001
ng/ml
mmHg
GFAP ng/ml
Linear (GFAP ng/ml)
CSF - Average of GFAP ng/ml
CSF - 6h PbrO2


UCH-L1 ng/ml
R= 0.29
P = *0.002
ng/ml
mmgh
UCH-L1 ng/ml
Linear (UCH-L1 ng/ml)
CSF - Average of UCH-L1 ng/ml
CSF - 6h PbrO2

BANYAN BIOMARKERS®

BANDITS
SEVERE TBI FEASIBILITY STUDY

PREDICTION OF MORTALITY

Comparison of Clinical, Radiologic, and Serum Marker as Prognostic Factors after Severe Head Injury

Author(s): Woertgen, Chris MD; Rothoerl, Ralf D. MD; Metz, Christoph MD; Brawanski,

The Journal of TRAUMA Injury, Infection and Critical Care

Reliable outcome prediction from severe head injury, especially in the early stage, is *still unresolved*.....

Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury

P.E. Vos, MD, PhD; K.J.B. Lamers, PhD; J.C.M. Hendriks, PhD; M. van Haaren, MD; T. Beems, MD; C. Zimmerman, MD; W. van Geel; H. de Reus; J. Biert, MD, PhD; and M.M. Verbeek, MSc, PhD

Abstract—*Objective*: To study the ability of glial (glial fibrillary acidic protein [GFAP] and S100b) and neuronal (neuron specific enolase [NSE]) protein levels in peripheral blood to predict outcome after sever
Eighty-five patients with severe traumatic brain injury (admission Glasgow Coma Sco
samples taken at the time of hospital admission were analyzed for S100b, GFAP,
demographic and clinical variables. Outcome was assessed using the Glasgow Outc
injury. *Results*: The median serum levels of S100b, GFAP, and NSE were raised 18.3
twofold (NSE) compared to normal reference values. S100b, GFAP, and NSE serum lev
injury severity score and CT findings but not with age, sex, or GCS. S100b, GFAP,
higher in patients who died or had a poor outcome 6 months post injury than in those w
S100b level >1.13 μg/L was the strongest predictor of death with 100% discriminatio
(>21.7 μg/L) levels also strongly predicted death (adjusted odds ratios 5.82 [for GFAP]
and NSE all strongly predicted poor outcome (adjusted odds ratios 5.12 [S100b], 8.82
sions: These results suggest that determination of serum levels of glial and neurona
assessment of the primary damage and prediction of outcome after severe traumatic b

NEUROLOGY 2004;62:1303–1310

Accurate determination of the initial severity of the primary brain damage after severe head injury is crucial in establishing neurologic prognosis and to balance the risks and benefits of treatment.[1] Outcome prediction remains difficult because neurologic assessment is often influenced by the use of sedatives, analgetics, or muscle relaxants. Therefore, biologic markers that reliably reflect the extent of brain damage and are easy to measure (i.e., in peripheral blood) have long been searched for.[2]

Previous studies have identified inflammatory response molecules, excitotoxic amino acids, oxidative stress markers, and enzymes in CSF.[3-7] But measurement of CSF biomarkers requires placement of ventricular catheters, which may influence CSF protein levels.[8,9] Advances in the analysis of brain specific proteins revealed elevated levels of serum S100b and neuron specific enolase (NSE) after stroke, traumatic brain injury, cardiopulmonary bypass surgery, and cardiac arrest.[10-16]

S100b is a Ca^{2+}-binding protein of astrocytes, oligodendrocytes, and Schwann cells[16,17] and NSE is a cytoplasmic glycolytic enzyme of neurons.[18-20] Serum S100b and NSE levels correlate with contusion volume, presence of subarachnoid hemorrhage on CT,

and clinical outcome
injury.[21-24]

Glial fibrillary aci
meric intermediate f
CSF concentrations o
pressure hydrocephal
patients who died fr
creased immunoreact
cortical contusion zon
peripheral blood.[29,30]
correlates with infar
functional status at d

The objective of th
predictive value of
brain-specific protein
clinical outcome at 6
brain injury.

Methods. Approval of this study was obtained from the local ethics committee of the UMC Nijmegen. Eighty-five patients with severe closed head injury admitted within 98 hours after the accident to the University Medical Center Nijmegen between February 1999 and June 2000 were included. Written informed consent was obtained from a next of kin because all eligible patients were in coma. Exclusion criteria were no blood sample taken, no informed consent, and no possibility of long-term follow up (for a period of 6 months). Severe traumatic brain injury was defined as

