Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: an observational cohort study

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Summary

Background The prognostic value of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) as day-of-injury predictors of functional outcome after traumatic brain injury is not well understood. GFAP is a protein found in glial cells and UCH-L1 is found in neurons, and these biomarkers have been cleared to aid in decision making regarding whether brain CT should be performed after traumatic brain injury. We aimed to quantify their prognostic accuracy and investigate whether these biomarkers contribute novel prognostic information to existing clinical models.

Methods We enrolled patients from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) observational cohort study. TRACK-TBI includes patients 17 years and older who are evaluated for TBI at 18 US level 1 trauma centres. All patients receive head CT at evaluation, have adequate visual acuity and hearing preinjury, and are fluent in either English or Spanish. In our analysis, we included participants aged 17–90 years who had day-of-injury plasma samples for measurement of GFAP and UCH-L1 and completed 6-month assessments for outcome due to traumatic brain injury with the Glasgow Outcome Scale–Extended (GOSE-TBI). Biomarkers were analysed as continuous variables and in quintiles. This study is registered with ClinicalTrials.gov, NCT02119182.

Findings We enrolled 2552 patients from Feb 26, 2014, to Aug 8, 2018. Of the 1696 participants with brain injury and data available at baseline and at 6 months who were included in the analysis, 120 (7·1%) died (GOSE-TBI=1), 235 (13·9%) had an unfavourable outcome (ie, GOSE-TBI ≤4), 1135 (66·9%) had incomplete recovery (ie, GOSE-TBI <8), and 561 (33·1%) recovered fully (ie, GOSE-TBI=8). The area under the curve (AUC) of GFAP for predicting death at 6 months in all patients was 0·87 (95% CI 0·83–0·91), for unfavourable outcome was 0·86 (0·83–0·89), and for incomplete recovery was 0·62 (0·59–0·64). The corresponding AUCs for UCH-L1 were 0·89 (95% CI 0·86–0·92) for predicting death, 0·86 (0·84–0·89) for unfavourable outcome, and 0·61 (0·59–0·64) for incomplete recovery at 6 months. AUCs were higher for participants with traumatic brain injury and Glasgow Coma Scale (GCS) score of 3–12 than for those with GCS score of 13–15. Among participants with GCS score of 3–12 (n=353), adding GFAP and UCH-L1 (alone or combined) to each of the three International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury models significantly increased their AUCs for predicting death (AUC range 0·90–0·94) and unfavourable outcome (AUC range 0·83–0·89). However, among participants with GCS score of 13–15 (n=1297), adding GFAP and UCH-L1 to the UPFRONT study model modestly increased the AUC for predicting incomplete recovery (AUC range 0·69–0·69, p=0·025).

Interpretation In addition to their known diagnostic value, day-of-injury GFAP and UCH-L1 plasma concentrations have good to excellent prognostic value for predicting death and unfavourable outcome, but not for predicting incomplete recovery at 6 months. These biomarkers contribute the most prognostic information for participants presenting with a GCS score of 3–12.

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Introduction

Outcome after traumatic brain injury is affected by pre-injury factors (eg, demographics, social history, and medical comorbidities), injury factors (eg, injury biomechanics and the type, extent, and location of primary and secondary brain injury), treatment factors, and environmental factors.[1] Structural brain injury visualised by CT (eg, contusions, subdural haemorrhages,

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Research in context

Evidence before this study

We conducted a PubMed search for studies examining the prognostic value of plasma glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) in patients with traumatic brain injury (TBI) published in English from April 1, 2004, to April 8, 2022, with the search terms ("glial fibrillary acidic protein" OR "ubiquitin carboxy-terminal hydrolase") AND "traumatic brain injury" AND "prognosis" and filtered by "Humans" in the publication title or abstract. 51 studies were retrieved, of which ten were prospective observational studies of more than 50 participants that examined the association between GFAP and UCH-L1 and clinical outcome (ie, global functional recovery measured by the Glasgow Outcome Scale Extended and or all-cause mortality). We also identified one systematic review that included studies meeting our selection criteria. These studies have consistently reported higher concentrations of GFAP and UCH-L1 in participants with poor clinical outcome compared with those with good clinical outcome. A few studies investigated whether these biomarkers contribute additional prognostic information to existing prognostic models.

Added value of this study

This study contributes new knowledge to the scientific literature on the prognostic value of GFAP and UCH-L1 in patients with acute traumatic brain injury. We used an assay that was CE-marked and cleared by the US Food and Drug Administration. Our large sample size enabled us to estimate the prognostic value of GFAP and UCH-L1 for predicting death, incomplete recovery (Glasgow Outcome Scale-Extended-TBI <8), and unfavourable outcome (ie, GOSE-TBI ≤4) with high precision. To our knowledge, this is also the first study to examine the association between brain injury biomarker concentrations and all-cause mortality following traumatic brain injury, using a time-to-event analysis. Our study also investigated the added prognostic contribution of GFAP and UCH-L1 to existing prognostic models (the International Mission for Prognosis and Analysis of Clinical Trials in TBI [IMPACT] Core and IMPACT Extended models for patients with traumatic brain injury and a Glasgow Coma Scale [GCS] score of 3–12 traumatic brain injury and the UPFRONT study model for patients with traumatic brain injury and a GCS score of 13–15).

Implications of all the available evidence

Our findings, which are corroborated by findings from previous smaller studies, suggest that day-of-injury plasma concentrations of GFAP and UCH-L1 provide information regarding a patient's 6-month risk of death and unfavourable outcome, but not incomplete recovery. Furthermore, in patients presenting with traumatic brain injury and a GCS score of 3–12, incorporating GFAP and UCH-L1 values into the IMPACT models significantly increases the prognostic value of these models. However, these biomarkers only modestly, but significantly, increased the prognostic value of the UPFRONT study model for predicting incomplete recovery in patients with a GCS score of 13–15. Therefore, GFAP and UCH-L1 concentrations can improve outcome prognostication, especially for patients with a GCS score of 3–12, enabling clinicians and researchers to provide a more accurate assessment of the expected course of recovery than currently possible.

or subarachnoid haemorrhages) and those visualised by MRI (eg, diffuse axonal or vascular injury) are well established as predictors of traumatic brain injury outcome.[2–5] During the past 10 years, several blood-based biomarkers of glial and neuronal cell injury obtained on the day of injury have been reported to be associated with structural brain injury visualised by neuroimaging.[6–9] The US Food and Drug Administration cleared the use of two such biomarkers—glial fibrillary acidic protein (GFAP; a structural protein found in astrocytes) and ubiquitin C-terminal hydrolase L1 (UCH-L1; an enzyme found in high abundance in neurons)—to aid clinicians in deciding whether to order a head CT for imaging structural brain injury following mild traumatic brain injury (ie, defined as Glasgow Coma Scale [GCS] score of 13–15).[10] These biomarkers are associated with clinically assessed injury severity and structural brain injury confirmed by CT and MRI.[6–9,11,12]

