Development and External Validation of the KIIDS-TBI Tool for Managing Children with Mild Traumatic Brain Injury and Intracranial Injuries

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Abstract

Background: Clinical decision support may improve the post-neuroimaging management of children with mild traumatic brain injuries (mTBI) and intracranial injuries. While the CHIIDA score has been proposed for this purpose, a more sensitive risk model may have broader use. Consequently, this study's objectives were to: 1) develop a new risk model with improved sensitivity compared to the CHIIDA model; and 2) externally validate the new model and CHIIDA model in a multicenter dataset.

Methods: We analyzed children < 18 years-old with mTBI and intracranial injuries included in the PECARN head injury dataset (2004-2006). We used binary recursive partitioning to predict the composite outcome of neurosurgical intervention, intubation for > 24 hours due to TBI, or death due to TBI. The new model was externally validated in a separate dataset that included children treated at any one of six centers from 2006-2019.

Results: Based on 839 patients from the PECARN dataset, a new risk model, the KIIDS-TBI model, was developed that incorporated imaging (e.g. midline shift) and clinical (e.g. GCS score) findings. Based on the model-predicted probability of the composite outcome, three cutoffs were evaluated to classify patients as 'high risk' for level of care decisions. In the external validation dataset consisting of 1,630 patients, the most conservative cutoff (i.e. any predictor present) identified 119/119 children with the composite outcome (sensitivity 100%), but had the lowest specificity (26.3%). The other two decision-making cutoffs had worse sensitivity (94.1%-96.6%) but improved specificity (67.4%-81.3%). The CHIIDA model lacked the most conservative cutoff and otherwise showed the same or slightly worse performance compared to the other two cutoffs.

Conclusions: The KIIDS-TBI model has high sensitivity and moderate specificity for risk-stratifying children with mTBI and intracranial injuries. Use of this clinical decision support tool may help improve the safe, resource-efficient management of this important patient population.

Introduction:

Mild traumatic brain injury (mTBI) in children is a major public health concern due to its high frequency and potential for substantial morbidity.[1-3] The primary objective of acute evaluation for children with mTBI is to appropriately identify and manage those individuals at high risk of neurological decline. However, there is limited evidence guiding the appropriate management of the 4-14% of children with mTBI who show radiographic evidence of intracranial injury (ICI) on CT imaging.[4,5] Most of these patients may not require any escalation in care, although some experience neurological decline and undergo acute neurosurgical intervention, creating uncertainty regarding decisions such as the appropriate level of care. Matching patient risk and acuity of care is imperative to ensure appropriately close intensive care unit (ICU) monitoring for high risk patients, while limiting the substantial resource use and mental distress associated with unnecessary hospital transfers and ICU admissions.[6-8] However, current practice is based largely on individual physician choice, is not evidence-based, and is heterogeneous, placing some children at risk of harm.[4,9]

In an attempt to develop evidence-based guidance, several studies have tried to stratify the risk of neurological decline among children with mTBI and ICI,[10,11] with the largest being the development and internal validation of the Children's Intracranial Injury Decision Aid (CHIIDA) tool.[4] However, external validation studies conducted to date have lacked adequate power or generalizability to validate the appropriateness of using such a risk model in routine practice.[12-14] Additionally, while the CHIIDA tool's published sensitivity is relatively high (93-94%),[4,12] a more sensitive risk model may expand potential clinical uses (e.g. in community hospital settings without immediate access to invasive neurotrauma specialty care).

Consequently, the objectives of this study were to: 1) develop the Kids Intracranial Injury Decision Support tool for TBI (KIIDS-TBI); and 2) compare its performance to that of the CHIIDA model for managing children with mTBIs and ICI.

Methods:

Study Population:

To derive the KIIDS-TBI model, we used the Public Use Database from the Pediatric Emergency Care Applied Research Network (PECARN) head injury study—the same dataset used to develop the CHIIDA model.[15] The details of that study have been published previously,[16] but in brief, included children with blunt head trauma who were treated at any one of 25 North American emergency departments (ED) from 2004-2006. All data analyzed were deidentified, and consequently were not subject to institutional review board (IRB) oversight.

To externally validate the KIIDS-TBI model, we leveraged a separate multicenter dataset retrospectively collected by the Pediatric TBI Research Consortium (PTRC). This cohort consisted of patients evaluated at any of six academic hospital ED's from 2006-2019. Some centers used existing TBI registries,[17,18] but there was no overlap between the derivation (PECARN) and validation (PTRC) cohorts. Data from the validation cohort were collected via retrospective chart review conducted by PTRC investigators at each center. For the PTRC study, waivers of informed consent and IRB approval were obtained at each site. A shared operations manual was used to help standardize definitions of the variables collected, and de-identified data were stored in a centralized Research Electronic Data Capture (REDCap) database.[19] After initial data collection, a centralized quality control analysis was completed to flag unusual or missing values, which were then investigated and corrected by site investigators, as needed.

Inclusion Criteria:

We included patients 18 years-old or younger presenting to a participating ED within 24 hours of blunt head trauma, with Glasgow Coma Scale (GCS) scores of 13-15, and who were found to have ICI on acute CT or magnetic resonance imaging (MRI). While the terminology around this population is heterogeneous, with some authors using the terms "complicated mild traumatic brain injury" or "minor traumatic brain injury," we chose to term these patients mTBI with ICI.[11,20] ICI was defined based on the criteria applied by the PECARN investigators, which included intracranial hemorrhage, cerebral edema, skull diastasis, midline shift, pneumocephalus, skull fracture depressed by at least the width of the skull, traumatic infarction, diffuse axonal injury, herniation, shear injury, or sigmoid sinus thrombosis. In the validation PTRC dataset, skull diastasis was not evaluated due to its marginal clinical significance, and shear injury and diffuse axonal injury were not distinguished from cerebral contusion.[16] Patients with penetrating

head trauma, current brain tumor diagnosis, pre-morbid cognitive impairment, or presence of ventriculoperitoneal shunts were excluded. In the validation PTRC cohort, patients were also excluded if the initial imaging suggested that the ICI was subacute or chronic, whereas this information was not available in the PECARN dataset.