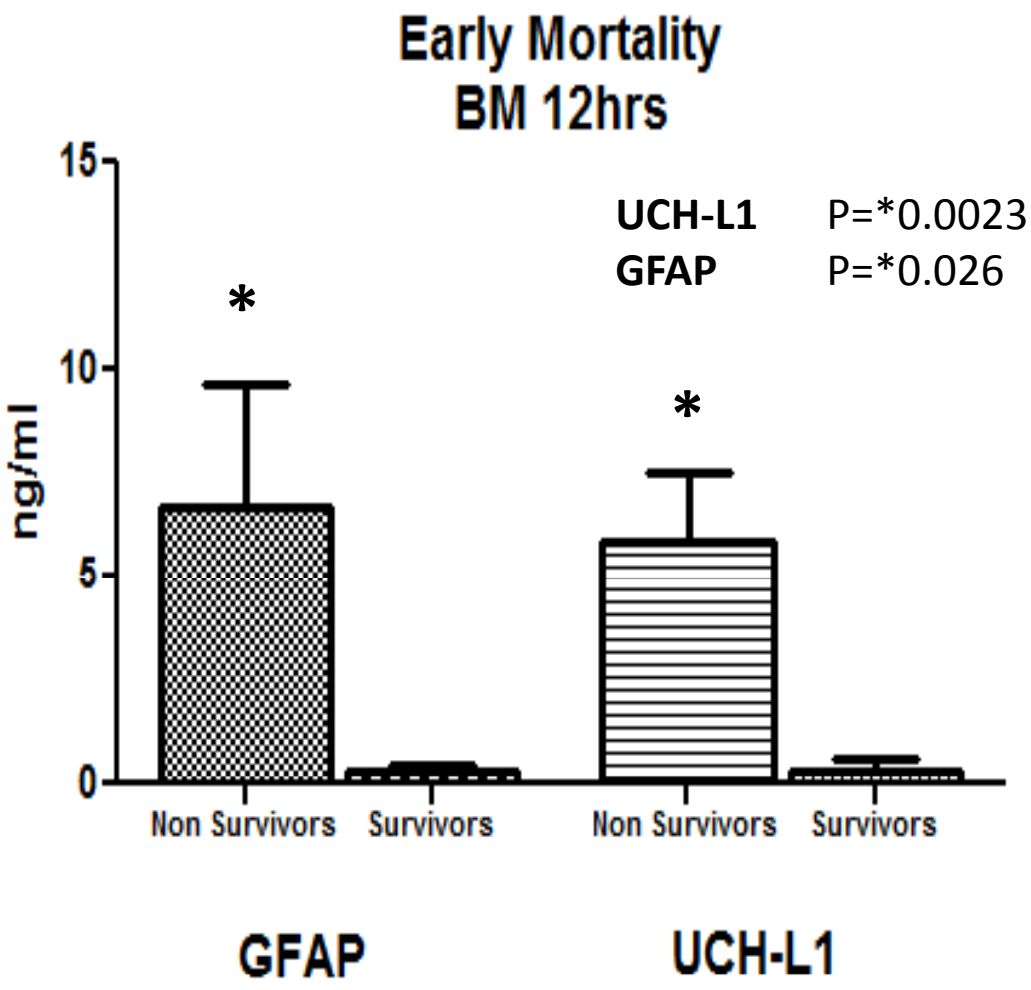
...tcome prediction from severe head injury, especially in the early stage, is still unresolved. 1-7 Predictions made during the first 24
...ury were correct for only 44% of these patients. 7 Clinical scores such as the Glasgow Coma Scale (GCS) score and diagnostic scores
...rshall Computed Tomographic Classification (MCTC) are well established and investigated, but there are still some concerns over these
...in assumes that patients with head injuries will need to be classified by a combination of clinical, radiographic, and laboratory
In the recent years, serum markers, e.g., neuron-specific enolase (NSE), CKBB, myelin basic protein, and S-100B, were described as
information for outcome prediction after severe head injury, stroke, and subarachnoid hemorrhage. 5,13-24 Particularly, the serum
...ium binding protein of astroglial cells in the central nervous system, S-100B, are recognized to have statistically significant correlations
...er severe head injury. 5,23,24 The aim of this study was to investigate the predictive value of the initial serum level of S-100B and to
...inding with the GCS score and the MCTC, the other known predictors of long-term outcome after severe head injury.

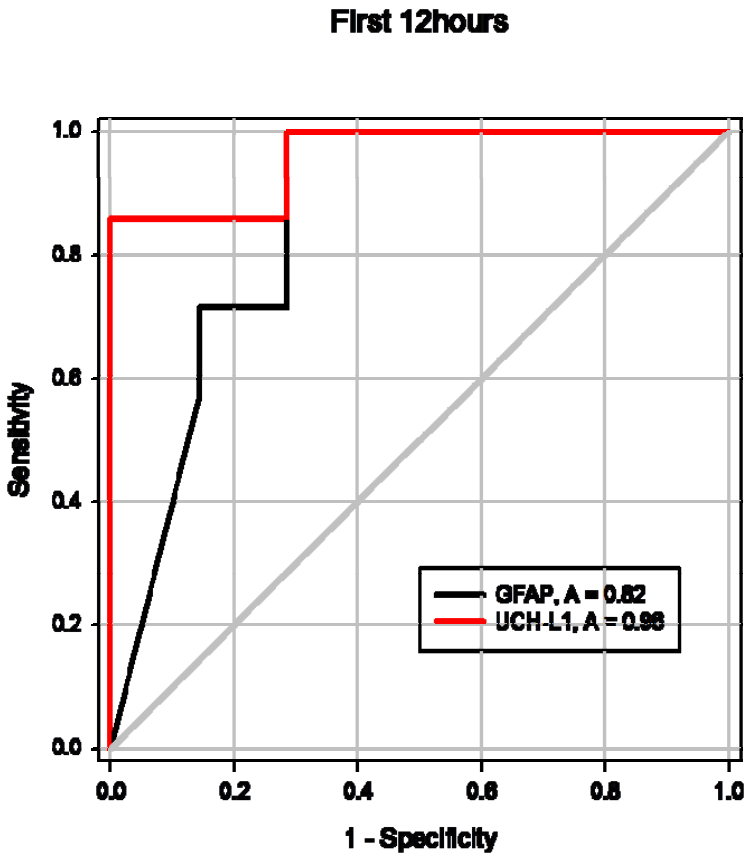
Accurate determination of the initial severity of the primary brain damage after severe head injury is crucial *in establishing neurologic prognosis and to balance the risks and benefits of treatment.*

