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Association of Brain Injury Biomarkers and Circulatory Shock Following Moderate-Severe Traumatic Brain Injury: A TRACK-TBI Study

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This work has not been previously presented in any format.

SUPPLEMENTARY MATERIAL

Supplemental digital content 1

Supplementary Tables 1–5 showing temporal changes in biomarker levels

Supplemental Digital Content 1.pdf

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Abstract

Introduction—Early circulatory shock following traumatic brain injury (TBI) is a multifactorial process; however, the impact of brain injury biomarkers on the risk of shock has not been evaluated. We examined the association between neuronal injury biomarker levels and the development of circulatory shock following moderate-severe TBI.

Methods—In this retrospective cohort study, we examined adults with moderate-severe TBI (Glasgow Coma Scale score <13) enrolled in the TRACK-TBI study, an 18-center prospective TBI cohort study. The exposures were day-1 levels of neuronal injury biomarkers (glial fibrillary acidic protein, ubiquitin C-terminal hydrolase-L1 [UCH-L1], S100 calcium binding protein B [S100B], neuron specific enolase), and of an inflammatory biomarker (high-sensitivity C-reactive protein). The primary outcome was development of circulatory shock, defined as cardiovascular Sequential Organ Failure Assessment score ≥ 2 within 72 hours of admission. Association between day-1 biomarker levels and the development of circulatory shock was assessed with regression analysis.

Results—The study included 392 subjects, with a mean age of 40 years; 314 (80%) were male and 165 (42%) developed circulatory shock. Median [interquartile range] day-1 levels of UCH-L1 (994.8 [518.7–1988.2] pg/ml vs. 548.1 [280.2–1151.9] pg/ml; p <.0001) and S100B (0.47 ug/ml [0.25–0.88] vs. 0.27 [0.16–0.46] ug/ml; p <.0001) were elevated in those who developed early circulatory shock compared to those who did not. In multivariable regression, there were associations between levels of both UCH-L1 (odds ratio, 1.63 [95% confidence interval, 1.25–2.12]; p<.0005) and S100B (odds ratio, 1.73 [95% confidence interval 1.27–2.36]; p<.0005) with the development of circulatory shock.

Conclusion—Neuronal injury biomarkers may provide improved mechanistic understanding and possibly early identification of patients at risk for early circulatory shock following moderate-severe TBI.

Keywords

traumatic brain injury; circulatory shock; biomarkers

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States[1] and worldwide. Compared to mild TBI, moderate-severe TBI has been associated with a greater incidence of hypotension, increased mortality, and worse functional outcomes[2]. The critical care management of moderate-severe TBI is aimed at limiting damage from the primary brain injury and reducing secondary brain injury, including by maintenance of hemodynamic stability and prevention of multi-organ dysfunction[3 4]. Early circulatory shock following moderate-severe TBI is a multifactorial process driven by the underlying brain injury, cardiac dysfunction, and impaired vascular autoregulation. Circulatory shock has long been recognized for its association with poor clinical outcomes following TBI, including cerebral ischemia, disrupted cerebral hemodynamics, and increased mortality[5–10].

Therefore, improving early recognition, diagnosis and treatment of circulatory shock could represent an important therapeutic target to improve moderate-severe TBI outcomes.

Blood-based biomarkers have the potential to identify patients who may be at risk for clinical deterioration and would benefit from novel therapies aimed at specific pathophysiologic mechanisms. Current research on neural injury biomarkers, including glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), S100 calcium binding protein B (S100B), and neuron specific enolase (NSE), and the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP), demonstrate promise to assist in the management of TBI[11–19]. Given that the development of circulatory shock is associated with primary brain injury severity, direct neuronal and glial injury may contribute to the dysfunction in circulatory autoregulation commonly seen following TBI[20]. As such, examining the association of these biomarkers with hemodynamic failure may elucidate mechanistic pathways contributing to the development of circulatory shock following brain injury, and may be useful for identifying patients at risk of circulatory shock. No studies to date have been conducted to explore an association of these biomarkers with the development of circulatory shock following TBI. To address this gap, the aim of our study was to determine the association of neuronal injury and inflammatory biomarker levels with the development of early circulatory shock following moderate-severe TBI.

METHODS

We conducted a retrospective cohort study of adult patients enrolled in the Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) study. TRACK-TBI was a prospective 18-center cohort study of patients evaluated in a level 1 trauma center Emergency Department within 24 hours of suffering blunt TBI, conducted between February 2014 and July 2018. This was a secondary retrospective analysis, as the current research question was not pre-specified when designing the original cohort. In addition to the collection of a multi-dimensional outcome battery over the year following injury, detailed hospital encounter data, including time-stamped diagnostic, pharmacy, and laboratory information, were collected in TRACK-TBI[21]. Subjects were excluded from the TRACK-TBI cohort if they met the following criteria: significant history of pre-existing conditions that would interfere with follow-up and outcome assessment; prisoners or patients in custody; pregnancy; on psychiatric hold; major debilitating baseline mental health disorders or major debilitating neurologic disease; participants in an interventional trial; or penetrating head or spinal cord injury with American Spinal Injury Association impairment scale score of C or worse[22]. Data were collected by trained research coordinators, using structured data collection tools. The present study was approved by the Institutional Review Board at Duke University (Reference 00100061).

Study population

We examined adults (age ≥17 years) in the TRACK-TBI cohort with moderate-severe TBI, defined as Glasgow Coma Scale (GCS) score <13 after resuscitation, who were admitted to an Intensive Care Unit (ICU) from the Emergency Department. To remove the confounding effects of extracranial injuries on the development of circulatory shock, we excluded patients

with significant extracranial injury, defined as non-head/neck Abbreviated Injury Scale score >3. Among these patients, we included only those who had biomarker data available on the day of hospital admission (day-1).

