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High-Sensitivity C-Reactive Protein Is a Prognostic Biomarker of Six-Month Disability after Traumatic Brain Injury: Results from the TRACK-TBI Study

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Abstract

Systemic inflammation impacts outcome after traumatic brain injury (TBI), but most TBI biomarker studies have focused on brain-specific proteins. C-reactive protein (CRP) is a widely used biomarker of inflammation with potential as a prognostic biomarker after TBI. The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study prospectively enrolled TBI patients within 24 h of injury, as well as orthopedic injury and uninjured controls; biospecimens were collected at enrollment. A subset of hospitalized participants had blood collected on day 3, day 5, and 2 weeks. High-sensitivity CRP (hsCRP) and glial fibrillary acidic protein (GFAP) were measured. Receiver operating characteristic analysis was used to evaluate the prognostic ability of hsCRP for 6-month outcome, using the Glasgow Outcome Scale-Extended (GOSE). We included 1206 TBI subjects, 122 orthopedic trauma controls (OTCs), and 209 healthy controls (HCs). Longitudinal biomarker sampling was performed in 254 hospitalized TBI subjects and 19 OTCs. hsCRP rose between days 1 and 5 for TBI and OTC subjects, and fell by 2 weeks, but remained elevated compared with HCs ($p < 0.001$). Longitudinally, hsCRP was significantly higher in the first 2 weeks for subjects with death/severe disability (GOSE <5) compared with those with moderate disability/good recovery (GOSE ≥5); AUC was highest at 2 weeks (AUC = 0.892). Combining hsCRP and GFAP at 2 weeks produced AUC = 0.939 for prediction of disability. Serum hsCRP measured within 2 weeks of TBI is a prognostic biomarker for disability 6 months later. hsCRP may have utility as a biomarker of target engagement for anti-inflammatory therapies.

Keywords: biomarkers; head trauma; traumatic brain injury

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Introduction

The management of patients with traumatic brain injury (TBI) relies upon neurological examination and radiographical imaging for assessment of injury severity and prognosis. Although outcome after TBI can range from complete recovery to death or severe disability, clinical assessments, such as the Glasgow Coma Scale (GCS) and standard neuroimaging, explain only a small fraction of the variance in outcome and are largely non-specific for pathophysiology, limiting our ability to identify patients appropriate for clinical trials of novel therapies.[1–3] Blood-based biomarkers have the potential to identify patients who may be at risk for clinical deterioration[4] and confirm target engagement by novel therapies aimed at specific pathophysiological mechanisms.

C-reactive protein (CRP) is a non-specific but sensitive biomarker of systemic inflammation that is known to rise in response to numerous conditions, including infection, cancer, surgery, burns, and tissue infarction, and is routinely used in clinical assessment of these conditions.[5–7] Anti-inflammatory therapies reduce CRP levels in these and other medical conditions, including cardiovascular disease,[8,9] cancers,[10,11] and various autoimmune diseases.[12–14] CRP belongs to the pentraxin family of calcium-dependent, ligand-binding plasma proteins, which activate the classical complement pathway by binding to the phosphocholine expressed on the surface of dead or dying cells and some bacteria.[15,16] As a member of the acute-phase protein class, CRP levels in serum increase up to 1000-fold in response to inflammation, often directly in proportion to injury severity.[5,17]

A growing body of evidence implicates CRP as a biomarker in neurological disease. Although CRP is produced primarily by hepatocytes, it can be generated by human neurons.[18] It is sharply upregulated in Alzheimer's disease[19] and after spontaneous intracerebral hemorrhage, proportional to hematoma volume.[20] In TBI, elevated levels of serum CRP within the first 24 h post-injury is associated with more-severe injury[21] and presence of intracranial lesions on neuroimaging.[22,23] It is also associated with post-injury headache and fatigue up to 30 days post-injury[24] and poor long-term outcomes, including premature mortality[21] and persistent post-concussional, psychiatric, and neurocognitive symptoms.[25] However, CRP in the acute phase is limited by a lack of specificity and is affected by concurrent polytrauma.[26,27] In previous studies, CRP has been observed to rise for 3–5 days after TBI[28] before gradually declining, potentially over the course of months.[24] Similar trends have been reported in ischemic stroke,[29–32] but no studies have explored the relationship between sustained CRP elevation and outcome after TBI. Monitoring subacute CRP elevations in these patients may provide important prognostic information for identifying patients at risk for unfavorable recovery.[33]

The current study is a pre-specified analysis of the prospective, multi-center Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study (ClinicalTrials.gov: NCT02119182; and see Methods). We assess the temporal evolution of high-sensitivity CRP (hsCRP) serum levels over the first 2 weeks post-injury and the utility of serum CRP as a prognostic biomarker for post-TBI outcome.

Methods

Subjects and study design

Patients presenting with TBI (GCS 3–15) to 1 of 18 participating level I U.S. trauma centers from February 26, 2014 to July 27, 2018 were identified and enrolled prospectively in the TRACK-TBI study, as previously described.[34,35] Written consent was obtained from subjects or their legal authorized representatives. Eligibility criteria included presentation within 24 h of injury with TBI warranting clinical evaluation with a non-contrast head computed tomography (CT) evaluation based on practice guidelines.[36] Exclusion criteria were positive pregnancy test or known pregnancy, imminent death or current life-threatening disease, incarceration, or evidence of serious psychiatric and neurological disorders that would interfere with consent or follow-up outcome assessment. The study was approved by the institutional review board of each enrolling site.