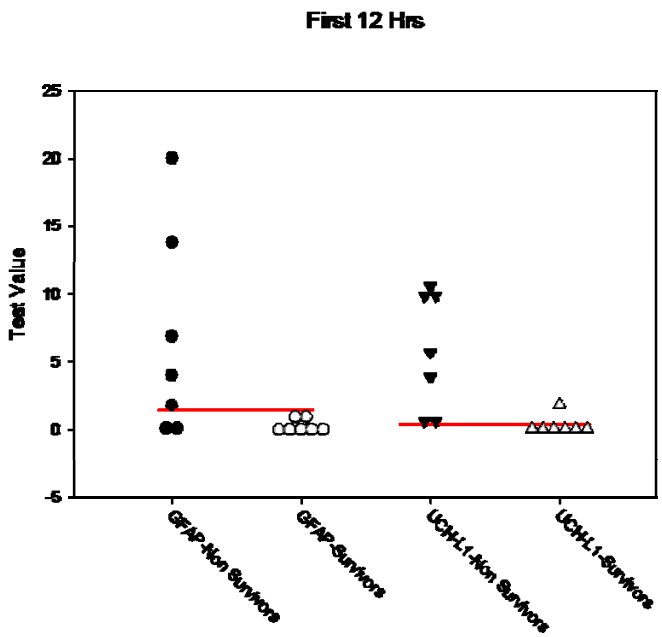
Outcome prediction remains difficult because neurologic assessment is often influenced by the use of sedatives, analgetics, or muscle relaxants. Therefore, biologic **markers that reliably reflect the extent of brain damage and are easy to measure** (i.e., in peripheral blood) **have long been searched for…**

Woertgen, C et al J Trauma, 1999, 47(6), p 1126
Vos PE, et al Neurology. 2004, 7;62(8):1303-10.

