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Biomarkers May Predict Unfavorable Neurological Outcome after Mild Traumatic Brain Injury

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Abstract

The objective of this study was to determine if initial or repeat measurements of serum concentrations of glial fibrillary acidic protein (GFAP) or ubiquitin C-terminal hydrolase L1 (UCH-L1) are predictive of an acute unfavorable neurological outcome in patients who present to the emergency department (ED) with brain injury and an initial Glasgow Coma Scale Score (GCS) of 14–15. This multi-center observational trial included brain-injured adults presenting to the ED, receiving a head computed tomography (CT) and venipuncture for biomarker concentration measurements within 6 h of injury. Subjects had repeat serum sampling and GCS scores every 4 h for the first 24 h, if available for assessment. We analyzed blood samples using an enzyme-linked immunosorbent assay approved by the Food and Drug Administration (FDA). Wilcoxin two-sample test was used to compare initial and repeat serum concentrations for both biomarkers between CT-positive patients who did not have an acute unfavorable neurological outcome and those patients who did. A total of 145 enrolled subjects had adequate data for analysis; 69 were CT-positive, 74 were CT-negative, and 2 were CT-inconclusive. Five subjects developed an acute unfavorable neurological outcome, defined as need for intracranial pressure monitoring, craniotomy, persistent neurological deficits, or death resulting from brain injury. Initial median serum concentrations of GFAP and UCH-L1 (obtained <6 h from injury) were significantly greater in CT-positive patients who had an acute unfavorable neurological outcome than in CT-positive patients who did not (GFAP: 5237 pg/mL [IQR 4511, 8180] versus 283.5 pg/mL [IQR 107, 1123]; $p=0.026$; UCH-L1: 3329 pg/mL [IQR 1423, 5010] versus 679.5 pg/mL [IQR 363, 1100] $p=0.014$). Repeat serum testing (6–<12 h from injury) showed that UCH-L1 serum concentration, but not GFAP, was also significantly greater in the acute unfavorable neurological outcome group than in those without an unfavorable outcome: 1088 pg/mL versus 374 pg/mL; $p=0.041$.

Keywords: biomarkers; mild traumatic brain injury; neurological deterioration

Introduction

BRAIN INJURY is a common reason for seeking care in an emergency department (ED), with ~2,900,000 traumatic brain injury (TBI) related ED visits in 2014.¹ The vast majority of these injuries are considered mild traumatic brain injury (mTBI), defined as a Glasgow Coma Scale score (GCS) of 13–15 inclusive.² Clinical decision guidelines have been developed to identify patients with mTBI at low risk for intracranial injury who could forego head computed tomography (CT).^{3–6} Investigators have also tried to identify factors that would help predict risk for neurological deterioration in CT-positive patients with mTBI.^{7–11} However, there is currently no validated clinical decision tool to safely and effectively risk stratify these patients.¹¹

Over the past decade, neuro-biomarkers have been shown to be useful in predicting the need for a head CT in ED patients with

mTBI.^{12–15} Research evaluating the utility of neuro-biomarkers to predict risk of acute neurological deterioration after mTBI is scarce. The primary objective of this investigation was to determine if initial or serial measurements of serum concentrations of glial fibrillary acidic protein (GFAP) or ubiquitin C-terminal hydrolase L1 (UCH-L1) could differentiate between patients with mild TBI (GCS >13) who developed an acute unfavorable neurological outcome (defined by the need for intracranial pressure monitoring, craniotomy, persistent neurological deficits, or death as a result of brain injury) and those CT-positive patients who did not.

Methods

Participants

This was an unplanned sub-analysis of a larger multi-center study entitled “A Prospective Evaluation of UCH-L1 and GFAP

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Biomarker Kinetics After Mild Brain Injury Trauma” (VIGILANT Clinical Trial NCT02541123). Approval by the local institutional review board and by the ethics board of the United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) Department of Defense was obtained at each study site. We followed the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies.¹⁶

Inclusion criteria

The parent study included patients 18–95 years of age, presenting to the ED within 6 h of sustaining a non-penetrating brain injury with an initial GCS score of 13–15. It began as a non-consecutive sample of brain-injured subjects, initially enrolling only those patients who were CT-positive. After enrolling 51 subjects, the protocol was amended to enroll subjects prior to their CT result, including CT-negative and CT-positive subjects. The parent study also included 40 uninjured control subjects.