TBI subjects were stratified into three clinical groups differentiated by clinical care path: 1) emergency department and discharged (ER) stratum; 2) admission stratum (ADM): patients admitted to the hospital but not to the intensive care unit (ICU); and 3) ICU stratum (ICU): patients admitted directly from ER or another hospital to the ICU.

Subjects were eligible for inclusion as orthopedic trauma controls (OTCs) if they presented with isolated trauma to their limbs, pelvis, and/or ribs and had an Abbreviated Injury Score <4 for those body regions. OTC subjects were identified and enrolled using the same process as that for patients with TBI, except for the head CT requirement. Subjects were ineligible from enrollment as an OTC if they had loss of consciousness, disturbance of consciousness, post-traumatic amnesia/retrograde amnesia, or other clinical findings suggestive of a TBI.

Finally, healthy controls (HCs) were recruited either based on a relationship with a TRACK-TBI participant or through public outreach within TRACK-TBI institutions, and the ability to provide informed consent. HCs were ineligible for enrollment if they had a history of TBI, concussion, or any traumatic injury causing polytrauma in the 12 months preceding enrollment. In this analysis, HCs were sex- and age-matched to TBI subjects.

The TRACK-TBI Phase 1 Biomarker Cohort ($n = 1706$) evaluated in this study was a prespecified interim analysis that included the first half of the enrolled TBI subjects and the OTC and HC groups (Fig. 1).

Clinical data collection

Demographic, injury, and outcome variables were collected in accordance with the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (TBI-CDE).[37,38] Demographic data were obtained through a combination of medical records and patient report. Injury Severity Score (ISS) was collected for all hospitalized (ADM, ICU) subjects. Outcome assessments occurred at 2 weeks and 3, 6, and 12 months post-injury. Three-month assessments were performed by telephone; other assessments were performed in person. For this study, the primary outcome was the 6-month Glasgow Outcome Scale-Extended (GOSE) administered to assess patient-reported global disability attributable only to the TBI. Complete recovery was defined as a GOSE = 8. Incomplete recovery was defined as GOSE <8. Unfavorable outcome was defined as GOSE <5 and favorable outcome as GOSE ≥5.

Sample collection and biomarker analysis

For subjects who consented to biospecimen collection, blood samples were collected within 24 h of injury (day 1) and at 2 weeks and 6 months. For subjects admitted to the hospital (ADM, ICU), additional blood samples were collected on days 3 and 5, when possible. Patients with available samples on day 1 and 2 weeks, and additionally day 3 and/or day 5, were considered to have ''serial samples'' and were included in longitudinal analyses. All samples were dated and time-stamped to compare with time of injury. The TBI-CDE Biospecimens and Biomarkers Working Group consensus recommendations for plasma and serum preparation were followed.[37] Plasma and serum aliquots were prepared for

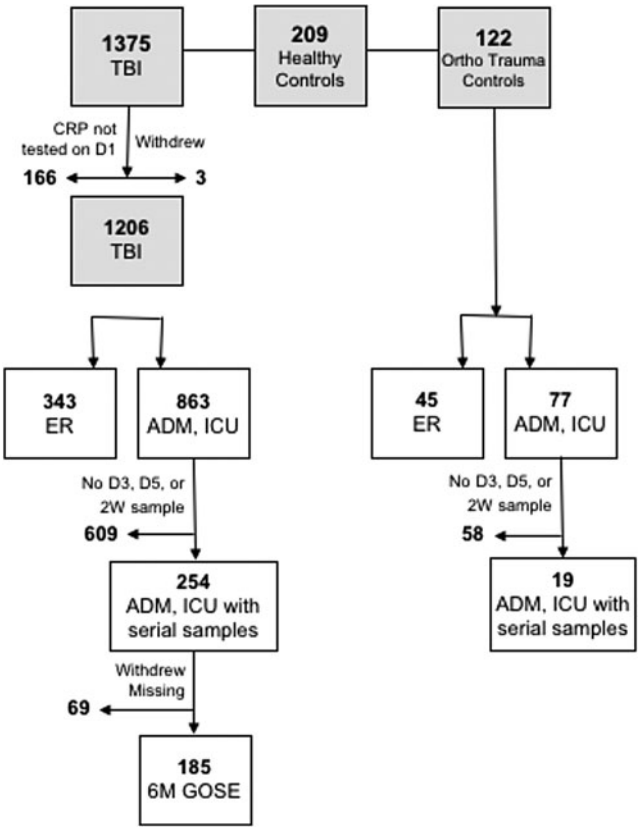

FIG. 1. TRACK-TBI phase 1 biomarker cohort CONSORT diagram. ADM = admission stratum: patients admitted to the hospital but not to the ICU. ICU = ICU stratum: patients admitted directly from ER or another hospital to the ICU. D1 = day 1. D3 = day 3. D5 = day 5. 2W = 2 weeks. Serial samples: available hsCRP samples on day 1 and 2 Weeks, and day 3 and/or day 5. GOSE = Glasgow Outcome Scale-Extended. CRP, C-reactive protein; CONSORT, Consolidated Standards of Reporting Trials; ER, emergency room; ICU, intensive care unit; TBI, traumatic brain injury; TRACK-TBI, Transforming Research and Clinical Knowledge in Traumatic Brain Injury.

each subject and frozen at −80°C for future analysis. All samples were deidentified using a unique study ID, specific to site and subject, and batch-shipped in temperature-controlled overnight express freight containers to the TRACK-TBI Biospecimens Repository at the University of Pittsburgh Medical Center (Pittsburgh, PA).