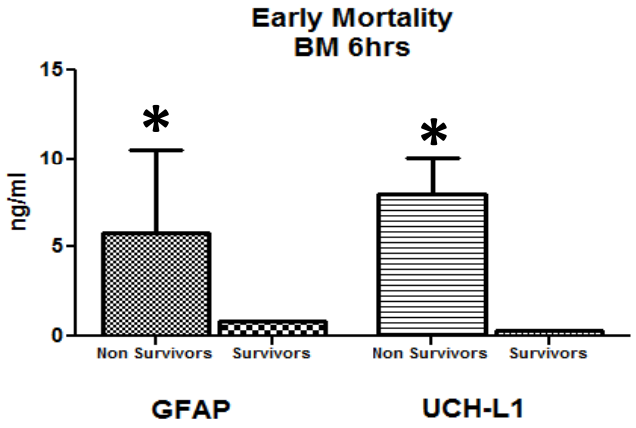
EARLY Mortality Serum

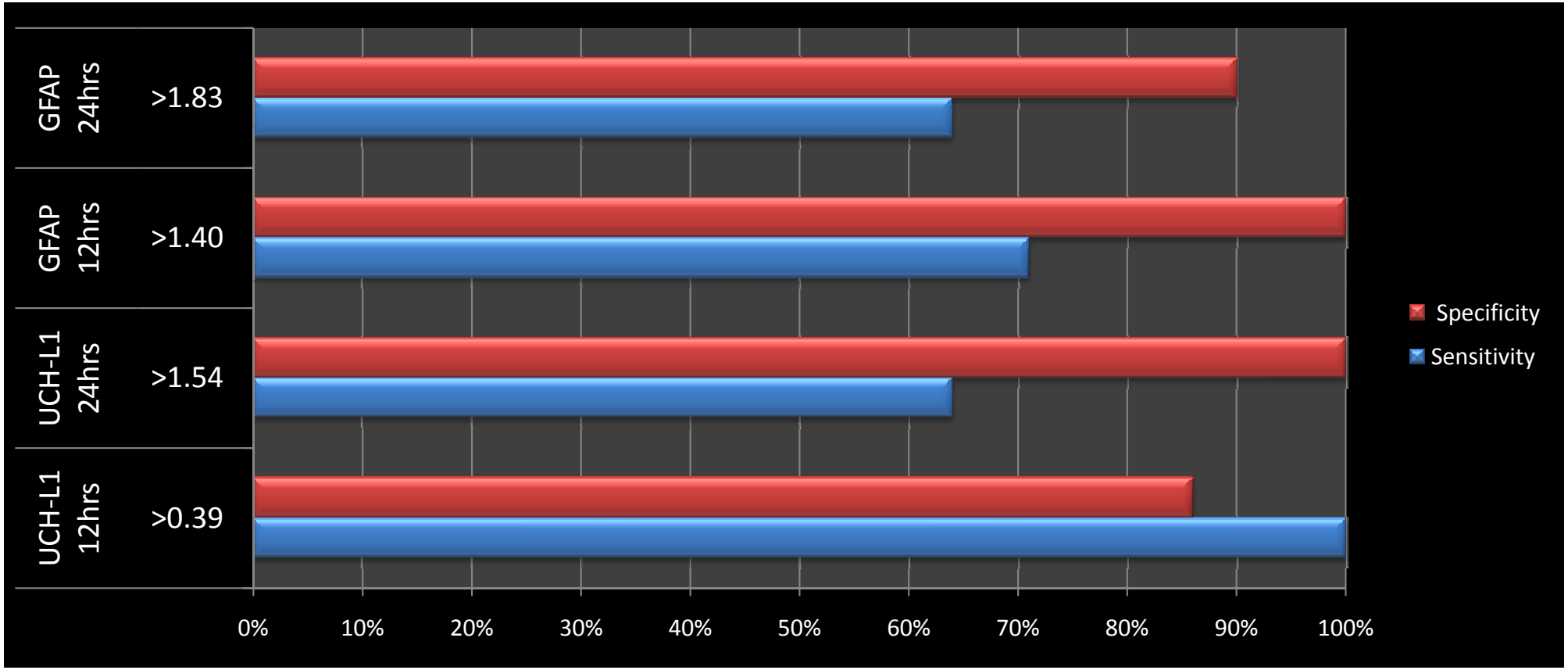






Biomarkers	Cut off (ng/ml)	Sensitivity	Specificity	PPV	NPV
UCH-L1 12hrs	>0.39	1	0.86	0.87	1
UCH-L1 24hrs	>1.54	0.64	1	1	0.71
GFAP 12hrs	>1.40	0.71	1	1	0.78
GFAP 24hrs	>1.83	0.64	0.9	0.8642	0.7123





SUMMARY AND CONCLUSIONS (1)

- Serum levels of UCH-L1 and GFAP are specific and sensitive indicators of severe TBI within the first 6 hrs after injury.
- CSF levels of UCH-L1, GFAP and SBDP145 are specific and sensitive biomarkers of severe TBI within the first 6 hrs after injury.
- Analyses of CT Marshall Scale scores indicated that serum levels of UCH-L1 and GFAP were significantly elevated with increasing injury severity.

SUMMARY AND CONCLUSIONS (2)

- Serum levels of UCH-L1 and GFAP were sensitive and specific predictors of early mortality prior to discharge when measured within the first 12 hrs after injury.
- CSF levels of UCH-L1 and GFAP were significantly correlated with decreasing tissue oxygenation, suggesting biomarker levels can be associated with secondary insults produced by inadequate oxygen substrate availability.
- Increased CSF biomarker levels could be associated with secondary insults detected by continuous physiological monitoring.

FUTURE STUDIES

- Continue accrual of severe TBI patients in multicenter trial feasibility study.
- Complete more extensive analyses of data set from first 101 patients.
- Continue separately funded research discovering biomarkers of penetrating and blast induced brain injuries.

BANDITS
MILD AND MODERATE TBI
PILOT STUDY

Care of War Veterans with Mild Traumatic Brain Injury — Flawed Perspectives

Charles W. Hoge, M.D., Herb M. Goldberg, B.A., B.Ed., and Carl A. Castro, Ph.D.

Researchers estimate that more than 300,000 U.S. veterans of the wars in Iraq and Afghanistan (20% of the 1.6 million) have sustained a mild traumatic brain injury (TBI), also known as concussion, with the majority going untreated.[1] In response, the Department of Defense and the Department of Veterans Affairs (VA) have implemented new postdeployment health initiatives, including screening, communication strategies, disability regulations, and specialty care services.

Unfortunately, the clinical def-

Defense and the VA — a blow or jolt to the head resulting in brief alteration in consciousness, loss of consciousness (lasting less than 30 minutes), or post-traumatic amnesia — is inadequate for achieving the objectives of these well-intentioned initiatives. The case definition lacks three essential criteria for use months after injury: symptoms, time course, and impairment. It pertains only to physiological disruption of brain function at the time of injury. Health initiatives crafted through consensus processes us-

tive responses to this single unvalidated question have accounted for two-thirds of all reported cases of concussion/mild TBI. The remaining cases are clinically similar to sports concussions, involving brief loss of consciousness (usually lasting seconds to

Researchers estimate that **more than 300,000** *U.S. veterans of the wars in Iraq and Afghanistan(*20% of the 1.6 million) have sustained *a mild traumatic brain injury* (TBI), also known as concussion, with the ***majority going untreated***….

Promising neuroimaging techniques, such as diffusion tensor imaging, *currently have limited clinical usefulness…* Lacking an accepted medical definition for postconcussive symptoms or impairment, the *VA created a disability category called "residuals of TBI."…*

symptoms, not the mild TBI itself, overlap with numerous ill-

nesses, including postwar health

itions that have been de-

ed for centuries. The cur-

emphasis on attributing post-

"postconcussive" symptoms

ne of two potentially stig-

zing diagnoses — mild TBI

TSD — reflects a lack of un-

derstanding that the strategies most likely to be effective are evidence-based treatments for functional somatic symptoms.

self-fulfilling prophecy.