Exposure, outcomes, and covariates

The exposures were the levels of four day-1 neuronal injury biomarkers and an inflammatory biomarker; biomarker levels at days 3, 5, and 14 were also collected for patients with available information. Biomarker data collected were GFAP (pg/ml), UCH-L1 (pg/ml), S100B (ug/l), NSE (ng/ml), and hsCRP (mg/l). The first batch of GFAP and UCH-L1 concentrations (n=170) were measured using the prototype point-of-care i-STAT™ Alinity™ System. The second batch of GFAP and UCHL1 concentrations (n=222) were measured on the prototype core lab Abbott ARCHITECT® platform for faster throughput. For the i-STAT™ Alinity™ assays, the test limit of detection (LoD) and limit of quantitation (LoQ) for GFAP were <15 pg/mL and <25 pg/mL respectively, and, for UCHL-1 <10 pg/mL and <20 pg/mL, respectively. For the ARCHITECT® assays, the GFAP LoD and LoQ were 2 pg/mL and 5 pg/mL, respectively, and the LoD and LoQ for UCHL-1 were10 pg/mL and 20 pg/mL, respectively. All samples were tested neat, without dilution, and in duplicate. Samples reading greater than the calibration range were reported as greater than the reportable range and were not diluted. ARCHITECT® values were converted to iSTAT equivalents using two previously derived equations: iSTAT= −12.36+1.02*ARCHITECT for GFAP (Spearman's correlation coefficient, 0.985) and iSTAT=−3.29+0.72*ARCHITECT for UCHL1 (Spearman's correlation coefficient, 0.933).[23] Biomarker measurements were blinded to outcome assessments. Biomarker levels were log-transformed for the statistical models because of the skewness of the distributions.

The primary outcome of interest was the development of circulatory shock, defined by the cardiovascular component of the Sequential Organ Failure Assessment (SOFA) score ≥ 2 within 72 hours of admission. The SOFA score was developed to assess acute morbidity in a range of organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological), for which both the sub-scores and the total score are associated with prognosis[24]. Covariates were ascertained by examination of time-stamped demographic, clinical, diagnostic, pharmacy, and laboratory information in the TRACK-TBI cohort; these included age, gender, race, ethnicity, injury cause, Injury Severity Score (ISS), computed tomography (CT) confirmed intracranial injury, CT Marshall Score, CT Rotterdam Score, and GCS upon arrival to the ED (3–8 vs. 9–12).

Statistical analysis

Descriptive statistics were used to examine demographics, clinical characteristics, and day-1 biomarker levels, stratified by early circulatory shock status. All biomarker levels were reported using median and interquartile range (IQR). Group comparisons used Wilcoxon Rank Sum test for continuous variables and Fisher's exact test for categorical variables. Categorical variables are reported as number (percentage) and continuous variables as mean and standard deviation (SD). Descriptive statistics were also used to examine biomarker levels at days-3, 5, and 14, stratified by early circulatory shock status. Multivariable logistic regression models were performed to assess the association between each of the day-1

biomarker levels and development of early circulatory shock. Models were fit with and without the following covariates: age, gender, race, non-head ISS, CT Rotterdam Score, and GCS. Odds ratios (OR) per unit increase in each biomarker level (in log scale) were presented with 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant. All analyses were performed using Statistical software R version 3.6 (http://www.r-project.org).

Results

The study population included 392 subjects, of which 165 (42%) developed circulatory shock (Figure 1). The mean age of participants was 39.9 ± 16.8 years; 313 (79.9%) participants were male, 307 (80.6%) participants were white, and 76 participants (19.9%) identified as Hispanic. The median ISS non-head/neck of the study cohort was 4 [IQR,1–10] and mean CT Rotterdam Score was 3.4±1.2. Mean GCS upon arrival was 5.8±3.1; 74.2% of patient cohort had severe TBI (GCS 3–8) and 25.8% had moderate TBI (GCS 9–12). Details of the demographic and clinical characteristics of the study population stratified by development of circulatory shock within 72 hours of admission are shown in Table 1.

Biomarker levels

Figure 2 shows the median (25^{th}/75^{th}) percentiles of day 1 biomarkers, stratified by early circulatory status. Median day-1 UCH-L1 levels were significantly elevated in those who developed early circulatory shock compared to those who did not (994.8 [IQR, 518.7–1988.2] pg/ml vs. 548.1 [IQR, 280.2–1151.9] pg/ml, respectively; p <.0001) Similarly, S100b levels were significantly elevated in those who developed early circulatory shock (0.47 ug/ml [0.25–0.88] vs. 0.27 [0.16–0.46] ug/ml; p <.0001). Temporal changes in biomarker levels on days 1, 3, 5 and 14 are shown in Figure 3 and in the supplementary material (Supplemental digital content 1: Supplementary tables 1–5). There were no significant differences in day-1 GFAP levels between those who did and did not develop circulatory shock. GFAP levels were significantly elevated on days-3, 5, and 14 amongst those who developed circulatory shock, with levels in both groups gradually declining by day-14. UCH-L1 levels were significantly elevated on day-1 and day-3 in those who developed early circulatory shock, and levels gradually declined in both groups by day-14. S100b levels were significantly elevated on days-1, 3, and 5 in those who developed circulatory shock, and also gradually declined in both groups over 14 days. There were no significant between-group differences in NSE levels on days-1, 3, 5 and 14; in both groups, NSE levels declined between day-1 and day-5 and then increased by day-14. There were no significant between-group differences in day-1 hsCRP levels; however, day-3, 5, and 14 hsCRP levels were significantly increased in those who developed early shock. Compared to day-1, hsCRP levels were higher on day-3 and day-5 in both groups.