Blinded sample analysis of hsCRP was carried out by a single laboratory (University College of Dublin) using the Abbott Architect c8000, MULTIGENT CRP Vario assay using the high-sensitivity method (CRP16). Anti-CRP antibody adsorbed to latex particles agglutinate when an antigen-antibody reaction occurs with CRP, resulting in a change in absorbance proportional to the quantity of CRP in the sample. Serum samples were thawed in batches at room temperature and centrifuged at 10,000 rfc for 10 min at 4°C before testing. Assays were performed in duplicate with a lower limit of quantification of 0.1 mg/L and a reportable range of 0.1–160.0 mg/L. Temporal trends of CRP were analyzed and reported. Glial fibrillary acidic protein (GFAP) concentrations were determined using prototype immunoassays on the i-STAT point-of-care platform (Abbott Laboratories, Abbott Park, IL), as previously described.[34] The i-STAT GFAP test uses the sandwich enzyme-linked immunosorbent assay method with electrochemical detection of the resulting enzyme signal.

Computing tomography imaging evaluation and analysis

Initial head CT scans were deidentified and uploaded to a central imaging database at the Laboratory of NeuroImaging (LONI; University of Southern California, Los Angeles, CA) and independently evaluated by a central board-certified neuroradiologist in accordance with TBI-CDE Neuroimaging Working Group consensus recommendations.[36] The study neuroradiologist was blinded to the identity and clinical information associated with each CT scan. The result of each review was uploaded to the TRACK-TBI clinical database under the respective subject's record. CT scans were read as positive (CT^+) if there was any evidence of acute intracranial pathology consistent with TBI (e.g., contusion, subarachnoid hemorrhage, and subdural hematoma).

Magnetic resonance imaging methods and analysis

Magnetic resonance imaging (MRI) was obtained at 7–18 days. Image sequences included T1, T2, fluid-attenuated inversion recovery, and T2*. The MRI protocol was standardized across all sites and General Electric, Siemens, and Phillips MRI platforms (available at https://tracktbi.ucsf.edu/researchers). Baseline phantom scans were performed at all centers to quantify differences between magnets and correct geometrical variances across scanners. Structural MRI abnormalities were quantified according to CDE standards and definitions[36] by a central board-certified neuroradiologist blinded to the identity and clinical history of the subject. MRI scans were read as positive (MRI^+) if there was any evidence of acute intracranial pathology consistent with TBI (e.g., contusion, traumatic axonal injury, and diffuse axonal injury).

Statistical analysis

Descriptive summary statistics were used to characterize the demographics and clinical attributes of the study cohort. hsCRP levels were reported using the median and 25th/75th percentiles and were compared using a Wilcoxon's rank-sum test between TBI subjects and OTC/HC; among TBI subjects with and without intracranial lesions on CT; among TBI CT-negative subjects with and without intracranial lesions on MRI; among TBI subjects by ISS total score categories (≤9, 10–16, 17–25, and >25); and among TBI subjects by GOSE outcomes (unfavorable, <5 vs. favorable, ≥5; and complete recovery, = 8 vs. incomplete recovery, <8). Receiver operating characteristic (ROC) analysis was performed to assess the ability of hsCRP level at each time point to predict GOSE at 6 months post-injury, and area under the ROC curve (AUC) was calculated with a 95% confidence interval (CI). AUCs of >0.9 were considered excellent, 0.8–0.9 as good, 0.7–0.8 as adequate, and <0.7 as poor. All data were analyzed and plotted using statistical software R (version 3.6.1; http://www.r-project.org).

Results

The TRACK-TBI Phase 1 Biomarker Cohort included 1706 subjects (1375 TBIs, 122 OTCs, and 209 HCs; Fig. 1). Serum was available for hsCRP assay in 1206 TBI subjects. Most TBI subjects were Caucasian, male, and had mild injury (GCS 13–15). The most common cause of injury was road traffic accidents, followed by falls. Full demographic and clinical data are presented in Table 1.

