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A high-performance core laboratory GFAP/UCH-L1 test for the prediction of intracranial injury after mild traumatic brain injury

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ABSTRACT

Background: A glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) blood biomarker panel can reliably eliminate the need to perform a head computed tomography (CT) scan in selected patients with traumatic brain injury (TBI). Currently, this FDA cleared panel can be run both on a core laboratory platform or a hand-held single-sample point of care platform. This study examined test characteristics of the panel as analyzed on a core lab-based fast high-throughput platform.

Methods: This secondary analysis of clinical data and banked blood samples obtained for the ALERT-TBI study included patients ≥18 years old with nonpenetrating head injury, a presenting Glasgow Coma Scale score 9–15, and a head CT was indicated. Included were patients with a GCS 13–15 who had sufficient banked blood for analysis. Test characteristics of the biomarker panel were determined relative to head CT findings for traumatic intracranial injury.

Results: Among the 1899 included subjects, mean age was 49.1 yrs. (18 to 98 yrs), 56.5 % male, and 70.6 % were Caucasian. The most common mechanism of injury was a fall (51.9 %) and 94.1 % presented with a GCS of 15. Head CT was positive for traumatic intracranial injury in 120 patients (6.3 %) of which the biomarker panel was a false negative in four patients. Sensitivity (95 % confidence interval) of the biomarker panel was 96.7 (91.7, 98.7), specificity 40.1 (37.8, 42.4), negative predictive value 99.4 (98.6, 99.8), and the negative likelihood ratio was 0.08 (0.03, 0.22).

Conclusions: The biomarker panel, measured on this core lab-based fast high-throughput platform, had high sensitivity and negative predictive values. The core laboratory platform has the advantage of speed and the ability to analyze multiple samples simultaneously suggesting additional utility when there is high need for CT imaging such as mass casualty or emergency department volume overload situations.

1. Introduction

The results of the Prospective Clinical Evaluation of Biomarkers of Traumatic Brain Injury (ALERT-TBI) trial suggested that a test combining glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) done within 12 h of head injury could reduce unnecessary head CT scanning by 30 % [1], and data from this trial were used to support Food and Drug Administration (FDA) clearance of the combined GFAP and UCH-L1 test (Banyans Biomarkers' Brain Trauma Indicator [BTI] February 2018) [1,2]. The BTI, when used in patients with mTBI in whom a head CT scan is felt to be clinically indicated, can, with a high degree of certainty, identify those at low risk for acute traumatic intracranial injury. The four hours required to perform the lab based BTI test, however, has precluded widespread clinical adoption for emergency department (ED) patients. Given the average wait time of over 3 h for a head computed tomography (CT) scan in the ED [3], a rapid GFAP/UCH-L1 test using the point of care i-STAT Alinity platform was found to be just as accurate [4] and received FDA clearance on January 8th 2021 [5]. However, neither of these tests were designed for both fast and high throughput sample analyses typically found in hospital-based core laboratories.

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The goal of this study was to determine test characteristics of a new TBI test using GFAP and UCH-L1 when performed on the rapid and high throughput core laboratory Alinity i platform (hereafter referred to as Alinity i). The importance of this study is two-fold. First, it will utilize the same population and specimens that can assess the accuracy of the platform as well as the consistency and validity of previous results using other lab platforms and, second, it will potentially suggest that the use of a fast and high throughput core laboratory platform could be of great value to reduce CT use and ED backup when a large number of patients are seeking care for TBI in situations such as mass casualty or when the ED is overloaded.

2. Methods

2.1. Study design and characteristics

This study, a secondary analysis of data and banked blood samples obtained for the ALERT-TBI trial included patients enrolled from December 2012 to March 2014 at 22 international sites; located in the United States and seven in Europe [1]. All sites received approval from their Institutional Review Board or the appropriate regulatory body. Informed consent was obtained from patients or if unable, an appropriate surrogate.