Association of day-1 biomarker levels with the development of early shock

Table 2 shows the association between day-1 biomarker levels and the development of early circulatory shock, before and after adjustment with covariates. Overall, 42% of the study population developed early circulatory shock. In multivariable logistic regression models, there were significant associations between day-1 levels of UCH-L1 (OR, 1.63 [95% CI

1.25–2.12]; p<.0005) and day-1 levels of S100B (OR, 1.73 [95% CI 1.27–2.36]; p<.0005) and the development of early circulatory shock.

DISCUSSION

We conducted a retrospective study to examine the association of day-1 brain biomarker levels with the development of early circulatory shock following moderate-severe TBI. We found significant differences in UCH-L1, S100B, GFAP and hsCRP in the 14 days following injury between those who did and did not develop early circulatory shock, and that day-1 levels of UCH-L1 and S100B were associated with the development of early circulatory shock.

This association between neuronal and glial injury and circulatory shock helps further elucidate the multifactorial etiology of circulatory shock following moderate-severe TBI[4 25]. Current research demonstrates that TBI-associated circulatory shock occurs secondary to the initial primary brain injury, during which mechanical forces lead to axonal shearing and necrosis, and the subsequent secondary injury which is driven by inflammation, blood–brain barrier disruption, apoptosis, metabolic disturbances, and oxidative stress[26]. The release of a cascade of autonomic and inflammatory mediators into the circulation leads to changes in central and peripheral autonomic tone and widespread catecholamine release through activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system[4 27–29]. This activation leads to a direct effect on the function of a range of organ systems, including cardiopulmonary dysfunction and subsequent shock[4 30]. Markers of neurological injury severity, such as low initial GCS (3–5), increase the risk of developing ICU hypotension 3.37 fold[20]. Taken together, this evidence suggests that circulatory shock following TBI is caused by a complex cascade of dysfunction driven by injury to the brain and its cellular components.

In this study, we observed a significant association between day-1 levels of UCH-L1 and S100B and the development of circulatory shock within 3 days of admission. UCH-L1 is a protein specifically expressed in neurons involved in either the addition or removal of ubiquitin from abnormal proteins (i.e., misfolded proteins, proteins damaged by oxidation, or denatured by other means) that are destined for proteasomal degradation[31]. In the first 24 hours after severe TBI, there is a significant increase in serum and cerebrospinal fluid UCH-L1, which is associated with increased hospital and 6-month mortality[13 32]. UCHL1 has also been shown to predict abnormal head CT findings following brain injury with a sensitivity of 100% and a specificity of 39% at a cut off value of >40pg/ml[33]. S100B is a low affinity calcium-binding protein expressed in astroglial and Schwann cells that regulates intracellular calcium levels; it is released during astroglial injury and becomes elevated in the cerebrospinal fluid and serum following injury[34]. S100B has been shown to correlate with GCS score and neuroradiological findings at the time of hospital admission of TBI patients[35–38]. A high level of S100B early after TBI can predict poor outcome, especially if it is accompanied by a second increase in serum S100B levels during the subacute phase[16 39]. Our data demonstrated that day-1 and day-3 levels of both UCH-L1 and S100B were significantly increased in the group that developed circulatory shock. Median levels of UCH-L1 and S100B subsequently declined over the 14-day interval for the study population.

These findings suggest that UCH-L1 and S100B may be useful biomarkers for detecting the development of circulatory shock after moderate-severe TBI, and further support the hypothesis that direct neuronal and astroglial injury contributes to the development of circulatory shock in patients with moderate-severe TBI.

We also observed unique patterns of elevation of GFAP, NSE and hsCRP levels in the first 14-days following moderate-severe TBI. GFAP, which was acutely elevated in both groups in our study cohort and declined over 14 days, is a monomeric intermediate filament protein of astrocytes and considered specific for central nervous system disease[40 41]. Previous studies demonstrate GFAP is elevated early after TBI and functions as a good predictor for TBI severity and abnormal head CT findings in patients with severe TBI[12 42–44]. In one study, GFAP outperformed S100B in its ability to predict intracranial abnormalities on CT scan in patients with TBI across the full injury spectrum of GCS 3–15 through 24 hours post-injury[44]. We did not observe significant differences in day-1 GFAP levels between those who developed circulatory shock and those who did not. Serum hsCRP, a non-specific but sensitive biomarker for systemic inflammation, has previously been shown to predict disability at 6-months after injury when measured within 2 weeks of TBI[17 45]. Though we did not observe an association with day-1 levels in those who developed circulatory shock, we did observe a slow increase in hsCRP at days-3, 5 and 14 that was significantly increased in those who developed early shock. As such, hsCRP and therefore systemic inflammation levels following injury may not correlate with neuronal or glial injury incident to the index event, but rather secondary to downstream inflammatory events such as ventilator associated pneumonia and secondary organ injury. NSE is a glycolytic enzyme which is released following acute neuronal damage in the brain; it has high specificity to the brain but limited accuracy to predict brain injury due to its release in the serum during hemolysis[34]. NSE was initially identified in the serum and cerebrospinal fluid of patients with head trauma and those in a state of coma, and its levels in cerebrospinal fluid were proportional to the severity of TBI and were associated with increased mortality in cases of moderate or severe TBI[18]. We found that serum NSE was not predictive of circulatory shock, and between group differences were not observed at any point during the 14-day interval of the study. As such, the utility of NSE in predicting or correlating with TBI severity and its complications may be limited.