High-sensitivity C-reactive protein rises in traumatic brain injury and orthopedic trauma controls and is increased in computed tomography–positive vs. computed tomography–negative cases

Day 1 hsCRP was higher in TBI subjects compared to HC (median [interquartile range], 9.091 [2.110–30.932] vs. 1.34 [0.642–

Table 1. Demographic and Clinical Characteristics of the TRACK-TBI Phase 1 Biomarker Cohort

	TBI (n = *1206*)	*OTC* (n = *122*)	p *value**	*HC* (n = *209*)
Patient care pathway				
ER discharge	343 (28.4%)	45 (36.9%)	0.0005	
ADM, hospital admit	437 (36.2%)	70 (57.4%)		
ICU, ICU admit	426 (35.3%)	7 (5.7%)		
Sex				
Female	390 (32.3%)	43 (35.3%)	0.5434	104 (50%)
Male	816 (67.7%)	79 (64.8%)		105 (50%)
Age (mean ± SD)	40.0 ± 17.0	39.2 ± 15.0	0.9173	39.0 ± 17.0
Years of education (mean ± SD)	13.4 ± 2.9	13.8 ± 2.6	0.0702	
Race				
White	924 (77.3%)	95 (81.2%)	0.6192	
Black	196 (16.4%)	15 (12.8%)		
Other	75 (6.3%)	7 (6.0%)		
Hispanic				
No	934 (78.2%)	91 (76.5%)	0.6443	
Yes	261 (21.8%)	28 (23.5%)		
Cause of injury				
Road traffic accident	705 (58.5%)	43 (38.0%)	0.0005	
Incidental fall	314 (26.1%)	40 (35.4%)		
Violence/assault	82 (6.8%)	1 (0.9%)		
Other	104 (8.6%)	29 (25.7%)		
GCS on ER arrival				
3–8	117 (9.8%)	0 (0%)	0.0005	
9–12	43 (3.6%)	0 (0%)		
13–15	1030 (86.6%)	122 (100%)		
CT				
CT^-	731 (61.3%)			
CT^+	461 (38.7%)			

Data are *n* (%) or mean ± SD.

**p* values were calculated comparing TBI and OTC using Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for categorical variables.

TBI, traumatic brain injury; OTC, orthopedic trauma control; HC, healthy control; ER, emergency department and discharged (ER) stratum; ADM, admission stratum: patients admitted to the hospital, but not to the ICU; ICU, ICU stratum: patients admitted directly from the ER or another hospital to the ICU; GCS, Glasgow Coma Scale; SD, standard deviation; CT, computed tomography.

2.785] mg/L; $p < 0.0001$). hsCRP values rose over the first 5 days in both TBI and OTC. In those with serial samples (day 1 and 2 weeks, as well as day 3 and/or day 5), there was no significant difference in hsCRP between TBI and OTC at any time point (Fig. 2), suggesting that OTCs were well matched to TBI subjects for systemic injury severity. Among patients with mild TBI (mTBI; GCS 13–15), a slight trend toward decreased hsCRP compared with OTC was observed at all time points, which did not reach significance. Please refer to Supplementary Table S1 for hsCRP numerical values for mTBI patients.

In TBI patients with day 1 samples, median hsCRP was higher in CT^+ cases compared to CT^- cases on day 1 (20.415 [5.979–54.244] vs. 4.233 [1.327–17.479] mg/L; $p < 0.0001$). Within CT^- cases, day 1 hsCRP was higher among MRI^+ cases compared with MRI^- cases (3.905 [1.840–16.219] vs. 2.94 [0.800–11.349] mg/L; $p = 0.0075$). In those with serial samples, hsCRP remained significantly higher in CT^+ versus CT^- cases at all time points, increasing from days 1 to 5 in CT^+ cases and plateauing between days 3 and 5 in CT^- cases.

Given that future clinical trials may require enrolling subjects within time windows shorter than 24 h, we investigated hsCRP elevation by blood-draw time intervals from 0 to 6, 7 to 12, 13 to 18, and 19–25 h post-injury. hsCRP increased temporally over the first 24 h in both CT^- and CT^+ TBI subjects, and hsCRP was significantly higher in CT^+ cases at all time points. Please refer to Supplementary Table S2 for hsCRP numerical values.

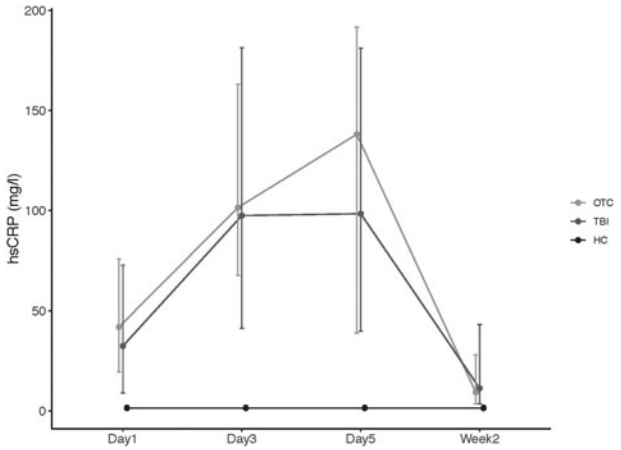

FIG. 2. hsCRP at days 1, 3, and 5 and 2 weeks, comparing TBI, OTC, and HC. Line plot indicates median and 25th–75th percentile. Among patients with serial hsCRP samples (day 1 and 2 weeks, and day 3 and/or day 5), Wilcoxon's rank-sum test found no significant difference in hsCRP level between TBI and OTC at any time point. Baseline hsCRP level in HC was measured at one time point and was significantly lower than TBI and OTC at all time points. HC, healthy controls; hsCRP, high-sensitivity C-reactive protein; OTC, orthopedic trauma controls; TBI, traumatic brain injury.