Predictor and Outcome Variables:

To derive the KIIDS-TBI score, we evaluated both presenting clinical characteristics (e.g. GCS score, post-traumatic seizure) and neuroimaging findings (e.g. hemorrhage type). A full list of potential predictors is provided in Table 1, which were defined in detail previously.[16] Because the PECARN (derivation) Public Use Dataset did not prospectively distinguish depressed fractures, radiologist impressions were reviewed for any mention of fracture depression or displacement in patients diagnosed with skull fractures. For the PTRC (validation) cohort, imaging findings were defined through a combination of abstraction from radiology reports by site investigators and primary image review to verify any unusual or ambiguous findings. GCS scores were recorded at the time of initial physician evaluation at the study site, with the exception of one PTRC center where some scores were recorded at a referring hospital. Injury severity and significant non-cranial injuries were recorded using previously published definitions.[16]

The primary outcome was the composite of neurosurgical intervention, intubation for more than 24 hours due to TBI, or death due to TBI. This outcome was chosen because of its previous use in the literature,[4,16] as well as its strong indication of patients who are likely to benefit from close neuromonitoring and early detection of any neurological change. Neurosurgical intervention was defined as craniotomy for hematoma evacuation or lobectomy, dural repair of cerebrospinal fluid leak, elevation of a depressed skull fracture, intracranial pressure monitor or external ventricular drain placement, or decompressive craniectomy. Scalp debridement and other minor procedures (e.g. lumbar drain placement for transient CSF leak) were not included in this definition, since they did not reflect the same severity of ICI.

Statistical Analysis:

The KIIDS-TBI model was developed using binary recursive partitioning, which was chosen based on previous studies that indicated this technique offered both a statistically powerful and easily interpretable approach for identifying low-risk subgroups.[16,21-23] This approach was also chosen to contrast with the multivariable logistic regression analysis used to develop the CHIIDA model, which required users to remember point values assigned to each predictor.[4] Recursive partitioning is a non-parametric multivariable modeling technique that identifies important predictors sequentially and splits these predictors at optimal cutoff points to stratify risk of the outcome in question. At each stage, the predictor variable with the strongest association with the outcome is identified, and the tree building continues until stopping criteria are met and further addition and splitting of variables does not improve model accuracy. This technique is used to classify observations according to risk profiles for the outcome of interest by using a treelike structure with decision nodes, making it easy for clinicians to interpret and apply. Recursive partitioning analysis may be preferable to multiple logistic regression when the objective is to derive a highly sensitive clinical decision rule.[24] Different from recursive partitioning, logistic regression assumes risk factors have an additive impact on the outcome.

Due to its clinical importance demonstrated in a large survey of pediatric neurotrauma providers,[9] midline shift was set as the first split. The remaining tree was grown using recursive partitioning. To maximize the rule's sensitivity, we assigned a relative cost of 100 to 1 for failing to identify a patient that experienced the composite outcome. We used a minimum terminal node size of 25 to prevent overfitting. We then used 10-fold cross-validation to select a final prediction tree.[25] Missing data were treated using surrogate splits for the recursive partitioning, and complete cases were summarized for descriptive statistics. The final KIIDS-TBI model was selected using the PECARN dataset prior to testing on the PTRC (validation) dataset.

Based on an expected event rate of 8.7%,[4] we anticipated needing at least 1,150 patients in the validation dataset to have at least 100 outcome events. A minimum of 100 events has been shown in simulation studies to be a conservative estimate of the sample needed to have 80% power to detect significant changes in model performance.[14] We validated the performance of both the KIIDS-TBI and CHIIDA models by assessing the sensitivity, specificity, positive (PPV) and negative predictive values (NPV), as well as positive and negative likelihood ratios with

95% confidence intervals (CI) at multiple risk thresholds. We also compared performance in children younger than two years versus those two years and older. We examined the association between post-ED disposition and patient risk, stratifying disposition into low (home, short-stay, and non-ICU floor unit) versus high (operating room or ICU) acuity settings. We assessed model calibration graphically by comparing observed versus expected outcomes in the validation dataset. All analyses were conducted in R version 4.0.1 (R Foundation; Vienna, Austria),[26] and recursive partitioning was performed using the rpart package.[27]

Results:

The characteristics of the PECARN study cohort have been reported previously,[4] but are presented alongside characteristics of the PTRC validation cohort in Table 2. Of 43,399 patients evaluated at 25 hospitals in the PECARN dataset, 839 had GCS scores of 13-15 and ICIs observed on CT. Out of 2,614 patients evaluated at any of six hospitals in PTRC dataset, 1,630 met the same inclusion criteria. Most (59.3%) patients were two years or older, male (63.6%), and presented with GCS scores of 15 (82.0%). The patients excluded from the analysis are shown in Figure S1 in the supplemental digital content (SDC). All patients in the PECARN cohort received CT scans for acute neuroimaging evaluation, whereas almost all patients (n=1,629; 99.9%) in the PTRC cohort received CT rather than MRI scans.

From the ED, 17 patients (1.0%) were discharged, while 596 (36.6%) were admitted to a short-stay or non-ICU floor; 954 (58.3%) were managed initially in an ICU, and 63 (3.9%) managed initially with surgical intervention. A total of 119 patients (7.3%) in the PTRC validation cohort experienced the composite outcome, including 113 patients (6.9%) who underwent neurosurgical intervention, 12 (0.7%) who had prolonged intubation for their head injury, and one patient (0.06%) who died from head injury. Among patients who underwent neurosurgical interventions in a more delayed fashion (i.e. not directly from the ED), most underwent either skull fracture elevation (n=34; 52%) or hematoma evacuation (n=31; 48%). Among those intubated longer than 24 hours due to head injury, 4 (33%) were intubated in the ED, 5 (42%) were taken from the ED directly to the operating room for intubation, and 3 (25%) were intubated in a delayed fashion.