This study has several limitations. First, vasopressor utilization was used a proxy for circulatory shock as part of cardiovascular SOFA score because detailed information on exact shock state and episodes of hypotension could not be gathered. As such, we could not control for different mechanisms of shock (i.e., distributive, hemorrhagic, cardiogenic, obstructive) nor the dosing of different vasopressors over time. Furthermore, vasopressors may have been used to augment cerebral perfusion pressure despite absence of circulatory shock, contributing to bias in our analysis. Second, the retrospective nature of the study limits the conclusions that can be drawn, and places it at risk for residual confounding. Third, the levels of biomarkers may have been affected by a number of other conditions, including acute and chronic inflammatory conditions, surgical interventions, and complications such as ventilator associated pneumonia or sepsis, which we did not account for in this study. We addressed this by limiting our exposure to day-1 biomarkers and our outcome to early circulatory shock to increase the likelihood that vasopressor treatments

were used for injury-induced hypotension rather than for subsequent complications such as septic shock or pulmonary embolism. Fourth, brain injury biomarkers could be associated with the development of other extracranial organ dysfunction in addition to circulatory shock, but this was not included in our analysis. As well as examination of the development of these additional multiple outcomes not being the focus of this study, the development of additional extracranial organ dysfunction would potentially occur on the causal pathway between brain injury and the development of circulatory shock (making this variable a mediator); our analysis was not designed to examine mediation. Nevertheless, we believe that future studies should consider the relationship between brain injury and the development of additional extracranial organ injuries, above and beyond circulatory shock. Lastly, despite the large sample size of TRACK-TBI overall, a relatively small number of cases met study inclusion criteria, potentially leading to decreased precision in the risk estimates from a lack of statistical power.

CONCLUSION

In conclusion, we observed an association between elevated day-1 levels of UCH-L1 and S100B biomarkers and the development of early shock, as well as significant differences in UCH-L1, S100B, GFAP and hsCRP in the 14 days following injury between those who did and did not develop early circulatory shock. Our data support the role of neuronal injury and inflammatory biomarkers for improved mechanistic understanding and possibly early identification of patients at risk for circulatory shock following moderate-severe TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Prevention CfDCa. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths-United States, 2014: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2019.
2. Mascia L, Sakr Y, Pasero D, et al. Extracranial complications in patients with acute brain injury: a post-hoc analysis of the SOAP study. Intensive Care Med 2008;34(4):720–7. doi: 10.1007/s00134-007-0974-7 [published Online First: 2008/01/05] [PubMed: 18175107]

3. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 2017;80(1):6–15. doi: 10.1227/NEU.0000000000001432 [published Online First: 2016/09/23] [PubMed: 27654000]
4. Krishnamoorthy V, Komisarow JM, Laskowitz DT, et al. Multi-Organ Dysfunction following Severe Traumatic Brain Injury: Epidemiology, Mechanisms, and Clinical Management. Chest 2021 doi: 10.1016/j.chest.2021.01.016 [published Online First: 2021/01/19]
5. Vavilala MS, Lee LA, Lam AM. Cerebral blood flow and vascular physiology. Anesthesiol Clin North Am 2002;20(2):247–64, v. doi: 10.1016/s0889-8537(01)00012-8 [published Online First: 2002/08/09] [PubMed: 12165993]
6. Czosnyka M, Smielewski P, Piechnik S, et al. Cerebral autoregulation following head injury. J Neurosurg 2001;95(5):756–63. doi: 10.3171/jns.2001.95.5.0756 [published Online First: 2001/11/13] [PubMed: 11702864]
7. Miller JD, Sweet RC, Narayan R, et al. Early insults to the injured brain. JAMA 1978;240(5):439–42. [published Online First: 1978/08/04] [PubMed: 660888]
8. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(2):294–302. doi: 10.1089/neu.2006.0032 [published Online First: 2007/03/23] [PubMed: 17375994]
9. Brenner M, Stein DM, Hu PF, et al. Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury. J Trauma Acute Care Surg 2012;72(5):1135–9. doi: 10.1097/TA.0b013e31824af90b [published Online First: 2012/06/08] [PubMed: 22673237]
10. Manley G, Knudson MM, Morabito D, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. Arch Surg 2001;136(10):1118–23. doi: 10.1001/archsurg.136.10.1118 [published Online First: 2001/10/19] [PubMed: 11585502]
11. Adrian H, Marten K, Salla N, et al. Biomarkers of Traumatic Brain Injury: Temporal Changes in Body Fluids. eNeuro 2016;3(6) doi: 10.1523/ENEURO.0294-16.2016 [published Online First: 2016/12/30]
12. Honda M, Tsuruta R, Kaneko T, et al. Serum glial fibrillary acidic protein is a highly specific biomarker for traumatic brain injury in humans compared with S-100B and neuron-specific enolase. J Trauma 2010;69(1):104–9. doi: 10.1097/TA.0b013e3181bbd485 [published Online First: 2010/01/23] [PubMed: 20093985]
13. Brophy GM, Mondello S, Papa L, et al. Biokinetic analysis of ubiquitin C-terminal hydrolase-L1 (UCH-L1) in severe traumatic brain injury patient biofluids. J Neurotrauma 2011;28(6):861–70. doi: 10.1089/neu.2010.1564 [published Online First: 2011/02/12] [PubMed: 21309726]
14. Diaz-Arrastia R, Wang KK, Papa L, et al. Acute biomarkers of traumatic brain injury: relationship between plasma levels of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein. J Neurotrauma 2014;31(1):19–25. doi: 10.1089/neu.2013.3040 [published Online First: 2013/07/20] [PubMed: 23865516]
15. Bogoslovsky T, Wilson D, Chen Y, et al. Increases of Plasma Levels of Glial Fibrillary Acidic Protein, Tau, and Amyloid beta up to 90 Days after Traumatic Brain Injury. J Neurotrauma 2017;34(1):66–73. doi: 10.1089/neu.2015.4333 [published Online First: 2016/06/18] [PubMed: 27312416]
16. Thelin EP, Johannesson L, Nelson D, et al. S100B is an important outcome predictor in traumatic brain injury. J Neurotrauma 2013;30(7):519–28. doi: 10.1089/neu.2012.2553 [published Online First: 2013/01/10] [PubMed: 23297751]
17. Xu LB, Yue JK, Korley F, et al. High-Sensitivity C-Reactive Protein Is a Prognostic Biomarker of Six-Month Disability after Traumatic Brain Injury: Results from the TRACK-TBI Study. J Neurotrauma 2020 doi: 10.1089/neu.2020.7177 [published Online First: 2020/11/10]
18. Berger RP, Beers SR, Richichi R, et al. Serum biomarker concentrations and outcome after pediatric traumatic brain injury. J Neurotrauma 2007;24(12):1793–801. doi: 10.1089/neu.2007.0316 [published Online First: 2007/12/28] [PubMed: 18159990]
19. Edalatfar M, Piri SM, Mehrabinejad MM, et al. Biofluid Biomarkers in Traumatic Brain Injury: A Systematic Scoping Review. Neurocrit Care 2021 doi: 10.1007/s12028-020-01173-1 [published Online First: 2021/01/07]