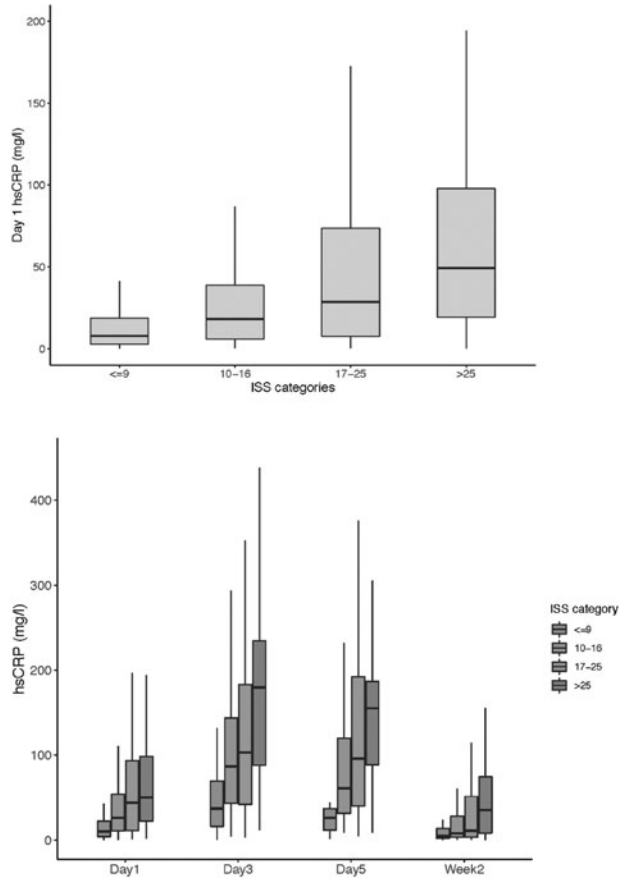

FIG. 3. Relationship between hsCRP and ISS at (**A**) day 1 and (**B**) days 1, 3, and 5 and 2 weeks. Boxplots indicate median and 25th–75th percentile (interquartile range; IQR) of hsCRP values. Upper whisker indicates the smaller value of: the maximum value or 75th percentile +1.5*IQR, and lower whisker indicates the larger value of: the minimum value or 25th percentile −1.5*IQR. ISS total score was separated into four score categories: ≤9, 10–16, 17–25, and >25. (A) Among all TBI patients with available day 1 hsCRP samples, Ddy 1 hsCRP rises with increasing ISS total score. (B) Among patients with serial hsCRP samples (day 1 and 2 weeks, and day 3 and/or day 5), hsCRP rises with increasing ISS total score at all time points. hsCRP, high-sensitivity C-reactive protein; ISS, Injury Severity Score; TBI, traumatic brain injury.