On the basis of this analysis, a different public health approach is recommended. This approach would establish case definitions and evaluation tools that fulfill criteria for causation, have clinical validity, and do not lead to misattribution; ensure that screening does not include nonspecific questions, is conducted near the time of injury, and maintains the independence of variables; use communication strategies that

On the basis of this analysis, a different public health approach is recommended. ***This approach would establish case definitions and evaluation tools that fulfill criteria for causation, have clinical validity, and do not lead to misattribution***…

Hoge CW et al, N Engl J Med. 2009 Apr 16;360(16):1588-91

Mild and Moderate TBI		
n	34	
Age, years Mean (SD)	42.66 ± 17.08	
Range	19-87	
F/M, n	13/21	
F/M, %	38.23/ 61.77 %	
Ethnicity	Not Hispanic or Latino	11
	Hispanic or Latino	2
	Other	1
Race	Caucasian	24
	Asian	
	Black or African American	9
	Other	1
GCS	13-15	29
	9-12	5
Mechanism of Injury:	Motor Vehicle Accident	9
	Moto Cycle Accident	4
	Fall	8
	Assault	3
	Other	10
CT	Normal	24
	Abnormal	9

Control Groups

Normal Controls (Serum)		
n	167	
Age, years Mean (SD)	36.91 ± 14.06	
Min-Max	18-74	
F/M, n	72/95	
F/M, %	43.1/ 56.9 %	
Ethnicity	Not Hispanic or Latino	146
	Hispanic or Latino	13
	N/A	8
Race	Caucasian	53
	Asian	7
	Black or African American	4
	Middle Eastern	1
Alcohol (Y/N)	114/47	
	N/A 6	
Drug	19/ 147	
	N/A 1	
Smoke (Y/N)	54/112	
	N/A 1	
Health	Excellent	78
	Good	74
	Average	13
	N/A	2

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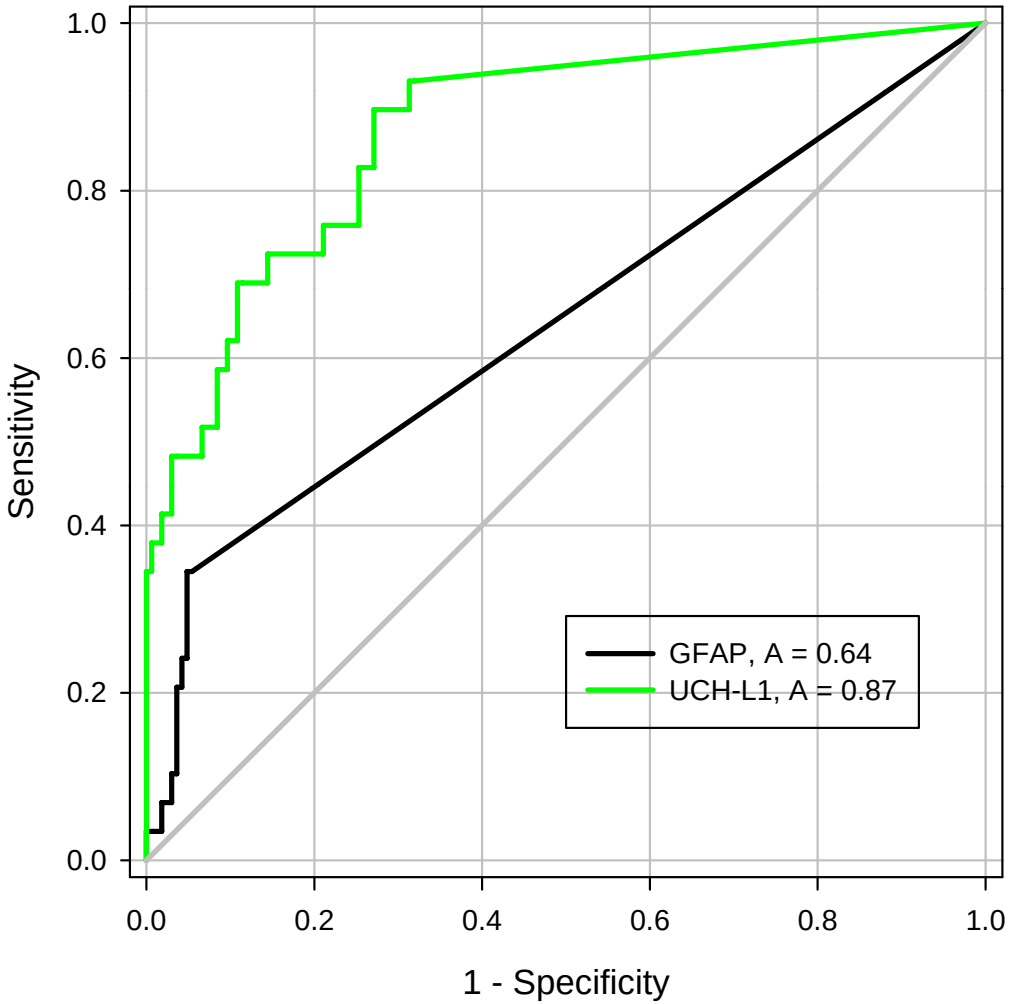
BANDITS
MILD AND MODERATE TBI
PILOT STUDY

ROC Curve Analysis of Diagnostic Utility

ROC Curves: Biomarkers in Mild (GCS 13-15) TBI

T= E

ORMC & Wash. Univ. St. Louis



Variables	GFAP	UCH-L1
ROC Curve Area	0.6428	**0.8735**
P Value	0.01421	**< 0.0001**
Sample Size - TBI	29	29
Sample Size - Normal	166	166

T=E	Normal Controls	MMTBI
UCH-L1	0.12 ± 0.02	3.48 ± 1.27
GFAP	0.07 ± 0.03	0.28 ± 0.17

T=E

Mean 3h35', Range 15'-14h35'