20. Corral L, Javierre CF, Ventura JL, et al. Impact of non-neurological complications in severe traumatic brain injury outcome. Crit Care 2012;16(2):R44. doi: 10.1186/cc11243 [published Online First: 2012/03/14] [PubMed: 22410278]
21. Bodien YG, McCrea M, Dikmen S, et al. Optimizing Outcome Assessment in Multicenter TBI Trials: Perspectives From TRACK-TBI and the TBI Endpoints Development Initiative. J Head Trauma Rehabil 2018;33(3):147–57. doi: 10.1097/HTR.0000000000000367 [published Online First: 2018/02/01] [PubMed: 29385010]
22. El Masry WS, Tsubo M, Katoh S, et al. Validation of the American Spinal Injury Association (ASIA) motor score and the National Acute Spinal Cord Injury Study (NASCIS) motor score. Spine (Phila Pa 1976) 1996;21(5):614–9. doi: 10.1097/00007632-199603010-00015 [published Online First: 1996/03/01] [PubMed: 8852318]
23. Korley FK, Datwyler SA, Jain S, et al. Comparison of GFAP and UCH-L1 Measurements from Two Prototype Assays: The Abbott i-STAT and ARCHITECT Assays. Neurotrauma Rep 2021;2(1):193–99. doi: 10.1089/neur.2020.0037 [published Online First: 2021/05/04] [PubMed: 33937911]
24. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11):1793–800. doi: 10.1097/00003246-199811000-00016 [published Online First: 1998/11/21] [PubMed: 9824069]
25. Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369(18):1726–34. doi: 10.1056/NEJMra1208943 [published Online First: 2013/11/01] [PubMed: 24171518]
26. Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav Immun 2012;26(8):1191–201. doi: 10.1016/j.bbi.2012.06.008 [published Online First: 2012/06/26] [PubMed: 22728326]
27. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. J Neurosurg 1984;61(1):76–86. doi: 10.3171/jns.1984.61.1.0076 [published Online First: 1984/07/01] [PubMed: 6726414]
28. Koiv L, Merisalu E, Zilmer K, et al. Changes of sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in patients with head injury. Acta Neurol Scand 1997;96(1):52–8. doi: 10.1111/j.1600-0404.1997.tb00238.x [published Online First: 1997/07/01] [PubMed: 9262133]
29. McDonald SJ, Sharkey JM, Sun M, et al. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. J Neurotrauma 2020;37(5):770–81. doi: 10.1089/neu.2019.6885 [published Online First: 2020/02/12] [PubMed: 32041478]
30. Tracey KJ. The inflammatory reflex. Nature 2002;420(6917):853–9. doi: 10.1038/nature01321 [published Online First: 2002/12/20] [PubMed: 12490958]
31. Tongaonkar P, Chen L, Lambertson D, et al. Evidence for an interaction between ubiquitin-conjugating enzymes and the 26S proteasome. Mol Cell Biol 2000;20(13):4691–8. doi: 10.1128/mcb.20.13.4691-4698.2000 [published Online First: 2000/06/10] [PubMed: 10848595]
32. Mondello S, Papa L, Buki A, et al. Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. Crit Care 2011;15(3):R156. doi: 10.1186/cc10286 [published Online First: 2011/06/28] [PubMed: 21702960]
33. Welch RD, Ayaz SI, Lewis LM, et al. Ability of Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and S100B To Differentiate Normal and Abnormal Head Computed Tomography Findings in Patients with Suspected Mild or Moderate Traumatic Brain Injury. J Neurotrauma 2016;33(2):203–14. doi: 10.1089/neu.2015.4149 [published Online First: 2015/10/16] [PubMed: 26467555]
34. Persson L, Hardemark HG, Gustafsson J, et al. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. Stroke 1987;18(5):911–8. doi: 10.1161/01.str.18.5.911 [published Online First: 1987/09/01] [PubMed: 3629651]
35. Raabe A, Grolms C, Keller M, et al. Correlation of computed tomography findings and serum brain damage markers following severe head injury. Acta Neurochir (Wien) 1998;140(8):787–91;

discussion 91–2. doi: 10.1007/s007010050180 [published Online First: 1998/11/12] [PubMed: 9810445]