The usefulness of GFAP and UCH-L1 for early prediction of long-term traumatic brain injury outcomes has not been adequately studied. Early and accurate prediction of traumatic brain injury outcomes is important both clinically and in research settings. Prognostic tools can guide discussions between clinicians and patients or family members regarding the expected course of recovery and therapeutic options. They might also inform participant selection in trials and could be used to adjust for baseline characteristics during the analysis of study results. Many existing studies evaluating the prognostic value of brain injury biomarkers are limited by modest sample sizes, which yield imprecise estimates of prognostic value. Increased precision in estimates of the prognostic value of these biomarkers could provide early and more accurate information on which to base clinical decisions and a more refined study design than currently exists. Additionally, these biomarkers might add novel prognostic information to existing validated prognostic models that are based on clinical variables and CT measures.

We aimed to quantify the prognostic value of day-of-injury plasma concentrations of GFAP and UCH-L1 to predict death (ie, Glasgow Outcome Scale–Extended

score attributable solely to TBI [GOSE-TBI] of 1), unfavourable outcome (ie, GOSE-TBI ≤4), and incomplete recovery (ie, GOSE-TBI <8) at 6 months in participants with traumatic brain injury of all severities (presenting with a GCS score of 3–15). We also aimed to establish whether these biomarkers contributed novel prognostic information to the International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury (IMPACT) Core and IMPACT Extended models for predicting death and unfavourable outcome[13] in participants with traumatic brain injury and a GCS score of 3–12, and the UPFRONT study model for predicting incomplete recovery in participants with traumatic brain injury and a GCS score of 13–15.[14]

Methods

Study design and participants

The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) cohort is a prospective observational study of a convenience sample of patients who were evaluated for traumatic brain injury at emergency departments of 18 level 1 trauma centres in the USA[15] from Feb 26, 2014, to Aug 8, 2018. We analysed data from participants aged 17 years and older who had day-of-injury plasma samples available for measurement of GFAP and UCH-L1 concentrations and who had completed a 6-month follow-up assessment. Traumatic brain injury was defined as injury to the brain that was at least as severe as injury described by the American Congress of Rehabilitation Medicine's criteria.[16] Participants of all injury severities were included in the study if they met the following criteria: evaluated for traumatic brain injury within 24 h of injury either in the emergency department or a hospital inpatient unit; received head CT by order of the evaluating clinician; had adequate visual acuity and hearing preinjury; and were fluent in either English or Spanish. We excluded patients with clinically significant polytrauma that would interfere with follow-up (on the basis of the judgment of the clinical team and research coordinators), penetrating traumatic brain injury, a contraindication to MRI, major debilitating psychiatric disorders (eg, schizophrenia or bipolar disorder) or neurological disorders (eg, stroke or dementia), or any other disorder that would interfere with assessment and follow-up or provision of informed consent. We also excluded patients who were prisoners or patients in custody; those who were pregnant; people under involuntary psychiatric treatment hold; individuals who could not speak English or Spanish; and patients currently participating in an interventional trial.[17] Written informed consent was obtained from participants or legally authorised representatives. The study was approved by the institutional review boards of enrolling sites.

Procedures

Demographic and clinical data were obtained by trained research assistants through medical record review or participant interviews at enrolment. The GCS score was based on the first and most accurately documented GCS score after resuscitation. Head CT scans were sent to a central imaging repository (Laboratory of Neuro Imaging, Los Angeles, CA, USA) and were assessed by one board-certified neuroradiologist (ELY) on the basis of the Common Data Elements in Radiologic Imaging of Traumatic Brain Injury.[18] Scans were classified by use of the Marshall head CT classification.[19] Global functional recovery at 6 months (GOSE score) was assessed either in person or via telephone by trained study personnel who were masked to biomarker concentrations. For participants with multisystem trauma, the GOSE assessment specifically elicited the interviewees' assessment of functional impairment that was solely attributable to the traumatic brain injury and not impairment related to other system injuries (denoted as GOSE-TBI).[20] The primary outcomes were death (GOSE-TBI=1) or unfavourable outcome at 6 months after injury (GOSE-TBI ≤4). Patients who died were assigned a GOSE-TBI of 1 irrespective of the cause of death. The secondary outcome was incomplete recovery at 6 months (GOSE-TBI <8). Outcome assessors were masked to biomarker measurements. Major extracranial injury was defined as an Abbreviated Injury Scale score of 3 or more in at least one of the extracranial domains. Since the Abbreviated Injury Scale is available only for patients who are admitted to hospital, those who were discharged home were assumed to have no major extracranial injury.

We obtained blood samples within 24 h of injury, and processed, aliquoted, and stored them in a –80°C freezer within 2 h of collection. Sample acquisition, processing, and storage were performed following the TBI-Common Data Elements Biospecimens and Biomarkers Working Group Guidelines.[21] Coded samples were then shipped overnight on dry ice to a central repository (University of Pittsburgh Medical Center, Pittsburgh, PA, USA), and from the central repository to a laboratory (Abbott Laboratories, Abbott Park, IL, USA) for analysis. Sample analysis was done in batches by personnel at Abbott who were masked to sample information. Plasma samples used in this analysis underwent one freeze–thaw cycle.

The first batch of plasma GFAP and UCH-L1 concentrations (n=963) was measured using the prototype point-of-care i-STAT Alinity System (Abbott Laboratories, Abbott Park, IL, USA). The second batch of plasma GFAP and UCH-L1 concentrations (n=733) were measured on the prototype core lab ARCHITECT platform (Abbott Laboratories, Abbott Park, IL, USA) for faster throughput. The two assays were highly correlated, and ARCHITECT values were converted to iSTAT equivalents by use of two previously derived equations: $iSTAT = -12 \cdot 36 + 1 \cdot 02 \times ARCHITECT$ for GFAP (*Spearman's correlation coefficientr*=0·985) and $iSTAT = -3 \cdot 29 + 0 \cdot 72 \times ARCHITECT$ for UCH-L1 (r=0·933).[22]