2.2. Patient selection

Eligible patients were those ≥18 years of age who presented to an ED or other healthcare facility with a non-penetrating head injury and an initial Glasgow Coma Scale Score (GSC) of 9–15. Blood samples had to be obtained withing 12-h of injury, and, based on the evaluation by the treating physician, a CT scan was required as part of routine care. Excluded were patients for whom injury time could not be determined, blood samples could not be obtained within 12 h, a CT scan was not deemed necessary, or appropriate consent was not obtained. For this study, only patients with a presenting GCS of 13–15 were included (Fig. 1).

2.3. Data obtained

General information was obtained from the patient (or surrogate) that included demographics, mechanism and time of injury, initial GCS, and other head injury-related information.

Head CT images obtained on all patients were interpreted by two board certified neuroradiologists. If there was disagreement between the two, a third board certified neuroradiologist adjudicated and that final interpretation was used. Images interpretation was complete (including isolated skull fractures, soft tissue injury, etc.) but the main finding for this study was any sign of study-defined traumatic intracranial injury defined as acute epidural hematoma, acute subdural hematoma, intraventricular hemorrhage, parenchymal hemorrhage/contusion, petechial hemorrhage/bland sheer injury, subarachnoid hemorrhage, brain edema/herniation, or ventricular compression/trapping. Skull fractures without any of the above intracranial findings were not considered positive.

Blood samples obtained were processed and stored locally (-80 °C) and shipped to a central storage facility. Banked plasma samples were then later shipped on dry ice to the Alinity i TBI study clinical testing sites. These specimens had not been thawed prior to use in the Alinity i TBI study. The stability of fresh and frozen plasma specimens was established as part of the FDA submission process. These frozen and de-identified plasma samples were tested at three clinical sites: University of Maryland (Baltimore, MD), Penn State Milton S. Hershey Medical