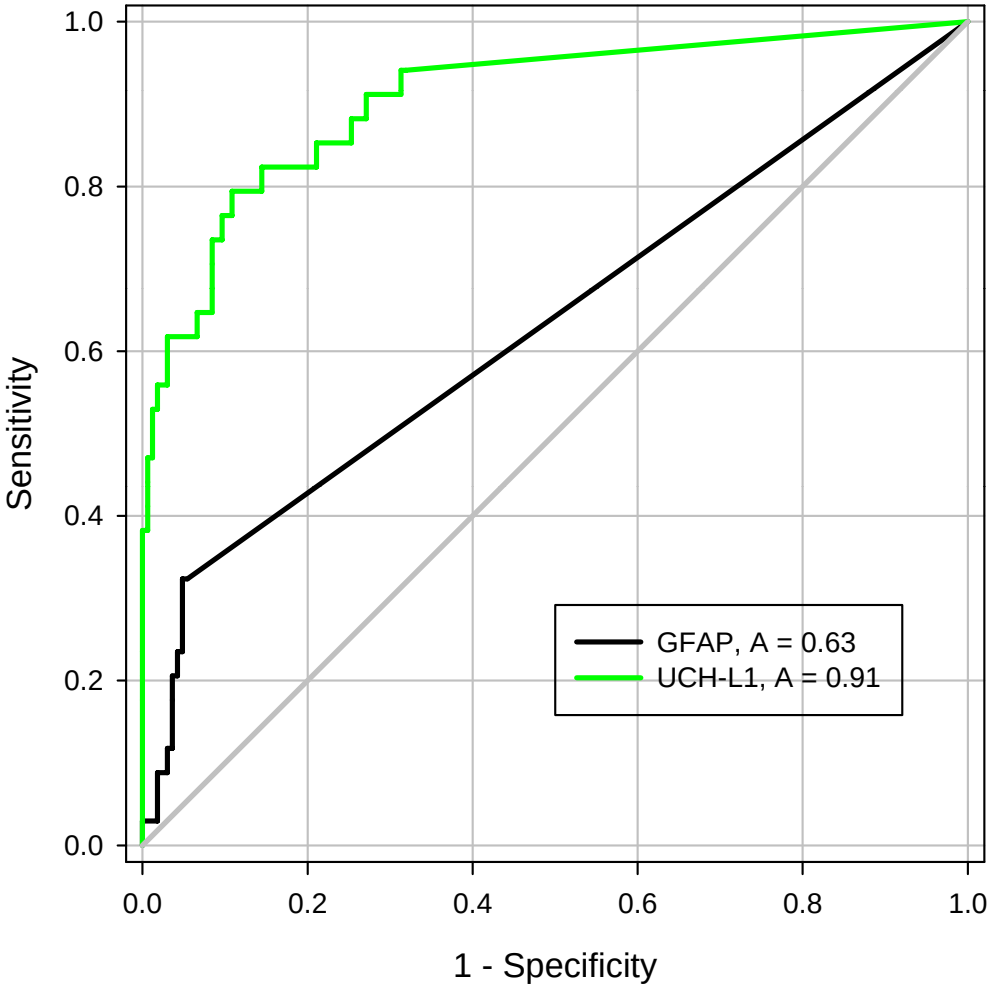
ORMC: Mean 1h43', Range 15'-4h

Wash.Univ.: Mean 4h59', Range 1h20'-14h35'