	Total (n=1696)	GCS 13–15 (n=1297)	GCS 3–12 (n=353)
Age, years	39 (26–56)	39 (26–56)	38 (25–55)
Sex			
Male	1156 (68·2%)	843 (65·0%)	275 (77·9%)
Female	540 (31·8%)	454 (35·0%)	78 (22·1%)
Race			
White	1306/1679 (77·8%)	987/1291 (76·5%)	278/344 (80·8%)
Black	264/1679 (15·7%)	218/1291 (16·9%)	43/344 (12·5%)
Other	109/1679 (6·5%)	86/1291 (6·7%)	23/344 (6·7%)
Ethnicity			
Non-Hispanic	1423/1679 (84·8%)	1101/1291 (85·3%)	288/344 (83·7%)
Hispanic	256/1679 (15·2%)	190/1291 (14·7%)	56/344 (16·3%)
Mechanism			
Road traffic incident	960/1687 (56·9%)	726/1292 (56·2%)	207/350 (59·1%)
Incidental fall	465/1687 (27·6%)	363/1292 (28·1%)	90/350 (25·7%)
Violence or assault	104/1687 (6·2%)	80/1292 (6·2%)	21/350 (6·0%)
Other	158/1687 (9·4%)	123/1292 (9·5%)	32/350 (9·1%)
Previous traumatic brain injury	503/1631 (30·8%)	428/1279 (33·5%)	70/311 (22·5%)
Past psychiatric history	411 (24·2%)	319/1297 (24·6%)	80/353 (22·7%)
Loss of consciousness			
No	184/1683 (10·9%)	172/1293 (13·3%)	9/345 (2·6%)
Yes	1420/1683 (84·4%)	1058/1293 (81·8%)	323/345 (93·6%)
Unknown	79/1683 (4·7%)	63/1293 (4·9%)	13/345 (3·8%)
Post-traumatic amnesia			
No	254/1683 (15·1%)	232/1293 (17·9%)	16/345 (4·6%)
Yes	1191/1683 (70·8%)	958/1293 (74·1%)	208/345 (60·3%)
Unknown	238/1683 (14·1%)	103/1293 (8·0%)	121/345 (35·1%)
Disposition			
Emergency department discharge	384 (22·6%)	379 (29·2%)	0
Non-ICU hospital admission	551 (32·5%)	543 (41·9%)	4 (1·1%)
ICU admission	761 (44·9%)	375 (28·9%)	349 (98·9%)
Major extracranial injury	319 (18·8%)	196 (15·1%)	110 (31·2%)
Marshall head CT classification			
1	819/1631 (50·2%)	790/1263 (62·5%)	22/326 (6·7%)
2	579/1631 (35·5%)	426/1263 (33·7%)	135/326 (41·4%)
3	35/1631 (2·1%)	10/1263 (0·8%)	24/326 (7·4%)
4	15/1631 (0·9%)	3/1263 (0·2%)	10/326 (3·1%)
5	170/1631 (10·4%)	32/1263 (2·5%)	125/326 (38·3%)
6	13/1631 (0·8%)	2/1263 (0·2%)	10/326 (3·1%)
Traumatic subarachnoid haemorrhage	596/1630 (36·6%)	310/1262 (24·6%)	256/326 (78·5%)
Epidural haemorrhage	133/1629 (8·2%)	67/1262 (5·3%)	57/326 (17·5%)
GCS motor score			
5 or 6	1388/1671 (83·1%)	1274/1286 (99·1%)	100/351 (28·5%)
4	58/1671 (3·5%)	3/1286 (0·2%)	53/351 (15·1%)
3	22/1671 (1·3%)	0	17/351 (4·8%)
2	23/1671 (1·4%)	0	23/351 (6·6%)
1	180/1671 (10·8%)	9/1286 (0·7%)	158/351 (45·0%)

(Table 1 continues on next page)

The i-STAT Alinity GFAP and UCH-L1 tests use the sandwich ELISA method with electrochemical detection of the resulting enzyme signal. The test time for each assay was approximately 15 min. The calibration range of the GFAP assay was 0–50 000 pg/mL. The limit of detection (LoD) was 15 pg/mL and limit of quantitation (LoQ) was 25 pg/mL, resulting in a reportable range of 15–50 000 pg/mL. Within-laboratory precision, measured by the coefficient of variation, was 2·8–14·2%. The UCH-L1 assay calibration range was 0–20 000 pg/mL. The LoD was 10 pg/mL and LoQ was 20 pg/mL, resulting in a reportable range of 10–20 000 pg/mL. The assay had a coefficient of variation of 5·0–10·0%. Samples with values greater than 50 000 pg/mL were not retested with dilution.

The prototype ARCHITECT GFAP and UCH-L1 assays are two-step sandwich assays that use a chemiluminescent microparticle immunoassay technology. The prototype GFAP assay calibration range was 0–50 000 pg/mL. The LoD was 2 pg/mL and LoQ was 5 pg/mL, for a reportable range of 2–50 000 pg/mL. The within-laboratory coefficient of variation was 2·0–5·6%. The prototype UCH-L1 assay calibration range was 10–25 000 pg/mL. The LoD was 10 pg/mL and LoQ was 20 pg/mL, for a reportable range of 10–25 000 pg/mL. The assay had a coefficient of variation of 2·0–5·7%. All samples were tested neat (without dilution) and in duplicate. Samples with values greater than the calibration range were reported as greater than the reportable range and were not diluted. Technicians performing biomarker measurements were masked to clinical outcome data.

Statistical analysis

Demographics, clinical characteristics, and biomarker concentrations were summarised for the study cohort and by GCS at hospital presentation and GOSE-TBI status at 6 months. For group comparisons, we used the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Biomarker concentrations were not normally distributed and were summarised by reporting medians and their corresponding IQR. Log-transformed biomarker concentrations were used for modelling. For both i-STAT and ARCHITECT, biomarker concentrations below the assay's LoD were analysed using the value reported by the assay, without transformation; GFAP values above the upper limit of the assays (ie, 50 000 pg/mL) were assigned the upper limit. Receiver operating characteristic analysis was performed to assess the discriminative ability of day-1 GFAP and UCH-L1 for predicting death (ie, GOSE-TBI=1), unfavourable outcome (ie, GOSE-TBI ≤4), and incomplete recovery (ie, GOSE-TBI <8) at 6 months after injury for participants with TBI of all severities, and separately for the subset of participants with a GCS score of 3–12 and those with a GCS score of 13–15. ROC curves were graphed and the area under the receiver operator characteristic curve (AUC) was calculated with its 95% confidence interval.