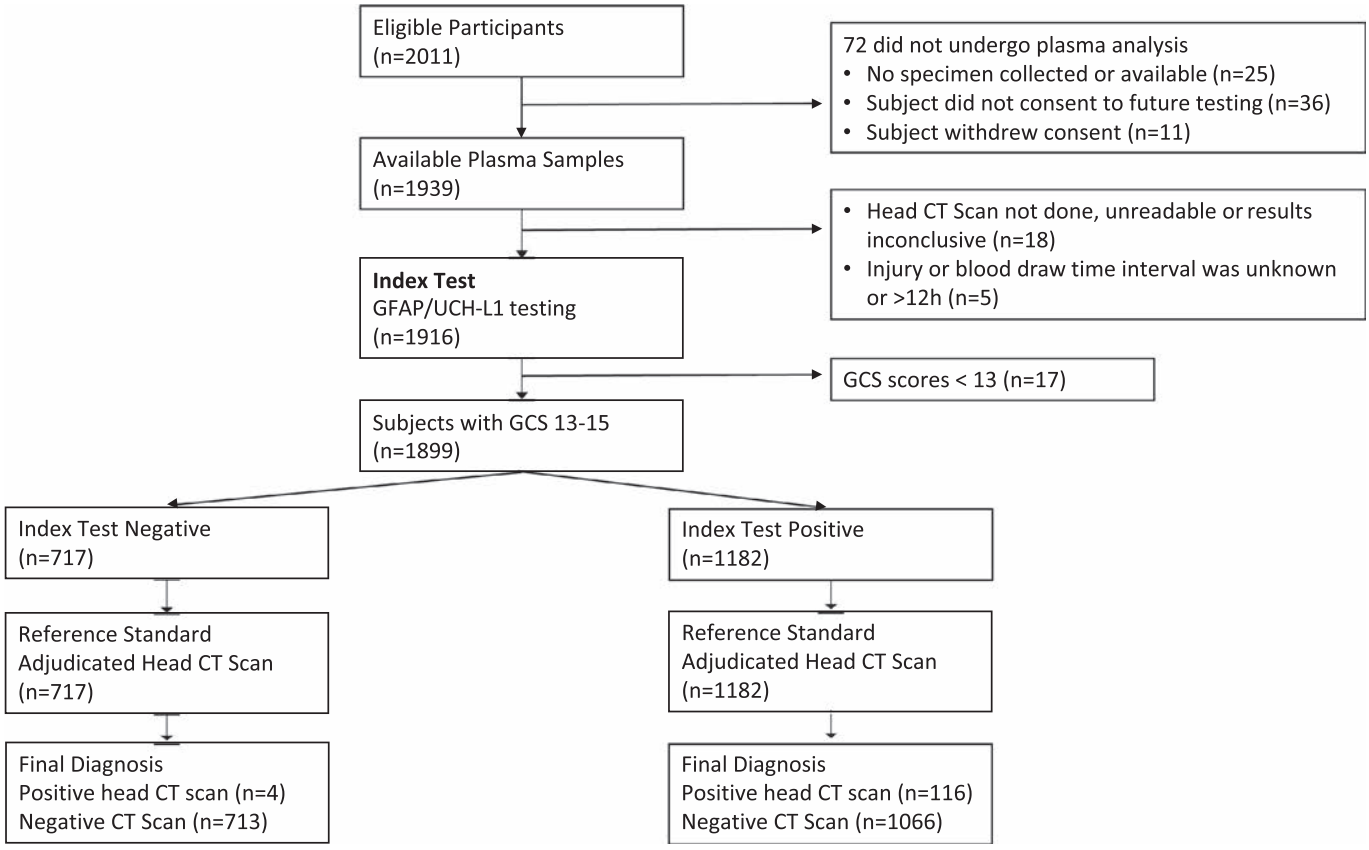

Fig. 1. STARD (Standards for Reporting Diagnostic accuracy studies) study flow diagram: CT (Computed Tomography); GCS (Glasgow Coma Scale); GFAP (Glial fibrillary acidic protein); UCH-L1 (Ubiquitin carboxyl-terminal hydrolase L1).

Center (Hershey, PA), and Inova Health System (Falls Church, VA). The 1939 specimens tested in the study were randomized across the three clinical sites. Site study personnel were blinded from the clinical result (i.e. CT scan) of each specimen. Specimens were thawed and tested using the TBI test on the Alinity i platform. Study personnel performed proficiency and reproducibility testing prior to testing the specimens. System reproducibility of the GFAP and UCH-L1 assays was evaluated by testing three lots of reagents, three lots of calibrators, and three lots of controls at each of three clinical testing sites. Three controls and seven human plasma panels were tested in four replicates at two separate times per day on five different days.

2.4. TBI Test

The Alinity i TBI test is a panel of in vitro diagnostic chemiluminescent microparticle immunoassays (CMIA) used for the quantitative measurements of GFAP and UCH-L1 in plasma and serum and provides a semi-quantitative interpretation of test results derived from a combination of these measurements. The Alinity i platform (Abbott Laboratories, IL, USA), is an automated immunoassay analyzer for the clinical laboratory with a throughput up to 200 tests per hour and a capacity of 47 assay reagent cartridges per module. The Alinity i TBI test consists of two distinct immunoassays for GFAP and UCH-L1 which are evaluated from a single plasma sample. The GFAP and UCH-L1 results are reported separately, and the Alinity i platform software provides a TBI interpretation relative to the respective cutoff values. In the current study, each plasma specimen was thawed and centrifuged at 10,000 RCF for 10 min. The specimen was transferred to a sample cup and placed in the Alinity i platform for testing. Sample analysis takes approximately 18 min and concentrations of the two biomarkers are displayed on the screen. The reportable interval for each assay extends from the limit of detection (LoD) to the upper limit of quantitation (LoQ). The reportable interval for GFAP is 3.2 pg/mL to 42,000 pg/mL, and for UCH-L1 is 18.3 pg/mL to 25,000 pg/mL. The Alinity i platform will not display a value for measurement beyond the reportable interval. The lower LoQ was 6.1 pg/mL for GFAP and 26.3 pg/mL for UCH-L1. The analytical measuring interval (AMI) is determined by the range of values that demonstrated acceptable performance for linearity, imprecision, and bias. The AMI for GFAP is 6.1 pg/mL to 42,000 pg/mL, and for UCH-L1 is 26.3 pg/mL to 25,000 pg/mL. Overall reproducibility, including within-run, between-run, between-day, between-lot, and between-site variance components ranged from 2.5 % CV (coefficient of variation) to 4.7 % CV for GFAP and 2.6 % CV to 6.6 % CV for UCH-L1.