36. Romner B, Ingebrigtsen T, Kongstad P, et al. Traumatic brain damage: serum S-100 protein measurements related to neuroradiological findings. J Neurotrauma 2000;17(8):641–7. doi: 10.1089/089771500415391 [published Online First: 2000/09/06] [PubMed: 10972241]
37. Raabe A, Grolms C, Sorge O, et al. Serum S-100B protein in severe head injury. Neurosurgery 1999;45(3):477–83. doi: 10.1097/00006123-199909000-00012 [published Online First: 1999/09/24] [PubMed: 10493369]
38. Raabe A, Seifert V. Protein S-100B as a serum marker of brain damage in severe head injury: preliminary results. Neurosurg Rev 2000;23(3):136–8. doi: 10.1007/pl00011944 [published Online First: 2000/11/22] [PubMed: 11086737]
39. Thelin EP, Nelson DW, Bellander BM. Secondary peaks of S100B in serum relate to subsequent radiological pathology in traumatic brain injury. Neurocrit Care 2014;20(2):217–29. doi: 10.1007/s12028-013-9916-0 [published Online First: 2013/10/23] [PubMed: 24146416]
40. Rosengren LE, Wikkelso C, Hagberg L. A sensitive ELISA for glial fibrillary acidic protein: application in CSF of adults. J Neurosci Methods 1994;51(2):197–204. doi: 10.1016/0165-0270(94)90011-6 [published Online First: 1994/03/01] [PubMed: 8051950]
41. Missler U, Wiesmann M, Wittmann G, et al. Measurement of glial fibrillary acidic protein in human blood: analytical method and preliminary clinical results. Clin Chem 1999;45(1):138–41. [published Online First: 1999/01/23] [PubMed: 9895354]
42. Pelinka LE, Kroepfl A, Schmidhammer R, et al. Glial fibrillary acidic protein in serum after traumatic brain injury and multiple trauma. J Trauma 2004;57(5):1006–12. doi: 10.1097/01.ta.0000108998.48026.c3 [published Online First: 2004/12/08] [PubMed: 15580024]
43. Vos PE, Jacobs B, Andriessen TM, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology 2010;75(20):1786–93. doi: 10.1212/WNL.0b013e3181fd62d2 [published Online First: 2010/11/17] [PubMed: 21079180]
44. Okonkwo DO, Puffer RC, Puccio AM, et al. Point-of-Care Platform Blood Biomarker Testing of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding Protein B for Prediction of Traumatic Brain Injuries: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study. J Neurotrauma 2020;37(23):2460–67. doi: 10.1089/neu.2020.7140 [published Online First: 2020/08/29] [PubMed: 32854584]
45. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340(6):448–54. doi: 10.1056/NEJM199902113400607 [published Online First: 1999/02/11] [PubMed: 9971870]

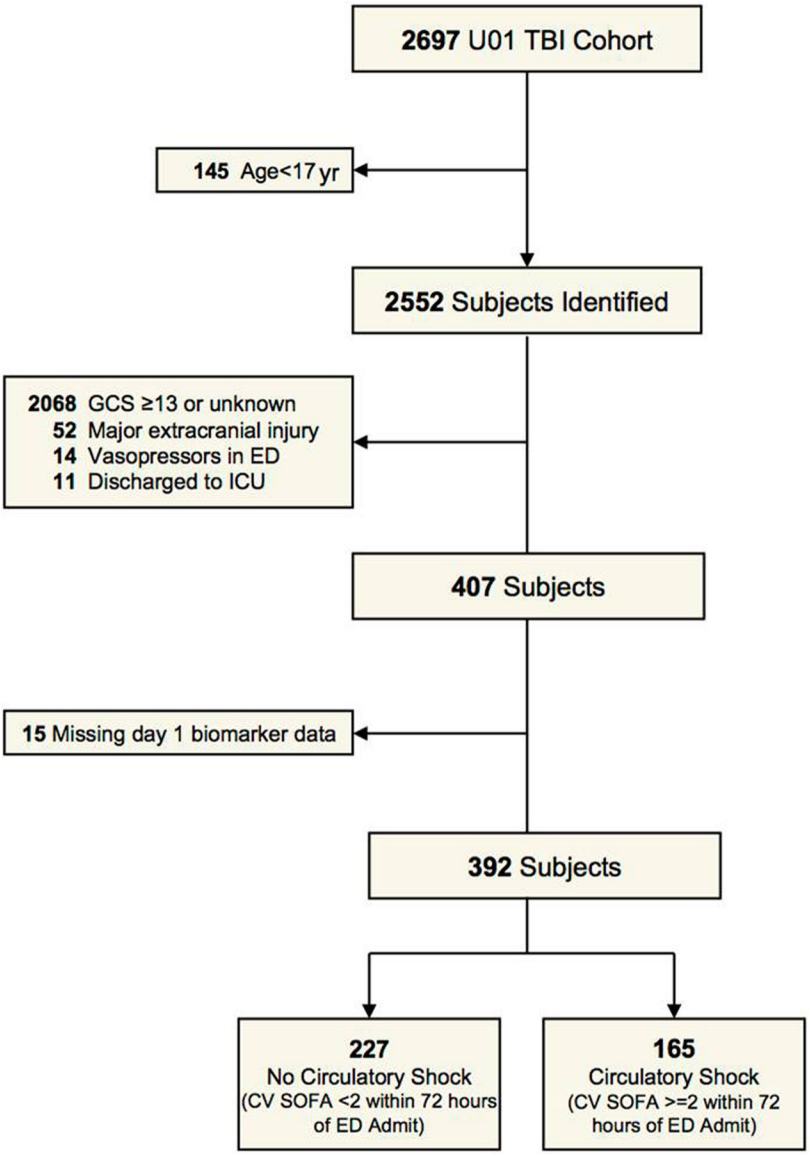

Figure 1. Study flowchart

CV SOFA, cardiovascular component of the Sequential Organ Failure Assessment score; ED, Emergency Department; GCS, Glasgow coma score; ICU, intensive care unit; TBI, traumatic brain injury