Kaplan-Meier curves were plotted to examine the association between day-of-injury biomarker concentration (categorised into quintiles) and time to all-cause mortality in the first 6 months since injury. Since there are no generally accepted biomarker cutoffs to distinguish high concentrations from low concentrations, we used quintiles to minimise bias. Cox proportional hazards models were performed to assess the association, adjusted for potential confounders such as age, sex, and presenting GCS score (as a continuous variable) of 12 or less versus 13–15. The proportional hazards assumptions were met.

We performed logistic regression models to assess whether adding day-of-injury concentrations of GFAP and UCH-L1 improved the prognostic value of modified IMPACT models for predicting unfavourable outcome and mortality. The IMPACT models were derived in a cohort of patients with traumatic brain injury and a GCS score of 3–12, and therefore the analysis regarding the added prognostic value of biomarkers was restricted to patients with traumatic brain injury and a GCS score of 3–12. Predictors in the IMPACT Core model are age, GCS motor score, and pupil reactivity. Predictors in the IMPACT Extended model are IMPACT Core, CT variables (ie, subarachnoid haemorrhage, epidural haemorrhage, and Marshall head CT score), hypotension, and hypoxia. Predictors in the IMPACT Lab model are IMPACT Extended and laboratory variables (ie, glucose and haemoglobin). As per a previous IMPACT model validation study, hypoxia was defined as peripheral oxygen saturation of less than 90% and hypotension was defined as systolic blood pressure of less than 90 mm Hg. We added major extracranial injury to the IMPACT models to adjust for this important predictor of outcome and, for this reason, we refer to the models as modified IMPACT models. Since the IMPACT models were derived to predict outcomes in patients with traumatic brain injury and a GCS score of 3–12, to establish whether biomarkers add prognostic value to clinical predictors in patients with traumatic brain injury and a GCS score of 13–15, we use the UPFRONT study model.[14] This model was developed to predict incomplete recovery in patients with traumatic brain injury and a GCS score of 13–15. To our knowledge there are no well validated models for predicting outcomes in patients with a GCS score of 3–8 and a GCS score of 9–12 separately. Predictor variables for the UPFRONT study model are age (ie, <40 years, 41–64 years, and 66–90 years), sex, years of education, previous psychiatric history, previous traumatic brain injury, alcohol intoxication on the day of injury, CT abnormalities, GCS score, duration of post-traumatic amnesia (ie, none, ≤24 h, or >24 h), and neck pain. We did not include neck pain as a predictor, because this variable was not collected in our dataset. However, as with the IMPACT models, we included major extracranial injury as a predictor (ie, modified UPFRONT study model). When biomarkers were added to the modified IMPACT and UPFRONT study models, we adjusted the models for time between injury and blood draw (ie, <9 h, 9–16 h, and ≥17 h). Missing values in the predictors were imputed by multiple imputation methods.[23] Pooled results from multiple imputed datasets were reported. Likelihood ratio tests were performed to examine whether adding the biomarkers improved the prognostic accuracy of the modified IMPACT and UPFRONT models. Model discrimination (ie, area under the curve [AUC]) and Nagelkerke's pseudo R^2 were also reported for each model.

Significance was set as p value of less than 0·05. Statistical analyses were conducted in R, version 4.1.2.

This study is registered with ClinicalTrials.gov, NCT02119182.

	Total (n=1696)	GCS 13–15 (n=1297)	GCS 3–12 (n=353)
(Continued from previous page)			
Pupillary reaction			
Both reacting	1348/1462 (92·2%)	1107/1114 (99·4%)	216/314 (68·8%)
One reacting	32/1462 (2·2%)	6/1114 (0·5%)	25/314 (8·0%)
None reacting	82/1462 (5·6%)	1/1114 (0·1%)	73/314 (23·2%)
Hypoxia	79 (4·7%)	23 (1·8%)	51 (14·4%)
Hypotension	69 (4·1%)	25 (1·9%)	41 (11·6%)
Time between injury and blood draw, h			
0–8	341/1614 (21·1%)	291/1247 (23·3%)	46/323 (14·2%)
9–16	496/1614 (30·7%)	370/1247 (29·7%)	110/323 (34·1%)
≥17	777/1614 (48·1%)	586/1247 (47·0%)	167/323 (51·7%)

Data are median (IQR), n (%), or n/N (%) when the denominator differs from the N value in the column heading, unless otherwise stated. GCS score at injury was missing for 46 participants. GCS=Glasgow Coma Scale. ICU=intensive care unit.

Table 1: **Demographic and clinical characteristics of study participants at presentation**

Role of the funding source

Abbott employees measured GFAP and UCH-L1 concentrations while masked to clinical data but had no other role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 2552 participants aged 17 years or older who were enrolled in the TRACK-TBI cohort between Feb 26, 2014, and Aug 8, 2018, 1696 participants had complete GFAP and UCH-L1 measurements (obtained from blood samples collected at enrolment) and 6-month GOSE-TBI scores (obtained 6 months after injury [ie, August, 2014–February, 2019]; appendix p 15). Global functional recovery at 6 months was assessed in-person for 1459 (86%) of 1696 patients and via telephone for 237 (14%) patients. Detailed demographic and clinical characteristics of the study population categorised overall and by presenting GCS score are shown in table 1. GCS score at injury could not be obtained for 46 participants, so these participants are not included in analyses of GCS

See Online for appendix

score. A comparison of the characteristics of participants with day 1 biomarker measurements who completed 6-month follow-up (n=1696), versus those who did not complete follow-up (n=728), is presented in the appendix (p 1). Male individuals and people of self-reported Hispanic ethnicity were somewhat less likely to complete follow-up assessments than were female individuals and people not of Hispanic ethnicity, respectively, and individuals who completed follow-up were significantly older than those who were lost to follow-up. The median time between injury and blood draw was 15·6 h (IQR 9·2–20·5, range 1·1–35·6). A histogram of the distribution of the time between injury and blood draw is presented in the appendix (p 16). At 6 months after injury, 561 (33·1%) of 1696 participants had recovered fully (ie, GOSE-TBI=8), 1135 (66·9%) had incomplete recovery (ie, GOSE-TBI <8), 235 (13·9%) had an unfavourable outcome (ie, GOSE-TBI ≤4), and 120 (7·1%) had died (GOSE-TBI=1). Participants with traumatic brain injury and a GCS score of 13–15 constituted 46 (19·6%) of 235 participants who had unfavourable at 6 months. Of the 1297 participants with traumatic brain injury and a GCS score of 13–15, four (1·1%) of 379 participants who were discharged home from the emergency department and 42 (4·6%) of 918 who were admitted to hospital had an unfavourable outcome at 6 months. The demographic and clinical characteristics of the participants who died (n=120) and those who recovered fully (n=561) by 6 months are presented in the appendix (pp 2–3).

