Clinical Significance of Nadir Hemoglobin in Predicting Neurologic Outcome in Infants With Abused Head Trauma

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Traumatic brain injury (TBI) is a leading cause of pediatric morbidity and mortality and is categorized as abusive head trauma (AHT) and accidental head injury. A retrospective chart review of 124 children aged <1 year diagnosed with TBI were analyzed. Outcomes were evaluated at discharge and 6 months later by using the Pediatric Cerebral Performance Category (PCPC) Scale. The receiver operating characteristic (ROC) curve was applied to determine the cutoff values for hemoglobin (HB) levels. In the study, 50 infants (40.3%) achieved a favorable neurologic outcome (PCPC ≤ 2) and 74 (59.7%) had poor neurologic outcomes (PCPC ≥ 3). Infants with poor neurologic outcomes had lower HB on admission and nadir HB (p < 0.05). Based on multivariate logistic regression analysis, the nadir HB was a predictor of poor neurologic outcomes at discharge and 6 months later in both AHT and accidental head injury. Nadir HB had the largest area under the ROC curve for predicting poor neurologic outcomes. We determined the appropriate cutoff value of nadir HB as 9.35 g/dl for predicting neurologic outcomes in infants with TBI. Furthermore, the cutoff value of nadir HB in predicting poor neurologic outcomes in infants caused by AHT and accidental head injury were taken as 9.36 and 8.75 g/dl, respectively.

Keywords: brain injury, trauma, intracranial hemorrhage, nadir, hemoglobin, infant

INTRODUCTION

Physical abuse and neglect are the major types of child maltreatment and affect an increasing number of children in the world (1). Despite the efforts of child protection medical services, physical abuse and neglect still remain important and serious problems. Based on the data of the National Child Abuse and Neglect Data System (NCANDS) in the United States of America, the number of fatalities fluctuated in the past 5 years. Younger children are the most frequent victims of child maltreatment because of their dependency and inability to protect themselves. Children aged <3 years old accounted for about three-quarters of all fatalities, especially infants (<1-year-old)
who accounted for half of all fatalities in the USA in 2015 due to child maltreatment (2). In the infant group suffering from child maltreatment, the primary cause of death is traumatic brain injury (TBI). In general TBI can be classified as abusive head trauma (AHT) and accidental head injury (3–5). Intracranial hemorrhage is frequent after TBI in infants due to the highly vascularized nature of the brain and is associated with poor outcomes. About two thirds of AHT and quarter of accidental head injury have the feature of subdural hemorrhage (SDH). And epidural hemorrhages (EDH) were significantly associated with accidental head injury rather than AHT (17 vs. 4 percent, respectively) (6). Therefore, it is important to analyze the risk factors associated with morbidity and mortality in infants with traumatic intracranial hemorrhage to develop guidelines for adequate treatment to prevent further complications such as higher brain dysfunction.

In adults with intracranial hemorrhage caused by TBI or stroke, several risk factors such as the volume of intracranial hemorrhage, the score on the Glasgow Coma Scale (GCS) on admission, or older age are predictors of poor outcomes. In particular, the common laboratory examination of HB can be used as a predictor for outcome, with low HB indicating poor functional outcomes after non-traumatic brain hemorrhage at discharge and at 3 months (7, 8). The pathophysiology of anemia in TBI or stroke is evidence of primary blood loss. The severe impact of anemia on brain function in various pathological conditions is somewhat unclear. It may be that lower HB impaired the function of brain oxygenation (9). However, evidence about the utility of HB in pediatric intracranial hemorrhage is limited, and its use is not endorsed in predicting outcomes of pediatric intracranial hemorrhage. The main objective of this study was to determine whether the HB level in traumatic intracranial hemorrhagic infants is associated with poor neurologic outcomes. Our hypothesis was that low HB is associated with increased mortality or poor neurologic outcomes.

**Methods**

**Study Design**

From January 2006 to 2017, we retrospectively collected data from infants aged <1 years old with intracranial hemorrhage (ICH) caused by TBI who were admitted to the pediatric intensive care unit (PICU) via the emergency department (ED) or outpatient department (OPD). A total of 124 infants with ICH confirmed by brain computed tomography (CT) at admission were included in this study. The study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital. All methods were performed in accordance with the relevant guidelines and regulations.

The data were collected, reviewed, de-identified, and anonymously analyzed by the authors, and the Ethics Committee waived the requirement for informed consent because of the anonymized nature of the data, and scientific purpose of the study.