The GFAP and UCH-L1 assay cut-offs were determined by analyzing a training dataset from a completely independent study population that is distinct from subjects evaluated in the pivotal study to validate the assay cut-offs. Frozen EDTA plasma samples from two study cohorts were utilized to establish the assay cut-offs. A total of 354 subjects with Glasgow Coma Scale (GCS) scores between 13 and 15 who had blood specimens collected within 12 h from the time of suspected head injury, a head CT scan determination, and were 18 years or older at the time of injury were included in the training dataset. Of the 354 subjects, 37.3 % (132/354) had a positive CT result. Using a 10-fold cross validation and bootstrapping method, the optimal cut-off values were selected as 35 pg/mL for the GFAP assay and 400 pg/mL for the UCH-L1 assay [6]. The cutoff values were determined to maximize sensitivity and negative predictive values prior to performing the tests for this study.

For the Alinity i TBI test, the GFAP cutoff is 35 pg/mL and UCH-L1 is 400 pg/mL. If either of the biomarkers were greater than or equal to the cutoff values, the test was reported as positive, and both had to be below the cutoff values to be reported as negative. The TBI test also provides actual values for each biomarker.

2.5. Primary outcome

The primary outcome was the presence or absence of traumatic intracranial injury on CT scan as defined above.

2.6. Data and statistical analysis

For general patient information, continuous data (age, biomarker values, etc.) are reported as mean (standard deviation [sd]) or median and 25th, 75th percentile as appropriate and categorical data as raw number and percents.

The Alinity i TBI test characteristics were compared to the gold standard CT results and include sensitivity, specificity, predictive values, and negative likelihood ratio (all with accompanying 95 % confidence intervals) for all included patients. We also examined the same test characteristics among the subgroups of those with GCS = 15 and GCS = 14 only, and those with blood sample obtained within two-hours of injury. Finally, exploratory analyses examined the risk ratio for CT positive at different concentration cutoff values (upper 5 %, 10 %, and 25 %). The later results must be considered as exploratory given that these are subgroups of the primary study population, and the risk ratios calculations were obtained using the different biomarker cutoff values as described above.

We followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [7] and the FDA guidelines (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-guidance-reporting-results-studies-evaluating-diagnostic-tests-guidance-industry-and-fda) for reporting our results. All analyses were performed using SAS ver 9.4 and R 3.5.3.

3. Results

This analysis included 1899 patients with complete data. The mean (sd) age was 49.1 (20.99), 56.5 % were male, and 70.2 % were white and the most common mechanism of injury was fall. The presenting GCS was 15 in most patients (94.1 %). The median (25th, 75th percentile) time from injury to blood sample obtained was 3.2 h (2.3, 4.0) and 340 patients had the blood sample obtained within two hours of injury. Table 1 summarizes this and other data and results for the subgroups of only patients with a GCS = 14, GSC = 15, and those with blood obtained within two hours of injury.

Head CT was positive for a traumatic intracranial injury in 120 (6.3 %) of all study patients, 21.1 % of patients with a GCS = 14, but in only 4.1 % of patients where blood samples were obtained within two hours. The combined biomarker TBI test was positive in 62.2 % of all study patients, 21.1 % of those with a GCS = 14, 61.4 % with a GCS = 15, and 74.0 % of patients in whom blood was obtained within two hours (Table 1). Table 1 also details the medians, ranges, in interquartile ranges of GFAP and UCH-L1 as determined on the Alinity itest.