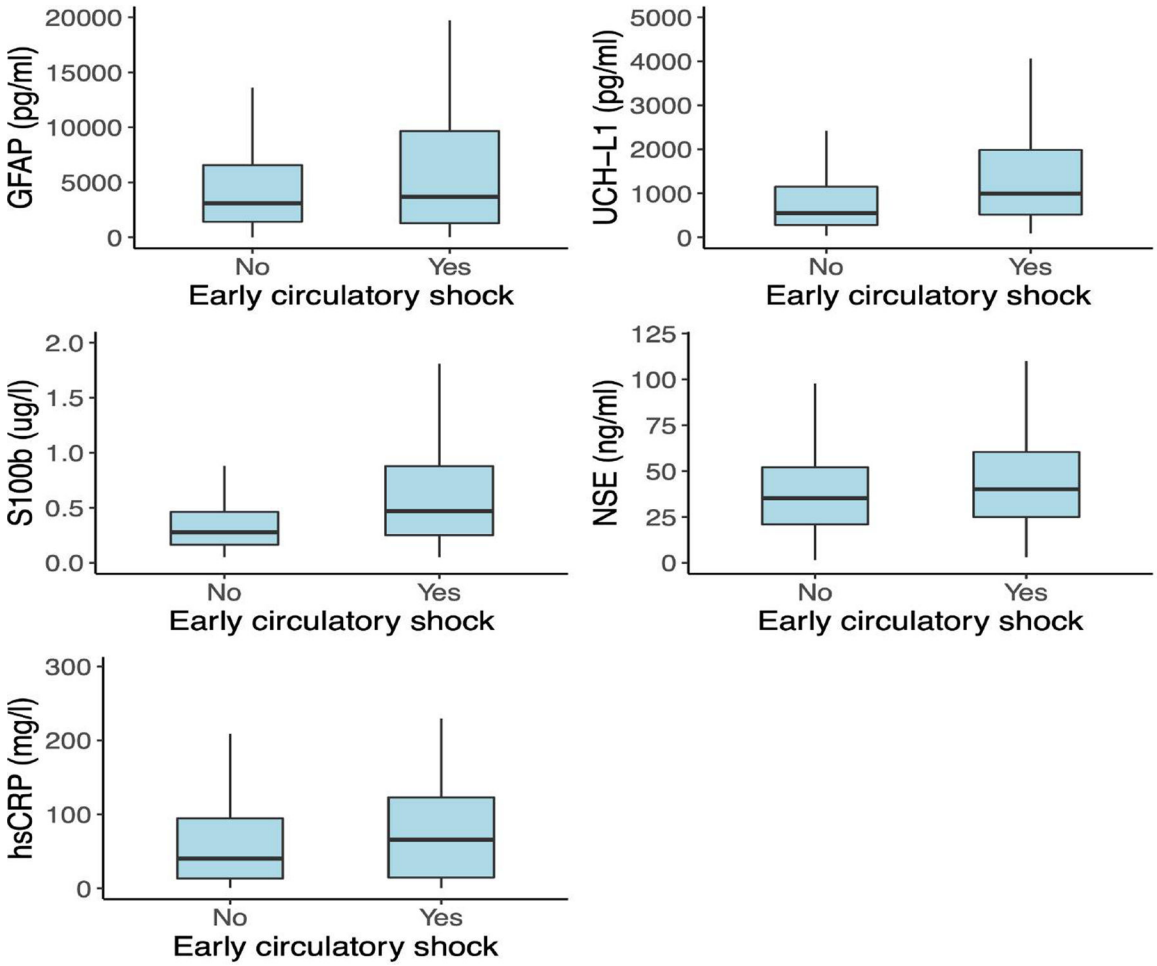

Figure 2. Boxplot of day 1 biomarker level stratified by early circulatory shock status

(Median and $25^{th}/75^{th}$ percentiles)

GFAP, glial fibrillary acidic protein; hsCRP, high-sensitivity C-reactive protein; NSE, neuron specific enolase; S100B, S100 calcium binding protein B; UCH-L1, ubiquitin C-terminal hydrolase-L1