KIIDS-TBI Model Derivation:

The KIIDS-TBI risk model is shown in Figure 1. Major risk factors included midline shift, depressed skull fracture, and epidural hematoma. Absent these factors, GCS score, and presence of subdural hematoma, extra-axial hematoma, or cerebral contusion further stratified lower risk patients. Patients were grouped into five risk levels based on the presence/absence of these findings, ranging from 0% to 27.9% risk in the PECARN derivation cohort. Among the 136 patients (16%) in the lowest risk level, the most common imaging findings were subarachnoid/intraventricular hemorrhage (48%), pneumocephalus (37%), and skull diastasis (15%). For purposes of clinical decision-making (i.e. level of care recommendations), we evaluated three cutoffs that distinguished patients recommended for a high level of care. Cutoff A would send patients in risk levels 2-5 to a high level of care, cutoff B would send risk levels 3-5, and cutoff C would only send patients in risk levels 4-5. The relationship between the three decision-making cutoffs and the five risk levels is displayed in Figure 1.

Model Validation:

The test performance of the three different decision-making cutoffs from the KIIDS-TBI model is shown in Table 3. All three cutoffs had high sensitivities—and correspondingly, small negative likelihood ratios. The most conservative approach, cutoff A, captured all 119/119 patients with the composite outcome, while cutoff B captured 115 (96.6%) and cutoff C captured 112 (94.1%). However, the specificity (26.3%) of cutoff A was notably lower than those for cutoffs B (67.4%) and C (81.3%). Reflecting a lower rate of the outcome (4.7%), the model showed slightly lower specificity (range 20.1%-80.7% across cutoffs A-C) and PPV (range 5.6%-18.7%) in children younger than two years. Otherwise, performance was similar across age groups (Table S1, SDC). The performance of the CHIIDA model in the validation cohort is shown in Table 4. Compared to the KIIDS-TBI model, the CHIIDA model lacked the most sensitive decision-making cutoff (A) and showed a decrease in sensitivity (81.5%) when using a score of more than five points to classify patients as high risk. Performance was otherwise the same or very similar between the models. Calibration plots of the KIIDS-TBI and CHIIDA models are shown in Figures S2a-S2b in the SDC, and likelihood ratios for each model are provided in Tables 3 and 4.

Risk Levels Versus Real-world Management Decisions:

Real-world post-ED dispositions (i.e., actual management decisions observed in the validation cohort) are stratified by KIIDS-TBI risk level and treating hospital in Figure 2. Within each KIIDS-TBI risk level, there was substantial variation in the proportion of patients actually admitted to a high level of care. Notably, in the lowest risk level, 3 of 6 centers admitted most patients to high levels of care. By comparison, in the highest risk level, the proportion of patients admitted to high levels of care ranged from 44% to 100% across the 6 study hospitals. In the validation dataset, 62% of patients were actually admitted to a high level of care, including 111 who experienced the composite outcome (sensitivity=93.3%). Among the 605 patients (38%) admitted to low levels of care, eight (1.3%) experienced the composite outcome (specificity 40.4%). Compared to this real-world practice, using decision cutoff A from the KIIDS-TBI model would increase the proportion of patients admitted to high levels of care (75.6%). By comparison, using cutoffs B and C would decrease the proportion admitted to high levels of care (37.2% and 24.2%, respectively).

Discussion:

In this study, we leveraged two large, multicenter datasets to develop and externally validate the KIIDS-TBI prediction model to risk-stratify children with mTBI and radiographic ICI. Using a recursive partitioning approach, we identified three decision-making cutoffs that could be used to guide level of care decisions. When applied to the external validation dataset, we found that these risk cutoffs effectively stratified patient risk of neurosurgical intervention, intubation for head injury, or death from head injury, forming the basis for the KIIDS-TBI CDS tool shown in Figure 3.

Several lines of evidence indicate that the current management of children with mTBI and radiographic ICI is not evidence-based and places some children at risk of harm. Previous evaluation of the PECARN dataset demonstrated that post-ED care setting assignment for such patients has been poorly aligned with patient risk.[4] Recently, a multicenter survey of North American neurotrauma providers indicated that more than 25% had experienced a child neurologically decline in the past year after initial post-ED admission to a low-acuity general floor. In the PTRC validation cohort, disposition decisions varied substantially across hospitals,

and many high-risk children were admitted to low acuity settings, and many low-risk patients were admitted to high acuity settings. This finding is consistent with evidence that individual physician decision-making remains a primary influence on post-ED care setting decisions for children with mTBI.[28] While close monitoring of high-risk patients remains of paramount importance for safe patient outcomes, universal ICU admission is neither practical nor advisable. Pediatric ICU beds are a limited resource and substantially increase the cost of hospital admission.[6-8] Additionally, ICU admission is associated with high rates of delirium in children,[29,30] constitutes a significant emotional burden for patients and families,[31,32] and may predispose to other overtreatment complications.

The first CDS tool for disposition based on a large multicenter cohort,[4] the CHIIDA model was an important advance in the evidence-based management of children with mTBI and ICI. Nonetheless, with a maximum sensitivity of 93-94% in past studies, the CHIIDA model may have limited utility at hospitals lacking non-ICU floor units experienced in caring for neurotrauma patients. Seeking to develop a more sensitive model with broader potential applications, this study developed and externally validated the KIIDS-TBI model. This model identified a subset of patients at very low risk of the composite outcome (cutoff A; 100% sensitivity). At the same time, including two other decision-making cutoffs (B and C) maintained excellent sensitivity (> 94%) but offered substantially higher specificity. Corresponding to these differences, cutoff A would have characterized 75.6% of patients as high risk, compared to 37.2% and 24.2% for cutoffs B and C, respectively. By comparison the CHIIDA model lacked the sensitivity offered by cutoff A and showed the same or slightly worse performance compared to cutoffs B and C, demonstrating the incremental improvements offered by the KIIDS-TBI model.