For all study patients, the test characteristics (%, 95 % CI) of the Alinity i TBI test are sensitivity 96.7 (91.7, 98.7), specificity 40.1 (37.8, 42.4), negative predictive value 99.4 (98.6, 99.8). The negative likelihood ratio is 0.08 (0.03, 0.22). Among patients with blood obtained within two hours, the sensitivity is 100 (78.5, 100), the negative predictive value is also 100 (96.7, 100), and negative likelihood ratio is 0.00 (0.00, 0.63). Caution is advised when interpreting these results due to the relatively small numbers and wider confidence intervals. The test characteristics for patients with GCS = 14 or GCS = 15 alone are summarized in Table 2.

Table 3 describes the four patients with false negative TBI test results. Of note, none of the patients would have been considered to have an injury that required neurosurgical intervention based on the CT findings. The results of the exploratory analysis are shown in Table 4 and demonstrate increased risk ratios for a positive CT for both proteins as their concentrations increase.

Table 1
Demographic and Presenting Features of Subjects

Characteristics	Subjects with GCS 13–15 (N = 1899)	Subjects with GCS 14 (n = 90)	Subjects with GCS 15 (n = 1787)	Subjects with GCS 13–15 and blood collected within 2 h of injury (n = 340)
Age, mean yrs. (SD)[range]	49.1 (20.99) [18, 98]	51.7 (20.7) [19, 87]	49.0 (21.00) [18, 98]	54.8 (22.1) [18, 95]
Male sex, No. (%)	1073 (56.5)	57 (63.3)	1003 (56.1)	206 (60.6)
Race/ethnicity, No. (%)				
White	1334 (70.2)	68 (75.6)	1246 (69.7)	304 (89.4)
Black or African American	493 (26.0)	17 (18.9)	475 (26.6)	27 (7.9)
Other/unknown race	72 (3.8)	3 (3.3)	66 (3.7)	9 (2.7)
Hispanic or Latino	90 (4.7)	2 (2.2)	87 (4.9)	8 (2.4)
GCS score No. (%)				
13	22 (1.2)		–	4 (1.2)
14	90 (4.7)	90 (100)	–	28 (8.2)
15	1787 (94.1)		1787 (100)	308 (90.6)
Mechanism of Injury, No. (%)				
Acceleration/Deceleration	394 (20.8)	8 (8.9)	382 (21.4)	27 (7.9)
Motor Vehicle Accident	577 (30.4)	21 (23.3)	569 (31.9)	58 (17.1)
Pedestrian Struck by Vehicle	67 (3.5)	1 (1.1)	66 (3.7)	9 (2.6)
Fall	987 (51.9)	58 (64.4)	913 (51.0)	222 (65.3)
Explosion	3 (0.2)	0 (0)	3 (0.2)	1 (0.3)
Assault	179 (9.4)	4 (4.4)	175 (9.8)	14 (4.1)
Sports Injury	47 (2.5)	3 (3.3)	44 (2.5)	14 (4.1)
Other	53 (2.8)	3 (3.3)	50 (2.8)	13 (3.8)
Unknown	7 (0.4)	2 (2.2)	5 (0.3)	3 (0.9)
LOC/PTA, No. (%)*				
LOC	802 (42.2)	48 (53.3)	742 (41.5)	115 (33.8)
PTA	625 (32.9)	50 (55.6)	564 (31.6)	114 (33.5)
Both LOC and PTA	468 (24.6)	41 (45.6)	416 (23.3)	79 (23.2)
Neither LOC nor PTA	892 (47.0)	27 (30.0)	860 (48.1)	140 (41.2)
Unknown	25 (1.3)	10 (11.1)	18 (1.0)	12 (3.5)
Intoxicated with alcohol or drugs, No. (%)				
Y	402 (21.2)	62 (68.9)	367 (20.5)	266 (78.2)
N	1497 (78.8)	28 (31.1)	1420 (79.5)	74 (21.8)
Head CT scan				
Traumatic injury on head CT, No. (%)	120 (6.3)	19 (21.1)	94 (5.3)	14 (4.1)
No Traumatic injury on head CT, No. (%)	1779 (93.7)	71 (78.9)	1693 (94.7)	326 (95.9)
Test Results				
Hours from injury to blood draw, median, [range], (IQR)	3.2 [0.3, 11.9] (2.3–4.0)	3.0 [0.3, 9.7] (1.8–3.7)	3.2 [0.3, 11.9] (2.3–4.0)	1.5 [0.3, 2.0] (1.2, 1.8)
GFAP, median, [range], (IQR) pg/mL	40.4 [2.6, 11,807.4] (20.1, 91.5)	81.9 [10.3, 8161.8] (24.1, 176.3)	39.4 [2.6, 11,807.4] (20.1, 88.3)	41.8 [7.4, 985.4] (21.7, 79.2) [n = 340]
UCH-L1, median [range], (IQR) pg/mL	256.4 [32.7, 9753.1] (140.5, 488.6)	357.5 [86.6, 4129.3] (174.3, 649.5)	253 [32.7, 9753.1] (137.9, 476.8)	340.5 [42.1, 9753.1] (193.1, 564.6) [n = 340]
Positive Test, No. (%)	1182 (62.2)	19 (21.1)	1097 (61.4)	228 (74.0)

