NOVEL BIOMARKERS FOR MILD TRAUMATIC BRAIN INJURY

Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) and Glial Fibrillary Acidic Protein (GFAP)

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EXECUTIVE SUMMARY

Emergency department testing with ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) may be considered for adult patients with mild traumatic brain injury (TBI; Glasgow Coma Score 14-15) to aid in decisions on obtaining a head CT. UCH-L1 and GFAP are expressed in the brain and measurable in peripheral blood samples. Elevated levels of both biomarkers are present in acute brain injury. If both are negative, head CT may be avoided but if either is positive, head CT is warranted.

EXISTING LITERATURE

Multiple studies have examined the combination of UCH-L1 and GFAP. The largest study to date comes from Bazarian et al. in Lancet Neurology, 2018.[1]

- Prospective, multicenter observation trial (2012-2014).
- Adults (≥18 years) with a GCS of 9-15 with a non-penetrating TBI who received a non-contrast head CT, who were < 12 hours from injury.
- UCH-L1 and GFAP were measured with the cutoff values of 327 pg/mL and 22 pg/mL, respectively.
- If either were above the cutoff, the overall test was "positive."
- Of 1,959 patients, 125 (6%) had intracranial injuries and 8 (<1%) had neurosurgical injuries.
- 66% had a positive test result and 34% were negative.
- The sensitivity for detecting intracranial injury was 97.6% (95% Confidence Interval [CI] 93.1%-99.5%).
- The specificity was 36.4% (95% CI 34.2% - 38.7%).
- The negative predictive value was 99.6% (95% CI 98.7%-99.9%), meaning there is <1% chance of a significant finding if the test is negative, and even lower for neurosurgical interventions.
- In 3 patients, the test was negative and the CT was positive.

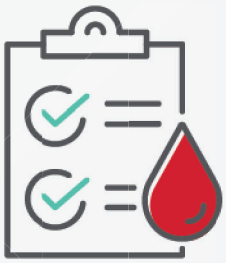
POTENTIAL USES FOR UCH-L1/GFAP[2, 3]

- Consider use in patients who have a mild TBI and a GCS of 14-15 in patients who present within 12 hours of injury.
- Because of the low specificity, we do not recommend use on very-low risk TBI. Consider in patients who you might otherwise CT because they are positive by the Canadian, NEXUS II, or New Orleans Criteria. These decision rules are also nearly 100% sensitive, so stacking both together will reduce the rate of false positive test results on the decision rule.
- When both UCH-L1 and GFAP are negative, you can have a shared-decision making conversation with the patient to say that the CT will most likely be negative and extremely unlikely to show anything requiring intervention so you can avoid a head CT.
- If UCH-L1 or GFAP is elevated, proceed with a non-contrast head CT.
- If UCH-L1 or GFAP is elevated, their head CT is negative, and they otherwise meet discharge criteria, let the patient know of the positive test result and that they may be at higher risk for concussion or continued symptoms.[2]
- UCH-L1 and GFAP can be used above the age thresholds for commonly used decision tools (e.g. Canadian, NEXUS II, or New Orleans Criteria).
- For all patients with TBI, give the standard concussion instructions and to follow-up with their primary care physician, a neurologist, or concussion clinic in line with local resources.[4]

*When **NOT** to use UCH-L1/GFAP to decide on obtaining a head CT*

- Do not use in GCS<14. Note that the FDA does allow for a GCS 13-15, however, we recommend using the test with caution in higher-risk patients as there is still concern in patients with lower GCS.
- Do not use in age <18 years.
- Do not use if the patient is on aspirin or other antiplatelet agent, or an anticoagulant.
- Do not use in patients with coagulopathy or known cirrhosis.
- Do not use in intoxicated patients or patients who are otherwise altered.
- Do not use >12 hours post injury.

PRECAUTIONS WHEN USING UCH-L1/GFAP



- There are different assays for UCH-L1 and GFAP. Cut-off values are different for each one and may change over time or be different at your lab. Use the 95% or 99% confidence interval reported in your lab.
- Do not let the possibility of UCH-L1 or GFAP levels override your clinical intuition. If you think the patient is best served with a head CT, skip the biomarkers and proceed with a head CT.