**Study Setting and Patient Selection**

The setting in our study was a tertiary medical center receiving cases transferred from local clinics, regional hospitals, and social and politic institutions (child protection agency subordinated by the government). The PICU of our hospital was a tertiary ICU with 29 beds for hospitalized patients aged <18 years. In our study, all the victims with ICH caused by child maltreatment by the definition of World Health Organization (WHO) (10) were admitted to the PICU. Victims with accompanying internal bleeding from other organs (except intracranial bleeding) were excluded. After review of the clinical history, physical examination findings, and past medical charts, TBI was categorized as AHT and accidental head injury according to predefined criteria (Table 1) (3–5). All the victims of AHT and accidental head injury were viewed by the child protection team. Our hospital was a Child Protection Medical Service Demonstration Center which consisting of well-trained medical doctors, nursing staff, and social workers for identifying abused and neglected victims.

**Study Protocol**

Information related to the cases of AHT and accidental head injury, including age (months), gender, initial presentations, Glasgow Coma Score (GCS), injury severity score (ISS), imaging examinations, length of stay in hospitals, and ICUs, laboratory data such as hemoglobin (HB) levels, neurologic outcomes, and mortality were obtained from the social welfare reporting system and medical records. Admission of victims to the PICU may indicate an urgent clinical condition requiring critical care following the guidelines of the Society of Critical Care Medicine (11), meeting at least one of its defined criteria. Rotterdam scoring system was used in the study to grade acute TBI on the basis of CT findings. It included four independently scored elements such as degree of basal cistern compression, degree of midline shift, traumatic subarachnoid, or intraventricular hemorrhage, and epidural hematoma (12). Neurologic outcome at discharge was evaluated by pediatric neurologists using the

| TABLE 1 | Classification scheme of head injuries as abuse or accident. |
|---|---|
| AHT: |
| a. Witnessed inflicted head injury |
| b. Confession of abuse by perpetrator |
| c. History of traumatic event which isn’t compatible with injury severity |
| d. Physical injuries consistent only with inflicted injuries (eg, old and new lesions, pattern bruises) |
| e. No history resulting in patient’s head injury |
| Accidental Head Injury: |
| a. History of traumatic event which is compatible with injury severity |
| b. Witnessed accident (eg, falls, sports-related injuries, isolated or unique event) |
| c. Absence of physical injuries which are consistent only with inflicted injuries (eg, old and new lesions, pattern bruises) |
| d. Vehicle accidents |

AHT, abusive head trauma.
Association Between HB Levels, Clinical Risk Factors, and Poor Outcomes

We performed a logistic regression model to identify indicators for predicting poor neurologic outcome at discharge and 6 months after discharge, and found that initial GCS score, ISS, nadir HB and Rotterdam CT score were all significant factors (Table 3). In the final model, only nadir HB remained as an independent predictor of poor neurologic outcome at discharge, but nadir HB and the initial GCS score were predictors of poor neurologic outcome at 6 months after discharge in the abused group. In the group with accidental head injury, only nadir HB appeared as an independent predictor for poor neurologic outcome at 6 months after discharge. And the detected mean time of nadir HB was 3.6 ± 3.5h after admission. In-hospital mortality was 9.7% (12 infants) (Table 4). Based on the results of univariate analysis, the initial GCS score, nadir HB and Rotterdam CT score were associated with in-hospital mortality. In the multivariate logistic regression model, only the initial GCS score (OR 0.528, 95% CI 0.389–0.716, p < 0.001) remained an independent predictor for in-hospital mortality (Table 5). Outcome at 6 months was available for 112 (90.3%) infants; and 12 infants died during admission. The nadir HB levels showed significant differences between groups with favorable and poor neurologic outcomes in the group with AHT (Figure 1) and accidental head injury (Figure 2) at discharge and 6 months after discharge (both p < 0.05).

Nadir HB had the highest area under the ROC curve (AUC) for predicting poor neurologic outcomes in all victims (Figure 3A). When divided into group with AHT (Figure 3B) and accidental head injury (Figure 3C), the nadir HB also had the largest AUC for predicting poor neurologic outcomes in each group. The AUCs of nadir HB, mean HB, and admission HB for predicting good or poor neurologic outcome in the all victims, victims with AHT and accidental head injury were calculated. The AUC of nadir HB was 0.884 (95% CI, 0.827–0.941) in the all group; 0.839 (95% CI, 0.718–0.96) in the group with AHT; and 0.919 (95% CI, 0.808–1) in the group with accidental head injury which were all significantly higher than both admission HB and mean HB in all groups (all p < 0.001) (Table 6). The best cutoff values of nadir HB in predicting poor neurologic outcomes are shown in Table 7. We identified nadir HB levels of 9.35 g/dl in the cohort, 9.36 g/dl in the group with AHT and 8.75 g/dl in the group with accidental head injury to predict poor neurologic outcomes at discharge.