* LOC: loss of consciousness, PTA: post-traumatic amnesia.

The results of the exploratory analysis are shown in Table 4 and demonstrates the risk of acute traumatic injury on head CT scan in subjects with GFAP and UCH-L1 concentrations in the upper 25th, 10th, and 5th percentiles compared to those below their respective cutoffs. Subjects with a GFAP result above 385 pg/mL (upper 5th percentile) are 72.4 times more likely to be CT positive compared to subjects with a GFAP below the cutoff (35 pg/mL). Subjects with a UCH-L1 result above 1538 pg/mL (upper 5th percentile) are 37.4 times more likely to be CT positive compared to subjects with a UCH-L1 below the cutoff (400 pg/mL).

4. Discussion

This study suggests that the Alinity i platform can provide the clinician with objective TBI test results and information to potentially exclude the need to obtain a head CT among patients presenting within

Table 2
Performance of rapid UCH-L1/GFAP Test for Predicting Acute Traumatic Intracranial Injury on Head CT Scan.

Performance Characteristic	Subjects with GCS 13–15 (n = 1899)	Subjects with GCS 14 (n = 90)	Subjects with GCS 15 (n = 1787)	Subjects with GCS 13–15 and blood collected within 2 h of injury (n = 340)
Sensitivity, % (95 % CI)	96.7 (91.7, 98.7)	100 (83.2, 100)	95.7 (89.6, 98.3)	100 (78.5, 100)
Specificity, % (95 % CI)	40.1 (37.8, 42.4)	67.6 (56.1, 77.3)	40.5 (38.2, 42.9)	35.0 (30.0, 40.3)
Positive Predictive Value, % (95 % CI)	9.8 (8.2, 11.6)	71.6 (59.9, 81.0)	8.2 (6.7, 10.0)	6.2 (3.7, 10.1)
Negative Predictive Value, % (95 % CI)	99.4 (98.6, 99.8)	100 (85.7, 100)	99.4 (98.5, 99.8)	100 (96.7, 100)
Positive Likelihood Ratio (95 % CI)	1.61 (1.53, 1.70)	1.48 (1.21, 1.78)	1.61 (1.50, 1.70)	1.52 (1.19, 1.66)
Negative Likelihood Ratio (95 % CI)	0.08 (0.03, 0.22)	0.00 (0.00, 0.53)	0.11 (0.04, 0.26)	0.00 (0.00, 0.63)

Table 3
Characteristics of False Negative Subjects ($n = 4$).

Sex	Age (years)	Time from Injury to Blood Draw (hours)	GCS	GFAP (pg/mL)	UCH-L1 (pg/mL)	Head CT Findings*
Male	62	8.9	15	21.0	95.2	Acute SDH
Female	49	5.9	15	30.1	97.8	SAH
Female	43	3.5	15	20.8	72.2	Parenchymal hematoma
Male	41	3.3	15	26.7	73.4	SAH

Abbreviations: GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; SAH, subarachnoid hemorrhage; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.
* No head CT findings were neurosurgically manageable injuries.