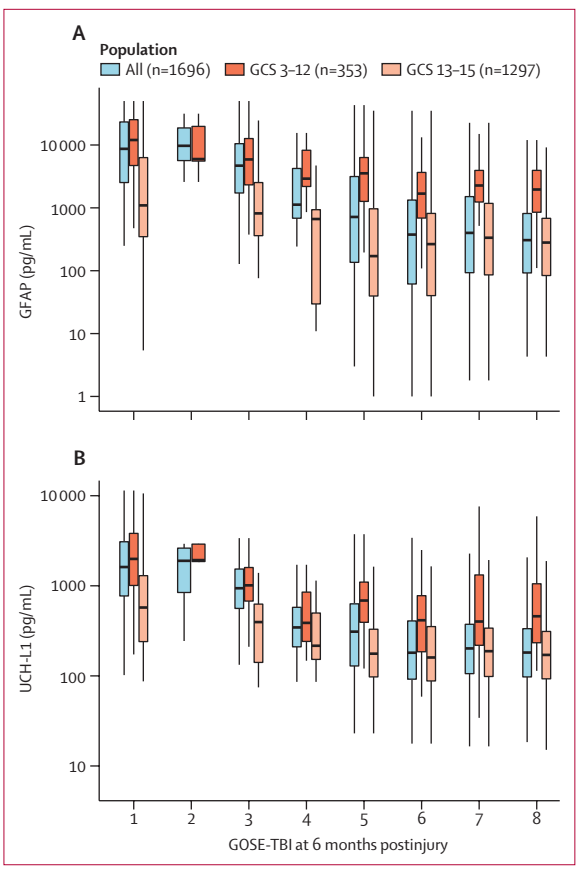

Figure 1: **The distribution of day-of-injury biomarker concentrations by 6-month clinical outcome**

Box plots of glial fibrillary acidic protein (GFAP; A) and ubiquitin C-terminal hydrolase L1 (UCH-L1; B) concentrations (in log10 scale) by 6-month GOSE-TBI in the overall cohort and separately for participants with a GCS score of 3–12 and participants with a GCS score of 13–15. The lower and upper ends of each box represent the 25th and 75th percentiles, respectively, and the line going through each box represents the median value. The upper whisker indicates the smaller value of the maximum value or 75th percentile + 1·5 × IQR, and lower whisker indicates the larger value of the minimum value or 25th percentile – 1·5 × IQR. The y-axis is marked in the raw scale. GCS=Glasgow Coma Scale. GOSE-TBI=Glasgow Outcome Scale–Extended-Traumatic Brain Injury.

139 (8·2%) participants had GFAP concentrations below the LoD, 194 (11·4%) had GFAP concentrations below the LoQ, two (0·1%) had UCH-L1 concentrations below the LoD, and nine (0·5%) had UCH-L1 concentrations below the LoQ; all other participants had detectable biomarker concentrations. Day-of-injury GFAP concentrations were higher in the 120 participants who died during the 6-month follow-up period (median 8680 pg/mL [IQR 2525–23 237]) and in the 115 participants with a 6-month GOSE-TBI of 2–4 (3998 pg/mL [1197–8932]) than in the 1461 participants with a 6-month GOSE-TBI of 5–8 (356 pg/mL [88–1242], p<0·0001; figure 1A). Similarly, UCH-L1 concentrations were higher in the participants who died during the 6-month follow-up period (median 1616 pg/mL [IQR 771–3083]) and in those with a 6-month GOSE-TBI of 2–4 (833 pg/mL [389–1453]) than in those with a 6-month GOSE-TBI of 5–8 (194 pg/mL [99–390], p<0·0001; figure 1B). These differences in biomarker concentrations by GOSE-TBI category were more pronounced in participants with a GCS score of 3–12 than in those with a GCS score of 13–15. Participants with biomarker concentrations in the highest quintile had a higher risk for all-cause mortality during the 6 months following injury than did those with biomarker concentrations in lower quintiles (figure 2). The number of participants with a GCS score of 13–15 who died is small and therefore we did not perform a survival analysis for this group. The range of biomarker concentrations corresponding to each biomarker quintile is described in the appendix (p 4). After adjusting for age, sex, and presenting GCS score (as a continuous variable), the hazard ratio (HR) for all-cause mortality within 6 months for participants with a day-of-injury biomarker concentration in the fifth quintile was significantly higher than for those with biomarker concentrations in the first quintile (HR 6·98 [95% CI 1·60–30·40] for GFAP, p=0·010; HR 22·38 [2·99–167·46] for UCH-L1, p=0·0020). The fifth quintile HRs were much higher in participants with a presenting GCS score of 3–12 than in the entire cohort (appendix p 5).

For incomplete recovery, unfavourable outcome, and mortality at 6 months, the AUC of GFAP and UCH-L1 combined was not significantly higher than the AUC of

each biomarker independently (table 2). Generally, these AUCs were higher for participants with a presenting GCS score of 3–12 than for those with a presenting GCS score of 13–15. For each of the 6-month outcomes examined, the AUCs for biomarkers measured with the Abbott ARCHITECT platform were higher than were the AUCs for biomarkers measured with the Abbott i-STAT platform (appendix p 6); however, these data should be interpreted with caution because the different platforms were used to measure biomarker concentrations in different subsets of the study population.

Among participants with traumatic brain injury and a GCS score of 3–12, GFAP only, UCH-L1 only, and GFAP and UCH-L1 together all significantly increased the prognostic accuracies of the modified IMPACT Core, IMPACT Extended, and IMPACT Lab models (table 3). Among participants with a GCS score 13–15, GFAP only, UCH-L1 only, and GFAP and UCH-L1 together all slightly increased the prognostic value of the modified UPFRONT study model (table 3). A detailed report of the models with and without biomarker concentrations is presented in the appendix (pp 7–14).

