Can S100B Serum Biomarker Testing Reduce Head Computed Tomography Scanning in Children With Mild Traumatic Brain Injury?

TAKE-HOME MESSAGE

S100B serum biomarker has high sensitivity and negative predictive value for detecting traumatic intracranial lesions in children with mild traumatic brain injury. However, how to incorporate this into existing risk-stratification tools is unclear, and reduced availability of the test currently limits its practical application in the emergency department (ED).

METHODS

DATA SOURCES

The authors searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, Scopus, and Google Scholar from inception to March 15, 2017. In addition, the authors searched reference lists of relevant studies.[1]

STUDY SELECTION

The meta-analysis included prospective cohort studies of children with mild traumatic brain injury who had S100B biomarker testing compared with the reference standards of head computed tomography (CT) or clinical follow-up. Authors did not indicate how they defined intracranial lesions on head CT. Studies were excluded for the following reasons: adult patients, non-English language, Glasgow Coma Scale (GCS) score of less than or equal to 12, insufficient data for analysis, literature reviews, and magnetic resonance imaging as the reference standard.

EBEM Commentators
Steven K. Roumpf, MD
IU Health Academic Health Center
Department of Emergency Medicine
Indiana University School of Medicine
Indianapolis, IN
Julie L. Welch, MD
Indiana Clinical and Translational Science Institute
Department of Emergency Medicine
Indiana University School of Medicine
Indianapolis, IN

Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is: **Oris C, Pereira B, Durif J, et al. The biomarker S100B and mild traumatic brain injury: a meta-analysis. *Pediatrics*. 2018;141: e20180037.**

Results

S100B serum biomarker in children with mild traumatic brain injury.

Analysis	Sensitivity (95% CI), %	NPV (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR– (95% CI)
Primary meta-analysis on 8 studies (n=601)	100 (98–100)	100 (99–100)	41 (26–57)	NR	NR
Secondary meta-analysis on individual participant-level data on 4 studies* (n=373)					
≤2 y and ≤3 h	100 (66.4–100)	NR	53.3 (34.3–71.7)	2.14 (1.46–3.14)	0
>2 y and ≤3 h	100 (85.8–100)	NR	21.1 (13.2–31)	1.27 (1.14–1.41)	0

NPV, Negative predictive value; *LR+*, positive likelihood ratio; *LR–*, negative likelihood ratio; *NR*, not reported.
*Four studies using the same S100B assay.

DATA EXTRACTION AND SYNTHESIS

Two authors independently screened studies for inclusion, assessed quality, and extracted data. Discrepancies were resolved by a third author. Study quality and risk of bias were assessed with the Quality Assessment of Diagnostic Accuracy Studies–2 criteria. Primary meta-analysis was performed with random-effects models. Heterogeneity was assessed with forest plots, 95% confidence intervals (CIs), and I^2 values. Because of potential variability from the use of different S100B serum assays, the authors performed a secondary meta-analysis on individual participant data from 4 studies that used the same S100B assay, the Cobas analyzer from Roche Diagnostics (Indianapolis, IN). Receiver operating characteristic cutoffs were calculated for a 100% sensitivity based on age (<2 versus >2 years) and blood draw times (≤3 versus >3 hours).

The authors identified 1,623 studies; 973 were excluded after review of title and abstract, leaving 57 studies for full-text review, of which 49 were excluded. The 8 included studies comprised 601 children with mild traumatic brain injury who underwent serum S100B biomarker testing compared with head CT or clinical follow-up as the references standard. S100B levels for detecting traumatic intracranial lesions in children with mild traumatic brain injury had a pooled sensitivity of 100% (95% CI 98% to 100%) and negative predictive value of 100% (95% CI 99% to 100%), whereas the pooled specificity was 41% (95% CI 26% to 57%), with significant heterogeneity (I^2>50%) that was driven primarily by one study. Results were similar when this study was removed and improved overall heterogeneity (I^2=0%). Sensitivity results were similar in the secondary analysis when S100B blood sampling times were less than or equal to 3 hours posttrauma (Table).

In terms of study quality, one study was deemed at high risk of bias, whereas 7 were at low to moderate risk. Bias was potentially introduced through patient selection, reference standard (eg, 6 studies used CT scan and 2 used either CT or clinical follow-up), variability in clinical risk-stratification tools, variability in S100B assays and reference ranges, flow, and timing (eg, only 2 studies recommended S100B levels at ≤3 hours posttrauma).