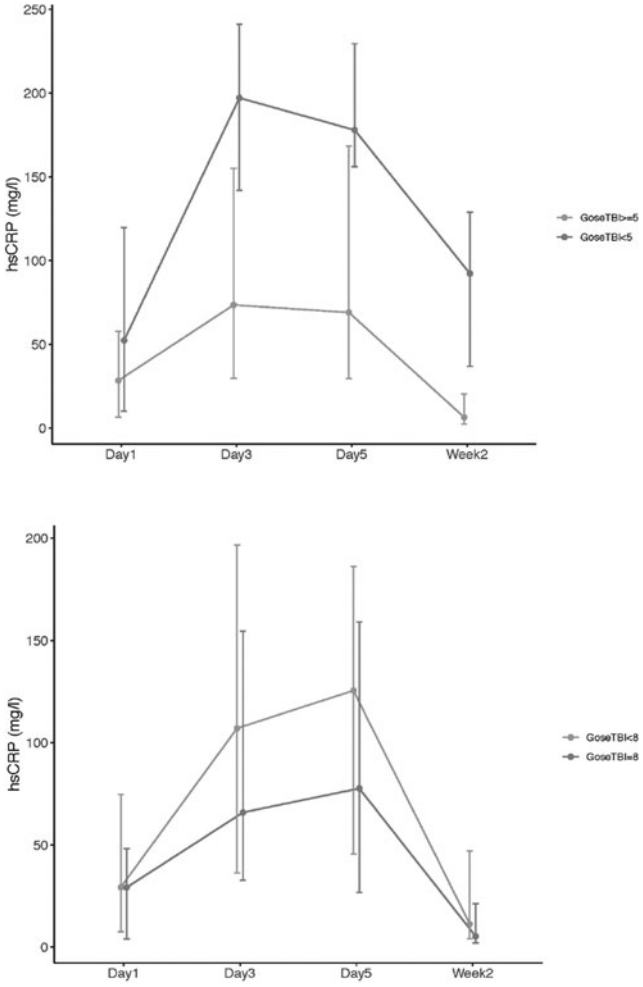

FIG. 4. hsCRP and outcome after TBI: (**A**) GOSE ≥5 versus <5 (**B**) GOSE = 8 versus <8. Line plots indicate median and 25th–75th percentile. (A) In patients with serial hsCRP samples (day 1 and 2 weeks, and day 3 and/or day 5), hsCRP level was compared between patients with unfavorable outcome (GOSE <5, indicating death/severe disability) and favorable outcome (GOSE ≥5). Patients with favorable outcome had significantly higher hsCRP level at all time points compared to patients with unfavorable outcome. (B) In patients with serial hsCRP samples, hsCRP level was compared between patients with complete recovery (GOSE = 8) and incomplete recovery (GOSE <8). Patients with incomplete recovery had significantly higher hsCRP level at the 2-week time point compared with patients with complete recovery, but were not significantly different at any other time point. GOSE, Glasgow Outcome Scale-Extended; hsCRP, high-sensitivity C-reactive protein; TBI, traumatic brain injury.

C-reactive protein rises with increasing overall Injury Severity Score

In subjects with recorded ISS and day 1 samples, day 1 hsCRP increased with ISS (Fig. 3A), with similar findings observed in mTBI subjects. In subjects with serial samples, median hsCRP increased with ISS at all time points (Fig. 3B). In mTBI subjects with serial samples, hsCRP increased with ISS at all time points, but reached significance only on days 1, 3, and 5.

C-reactive protein is a prognostic biomarker for predicting death/severe disability (Glasgow Outcome Scale-Extended [GOSE] <5) vs. moderate disability/good recovery (GOSE ≥5)

In TBI patients with serial samples, hsCRP level at each of the four time points was significantly elevated in subjects with death/severe disability (GOSE <5) compared to those with moderate disability/good recovery (GOSE ≥5; Fig. 4A). The AUC of hsCRP for discriminating 6-month disability was highest at 2 weeks (AUC = 0.892; Table 2). The same analysis was performed in mTBI subjects and revealed similar findings with 2-week hsCRP (AUC = 0.928). When stratified based on degree of peripheral injury (peripheral ISS [excluding head/neck] ≤9, = 10–16, and ≥17), predictive value of 2-week hsCRP remained high across all stratifications (AUC = 0.897, 0.922, and 0.800, for ISS ≤9, = 10–16, and ≥17, respectively). When stratified based on GCS (3–12, 13–15), predictive value of 2-week hsCRP was found to be higher in the subset of patients with milder injury (AUC = 0.779 and 0.928 for GCS 3–12 and 13–15, respectively).

Table 2. Predictive Performance of Acute Measurement of hsCRP on GOSE at 6 Months after Traumatic Brain Injury

	AUC (95% CI)
GOSE <5 vs. GOSE ≥5	
Day 1	0.640 (0.521–0.760)
Day 3	0.800 (0.729–0.871)
Day 5	0.777 (0.691–0.862)
2-week	0.892 (0.839–0.944)
Multiple time points	0.872 (0.818–0.925)
GOSE <8 vs. GOSE = 8	
Day 1	0.570 (0.477–0.662)
Day 3	0.569 (0.474–0.665)
Day 5	0.607 (0.480–0.735)
2-week	0.615 (0.525–0.705)
Multiple time points	0.608 (0.519–0.698)

GOSE <5 indicates unfavorable outcome (severe disability/death). GOSE = 8 indicates complete recovery.

hsCRP, high-sensitivity C-reactive protein; GOSE, Glasgow Outcome Scale-Extended; AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval.

Notably, among TBI subjects, combining 2-week hsCRP (AUC = 0.892) and 2-week GFAP (AUC = 0.890) improved discrimination of 6-month GOSE <5 versus GOSE ≥5 to AUC = 0.939 (95% CI, 0.900–0.978), higher than either marker individually (Table 3; ROC curves shown in Fig. 5).

When comparing the AUC of the model using age and GCS score category only compared to the model using age, GCS score category, and hsCRP, the addition of 2-week hsCRP significantly improved predictive ability of the model (Supplementary Table S3). Imaging results were not included as CT^+ versus CT^- status was not significant in the age + GCS model.

Table 3. Combined Predictive Performance of Acute Measurement of hsCRP and GFAP on GOSE ≥5 vs. <5 at 6 Months after Traumatic Brain Injury

	AUC (95% CI)
Day 1	
logGFAP	0.768 (0.662–0.875)
loghsCRP	0.640 (0.521–0.760)
logGFAP + loghsCRP	0.769 (0.663–0.876)
Day 3	
logGFAP	0.873 (0.798–0.949)
loghsCRP	0.800 (0.729–0.871)
logGFAP + loghsCRP	0.904 (0.846–0.963)
Day 5	
logGFAP	0.900 (0.827–0.972)
loghsCRP	0.777 (0.691–0.862)
logGFAP + loghsCRP	0.913 (0.853–0.973)
2-week	
logGFAP	0.890 (0.823–0.956)
loghsCRP	0.892 (0.839–0.944)
logGFAP + loghsCRP	0.942 (0.905–0.979)

GOSE <5 indicates unfavorable outcome (severe disability/death).

hsCRP, high-sensitivity C-reactive protein; GFAP, glial fibrillary acidic protein; GOSE, Glasgow Outcome Scale-Extended; AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval.