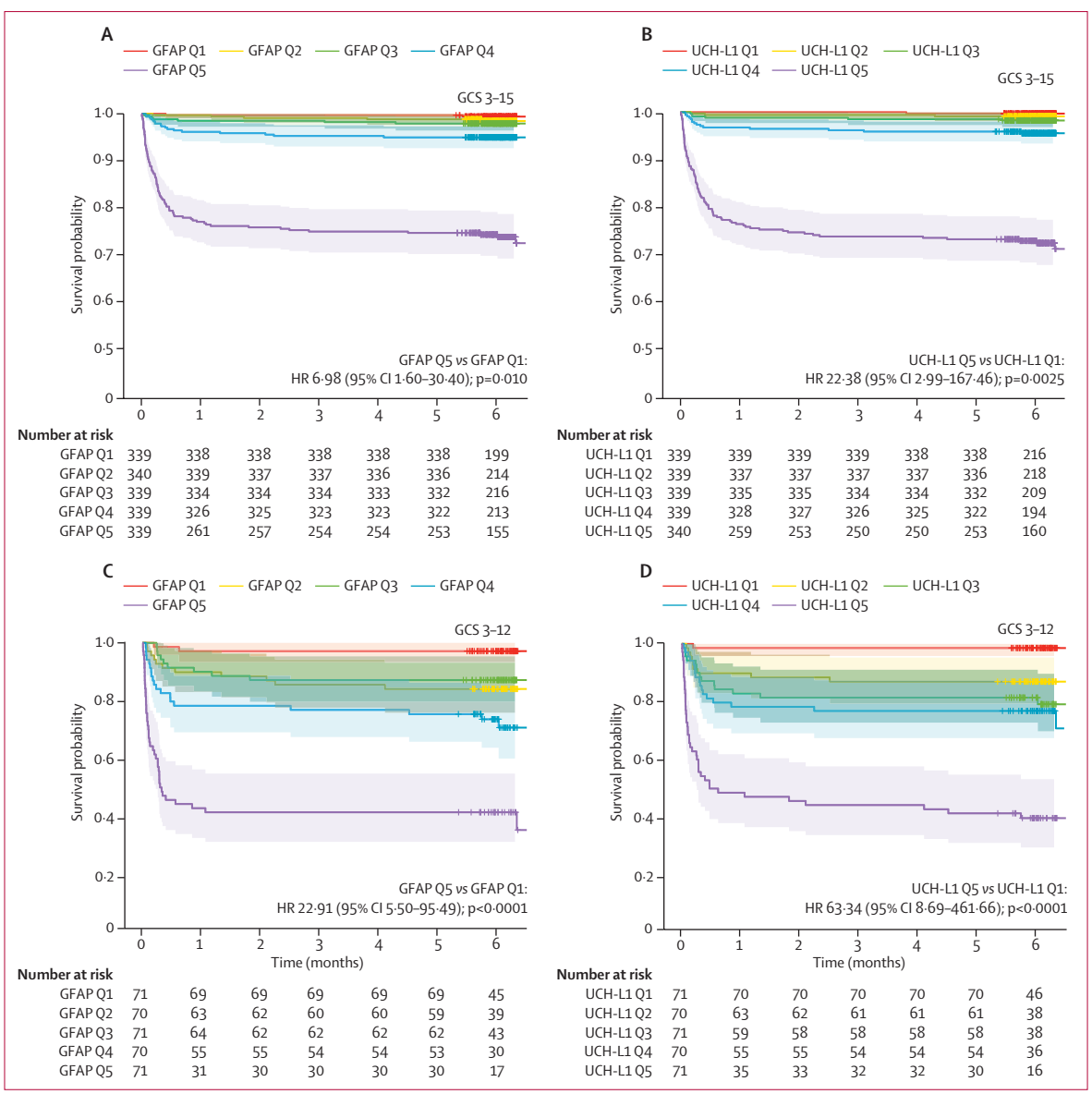

Figure 2: **Association between day-of-injury biomarker concentrations and time to death in the first 6 months following traumatic brain injury**
Kaplan-Meier plots of the association between all-cause mortality during the first 6 months following injury and day-of-injury GFAP in all participants (A), UCH-L1 in all participants (B), GFAP in participants with an initial GCS score of 3–12 (C), and UCH-L1 in participants with initial GCS score of 3–12 (D). Biomarker concentrations are presented in quintiles. The shaded area indicates the 95% CIs; tick marks indicate censoring (ie, death). The range of biomarker concentrations corresponding to each biomarker quintile is described in the appendix (p 4). Q=quintile.

Discussion

Early and accurate prediction of traumatic brain injury outcomes is important for guiding clinical care decisions, counselling patients and families, and for risk-adjusted outcomes analyses in clinical trials. Our study reports three key findings. First, day-of-injury GFAP and UCH-L1 concentrations predict unfavourable outcome (ie, GOSE-TBI ≤4) and death (ie, GOSE-TBI=1) at 6 months with good to excellent discriminative ability. However, they do not accurately predict incomplete recovery (ie, GOSE-TBI <8). The risk prediction ability of these biomarkers is modest in patients with traumatic brain injury and a GCS score of 13–15 but stronger in patients with traumatic brain injury and a GCS score of 3–12. The risk of death during the 6 months that follow traumatic brain injury is highest in patients with biomarker concentrations in the fifth quintile, with most of the deaths occurring during the first month. Second, day-of-injury GFAP and UCH-L1 concentrations substantially increase the prognostic value of the suite of IMPACT models for predicting outcomes in patients with traumatic brain injury and a GCS score of 3–12; however, they only modestly increase the prognostic value of the UPFRONT study model for predicting incomplete recovery in patients with traumatic brain injury and GCS score of 13–15. Third, when we examined biomarkers only, we found no difference between the AUC of GFAP and UCH-L1 combined versus the AUC of either biomarker alone. When we examined the incremental prognostic value of biomarkers over clinical predictors alone for predicting mortality, we found that on the basis of the likelihood ratio test, both biomarkers are independent predictors and improved model fit. For predicting mortality, adding both biomarkers to the IMPACT Extended and Lab models did not result in a significantly higher AUC than did adding one biomarker.

	All patients	Patients with GCS score 13–15	Patients with GCS score 3–12
Predicting incomplete recovery (GOSE-TBI 1–7 *vs* 8)			
GFAP	0·62 (0·59–0·64)	0·53 (0·50–0·56)	0·68 (0·61–0·76)
UCH-L1	0·61 (0·59–0·64)	0·53 (0·50–0·56)	0·65 (0·56–0·74)
GFAP and UCH-L1	0·62 (0·60–0·65)	0·53 (0·50–0·56)	0·70 (0·63–0·76)
Predicting unfavourable outcome (GOSE-TBI 1–4 *vs* 5–8)			
GFAP	0·86 (0·83–0·89)	0·67 (0·58–0·76)	0·77 (0·73–0·83)
UCH-L1	0·86 (0·84–0·89)	0·70 (0·62–0·79)	0·76 (0·71–0·81)
GFAP and UCH-L1	0·89 (0·86–0·91)	0·72 (0·64–0·80)	0·81 (0·77–0·86)
Predicting mortality (GOSE-TBI 1 *vs* 2–8)			
GFAP	0·87 (0·83–0·91)	0·72 (0·60–0·84)	0·79 (0·73–0·85)
UCH-L1	0·89 (0·86–0·92)	0·77 (0·66–0·88)	0·81 (0·76–0·86)
GFAP and UCH-L1	0·90 (0·87–0·94)	0·78 (0·66–0·89)	0·84 (0·80–0·89)

Data are AUC (95% CI). For each GCS category and each outcome grouping, the AUCs of GFAP and UCH-L1, GFAP only, and UCH-L1 only did not differ. GCS=Glasgow Coma Scale. AUC=area under the curve. GOSE-TBI=Glasgow Outcome Scale–Extended-Traumatic Brain Injury.