12 h of a suspected head injury and having a GCS 13–15 on presentation. These results are in-line with and help to broadly confirm the results of the TBI test panel as determined in the initial ALERT-TBI trial and the study that utilized the point of care i-STAT Alinity hand-held single sample platform, both of which are FDA cleared for clinical use [1,4]. More recently (the TBI test performed on the core laboratory Alinity i platform was cleared for marketing [6].

In addition to confirming the important test characteristics and clinical usefulness, the ability of this platform to analyze many samples (up to 200 per hour) and other analytes simultaneously suggests that this platform is potentially attractive for several reasons. Despite the need to obtain blood and send the samples to the core lab for centrifugation, results can be obtained in as little as 18 min [6] The screening process can reduce the need to obtain a head CT for this selected group of mTBI patients and can potentially improve overall efficiency. Although it is variable, one hospital found the median (25th, 75th) percentile for time (hours:minutes) of head CT imaging completion to preliminary results availability was 0:57 (0:36, 1:35) and the patient ED arrival time to CT preliminary results was 3:13 (2:17, 4:26) [3]. This study, published in 2017 (pre-COVID), may not reflect all institutions' times or current data but the use the TBI blood test can not only help reduce CT use but may be an important part of reducing ED length of stay when patients must wait to be seen by a physician. Ultimately, this hospital lab-based test has the potential advantages of being faster than obtaining CT results (under certain conditions) and can perform multiple tests simultaneously.

We postulate that the ability to provide the TBI test results to clinicians is particularly important when the ED is overloaded, there is a multiple patient injury or mass casualty situation, or the CT must be prioritized for critically ill, polytrauma, stroke, or other patients with a higher triage acuity. As we learned with the recent COVID-19 and Monkey Pox outbreaks, there is also a need to reduce the number of people in ED waiting area and to reduce the number of patients going through the CT scanner since time and labor are required to disinfect the area.

Why a blood test when others suggest using CDRs alone? In contrast to the Canadian CT Head (CCTH) [8] or New Orleans Criteria (NOC) [9] clinical decision rules, the blood test panel does not have an upper age (≥ 65 for CCTHR or > 60 for the NOC) that suggests a CT is needed for adults, it can be used in patients with a GCS 13 (under the right clinical circumstances) or, in the case of the CCTH rule, there is no need to transition from a GCS score of 13 or 14 to a GCS score or 15 within two hours of injury. In fact, the NOC has a lower specificity that indicates reduced potential to decrease use compared to the CCTH rule [10]. Additionally, the CCTH rule, first published in 2001, has been slow to adopt [11,12] and when adopted, resulted in only small decreases in CT use and proportion of positive CT scans [12,13], Finally, even when the CCTH rule is used, it has been suggested that the addition of measuring GFAP has improved diagnostic capability above clinical decision making alone [14],

Table 4
Risk of acute traumatic injury on head CT scan in subjects with GFAP and UCH-L1 concentrations in the upper 25th, 10th, and 5th percentiles compared to those below cutoff.

Protein	Upper Percentile (concentration)	Risk Ratio with Haldane's Correction Applied (95 % CI)
UCH-L1	5th (>1538 pg/mL)	37.4 (14.5, 117.9)
	10th (>954 pg/mL)	29.7 (11.9, 91.8)
	25th (>489 pg/mL)	22.7 (9.3, 69.0)
GFAP	5th (>385 pg/mL)	72.4 (29.9, 220.8)
	10th (>213 pg/mL)	51.0 (21.1, 155.0)
	25th (>92 pg/mL)	32.2 (13.4, 97.3)

This analysis platform has other potential advantages. It provides for a larger analytic interval for both proteins, mostly at the upper end but also lowers the lower limit of quantification. Higher values of these biomarkers may help clinicians understand patient injury even in the absence of a positive CT. One study has demonstrated that patients with a negative head CT but having traumatic cranial abnormalities found on magnetic resonance imaging (MRI) have, on average, higher GFAP levels suggesting there are still structural injuries to the brain [15]. The diagnostic, prognostic, therapeutic, and other clinical ramifications, however, are yet to be fully understood.