Our sub-analysis included those subjects with a documented brain injury, a GCS >13 on presentation, capable of informed consent, who received a head CT and had blood obtained for serum analysis within 6 h of injury (Fig. 1). We excluded the five subjects with a GCS of 13 who were enrolled in the parent study, because

previous reports have demonstrated that this is inherently a higher risk group, and most clinical guidelines suggest closely observing these patients.^{11,17} All subjects had blood obtained for repeat biomarker concentration measurements every 4 h for up to 24 hours from the initial blood draw, if they were available to the research assistant. Repeat GCS and neurological assessments were performed with each blood draw by research assistants trained in their administration, using a written scorecard.

Imaging

All CTs were ordered by the treating physicians based on their clinical judgement. Treatment was predicated on the real-time CT reading at the individual institutions. A neuroimaging review committee (NRC) consisting of three independent neuroradiologists reviewed all CTs. CT results reported in this study are based on the adjudication readings of the NRC (Fig. 1, flow diagram).

Biomarker collection, processing, and measurement

The initial blood sample for biomarker analysis was obtained within 6 h of brain injury in all patients, and the repeat sample was obtained between 6 and 12 h of brain injury. The elapsed time between the reported time of brain injury and the time of blood collection for biomarker analysis defines “time from injury” for

FIG. 1. This subject enrollment flow diagram includes all the subjects enrolled into the parent VIGILANT trial. The sub-analysis we performed begins with the 149 brain-injured subjects who were evaluated. Because we analyzed and reported our results based on the computed tomography (CT) interpretation, the two CT-inconclusive subjects were not included in the bottom row. Neither of these subjects showed any neurological deterioration.

our statistical analyses. Blood samples (5 mL) were collected and processed to serum within 30 min of collection, frozen at -80°C , and shipped on dry ice to a central laboratory for analysis. Samples were analyzed using the Food and Drug Administration (FDA approved) Banyan BTITM (Brain Trauma Indicator) test for GFAP and UCH-L1, a sandwich enzyme-linked immunosorbent assay. The reportable range for GFAP using this assay is 10–320 pg/mL. The range for UCH-L1 is 80–2560 pg/mL. Samples with initial biomarker concentrations at the upper limit of the reportable range were diluted and re-analyzed to determine the actual serum concentration. The lower limit of quantification for this assay is 10 pg/mL for GFAP and 80 pg/mL for UCH-L1. For both assays, the intra- and inter-run coefficient of variation was $<10\%$. Laboratory personnel performing these measurements were blinded to clinical data.

Data analysis

Our primary analysis compared initial and repeat median serum concentration of GFAP and UCH-L1 between patients with an initial GCS of 14 or 15 and an acute intracranial injury on their initial head CT, who developed an acute unfavorable neurological outcome and those that did not, using a Wilcoxon two-sample test for pairwise comparisons.

We performed a secondary analysis using a Kruskal–Wallis test to independently compare the GFAP and UCH-L1 serum concentrations at two time points (<6 h and $6- <12$ h from injury) across three clinical groups: CT-positive patients who were stable or improved at all assessments, CT-positive patients who had a transient decrease in their neurological status at one or more assessments but did not have an unfavorable outcome, and those (all CT-positive) who had an acute unfavorable neurological outcome.

As this was an exploratory analysis, there were no adjustments for multiple comparisons and as it was a secondary analysis of previously acquired data, we did not perform a power analysis to determine enrollment. We used SAS version 9.4 for analyses.

Results

Of 156 brain-injured subjects enrolled in the parent study, 149 were included in the current analysis (Fig. 1). Seventy (47.6%) had an acute injury on head CT, 77 (51.7%) had no acute injury, and two CTs (1.3%) were inconclusive, as determined by the NRC. The two subjects with inconclusive CT results were excluded from analysis, reducing the study population to 147. Of these 147 subjects, 143 (97%) had an initial serum biomarker concentration and at least two neurological and GCS assessments recorded within the first 24 h, and therefore were analyzable for a change in GCS score or neurological deterioration (Fig. 1).

Subject characteristics

Table 1 describes demographic and clinical characteristics for our patient population, stratified by neurological outcome and CT result. Most subjects ($n=123$) were neurologically stable or improved over the course of the first 24 h after enrollment, and remained that way the duration of their study participation. Seventeen subjects (12 CT-positive) had a transient decrease in their GCS score at some point in the first 24 h following enrollment, but did not develop an acute unfavorable neurological outcome.

Five subjects (all CT-positive) developed an acute unfavorable neurological outcome. Table 2 provides details of the specific CT lesions in the subjects with an acute unfavorable neurological outcome, along with their initial biomarker concentrations and eventual outcome.