Table 2: **Prognostic value of GFAP and UCH-L1 for predicting 6-month outcomes, by injury severity at presentation**

Similarly, for predicting unfavourable outcome, adding GFAP and UCH-L1 to the IMPACT models significantly increased the AUC compared with UCH-L1 alone. However, for predicting mortality, adding GFAP and UCH-L1 did not significantly improve the AUC of the IMPACT models compared with UCH-L1 alone. Similarly, there was no difference in the AUC of the UPFRONT study model with both biomarkers versus the UPFRONT study model with one biomarker. It is possible that other biomarkers of neurodegeneration, such as NF-L and total Tau, might be useful in predicting outcomes in patients with traumatic brain injury and a GCS score of 13–15.

Our findings regarding the prognostic value of day-of-injury GFAP and UCH-L1 corroborate and extend findings from previous smaller studies. In a study of 172 patients with predominantly severe traumatic brain injury (121 [70%] of 172), day-of-injury GFAP and UCH-L1 were associated with 12-month outcomes measured by the Glasgow Outcome Scale (pseudo-R^2 0·217 for GFAP and 0·271 for UCH-L1).[24] In another study of 267 participants in a placebo-controlled clinical trial of progesterone in moderate and severe traumatic brain injury, the unadjusted odds ratio of having an unfavourable outcome at 6 months per pg/mL change in biomarker was 1·75 (95% CI 1·51–2·03) for GFAP and 2·20 (1·63–2·99) per pg/mL for UCH-L1.[25] Furthermore, among 243 participants with an initial GCS score of 3–12 in the placebo group of a clinical trial of tranexamic acid, the AUCs of day-of-injury GFAP and UCH-L1 concentrations for predicting unfavourable outcome at 6 months were 0·71 (95% CI 0·61–0·81) for GFAP and 0·68 (0·57–0·80) for UCH-L1.[26] In the TRACK-TBI pilot study of 206 participants, we reported that the AUC of day-of-injury GFAP and UCH-L1 concentrations for predicting unfavourable outcome at 6 months were 0·76 (95% CI 0·60–0·91) for GFAP and 0·74 (0·61–0·87) for UCH-L1.[11] As a consequence of the larger sample size in this study than in previous studies, our estimates of the prognostic value of GFAP and UCH-L1 have greater precision (ie, narrower confidence intervals) than previous estimates. However, the absence of a significant increase in prognostic value by combining GFAP and UCH-L1 differs from our smaller TRACK-TBI pilot study.[11]

Our study results show that structural brain injury detected by biofluid-based biomarkers of brain injury is an important independent predictor of unfavourable outcome, including death after traumatic brain injury, particularly in patients with a presenting GCS score of 3–12. However, structural brain injury detected by these biomarkers is not as good a predictor of incomplete recovery. Previous studies have shown that psychological factors, such as emotional distress and maladaptive coping, preinjury mental health problems, education, and older age, are important predictors of incomplete recovery in patients with traumatic brain injury and a GCS score of 13–15.[14] Structural brain injury detected by CT and MRI has been previously reported as an independent predictor

of risk of incomplete recovery in patients with traumatic brain injury and a GCS score of 13–15.[4,5] Therefore, although structural brain injury measured by GFAP and UCH-L1 might play a predominant role in predicting poor outcome in patients with traumatic brain injury and a GCS score of 3–12, its role in predicting the outcome of patients with traumatic brain injury and a GCS score of 13–15 is not yet fully understood. The poor prognostic performance of these biomarkers for predicting incomplete recovery in patients with traumatic brain injury and a GCS score of 13–15 can be partly attributed to the potential ceiling effect of the GOSE-TBI in the

	Predicting unfavourable outcome (GOSE-TBI 1–4 *vs* 5–8)*				Predicting mortality (GOSE-TBI 1 *vs* 2–8)			
	AUC (95% CI)	R^2	LRT p value	AUC p value	AUC (95% CI)	R^2	LRT p value	AUC p value
Modified IMPACT Core (GCS 3–12)								
Without GFAP or UCH-L1	0·78 (0·73–0·83)	0·31	..	..	0·85 (0·80–0·89)	0·42	..	..
With GFAP only	0·85 (0·81–0·89)	0·49	<0·0001†	<0·0001†	0·90 (0·86–0·93)	0·56	<0·0001†	0·0010†
With UCH-L1 only	0·83 (0·79–0·87)	0·43	<0·0001†	0·0020†	0·92 (0·88–0·94)	0·59	<0·0001†	0·0001†
With GFAP and UCH-L1	0·86 (0·82–0·90)	0·50	<0·0001	<0·0001	0·92 (0·88–0·95)	0·61	<0·0001	<0·0001
Versus GFAP only	..	..	0·012	0·095	..	..	<0·0001	0·031
Versus UCH-L1 only	..	..	<0·0001	0·011	..	..	0·0064	0·20
Modified IMPACT Extended (GCS 3–12)								
Without GFAP or UCH-L1	0·84 (0·79–0·88)	0·44	..	..	0·90 (0·85–0·93)	0·54	..	..
With GFAP only	0·89 (0·85–0·92)	0·56	<0·0001†	<0·0001†	0·93 (0·89–0·96)	0·64	<0·0001†	0·010†
With UCH-L1 only	0·86 (0·82–0·90)	0·50	<0·0001†	0·033†	0·94 (0·90–0·96)	0·66	<0·0001†	0·0018†
With GFAP and UCH-L1	0·89 (0·85–0·92)	0·56	<0·0001†	<0·0001†	0·94 (0·90–0·96)	0·68	<0·0001†	0·0017†
Versus GFAP only	..	..	0·32	0·54	..	..	<0·0001	0·10
Versus UCH-L1 only	..	..	<0·0001	0·0063	..	..	0·0023	0·33
Modified IMPACT Lab (GCS 3–12)								
Without GFAP or UCH-L1	0·84 (0·80–0·88)	0·50	..	..	0·90 (0·85–0·93)	0·54	..	..
With GFAP only	0·89 (0·85–0·92)	0·57	<0·0001†	0·0011†	0·93 (0·89–0·96)	0·65	<0·0001†	0·011†
With UCH-L1 only	0·87 (0·82–0·90)	0·51	<0·0001†	0·030†	0·94 (0·90–0·96)	0·66	<0·0001†	0·0017†
With GFAP and UCH-L1	0·89 (0·85–0·92)	0·57	<0·0001	0·0010	0·94 (0·91–0·96)	0·68	<0·0001	0·0016
Versus GFAP only	..	..	0·29	0·43	..	..	<0·0001	0·11
Versus UCH-L1 only	..	..	<0·0001	0·0007	..	..	0·0038	0·32
Modified UPFRONT study model (GCS 13–15) for predicting incomplete recovery (GOSE-TBI 1–7 *vs* 8)								
Without GFAP or UCH-L1	0·67 (0·64–0·70)	0·12	..	..	NA	NA	NA	NA
With GFAP only	0·69 (0·66–0·72)	0·14	0·0005†	0·044†	NA	NA	NA	NA
With UCH-L1 only	0·69 (0·66–0·72)	0·14	<0·0001†	0·051†	NA	NA	NA	NA
With GFAP and UCH-L1	0·69 (0·66–0·72)	0·14	<0·0001	0·025	NA	NA	NA	NA
Versus GFAP only	..	..	0·0038	0·32	NA	NA	NA	NA
Versus UCH-L1 only	..	..	0·029	0·30	NA	NA	NA	NA