Considering the relative tradeoffs across risk cutoffs, we proposed a final CDS tool (Figure 3). In this final tool, patients with high-risk features (midline shift, depressed skull fractures greater than the width of the skull, or epidural hematomas) represented 26% of the population and should typically be triaged to a high acuity setting. Other patients are generally at low risk (< 3%) and can be further stratified based on GCS score and additional imaging findings. Notably, these CDS components closely reflected results from a large survey of neurotrauma providers. In

that survey, high-risk model predictors were listed as more important factors considered by clinicians when determining the need for ICU admission.[9] This consistency and face validity supports the likelihood that the CDS tool will be acceptable to clinicians, while providing an evidence-based framework that improves safety and reduces existing variations in practice. Patients without any risk factors (cutoff A) represent a uniquely low risk group that warrants particular attention. In the combined development and validation cohorts including 2,469 patients, no patients in this group experienced the composite outcome (95% CI 0-0.7%). Nonetheless, with specificity of 26%, this cutoff is likely too conservative to be useful at many large trauma centers. Consequently, this cutoff may be most valuable in those trauma centers where nearly all patients are currently admitted to an ICU, and of greater long-term potential, in community hospital settings. To date, some groups have attempted to identify children with mTBIs and radiographic ICI that do not require transfer to a tertiary pediatric trauma center,[33,34] and a small proportion of these children (< 5%) are already discharged from the ED. However, such practices are not routine and evidence guiding these decisions is lacking. While each hospital's capabilities and proximity to a trauma center should be considered, some of these very low risk patients might be observed in community hospital settings, a point of considerable importance in the highly distributed United States trauma system.[6,35] Future prospective validation may help justify this application or, similarly, using the KIIDS-TBI model to identify children safe for discharge after extended ED observation.

This study has several limitations. First, the data for the validation cohort were gathered retrospectively, which may have limited the accuracy with which some variables were captured. However, most model predictors were objective imaging findings, and study outcomes represented major events that were well documented in the medical record, limiting any bias from the retrospective review. Second, the risk model did not evaluate the severity of imaging findings (e.g. hematoma size). While this approach potentially broadens the decision tool's usability among clinicians less comfortable with detailed neuroimaging evaluations, the lack of quantitative measures could have limited predictive performance. This possibility should be explored in future work. Third, nearly all patients included in both datasets had acute CT imaging to identify their ICI. Given that acute MRI may have increased sensitivity for identifying some types of ICI,[36,37] future studies will be needed to verify model performance in

children initially evaluated with MRI. Fourth, because the public use PECARN dataset did not report the number of hours between injury to ED presentation, we could not evaluate that variable as a potential predictor for the KIIDS-TBI model. However, in the PTRC dataset, patients with and without the composite outcome both presented to the ED in a similar timeframe (median 1 hour for both), suggesting that hours from injury to ED presentation would be unlikely to impact our results. Finally, the model was not designed to predict non-neurological outcomes that could impact patient management. Although this limitation should not minimize potential safety benefits (i.e. focusing attention on patients at high risk), observed reductions in resource use may be diminished when social and non-cranial concerns are considered.

Conclusion:

In this largescale, multicenter development and external validation, the KIIDS-TBI CDS tool showed high sensitivity and moderate specificity in detecting clinically relevant outcomes for children with mTBIs and radiographic ICI. Additionally, the tool offers the first rigorous evidence identifying a subset of very low risk patients who may avoid routine transfer to a pediatric trauma center in some circumstances. Future work should focus on developing implementation strategies, demonstrating the tool's influence on care delivery, and identifying potential unintended consequences that could emerge during clinical use.[38] A prospective implementation trial is now indicated to test the impact of the CDS tool on patient safety and resource use.

References:

1. Mannix R, O'Brien MJ, Meehan WP, 3rd. The epidemiology of outpatient visits for minor head injury: 2005 to 2009. Neurosurgery 2013;73:129-34; discussion 34.

2. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA2003.

3. 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.

4. Greenberg JK, Yan Y, Carpenter CR, et al. Development and Internal Validation of a Clinical Risk Score for Treating Children With Mild Head Trauma and Intracranial Injury. JAMA Pediatr 2017;171:342-9.

5. Babl FE, Borland ML, Phillips N, et al. Accuracy of PECARN, CATCH, and CHALICE head injury decision rules in children: a prospective cohort study. Lancet 2017;389:2393-402.

6. Wang HE, Yealy DM. Distribution of specialized care centers in the United States. Ann Emerg Med 2012;60:632-7 e7.

7. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010;38:65-71.

8. Patient Pricing Information. 2020. (Accessed September 26, 2020, at http://www.uhhospitals.org/rainbow/patients-and-visitors/billing-insurance-and-medical-records/patient-pricing-information.)

9. Greenberg JK, Jeffe DB, Carpenter CR, et al. North American survey on the post-neuroimaging management of children with mild head injuries. J Neurosurg Pediatr 2018;23:227-35.

10. Greenberg JK, Stoev IT, Park TS, et al. Management of children with mild traumatic brain injury and intracranial hemorrhage. J Trauma Acute Care Surg 2014;76:1089-95.

11. Burns EC, Burns B, Newgard CD, et al. Pediatric minor traumatic brain injury with intracranial hemorrhage: identifying low-risk patients who may not benefit from ICU admission. Pediatr Emerg Care 2019;35:161-9.

12. Neumayer KE, Sweney J, Fenton SJ, Keenan HT, Flaherty BF. Validation of the “CHIIDA” and Application for PICU Triage in Children with Complicated Mild Traumatic Brain Injury. J Pediatr Surg 2019.

13. Jain R, Karnik H, Kotwani D. Utility and Predictive Value of CHIDA Score in Pediatric Traumatic Brain Injury: A Pilot Study. Journal of Neuroanaesthesiology and Critical Care 2018;5:A019.

14. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol 2005;58:475-83.

15. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. PECARN, 2015. (Accessed October 2, 2020, 2016, at http://www.pecarn.org/studyDatasets/StudyDetails?studyID=4.)

16. Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet 2009;374:1160-70.