Commentary

Traumatic brain injury is a common complaint in children presenting to EDs and is a major public health concern.[2] Mild traumatic brain injury, defined as a GCS score of 13 to 15,[3] is a common cause of pediatric hospital admission.[4] Clinical risk-stratification tools, such as the Pediatric Emergency Care Applied Research Network (PECARN) algorithm, have been developed for pediatric mild traumatic brain injury and have reduced the use of head CT scans in children by up to 90%.[5] This study addressed whether the serum biomarker S100B has prognostic value in concert with clinical risk stratification to predict traumatic intracranial lesions in children with mild traumatic brain injury.

S100B is a glial-specific protein expressed primarily by astrocytes and is one of the most studied protein biomarkers of cerebral damage in traumatic brain injury.[6] After cerebral trauma, S100B is released by the glial cells into the cerebrospinal fluid and subsequently into the bloodstream through a disrupted blood-brain barrier. S100B has a serum half-life of 30 to 120 minutes, with 100% renal clearance.[6] It has been shown in adults to be a promising screening tool to supplement the clinician's decision not to perform head CT imaging in certain low-risk head injury patients.[7] However, the use of this test has not been well established in the pediatric population.

The results of the primary meta-analysis suggest that S100B is a biomarker of exclusion and cannot confirm traumatic intracranial lesions. The high negative predictive value of 100% (95% CI 99% to 100%) implies that S100B could reduce the number of CT scans in children with mild traumatic brain injury; however, the low specificity implies that the test must be thoughtfully integrated into a traumatic brain injury clinical algorithm. The secondary analysis suggests that S100B results are also influenced by age, sampling time, and reference range.

This review has several limitations. Despite the premise of using this assay in conjunction with a clinical algorithm such as PECARN, only 1 of the 8 studies actually examined the PECARN decision rule in association with S100B measurement. Further prospective study and validation are necessary to apply this test to patients who failed the PECARN rule. Additionally, inconstant S100B cutoffs were used in the studies, and comparative criterion standards were variable (head CT versus clinical follow-up),

so further standardization for age-applicable reference ranges and consistent comparisons are also needed. This study did not examine cost or practical applicability in the ED. Despite its high sensitivity and high negative predictive value, serum S100B has low specificity and low positive predictive value, thus somewhat limiting its ability to reduce the number of CT scans and hospital costs.[8] In addition, many facilities may not have immediate access to the results of the test, with personal experience showing a turnaround time of 3 to 18 days at our facility.

S100B has potential as a supplemental tool for mild traumatic brain injury in children, but further study, standardization, and validation are necessary for practical use. This conclusion is consistent with the recent 2018 Centers for Disease Control and Prevention guidelines for mild traumatic brain injury in children. Insufficient evidence was found to recommend biomarkers for the diagnosis of mild traumatic brain injury in children, and the guidelines also stated that health care professionals should not use biomarkers in pediatric mild traumatic brain injury outside of a research setting.[9]

1. Oris C, Pereira B, Durif J, et al. The biomarker S100B and mild traumatic brain injury: a meta-analysis. *Pediatrics*. 2018;141:e20180037.
2. Thurman DJ. The epidemiology of traumatic brain injury in children and youths: a review of research since 1990. *J Child Neurol*. 2016;31:20-27.
3. Kristman VL, Borg J, Godbolt AK, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;95(3 suppl):S265-S277.
4. Cassidy JD, Carroll LJ, Peloso PM, et al; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004;43(suppl):28-60.
5. Babl FE, Borland ML, Phillips N, et al. Paediatric Research in Emergency Departments International Collaborative. Accuracy of PECARN, CATCH, and CHALICE head injury decision rules in children: a prospective cohort study. *Lancet*. 2017;389:2393-2402.
6. Thelin EP, Nelson DW, Bellander BM. A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. *Acta Neurochir (Wien)*. 2017;159:209-225.
7. Zongo D, Ribéreau-Gayon R, Masson F, et al. S100-B protein as a screening tool for the early assessment of minor head injury. *Ann Emerg Med*. 2012;59:209-218.
8. Ruan S, Noyes K, Bazarian JJ. The economic impact of S-100B as a pre-head CT screening test on emergency department management of adult patients with mild traumatic brain injury. *J Neurotrauma*. 2009;26:1655-1664.
9. Lumba-Brown A, Yeates KO, Sarmiento K, et al. Centers for Disease Control and Prevention guideline on the diagnosis and management of mild traumatic brain injury among children. *JAMA Pediatr*. 2018;172:e182853.