The time between injury and blood sampling was included as a predictor in models with biomarker values. R^2 refers to Nagelkerke's R^2. GOSE-TBI=Glasgow Outcome Scale–Extended-Traumatic Brain Injury. AUC=area under the curve. LRT=likelihood ratio test. IMPACT=International Mission for Prognosis and Analysis of Clinical Trials in TBI. GCS=Glasgow Coma Scale. *Except for the UPFRONT study model, which was used to predict incomplete recovery (GOSE-TBI 1–7 *vs* 8). †The p value refers to a comparison between models without GFAP or UCH-L1 and models with the biomarker or biomarkers corresponding to that row.

Table 3: **Prognostic value of the modified IMPACT (GCS 3–12) and UPFRONT study (GCS 13–15) models with and without GFAP and UCH-L1**

population with traumatic brain injury and a GCS score of 13–15.

For patients with traumatic brain injury and a GCS score of 3–12, adding day-of-injury GFAP and UCH-L1 concentrations to the IMPACT models significantly increased the prognostic accuracy of these models. This finding is important and has implications for both traumatic brain injury research and clinical care. Accounting for the baseline prognosis (ie, before intervention) is crucial to attaining sufficient statistical power without cost-prohibitive sample sizes, particularly in phase 3 traumatic brain injury trials.[27] In traumatic brain injury clinical trials in which the GOSE-TBI is analysed using a sliding dichotomy, the IMPACT model is often used to establish baseline prognosis.[28,29] Improving the prognostic value of the IMPACT model by adding GFAP and UCH-L1 values could improve the efficiency of clinical trials. A large-scale validation of the IMPACT model with the addition of GFAP and UCH-L1 is needed so that, ultimately, clinicians can use this tool to provide a more accurate prognosis to patients and their family members than do the current models.

Our study has several limitations. We focused primarily on functional recovery as measured by the GOSE-TBI, and therefore we cannot determine whether GFAP and UCH-L1 have prognostic value for predicting other outcomes, such as cognition and mental health. Furthermore, our study population consisted of adult patients seen at US level 1 trauma centres, who were sampled conveniently and might have been medically healthier than the general population of patients with traumatic brain injuries (ie, patients with some comorbidities were excluded). We also excluded patients with clinically significant polytrauma that would interfere with follow-up. Additionally, approximately 30% of our cohort reported previous traumatic brain injury, according to the patient's or their representative's self-report. Thus, it is unknown whether our findings are applicable to paediatric patients or to patients outside the level 1 trauma setting, or in those who would not meet study inclusion or exclusion criteria. Additionally, small amounts of GFAP and UCH-L1 can be released from extracranial sources, including orthopaedic injury.[30] Although the two different assays that we used were highly correlated, using different assays could have an influence on the precision in biomarker concentrations reported. Also, the variability in sampling times of blood draws could have influenced the prognostic value of these biomarkers. We converted biomarker concentrations from the Abbott ARCHITECT to i-STAT equivalents; this conversion could have introduced a measurement error to our analyses. Finally, several patients were lost to follow-up at 6 months, and therefore the participants who were analysed are different from those who were enrolled on some of the covariates examined (appendix p 1).

Day-of-injury GFAP and UCH-L1 concentrations have good to excellent prognostic value for predicting death and unfavourable outcome at 6 months, but not for incomplete recovery. Furthermore, for patients presenting with a GCS score of 3–12, day-of-injury GFAP and UCH-L1 significantly improved the prognostic value of the IMPACT models. However, for patients with traumatic brain injury and a GCS score of 13–15, these biomarkers improved the value of the UPFRONT study model only modestly, but significantly. Therefore, in addition to their known diagnostic value, day-of-injury GFAP and UCH-L1 concentrations, in conjunction with the IMPACT models, can provide a more accurate appraisal than IMPACT models alone of the likelihood of unfavourable outcome, including death, following traumatic brain injury of GCS score 3–12. Additional studies are needed to evaluate the reproducibility of these findings before broad clinical adoption.

The TRACK-TBI Study Investigators

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FKK, AMP, KKWW, LDN, ELY, JKY, RCG, PM, RD-A, DOO, SRT, AJM, and GTM contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of the report. XS and SJ contributed to the study design, data analysis, data interpretation, and writing of the report. FKK, RD-A, GTM, XS, and SJ accessed and verified the data and were responsible for the decision to submit the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All TRACK-TBI Study Investigators contributed to data acquisition and critical revision of the manuscript.

Declaration of interests

FKK previously consulted for Abbott Laboratories. FKK and CR have received research funding from Abbott Laboratories. GTM received research funding from a collaboration between Abbott Laboratories and the US Department of Defense. RD-A consulted for MesoScale Discoveries, BrainBox Solutions, and NovaSignal. All other authors and collaborators declare no competing interests.

Data sharing

The deidentified patient level data that support the findings of this study are available and will be made publicly available on the Federal Interagency Traumatic Brain Injury Research Informatics System following deadlines agreed on with federal funding partners.

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