C-reactive protein is a poor predictor of complete recovery (Glasgow Outcome Scale-Extended [GOSE]= 8) vs. incomplete recovery (GOSE <8)

Median hsCRP differed between subjects who experienced complete recovery (GOSE = 8) from those with incomplete recovery (GOSE <8) at only the 2-week time assessment (Fig. 4B). The AUC of hsCRP for discriminating complete recovery at 6 months increased with time after injury, but was poor at all time points (Table 2), similar to findings in the mTBI subjects with 2-week hsCRP (AUC = 0.547).

Discussion

hsCRP, a measure of systemic inflammation, is a prognostic biomarker for poor 6-month outcome after TBI when measured acutely. hsCRP is elevated in the first 2 weeks after TBI, proportional to the severity of systemic injury and more so in subjects with intracranial lesions on CT or MRI scans. Elevation of hsCRP in TBI subjects was indistinguishable from orthopedic controls at all time points after injury. In TBI subjects, hsCRP at all time points increased linearly with worsening ISS, a clinical measure of injury severity in six body regions.

Prognostically, hsCRP measured through the first 2 weeks post-injury was significantly higher in subjects with outcome of death/severe disability (GOSE <5) compared with those with favorable outcome (GOSE ≥5) at 6 months. Using ROC analysis, only 2-week hsCRP demonstrated good discriminative ability (AUC >0.8) for discriminating between favorable (GOSE ≥5) and unfavorable outcome (GOSE <5). In comparing subjects with full recovery (GOSE = 8) and those who were not fully recovered (GOSE <8), hsCRP was significantly higher in fully recovered patients only at the latest time point (2 weeks), with poor discriminative ability (AUC <0.7). These findings indicate that subacute hsCRP is a useful prognostic biomarker for detecting death/severe disability after TBI, particularly in combination with the prognostic biomarker, GFAP, and demonstrate the important association between both systemic injury and inflammation with outcome after TBI.

The mechanism of injury in TBI is characterized by an initial primary injury, during which mechanical forces lead to axonal shearing and necrosis, followed by a later secondary injury, driven by inflammation, blood–brain barrier (BBB) disruption, apoptosis, metabolic disturbances, and oxidative stress, which may have long-lasting effects.[39] In patients with isolated TBI, injury to the BBB allows peripheral inflammatory factors to access the brain tissue, leading to activation of neuroinflammatory cascades.[40] It is reasonable to hypothesize that concurrent polytrauma leads to greater systemic inflammation that can breach the BBB, further exacerbating inflammation both systemically and in the brain.[41] Previous studies support this hypothesis. Polytrauma in TBI results in increased levels of inflammatory cytokine interleukin (IL)-6, compared with patients with isolated TBI.[42,43] Animal studies in rodent models of concurrent polytrauma in TBI have also found increased levels of inflammatory markers, including IL-6, tumor necrosis factor alpha, and chemokine (C-C motif) ligand 2,[44,45] in the acute phase of injury. Further, peripheral delivery of IL-1ß in a rat model of TBI led to significantly worse behavioral outcomes compared with control vehicle-treated animals,[46] demonstrating a link between systemic inflammatory response and unfavorable outcome in TBI.

Several clinical studies have examined the role of concurrent polytrauma on mortality and functional outcome after TBI, as reviewed in detail by McDonald and colleagues.[41] Overall findings