17. Burns EC, Burns BS, Newgard CD, et al. Pediatric Minor Traumatic Brain Injury with Intracranial Hemorrhage: Identifying Low Risk Patients Who May Not Benefit From ICU Admission. Pediatr Emerg Care 2016;In Press.

18. Noje C, Jackson EM, Nasr IW, et al. Trauma bay disposition of infants and young children with mild traumatic brain injury and positive head imaging. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2019;20:1061.

19. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.

20. Lewis LM, Schloemann DT, Papa L, et al. Utility of serum biomarkers in the diagnosis and stratification of mild traumatic brain injury. Acad Emerg Med 2017;24:710-20.

21. Holmes JF, Lillis K, Monroe D, et al. Identifying children at very low risk of clinically important blunt abdominal injuries. Ann Emerg Med 2013;62:107-16. e2.

22. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-Spine Rule for Radiography in Alert and Stable Trauma Patients. JAMA 2001;286:1841-8.

23. Kuppermann N, Dayan PS, Levine DA, et al. A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. JAMA pediatrics 2019;173:342-51.

24. Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. Ann Emerg Med 1999;33:437-47.

25. Kuhn M, Johnson K. Applied Predictive Modeling. New York: Springer; 2013.

26. R: A Language and Environment for Statistical Computing. 4.0.1 ed. Vienna, Austria: R Foundation for Statistical Computing; 2020.

27. Therneau T, Atkinson B. rpart: Recursive Partitioning and Regression Trees. 2019.

28. Greenberg JKJ, D. B.; Carpenter, C. R.; Yan, Y.; Pineda, J. A.; Lumba-Brown, A.; Keller, M. S.; Berger, D.; Bollo, R. J.; Ravindra, V. M.; Naftel, R. P.; Dewan, M. C.; Shah, M. N.; Burns, E. C.; O'Neill, B. R.; Hankinson, T. C.; Whitehead, W. E.; David Adelson, P.; Tamber, M. S.; McDonald, P. J.; Ahn, E. S.; Titsworth, W.; West, A. N.; Brownson, R. C.; Limbrick, D. D. North American survey on the post-neuroimaging management of children with mild head injuries. J Neurosurg Pediatr 2019;23:227-35.

29. Traube C, Silver G, Gerber LM, et al. Delirium and Mortality in Critically Ill Children: Epidemiology and Outcomes of Pediatric Delirium. Crit Care Med 2017;45:891-8.

30. Alvarez RV, Palmer C, Czaja AS, et al. Delirium is a Common and Early Finding in Patients in the Pediatric Cardiac Intensive Care Unit. J Pediatr 2018;195:206-12.

31. Nelson LP, Gold JI. Posttraumatic stress disorder in children and their parents following admission to the pediatric intensive care unit: a review. Pediatr Crit Care Med 2012;13:338-47.

32. Colville G, Darkins J, Hesketh J, Bennett V, Alcock J, Noyes J. The impact on parents of a child's admission to intensive care: integration of qualitative findings from a cross-sectional study. Intensive Crit Care Nurs 2009;25:72-9.

33. Azim AJ, F. S.; Rhee, P.; O'Keeffe, T.; Tang, A.; Vercruysse, G.; Kulvatunyou, N.; Latifi, R.; Joseph, B. Big for small: Validating brain injury guidelines in pediatric traumatic brain injury. J Trauma Acute Care Surg 2017;83:1200-4.

34. Tallapragada KP, R. S.; Dexter, M. Paediatric mild head injury: is routine admission to a tertiary trauma hospital necessary? ANZ J Surg 2018;88:202-6.

35. Ahmed A-K, Duhaime A-C, Smith TR. Geographic proximity to specialized pediatric neurosurgical care in the contiguous United States. 2018;21:434.

36. Lindberg DM, Stence NV, Grubenhoff JA, et al. Feasibility and accuracy of fast MRI versus CT for traumatic brain injury in young children. Pediatrics 2019;144.

37. Shope C, Alshareef M, Larrew T, et al. Utility of a pediatric fast magnetic resonance imaging protocol as surveillance scanning for traumatic brain injury. Journal of Neurosurgery: Pediatrics PED 2021:1.

38. Ash JS, Sittig DF, Campbell EM, Guappone KP, Dykstra RH. Some unintended consequences of clinical decision support systems. AMIA Annual Symposium Proceedings; 2007: American Medical Informatics Association. p. 26.

Supplemental Information linked to the online version of the paper at Wiley-Blackwell:

- Figures S1, S2
- Table S1

Figure Legends:

Figure 1: The recursive partitioning model used to create the KIIDS-TBI tool. Numbers in each oval reflect the number of outcome events out of the number "at risk" at each stage of the

tree. Risk estimates are from the PECARN (derivation) cohort. Three different decision-making cutoffs for distinguishing high-risk patients are shown, where "high-risk" refers to the patients in risk levels above each cutoff.

Figure 2: The proportion of patients actually admitted to a high level of care from the ED (i.e., real-world outcome) stratified by KIIDS-TBI risk level. Results are shown separately for each hospital participating in the PTRC validation dataset.

Figure 3: The KIIDS-TBI clinical decision support tool for managing children with mTBI and intracranial injuries. Risk estimates are based on the combined derivation and validation cohorts.

Table 1: Potential predictors considered during decision tool development.

Clinical variables

- Post-traumatic seizure
- Non-cranial significant injury
- Severe mechanism of injury*
- Post-traumatic vomiting
- GCS score
- Patient age

Imaging Variables

- Cerebellar hemorrhage
- Cerebral contusion/intraparenchymal hemorrhage
- Epidural hematoma
- Extra-axial hematoma**
- Intraventricular hemorrhage
- Subarachnoid hemorrhage
- Subdural hematoma
- Traumatic infarction
- Skull diastasis
- Diffuse axonal injury
- Herniation
- Shear injury
- Sigmoid sinus thrombosis
- Midline shift
- Pneumocephalus
- Non-depressed skull fracture
- Depressed skull fracture

- Cerebral edema

*Defined as a motor vehicle collision with patient ejection, death of a passenger, or rollover; pedestrian or bicyclist without helmet struck by a motor vehicle; falls greater than 5 feet (children > 2 years) or 3 feet (children < 2 years); or head struck by a high-velocity object.[16]

**Extra-axial hematoma refers to a hemorrhage that could not be distinguished as either subdural or epidural.

Table 2: Characteristics of the patients included in the PECARN derivation cohort as well as the PTRC external validation cohort. Values represent No. (%) unless indicated otherwise.