Biomarker analysis

Among subjects with an acute intracranial injury on their initial CT scan, initial median serum concentrations for both GFAP and UCH-L1 were significantly greater in those who developed an acute unfavorable neurological outcome than in those who did not: 5237 pg/mL (interquartile range [IQR] 4511, 8180) versus 284 pg/mL (IQR 107, 1123); $p=0.026$ and 3329 pg/mL (IQR 1423, 5010) versus 680 pg/mL (IQR 363, 1100); $p=0.014$ respectively (Table 3). Figures 2A and 2B demonstrate median serum biomarker concentrations for those patients who developed an acute unfavorable neurological outcome and those who did not, along with the entire spread of data, for both the initial and repeat serum samples.

Median serum concentration of UCH-L1 decreased on repeat measurements across all groups and time points except one, but was still significantly greater at the $6- <12$ h time period in those patients with an acute unfavorable neurological outcome than in those without; 1088 pg/mL versus 374 pg/mL; ($p=0.041$). At the $6- <12$ h post-injury time frame, GFAP no longer showed a significant difference between those patients with an unfavorable outcome and CT-positive patients without an unfavorable outcome (Table 3).

CT-positive subjects with a transient decrease in their GCS score were found to have a median serum GFAP concentration, which was midway between that of CT-positive subjects who were stable/improved and that of those with an acute unfavorable outcome (Table 1). This was not the case for UCH-L1.

Discussion

Clinical decision rules for obtaining a head CT in adults with mTBI have good sensitivity for detecting patients with intracranial lesions that require neurosurgical intervention.¹⁷ This high sensitivity is in large part because the vast majority of patients who meet guideline criteria for not requiring a head CT will not have an acute intracranial lesion. However, in the subpopulation of patients with mTBI and an acute intracranial lesion, our study and others show that the need for neurosurgical intervention is not trivial, ranging between 3.5% and 8.8%, despite the initial low risk.^{10,11}

Intensive care unit (ICU) admission practices for patients with mTBI and an acute intracranial injury on head CT vary widely.¹⁸ Over-utilization of the ICU for these patients increases healthcare costs and can lead to decreased ICU bed availability, delays in admitting other critically sick or injured patients, and subsequent ED crowding. Under-use of the ICU may lead to worse outcomes because of undetected or delayed recognition of clinical deterioration.

A recent systematic review and meta-analysis of patients with mTBI (GCS of 13–15), and a positive head CT showed a pooled prevalence of clinical deterioration of 11.7%, and a pooled estimate of neurosurgical intervention risk of 3.5%.¹¹ This is somewhat lower than the 8.8% neurosurgical intervention found in a large multi-year query of the National Trauma Databank.¹⁰ Univariate analyses across most studies showed increasing age, a lower initial GCS, specific injury patterns on CT, and anticoagulation to be significant risk factors for deterioration.

Heterogeneity in populations and definitions, confounding variables, and conflicting results among studies precluded pooling of study populations for the construction of a model that could reliably identify a population at very low risk for deterioration.¹¹

We found that brain-injured patients who present to an ED with an initial GCS score of 14 or 15 and a negative initial head CT rarely deteriorate to the point of requiring neurosurgical intervention (we had none). However, in our study, patients with a positive

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY CLINICAL CATEGORY AND INITIAL CT RESULT