ROC Curves: Biomarkers in Mild (GCS 13-15) TBI

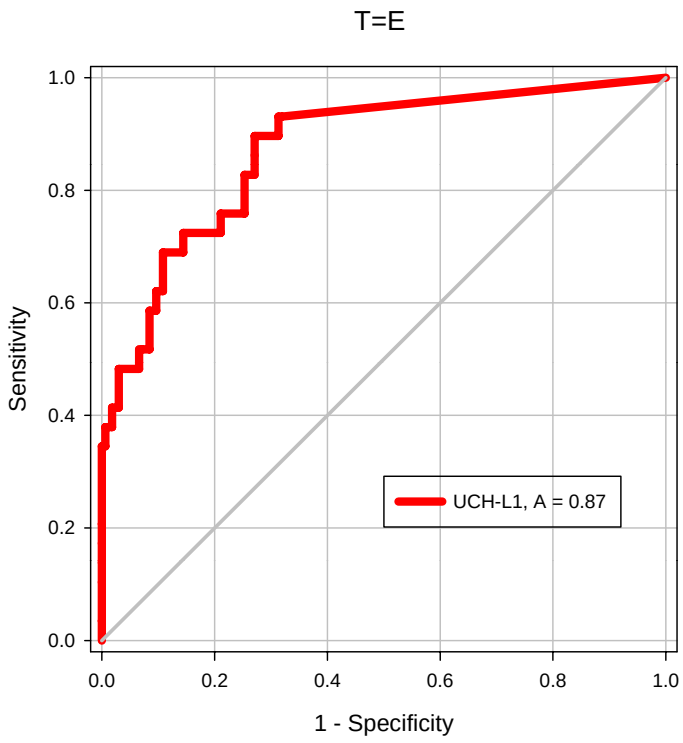
T= 6

ORMC & Wash. Univ. St. Louis



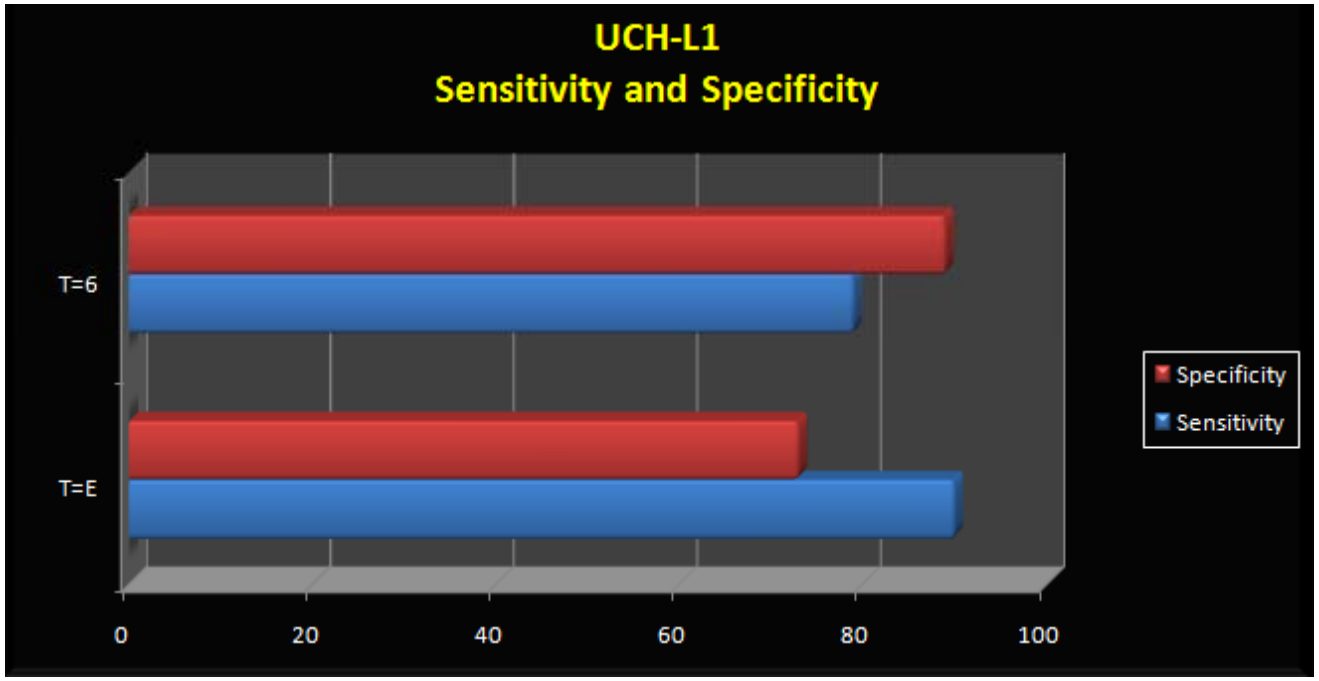
TEST Variables	GFAP	UCH-L1
ROC Curve Area	0.6328	**0.9072**
P Value	0.01478	**< 0.0001**
Sample Size - TBI	34	34
Sample Size - Normal	166	166

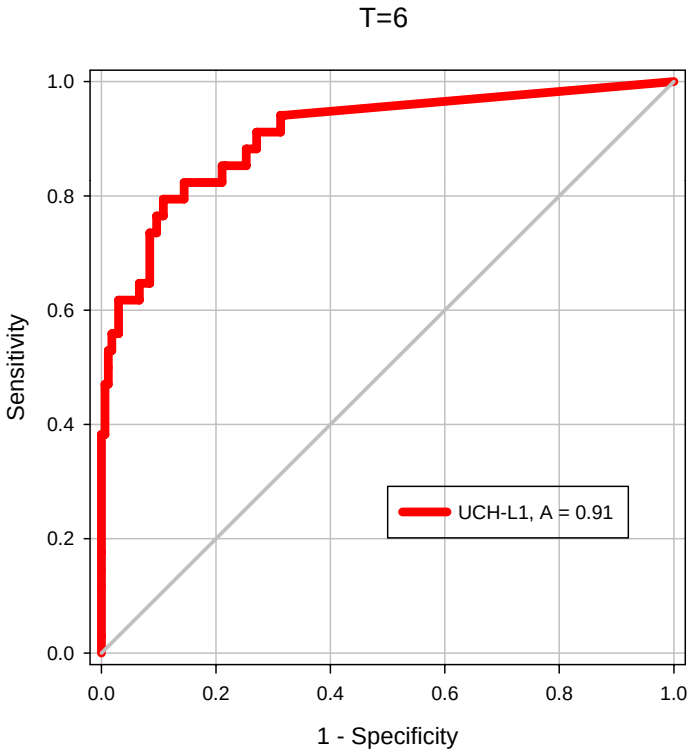
T=6	Normal Controls	MMTBI
UCH-L1	0.12 ± 0.02	3.44 ± 1.08
GFAP	0.07 ± 0.03	0.27 ± 0.14



UCH-L1 T=E

- Cut off (ng/ml) > 0.1105
- Sensitivity 90%
- PPV 77%
- Specificity 73%
- NPV 88%