	PECARN Cohort		PTRC Cohort	
	No Composite Outcome (n=766)	Composite Outcome (n=73)	No Composite Outcome (n=1,511)	Composite Outcome (n=119)
Median age (IQR)	5 (12)	7 (11)	3 (10)	5 (7)
Age > 2 years	497 (64.9)	52 (71.2)	878 (58.1)	89 (74.9)
Median (IQR) hours from injury to ED	NR	NR	1 (2)	1 (3)
Sex				
Male	494 (64.5)	46 (63.0)	963 (63.7)	73 (61.3)
Female	272 (35.5)	27 (37.0)	548 (36.3)	46 (38.7)
Mechanism of injury				
Fall	362 (47.3)	26 (35.6)	780 (53.8)	56 (47.1)
Struck by moving object	35 (4.6)	8 (11.0)	87 (6.0)	16 (13.4)
Motor vehicle collision	83 (10.8)	11 (15.1)	174 (12.0)	11 (9.2)
Other	286 (37.3)	28 (38.4)	408 (28.2)	36 (30.3)
Presenting GCS score				
13	52 (6.8)	11 (15.1)	64 (4.2)	9 (7.6)
14	146 (19.1)	19 (26.0)	198 (13.1)	22 (18.5)
15	568 (74.2)	43 (58.9)	1249 (82.7)	88 (73.9)
Non-cranial significant injury	142 (18.6)	18 (25.0)	174 (12.9)	14 (13.0)
Severe mechanism of injury	293 (38.9)	34 (46.6)	488 (35.7)	50 (45.9)

Concern for non-accidental trauma	NR	NR	164 (10.9)	13 (10.9)
History of loss of consciousness	270 (39.7)	25 (41.7)	372 (27.6)	23 (21.5)
History of post-traumatic seizure	29 (4.0)	4 (5.9)	90 (6.3)	8 (7.0)
CT Findings*				
Subdural hematoma	194 (25.3)	13 (17.8)	561 (37.1)	13 (10.9)
Subarachnoid hemorrhage	156 (20.4)	7 (9.6)	442 (29.3)	20 (16.8)
Epidural hematoma	81 (10.6)	27 (37.0)	166 (11.0)	56 (47.1)
Contusion	239 (31.2)	28 (38.4)	222 (14.7)	16 (13.4)
Skull fracture depressed > the width of the skull*	103 (13.8)	34 (46.6)	80 (5.3)	63 (52.9)
Midline shift	36 (4.7)	22 (30.1)	58 (3.8)	35 (29.4)
Extra-axial hematoma	135 (17.6)	12 (16.4)	142 (9.4)	10 (8.4)
Pneumocephalus	143 (18.7)	20 (27.4)	284 (18.8)	29 (24.3)
Linear fracture	315 (42.3)	25 (34.2)	584 (38.6)	20 (16.8)
ED Disposition				
Home	68 (8.9)	0 (0)	17 (1.1)	0 (0)
Short-stay (< 24 hours)	71 (9.3)	1 (1.4)	35 (2.3)	0 (0)
General ward	311 (40.8)	11 (15.1)	553 (36.6)	8 (6.7)
ICU	274 (35.9)	35 (47.9)	891 (59.0)	63 (52.9)
Operating room	5 (0.7)	24 (32.9)	15 (1.0)	48 (40.3)
Other	34 (4.5)	2 (2.7)	0 (0)	0 (0)
Median (IQR) length of hospital stay	NR	NR	2 (2)	3 (3)
Median (IQR) length of ICU stay	NR	NR	1 (2)	2 (2)

NR=not reported.

IQR=interquartile range.

*Percentages do not add to 100 because some participants had multiple imaging findings.

[**]In the PECARN (derivation) dataset, this variable was defined based on radiology report descriptions of fracture depression.

Table 3: Test characteristics comparing three decision-making cutoffs from the KIIDS-TBI model evaluated in the PTRC validation dataset.

	Observed Outcomes*	Cutoff A	Cutoff B	Cutoff C
High acuity disposition				
Composite outcome	111	119	115	112
No composite outcome	891**	1113	492	283
Low acuity disposition				
Composite outcome	8	0	4	7
No composite outcome	605	398	1019	1228
Sensitivity (95% CI)	93.3% (87.2-97.1)	100% (96.9-100)	96.6% (91.6-99.1)	94.1% (88.3-97.6)
Specificity (95% CI)	40.4% (37.9-43.0)	26.3% (24.1-28.6)	67.4% (65.0-69.8)	81.3% (79.2-83.2)
PPV (95% CI)	11.1% (9.2-13.2)	9.7% (8.1-11.4)	18.9% (15.9-22.3)	28.4% (24.0-33.1)
NPV (95% CI)	98.7% (97.4-99.4)	100% (99.1-100)	99.6% (99.0-99.9)	99.4% (98.8-99.8)
LR+ (95% CI)	1.57 (1.47-1.67)	1.36 (1.32-1.40)	2.97 (2.74-3.21)	5.03 (4.48-5.63)
LR- (95% CI)	0.17 (0.08-0.33)	0.00	0.05 (0.02-0.13)	0.07 (0.04-0.15)

PPV=positive predictive value; NPV=negative predictive value. LR+=positive likelihood ratio. LR-=negative likelihood ratio. Note, the 95% CI of the LR- is not defined for threshold 1.