	Stable/Improving ^a			Transient neurological dysfunction ^b			Unfavorable neurological outcome ^c
	All (n=123)	CT positive (n=52)	CT negative (n=69)	All (n=17)	CT positive (n=12)	CT negative (n=5)	
Age (years)							
n	123	52	69	17	12	5	5
Mean (SD)	48.9 (20.3)	55.9 (18.2)	43.8 (20.2)	58.4 (20.9)	58.9 (22.3)	57.0 (19.5)	52.6 (20.4)
Sex							
Male	84 (68.3%)	32 (61.5%)	51 (73.9%)	11 (64.7%)	8 (66.7%)	3 (60.0%)	2 (40.0%)
Female	39 (31.7%)	20 (38.5%)	18 (26.1%)	6 (35.3%)	4 (33.3%)	2 (40.0%)	3 (60.0%)
Ethnicity							
Hispanic or Latino	5 (4.1%)	1 (1.9%)	4 (5.8%)	0	0	0	0
Not Hispanic or Latino	118 (95.9%)	51 (98.1%)	65 (94.2%)	16 (94.1%)	11 (91.7%)	5 (100.0%)	5 (100.0%)
Race							
Black or African American	30 (24.4%)	10 (19.2%)	20 (29.0%)	1 (5.9%)	1 (8.3%)	0	2 (40.0%)
White	89 (72.4%)	41 (78.8%)	46 (66.7%)	16 (94.1%)	11 (91.7%)	5 (100.0%)	3 (60.0%)
GCS at Initial Visit							
14	13 (10.6%)	9 (17.3%)	4 (5.8%)	3 (17.6%)	3 (25.0%)	0	3 (60.0%)
15	110 (89.4%)	43 (82.7%)	65 (94.2%)	14 (82.4%)	9 (75.0%)	5 (100.0%)	2 (40.0%)
Loss of consciousness							
No	19 (15.4%)	15 (28.8%)	4 (5.8%)	5 (29.4%)	4 (33.3%)	1 (20.0%)	0
Yes	97 (78.9%)	36 (69.2%)	59 (85.5%)	11 (64.7%)	7 (58.3%)	4 (80.0%)	5 (100.0%)
Unknown	7 (5.7%)	1 (1.9%)	6 (8.7%)	1 (5.9%)	1 (8.3%)	0	0
GFAP (pg/mL) at initial visit							
n	123	52	69	17	12	5	5
Median (Q1,Q3)	164 (36, 445)	281 (111, 941)	56 (17, 250)	266 (214, 1584)	965 (168, 1771)	222 (214, 259)	5237 (4511, 8180)
UCH-L1 (pg/mL) at initial visit							
n	123	52	69	17	12	5	5
Median (Q1,Q3)	599 (257, 966)	680 (376, 1077)	488 (186, 853)	534 (322, 1740)	496 (319, 1575)	799 (337, 3059)	3329 (1423, 5010)
Time from injury to initial blood draw (in hours) ^d							
n	121	50	69	17	12	5	5
Mean (SD)	4.36 (1.079)	4.43 (1.006)	4.32 (1.147)	4.58 (0.998)	4.58 (0.834)	4.58 (1.439)	3.55 (0.335)
Time from injury to repeat blood draw (in hours) ^d							
n	117	50	65	15	11	4	5
Mean (SD)	9.15 (1.273)	9.11 (1.311)	9.21 (1.251)	9.04 (1.002)	8.80 (0.704)	9.72 (1.488)	7.61 (0.447)

^aThis group includes 123 patients, but two had inconclusive CT results and were excluded from further analysis, leaving a total of 121.^bIncludes 17 subjects that had a 1 point or greater decrease in GCS score at some point in their course, but who did not develop an unfavorable neurological outcome.^cUnfavorable neurological outcome is defined as requiring emergency neurosurgery, persistent neurological deficits, or death resulting from a brain injury.^dA subject is counted, at most, once per time from injury category. If a subject has more than one blood draw in the given visit window category, then the result closest to the midpoint value is summarized. If a subject has two results equidistant from the midpoint, then the result prior to the midpoint value is summarized.

CT, computed tomography; SD, standard deviation; GCS, Glasgow Coma Score; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1.

TABLE 2. CT RESULTS, BIOMARKER CONCENTRATIONS, AND CLINICAL OUTCOMES AMONG SUBJECTS WITH AN ACUTE UNFAVORABLE NEUROLOGICAL OUTCOME

Subject ID	Age	CT result	GFAP ^a (pg/mL)	UCH-L1 ^a (pg/mL)	Outcome
121-008	47	SDH/SAH / parenchymal hematoma ?EDH	8180/4050	3329/1088	Craniotomy / Death
124-003	68	SAH	5237/1216	1423/688	Craniotomy
124-021	20	Bifrontal hemorrhagic contusions, SDH	4511/5317	5594/3879	Craniotomy
124-037	70	SDH / Parenchymal hematoma	11536/9110	5010/3113	Vegetative / Death
127-003 ^b	58	Bilateral hematoma/acute on chronic with midline shift	47/25	612/277	Death

^aThe first value is the initial concentration (within 6 h of brain injury) and the second value is from a repeat serum sample 4 h after the initial sample.

^bSubject 127-003 had a significant previous brain injury.

CT, computed tomography; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1; SDH, subdural hematoma; SAH, subarachnoid hematoma;

EDH, epidural hematoma.

initial head CT and a GCS score ≥ 14 had a 7.1% risk of an acute unfavorable neurological outcome resulting in a neurosurgical intervention, a persistent neurologic deficit, or death.