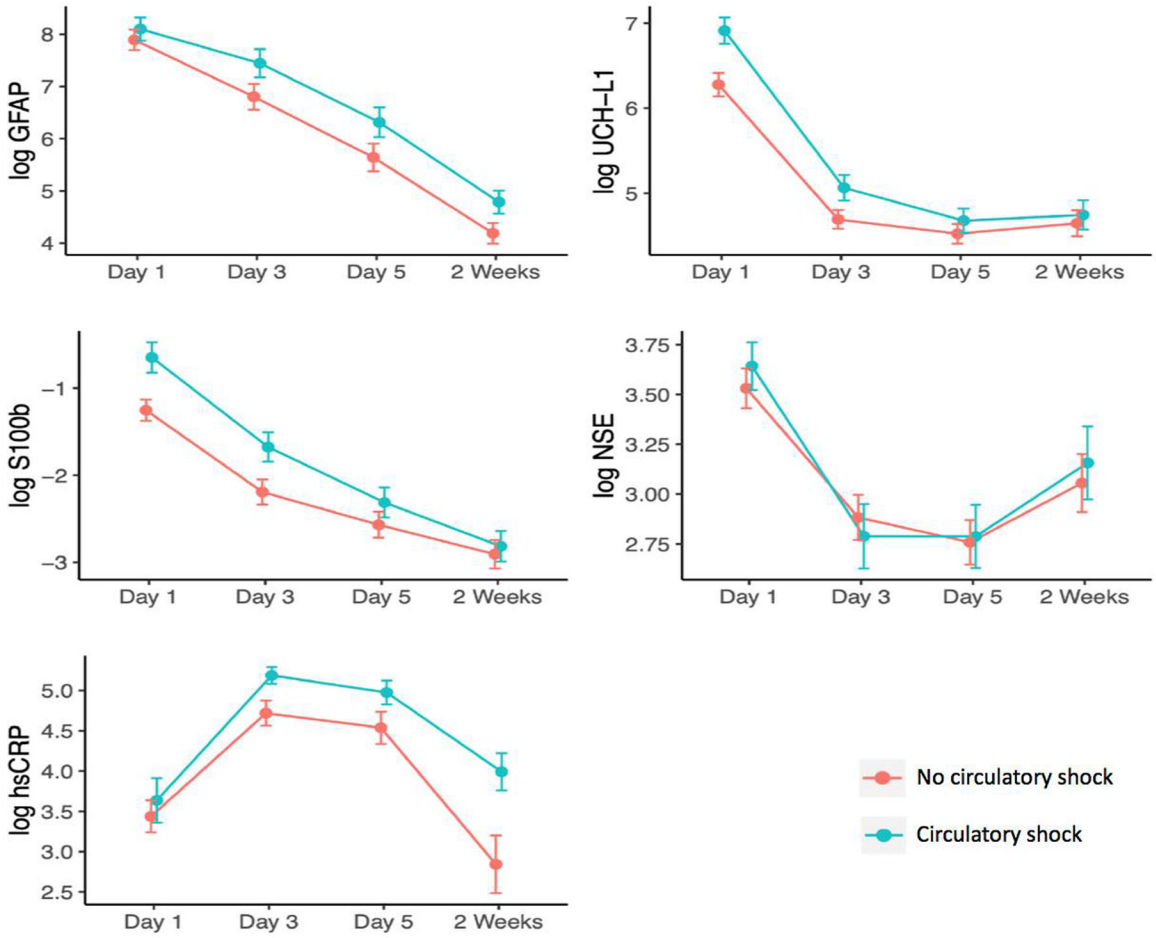

Figure 3. Biomarker levels (log transformed) at days 1, 3, 5 and 14 stratified by early circulatory shock status

GFAP, glial fibrillary acidic protein; hsCRP, high-sensitivity C-reactive protein; NSE, neuron specific enolase; S100B, S100 calcium binding protein B; UCH-L1, ubiquitin C-terminal hydrolase-L1

Table 1

Demographic and clinical characteristics of the study population

Variable	Total	Circulatory Shock		
		No	Yes	p value
Subjects	392	227	165	
Age [mean (SD)]	39.9.6 (16.6)	38.5 (16.6)	41.7 (16.6)	0.036
Unknown [no.]	0	0	0	
Age [no. (%)]				
17–39 years	211 (53%)	129 (57%)	82 (50%)	0.369
41–60 years	133 (34%)	72 (32%)	61 (37%)	
>60 years	48 (13%)	26 (11%)	22 (13%)	
Unknown	0	0	0	
Sex [no. (%)]				
Male	313 (80%)	182 (80%)	131 (79%)	0.899
Female	79 (20%)	45 (20%)	33 (21%)	
Unknown	0	0	0	
Race [no. (%)]				
White	307 (80%)	171 (77%)	138 (85%)	0.001
Black	47 (12%)	39 (18%)	8 (5%)	
Other	27 (7%)	13 (6%)	16 (10%)	
Unknown	11	5	6	
Hispanic [no. (%)]				
No	306 (80%)	171 (77%)	135 (84%)	0.122
Yes	76 (20%)	50 (23%)	26 (16%)	
Unknown	10	6	4	
Injury Cause [no. (%)]				
Road traffic incident	222 (57%)	127 (57%)	95 (58%)	0.038
Incidental fall	96 (25%)	57 (26%)	39 (24%)	
Violence / assault	34 (9%)	25 (11%)	9 (5%)	
Other	36 (9%)	14 (6%)	22 (13%)	
Unknown	4	4	0	
ISS non-head/neck [mean (SD)]	5.8 (6.3)	5.4 (6.2)	6.5 (6.4)	0.134
Unknown [no.]	5	3	2	
CT Rotterdam Score [mean (SD)]	3.4 (1.2)	3.1 (1.2)	3.8 (1.2)	<0.0001
Unknown [no.]	29	13	16	
GCS ED Arrival [mean (SD)]	5.8 (3.1)	6.3 (3.2)	5.1 (2.9)	<0.0001
Unknown [no.]	0	0	0	
GCS ED Arrival [no. (%)]				
Severe (3–8)	291 (74%)	157 (69%)	134 (81%)	0.007
Moderate (9–12)	101 (26%)	70 (31%)	31 (19%)	

Variable	Total	Circulatory Shock		
		No	Yes	p value
Unknown	0	0	0	
CT Intracranial Injury				
CT negative	22 (6%)	21 (10%)	1 (1%)	0.0002
CT positive	346 (94%)	196 (90%)	150 (99%)	
Unknown	24	10	14	
CT Marshall Score				
I-II	183 (50%)	133 (62%)	45 (34%)	0.0005
III-IV	36 (10%)	22 (10%)	14 (9%)	
V-VI	144 (40)	59 (28%)	85 (57%)	
Unknown	29	13	16	

CT, computed tomography; ED, Emergency Department; ISS, injury severity score; SD, standard deviation

Table 2

Association of day-1 biomarkers with early circulatory shock

	Unadjusted			Adjusted[1]		
Biomarker	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
log GFAP	1.10	0.96–1.26	.175	1.07	0.91–1.27	.417
log UCH-L1	1.82	1.47–2.25	<.001	1.63	1.25–2.12	<.001
log S100B	1.94	1.51–2.48	<.001	1.73	1.27–2.36	<.001
log NSE	1.24	0.92–1.66	.160	1.04	0.73–1.48	.840
log hsCRP	1.10	0.94–1.30	.243	1.05	0.87–1.27	.582

[1] Adjusted models include age, gender, race (black, other vs. white), GCS (3–8 vs. 9–12), non-head ISS, and CT Rotterdam score

CI, confidence interval; GFAP, glial fibrillary acidic protein; hsCRP, high-sensitivity C-reactive protein; NSE, neuron specific enolase; OR, odds ratio; S100B, calcium binding protein B; UCH-L1, ubiquitin C-terminal hydrolase-L1