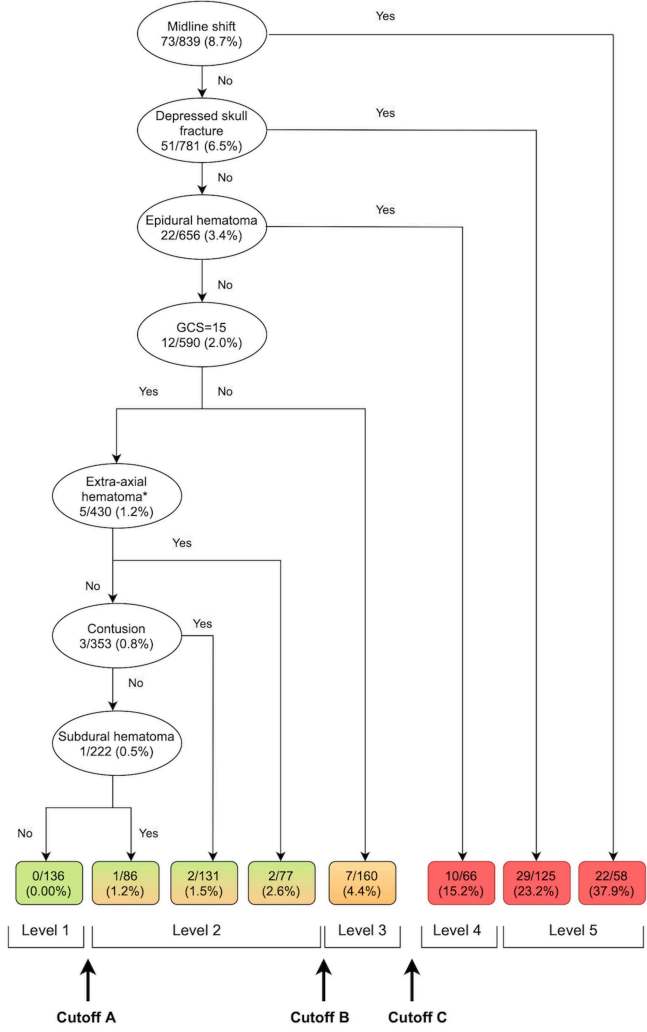
* Actual post-ED disposition decisions and composite outcome events observed in the PTRC validation cohort.

** n=15 patients sent to the operating room for reasons other than their head injury were excluded from this estimate to avoid falsely decreasing specificity and PPV.

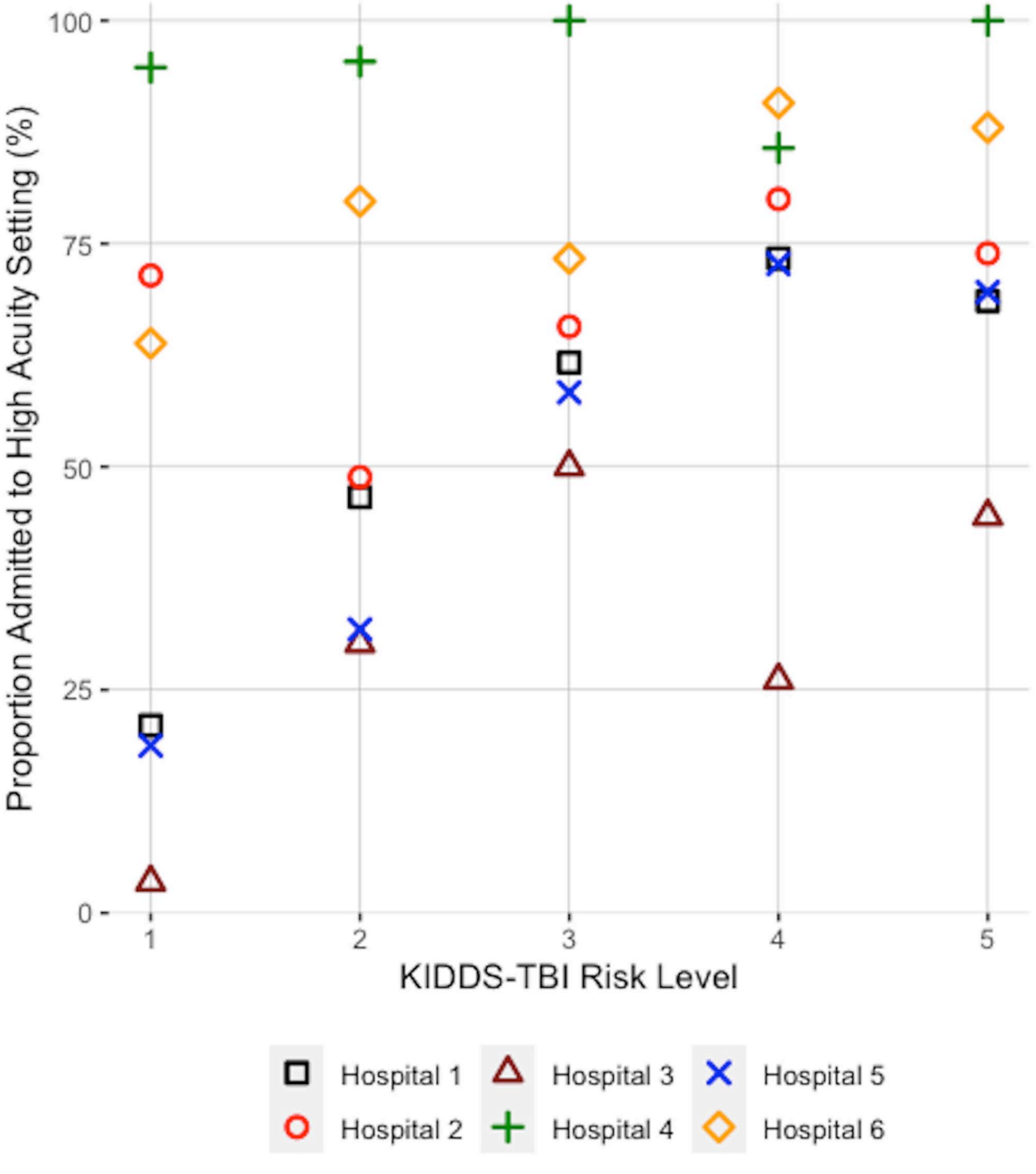
Table 4: Test characteristics of the CHIIDA model using cutoffs of > 0 points (i.e., any risk factor present), > 2 points, or > 5 points to classify patients as high risk. Of note, using the CHIIDA score with a cutoff of > 0 points to classify high risk patients is identical to using cutoff B from the KIIDS-TBI model shown in Table 3.