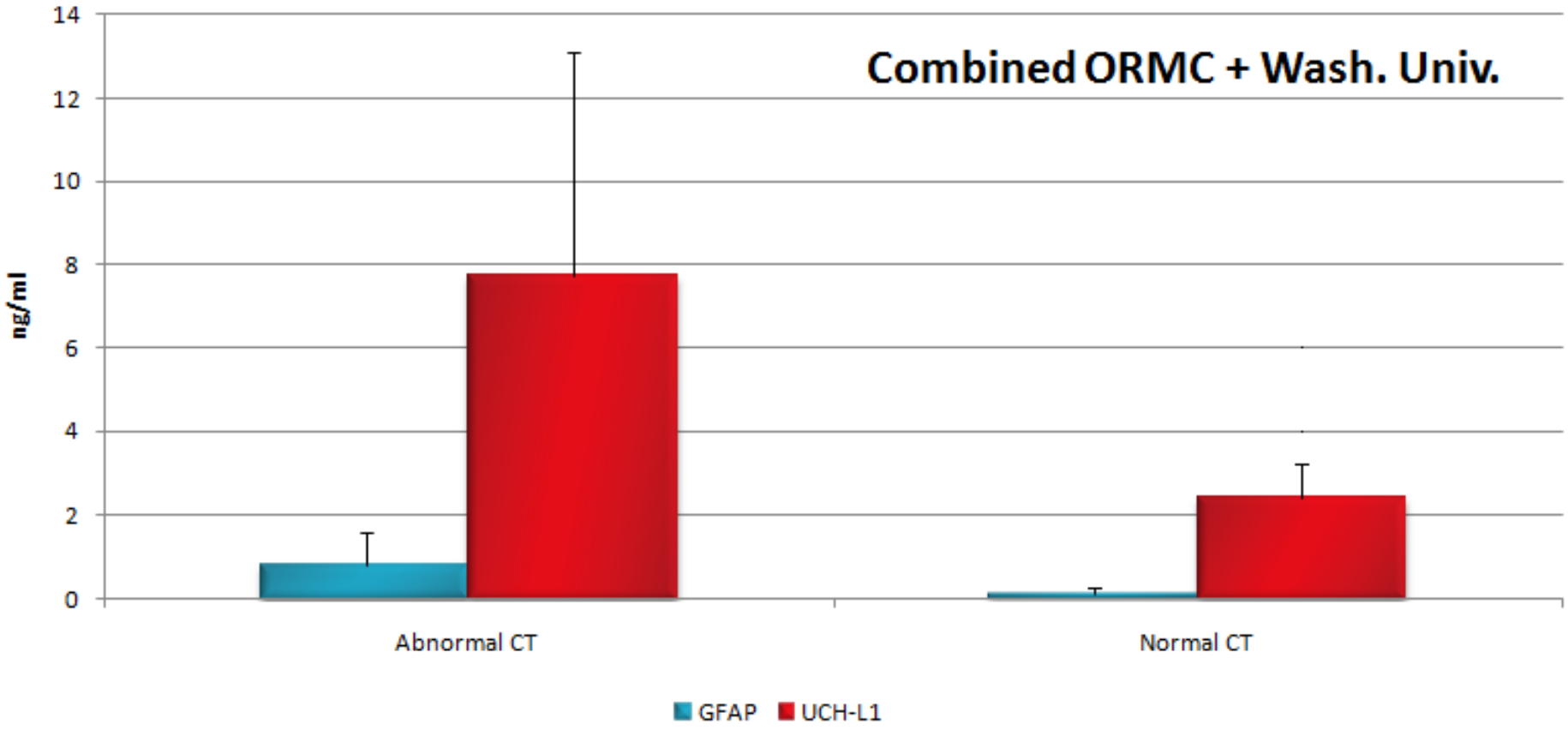
UCH-L1 T=6

- Cut off (ng/ml) > 0.3724
- Sensitivity 79%
- PPV 88%
- Specificity 89%
- NPV 81%

BANDITS
MILD AND MODERATE TBI
PILOT STUDY

Biomarkers vs. CT Scan

Biomarkers & CT in Mild TBI



MILD (GCS 13-15)	# Subjects	GFAP (ng/ml)	UCH-L1 (ng/ml)
CT Normal	**22**	**0.12 ± 0.05**	**2.45 ± 0.81**
CT Abnormal	**6**	**0.83 ± 0.79**	**7.74 ± 5.36**

Note: Biomarker Levels at T=E (***Mean 3h35', Range 15'-14h35'***)

SUMMARY AND CONCLUSIONS

- Separate pilot studies conducted at 2 sites have indicated that UCH-L1 and GFAP are sensitive and specific predictors of mild TBI when assayed approximately 3-6 hrs after injury.

- Although limited by a small subject population, data suggest that higher levels of UCH-L1 and GFAP are associated with the presence of lesions detectable on CT.

BANDITS
MILD AND MODERATE TBI
FEASIBILITY STUDY

Determine that the thing can and shall be done,

and then we shall find the way

STATUS MILD AND MODERATE TBI OF FEASIBILITY STUDY (1)

- Site identification completed Fall, 2008 – Washington University, St. Louis; Wayne State – University Detroit;
- Preliminary PI meeting held November, 2008
- Funding available to Banyan, March, 2009
- 300 Mild-Moderate TBI patients will be recruited
- Protocol reviewed by sites, submitted to HRPO and site IRBs.

STATUS MILD AND MODERATE TBI OF FEASIBILITY STUDY (2)

- TEMPO WEB-based data management system constructed and on-line for pilot study at Orlando
- Site inspection visits completed
- Preparation of SOPs and training materials in progress
- Site training in mid September, 2009
- Initiation of subject enrollment by Oct 1st, 2009

FUTURE STUDIES

- Conduct independently funded studies examining relationships between biomarkers and brain pathology in mild TBI patients assessed by various magnetic resonance imaging protocols including diffusion tensor and susceptibility weighed imaging.
- Examine potential biomarkers of repeated blast exposure in "Breacher Study".

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- Gillian Robinson