The incremental value and cost associated with using a blood biomarker test has been questioned [16] but there are now two cost-modeling studies that suggest the test is cost effective. One, in the United States, suggested that if the test is less than about $73 per test (2019 dollars), it is cost effective if the probability of traumatic intracranial injury is 0.10 [17]. In the French health care system, the GFAP/UCH-L1 test panel was also found to be cost saving and may marginally improve quality-adjusted life-years [18].

Although the recent ACEP guideline for mTBI management has little reference to these biomarkers [19], other global consensus guidelines support implementation. The TBI test panel (GFAP/UCH-L1) is now incorporated into the French multidisciplinary reference for management of mTBI patients. The French recommendations suggest the use of these biomarkers up to 12 h post-injury to limit CT use the recommendation had high agreement among their experts [20]. Other recommendations for adoption of the TBI blood test include the National Academies of Sciences, Engineering, and Medicine (Forum on Traumatic Brain Injury) [21], American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild TBI [22], and the Spanish Emergency Medicine Society consensus statement. Others are forthcoming in draft from National Institute of Neurological Disorders and Stroke TBI Classification, and Portuguese and German stakeholders.

5. Limitations

There are several limitations to consider when evaluating the results of the study. This is a non-interventional study in which clinicians used their local guidelines or unstructured judgment as to CT need and only those getting a CT were included. The Alinity i requires blood to be sent to a core lab for processing. A positive head CT alone may not be a clinically relevant outcome and does not implicate the need for treatment such as neurosurgical care. The “Brain Injury Guidelines” (BIG), however, still recommend at least six-hours of observation for patients with these low-grade intracranial injuries [23,24], and the CCTHR is not designed to recommend CT use for patients with “clinically unimportant injury”. There has not been a randomized clinical trial that prospectively examined the actual effect on CT use and patient outcomes when CDRs were implemented in all cases and the TBI test results were randomly available to treating clinicians.

Another limitation is this study did not include pediatric patients. It is possible that pediatric patients with mTBI may benefit more than adults, if the TBI test was available, when one considers that the potential CT radiation risk and diagnostic uncertainty are greater in pediatric patients [25]. This concept, however, remains to be clearly determined. Finally, the need for a two-biomarker panel has been debated. The need for both is demonstrated by the different kinetics with UCH-L1 rising earlier and dropping rapidly where GFAP rises a short time later and remains elevated longer [26].

6. Conclusion

The Alinity i TBI biomarker panel (GFAP and UCH-L1) can provide the clinician with a high degree of certainty and provides rapid, quantifiable, and objective information that can potentially reduce CT use among patients with TBI. The Alinity i can provide this information quickly into the electronic health record and can run many samples simultaneously. This may have importance during ED overload, mass casualty, or other instances when blood samples are delivered to the core lab for analysis.

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CRediT authorship contribution statement

Robert D. Welch: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Jeffrey J. Bazarian:** Writing – review & editing, Methodology, Investigation. **James Y. Chen:** Writing – review & editing, Data curation. **Raj Chandran:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Saul A. Datwyler:** Writing – review & editing, Resources, Conceptualization. **Beth McQuiston:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Krista Caudle:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Robert D. Welch, MD, MS reports a relationship with Abbott Laboratories that includes: consulting or advisory and speaking and lecture fees. Robert D. Welch reports a relationship with bioMérieux Inc. that includes: consulting or advisory. Jeff Bazarian, MD, MPH reports a relationship with Abbott Laboratories that includes: consulting or advisory and funding grants. Jeff Bazarian, MD, MPH reports a relationship with bioMérieux SA that includes: consulting or advisory. Raj Chandran, PhD reports a relationship with Abbott Laboratories that includes: employment and equity or stocks. Saul Datwyler, PhD reports a relationship with Abbott Laboratories that includes: employment and equity or stocks. Beth McQuiston, MD reports a relationship with Abbott Laboratories that includes: employment and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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