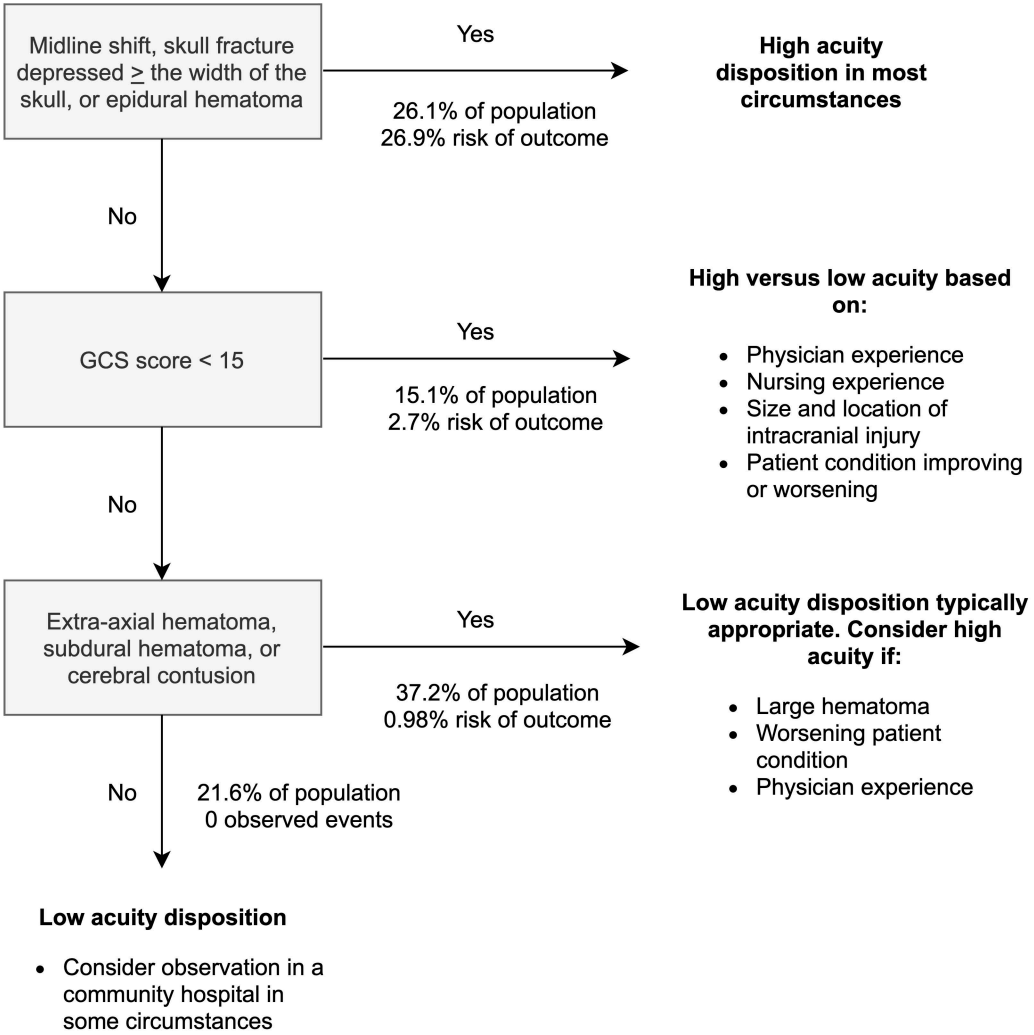
High acuity disposition	> 0 points	> 2 points	> 5 points
Composite outcome	115	112	97
No composite outcome	492	283	158
Low acuity disposition			
Composite outcome	4	7	22
No composite outcomes	1019	1228	1353
Sensitivity (95% CI)	96.6% (91.6-99.1)	94.1% (88.3-97.6)	81.5 (73.4-88.0)
Specificity (95% CI)	67.4% (65.0-69.8)	78.0 (75.8-80.0)	89.5 (87.9-91.0)
PPV (95% CI)	18.9% (15.9-22.3)	25.2 (21.2-29.5)	38.0 (32.1-44.3)
NPV (95% CI)	99.6% (99.0-99.9)	99.4% (98.8-99.8)	98.4 (97.6-99.0)
LR+ (95% CI)	2.97 (2.74-3.21)	4.27 (3.85-4.74)	7.80 (6.57-9.25)
LR- (95% CI)	0.05 (0.02-0.13)	0.08 (0.04-0.15)	0.21 (0.14-0.30)

PPV=positive predictive value; NPV=negative predictive value. LR+=positive likelihood ratio. LR-=negative likelihood ratio.



*Extra-axial hematoma refers to a hemorrhage that could not be distinguished as either subdural or epidural.


Proportion Admitted to High Acuity Setting (%)
100
75
50
25
0
1
2
3
4
5
KIDDS-TBI Risk Level
Hospital 1
Hospital 2
Hospital 3
Hospital 4
Hospital 5
Hospital 6


Midline shift, skull fracture depressed ≥ the width of the skull, or epidural hematoma
Yes
26.1% of population
26.9% risk of outcome
High acuity disposition in most circumstances
No
GCS score < 15
Yes
15.1% of population
2.7% risk of outcome
High versus low acuity based on:
Physician experience
Nursing experience
Size and location of intracranial injury
Patient condition improving or worsening
No
Extra-axial hematoma, subdural hematoma, or cerebral contusion
Yes
37.2% of population
0.98% risk of outcome
Low acuity disposition typically appropriate. Consider high acuity if:
Large hematoma
Worsening patient condition
Physician experience
No
21.6% of population
0 observed events
Low acuity disposition
Consider observation in a community hospital in some circumstances