OTHER CONSIDERATIONS

- Other biomarkers have been examined in the setting of mild TBI (e.g. S100 calcium protein-binding protein B or dS100B) but have not been found to have the diagnostic accuracy of UCH-L1 and GFAP. As such, the UCH-L1/GFAP combination is preferred over these other biomarkers in evaluating mild TBI.
- UCH-L1 and GFAP can be used above the age thresholds for commonly used decision tools (e.g. Canadian, NEXUS II, or New Orleans Criteria).

SUMMARY

Emergency department testing with UCH-L1 (ubiquitin C-terminal hydrolase-L1) and glial fibrillary acidic protein (GFAP) is approved by the FDA for adult patients with mild traumatic brain injury to aid in decisions on obtaining a head CT. UCH-L1 and GFAP are blood biomarkers that rise early after TBI, and can be an indicator of more serious injury (e.g. intracranial hemorrhage [ICH]). These markers can be used within 12 hours of injury. When both UCH-L1 and GFAP are negative, a CT can be avoided with patient consent. When either is positive, head CT is warranted to rule out ICH. These tests may be useful in identifing higher risk patients for subsequent concussion follow-up and management.[5]

COI STATEMENT:

The authors of this White Paper received no compensation and authored this White Paper as part of their work as leaders on the USACS CMO Team. This work was supported via an unrestricted medical education grant to USACS from Abbott Point of Care.

Reference:

1. Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, Gunnar Brolinson P, Büki A, Chen JY, Christenson RH, Hack D, Huff JS, Johar S, Jordan JD, Leidel BA, Lindner T, Ludington E, Okonkwo DO, Ornato J, Peacock WF, Schmidt K, Tyndall JA, Vossough A, Jagoda AS. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol. 2018 Sep;17(9):782-789. doi: 10.1016/S1474-4422(18)30231-X. Epub 2018 Jul 24. PMID: 30054151.
2. Korley FK, Jain S, Sun X, Puccio AM, Yue JK, Gardner RC, Wang KKW, Okonkwo DO, Yuh EL, Mukherjee P, Nelson LD, Taylor SR, Markowitz AJ, Diaz-Arrastia R, Manley GT; TRACK-TBI Study Investigators. 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. Lancet Neurol. 2022 Sep;21(9):803-813. doi: 10.1016/S1474-4422(22)00256-3. PMID: 35963263; PMCID: PMC9462598.
3. Chen H, Ding VY, Zhu G, Jiang B, Li Y, Boothroyd D, Rezaii PG, Bet AM, Paulino AD, Weber A, Glushakova OY, Hayes RL, Wintermark M. Association between Blood and Computed Tomographic Imaging Biomarkers in a Cohort of Mild Traumatic Brain Injury Patients. J Neurotrauma. 2022 Oct;39(19-20):1329-1338. doi: 10.1089/neu.2021.0390. Epub 2022 Jun 13. PMID: 35546284.
4. Papa L, Brophy GM, Welch RD, Lewis LM, Braga CF, Tan CN, Ameli NJ, Lopez MA, Haeussler CA, Mendez Giordano DI, Silvestri S, Giordano P, Weber KD, Hill-Pryor C, Hack DC. Time Course and Diagnostic Accuracy of Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild Traumatic Brain Injury. JAMA Neurol. 2016 May 1;73(5):551-60. doi: 10.1001/jamaneurol.2016.0039. PMID: 27018834; PMCID: PMC8805143.
5. Lewis LM, Schloemann DT, Papa L, Fucetola RP, Bazarian J, Lindburg M, Welch RD. Utility of Serum Biomarkers in the Diagnosis and Stratification of Mild Traumatic Brain Injury. Acad Emerg Med. 2017 Jun;24(6):710-720. doi: 10.1111/acem.13174. Epub 2017 May 18. PMID: 28170122.

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