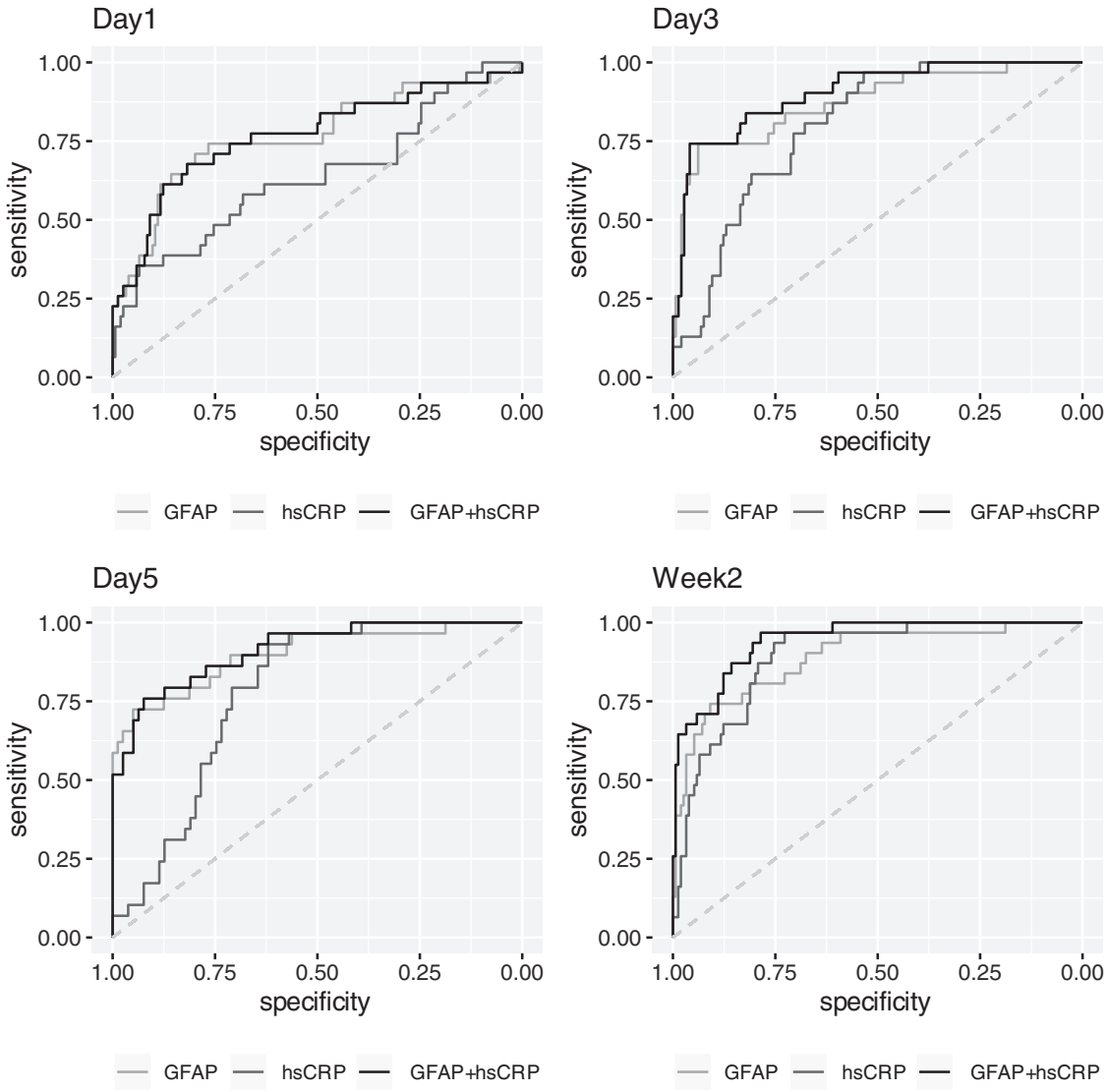

FIG. 5. Receiver operating characteristic (ROC) curves for hsCRP and GFAP in predicting GOSE ≥5 versus <5 at 6 months after traumatic brain injury. ROC curves for GFAP alone, hsCRP alone, and GFAP + hsCRP at (**A**) day 1, (**B**) day 3, (**C**) day 5, and (**D**) 2 weeks post-injury. GOSE <5 indicates unfavorable outcome (severe disability/death). GFAP, glial fibrillary acidic protein; GOSE, Glasgow Outcome Scale-Extended; hsCRP, high-sensitivity C-reactive protein.

suggest that TBI, compounded by concurrent polytrauma, results in increased mortality[47–49] and worsened functional outcomes.[47,48,50,51] In a large retrospective study of 39,274 TBI patients with and without major extracranial injury, van Leeuwen and colleagues found that patients with both TBI and major extracranial injury had significantly higher mortality, with a stronger effect noted in mild and moderate TBI (odds ratio of 2.14 and 1.46, respectively) than in severe TBI (odds ratio of 1.18),[49] a trend that has been previously observed.[52,53] Functional outcome, measured using GOS or GOSE score, was also worse in TBI patients with concurrent polytrauma,[48,51,54] although a few studies have reported no difference[42,55] or even improved outcome in polytrauma patients.[53] This divergence may be attributable to the observation that patients with TBI and concurrent polytrauma are often significantly younger than patients with isolated TBI, which may mask the effects of concurrent polytrauma on outcome.[41]

A broad span of therapeutic agents have been shown to reduce systemic inflammation and hsCRP level in cardiovascular disease,[56] including statins,[57] cyclooxygenase inhibitors,[58] angiotensin-converting enzyme inhibitors,[59] and more targeted therapies, such as canakinumab[9] (IL-1β monoclonal antibody). Targeting systemic inflammation in cardiovascular disease has been shown to improve outcomes, for instance reducing atherosclerotic burden[57] and decreasing rate of recurrent cardiovascular events.[9] Similar investigations are ongoing in the treatment of autoimmune disease[13,14,60,61] and cancers,[10,11,62] with growing evidence for the significant relationship between CRP level and outcomes. Future efforts may explore the application of similar therapies in TBI.

Our study has several important limitations. ISS is a crude measure of polytrauma and was only available in hospitalized TRACK-TBI participants, making it impossible to correlate ISS with hsCRP levels in less severely injured subjects who did not require in-patient care. A granular assessment of how much disability was attributable to central nervous system (CNS) versus extra-CNS injury is beyond the scope of this study. In addition,

hsCRP levels are also affected by a number of other conditions, including acute and chronic inflammatory conditions, surgical interventions, and complications such as ventilator associated pneumonia, which we do not account for in this study. The role of systemic inflammation in TBI requires further exploration and is likely to have important implications for prognostication and future clinical trial design.

Conclusions

Serum hsCRP measured within 2 weeks of TBI discriminates unfavorable from favorable recovery at 6 months. Our data support the role of hsCRP as a prognostic marker with potential utility for both early identification of subjects at risk for poor outcome and as a tool for subject stratification and cohort enrichment for clinical trials of anti-inflammatory treatments.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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