The literature suggests certain criteria are predictive of adverse outcomes, most notably the injury pattern on CT, particularly

swelling and midline shift. Clinical decision rules and specific head CT criteria to reduce the number of patients with mTBI admitted to an ICU have been previously developed.^{7–10,19–21} Nishijima and coworkers found that four variables predicted need for ICU admission: GCS <15 , non-isolated brain injury, age >65 years, and

TABLE 3. INITIAL AND REPEAT SERUM GFAP AND UCH-L1 CONCENTRATION IN CT-POSITIVE SUBJECTS WITH AND WITHOUT AN ACUTE UNFAVORABLE NEUROLOGICAL OUTCOME

Parameter	Time from injury category	Stable/improving or transient neurological dysfunction ^a (n = 64)	Unfavorable neurological outcome ^b (n = 5)
GFAP (pg/mL)	0-<6 h		
	n	62	5
	Mean (SD)	963.2 (1520.5)	5902.2 (4289.2)
	Median	283.5	5237.0
	Q1, Q3	107.0, 1123.0	4511.0, 8180.0
	Min, Max	8, 7580	47, 11536
	p value ^c		0.0259 ^[3]
	6-<12 h		
	n	61	5
	Mean (SD)	1282.1 (2008.8)	3943.6 (3584.1)
UCH-L1 (pg/mL)	0-<6 h		
	n	62	5
	Mean (SD)	1009.63 (1032.931)	3193.60 (2172.513)
	Median	679.50	3329.00
	Q1, Q3	363.00, 1100.0	1423.00, 5010.0
	Min, Max	63.0, 5068.0	612.0, 5594.0
	p value ^c		0.0143 ^[3]
	6-<12 h		
	n	61	5
	Mean (SD)	531.25 (424.105)	1809.00 (1589.719)
	Median	374.00	1088.00
	Q1, Q3	210.00, 703.0	688.00, 3113.0
	Min, Max	63.0, 1869.0	277.0, 3879.0
	p value ^c		0.0411 ^c

A subject is counted, at most, once per time from injury category. If a subject had more than one blood draw in the given visit window category, then the result closest to the midpoint value is summarized. If a subject had two results equidistant from the midpoint, then the result prior to the midpoint value is summarized.

^aSubjects were defined as having transient neurological dysfunction if they had a one or more-point decrease in GCS score or a transient neurological deficit but did not go on to have an unfavorable neurological outcome.

^bUnfavorable neurological outcome is defined as requiring emergency neurosurgery, persistent neurological deficits, or death resulting from a brain injury.

^cp value is from a Wilcoxon two-sample test and compares pairwise those patients with an acute abnormality on their initial head CT scan who are stable/improving or had transient neurological dysfunction with those patients with an acute unfavorable neurological outcome.

CT, computed tomography; SD, standard deviation; GCS, Glasgow Coma Score; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1.

FIG. 2. (A) Transient neurological dysfunction includes subjects that had a transient 1 or more-point decrease in their Glasgow Coma Scale (GCS) score but did not die or require surgery. Unfavorable neurological outcome is defined as requiring emergency neurosurgery, having persistent neurological deficits, or death as a result of a brain injury. Initial serum concentration measurements were within 6 hours of injury, repeat measurements were within 12 h of injury. Upper and lower bound of each box indicates the 75th and 25th percentiles, respectively (i.e., the interquartile range [IQR]). In each box, the square marker symbol and horizontal line indicate the mean and median, respectively. Median values at consecutive time points are connected by a line. (B) Transient neurological dysfunction includes subjects that had a transient 1 or more-point decrease in their GCS score but did not die or require surgery. Unfavorable neurological outcome is defined as requiring emergency neurosurgery, having persistent neurological deficits, or death as a result of a brain injury. Initial serum concentration measurements were within 6 h of injury, repeat measurements were within 12 h of injury. Upper and lower bound of each box indicates the 75th and 25th percentile, respectively (i.e., the IQR). In each box, the square marker symbol and horizontal line indicate the mean and median, respectively. Median values at consecutive time points are connected by a line. Color image is available online.

swelling or shift on initial CT.⁹ The CT lesions seen in our five patients who had an acute unfavorable neurological outcome varied, with only one showing significant midline shift (Table 2). Although certain demographic, clinical, and imaging characteristics are useful in risk stratifying patients with mTBI for delayed adverse neurological outcomes, the use of biomarkers may add additional useful information. We are unaware of any previous

studies evaluating the potential utility of serum biomarkers to stratify patients, with or without an acute injury on head CT, for risk of acute neurological deterioration.

In this small study, initial serum concentrations of GFAP and UCH-L1, obtained within 6 h of brain injury, were statistically greater in patients who went on to have an acute unfavorable neurological outcome than in those who did not. The repeat testing

was less clear. Median serum UCH-L1 concentrations decreased in all groups on repeat testing during the time window of 6–12 h. This is consistent with previous studies.^{22,23} Median GFAP concentration modestly increased on repeat testing in all groups except those with an unfavorable outcome. The decrease in GFAP concentration on repeat testing in those patients who had an unfavorable outcome seems counterintuitive, and it should be noted that the IQR is large and the number of subjects small. Papa and coworkers looked at the kinetics of GFAP and UCH-L1 in TBI patients and demonstrated that UCH-L1 concentration peaks early and decreases rapidly in patients with acute intracranial lesions, whereas GFAP increases after 4 h to peak near 16 h, before slowly declining.²² Welch and coworkers evaluated the kinetics of GFAP and UCH-L1 in patients with mTBI and found that GFAP, but not UCH-L1, increased modestly over time in patients with an acute intracranial lesion compared with those without.²³ This effect peaked at ~6 h post-injury and remained constant out to 24 h. The number of subjects requiring neurosurgical intervention were small in both of these studies. Larger studies are needed to further clarify the kinetics of GFAP and UCH-L1 in patients who deteriorate to the point of requiring neurosurgical intervention.

Finally, we noted a potential confounding factor that may warrant further investigation. Although four of the five subjects with acute unfavorable neurological outcomes had initial GFAP concentrations >5000 pg/mL, one had an initial serum concentration <100 pg/mL (Table 2). There was also an outlier with a very low initial serum GFAP concentration in the cohort with a transient decrease in GCS score. Both subjects had a history of a significant previous brain injury. A recent article evaluating autoimmunity after ischemic stroke and brain injury reported increased concentration of autoantibodies to S100 calcium-binding protein B (S100B) in subjects with repetitive head trauma.²⁴

These have been reported with GFAP as well and could interfere with the immunoassay, leading to falsely low serum concentration measurements.²⁵

There are several limitations to this study. Most importantly, the results are in a very small population (neurological deterioration $n = 5$). There were several outliers, including the two subjects with a previous brain injury mentioned previously. In a small study, having a few outliers may significantly affect the results. Additionally, although the five patients with an acute unfavorable neurological outcome had hard end-points, it is not clear what, if any, clinical significance can be placed on a transient unexplained decrease in the GCS score. Another limitation was the fact that although GCS scores were obtained and recorded by trained personnel, the same person may not have obtained consecutive GCS scores on any given patient, increasing the possibility of measurement variability. The inclusion criteria did not require that physicians utilize one of the validated clinical decision rules for obtaining a head CT, but rather allowed this to be decided by clinical judgement. We do not know how often various clinical decision rules were utilized for determining the need for head CT. Finally, many patients did not have biomarker samples at each time point, including some who did not have a 6–12-h sample, further reducing the number of subjects for analysis. A significantly larger study is needed to better evaluate whether these biomarkers (or others) could play an important role in helping predict which brain-injured patients with mTBI may be at increased risk for clinical deterioration.

Conclusion

In this small exploratory study, initial median serum concentrations of GFAP and UCH-L1 (obtained <6 h from injury) were

significantly greater in CT-positive patients who had an acute unfavorable neurological outcome than in CT-positive patients who did not. Repeated measurement of UCH-L1 (at 6–< 12 h post-injury) but not GFAP also differentiated between these two groups. Further study is required to verify these findings.

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Author Disclosure Statement

Lawrence Lewis reports grant money to Washington University to conduct research conceived and sponsored by Banyan Biomarkers, Inc. Linda Papa reports grant money to Orlando Regional Medical Center to conduct research conceived and by Banyan Biomarkers, Inc. She has also served as an unpaid consultant for Banyan Biomarkers, Inc. Jeffrey Bazarian reports grant money to the University of Rochester School of Medicine to conduct research conceived and sponsored by Banyan Biomarkers, Inc. Art Weber worked at Banyan Biomarkers, Inc at the time of this study. Rob Howard of Veridical Solutions has worked as a paid consultant for Banyan Biomarkers, Inc. Robert Welch reports grant money to Wayne State University to conduct research conceived and sponsored by Banyan Biomarkers, Inc.

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