In addition, we compared RBC transfused and non-transfused patients in Table 8 which reporting that the RBC transfused group had more critical initial presentations and worse outcomes including lower initial GCS, higher ISS, more episodes of hypotension, lower
### TABLE 2 | Correlation between poor outcome and characteristics in the group with AHT and accidental head injury.

| Characteristics                        | AHT (n = 78) | P-value | Accidental head injury (n = 46) | P-value |
|----------------------------------------|-------------|---------|---------------------------------|---------|
|                                        | PCPC 1–2 | PCPC 3–6 |                                 |         |
| Patients, n (%)                        | 12 (15.3) | 66 (84.7) | 38 (82.6) | 8 (17.4) | 0.18 |
| Age month, mean (SD)                   | 5.9 ± 4.3 | 5.1 ± 3.3 | 6.4 ± 3.7 | 8.1 ± 4.3 | 0.92 |
| Sex (male, n, %)                       | 9 (75) | 31 (46.9) | 21 (55.2) | 4 (50) | 0.92 |
| LOS in ICU, median (IQR)               | 4 (3–11) | 13 (7–23) | 4 (3–7) | 9 (6–11) | 0.024* |
| Mortality, n (%)                       | 0 | 8 (12.1) | 0 | 1 (12.5) | <0.01* |
| Initial presentation                   |           |         |                                 |         |
| Initial GCS, median (IQR)              | 14 (11–15) | 10 (6–13) | 15 (15–15) | 8 (6–9) | <0.01* |
| Initial ISS, mean (SD)                 | 21.5 ± 4.7 | 30.3 ± 18.3 | 15.3 ± 3.3 | 23.4 ± 20.9 | 0.15 |
| Hypotension, n (%)                     | 0 (0) | 14 (21.2) | 0 (0) | 2 (25) | 0.028* |
| Retinal hemorrhage, n (%)              | 7 (58.3) | 45 (68.1) | 1 (2.8) | 2 (25) | 0.12 |
| Brain CT findings, n (%)               |           |         |                                 |         |
| SDH                                    | 9 (75) | 47 (71.2) | 18 (47.3) | 7 (87.5) | 0.09 |
| EDH                                    | 1 (8.3) | 0 | 13 (34.2) | 3 (37.5) | 0.8 |
| SAH                                    | 2 (16.6) | 22 (33.3) | 6 (15.7) | 3 (37.5) | 0.35 |
| IVH                                    | 0 | 7 (10.6) | 1 (2.8) | 1 (12.5) | 0.77 |
| DAI                                    | 2 (1.6) | 14 (21.2) | 1 | 1 (12.5) | 0.38 |
| Skull Fracture, n (%)                  | 1 (8.3) | 8 (12.1) | 16 (42.1) | 2 (25) | 0.61 |
| Rotterdam CT score, median (IQR)       | 2 (2–3) | 3 (2–4) | 2 (2–3) | 3 (2–3) | 0.02* |
| Laboratory findings, median (IQR)      |           |         |                                 |         |
| Admission Hb g/dL                      | 10.3 (9.5–11.3) | 9 (7.6–9.9) | 10.7 (9.4–12.1) | 8.5 (7.6–8.8) | <0.01* |
| Mean Hb g/dL                           | 10.4 (9.5–11) | 10.2 (9.3–10.8) | 10.9 (10.2–12) | 8.7 (8.6–9.5) | <0.01* |
| Nadir Hb g/dL                          | 10.3 (9–10.4) | 8.1 (7.3–9.1) | 10.4 (9.2–11.9) | 7.2 (6.3–7.6) | <0.01* |
| Acute Neurosurgical Interventions, n (%) | 8 (66.6) | 43 (65.1) | 11 (28.9) | 6 (87.5) | 0.01* |
| Burr hole drainage                     | 7 (58.3) | 39 (59.1) | 5 (13.1) | 3 (37.5) | 0.25 |
| External ventricular drainage          | 1 (8.3) | 3 (4.5) | 1 (2.8) | 1 (12.5) | 0.77 |
| Intracranial pressure monitor         | 0 | 11 (16.6) | 0 | 1 (12.5) | 0.38 |
| Craniotomy and hematoma evacuation     | 2 (16.6) | 4 (6.1) | 5 (13.1) | 2 (25) | 0.76 |
| Decompressive craniectomy              | 0 | 1 (1.5) | 0 | 0 | – |
| Treatment, n (%)                       |           |         |                                 |         |
| Mechanical ventilation                 | 4 (33.3) | 40 (60.6) | 2 (5.9) | 4 (50) | <0.01* |
| RBC transfusion                        | 3 (25) | 47 (71.2) | 5 (13.2) | 6 (75) | <0.01* |

*: %; *: p < 0.05 statistic significant; AHT, abusive head trauma; ICU, intensive care unit; LOS, length of stay; GCS, glasgow coma scale; ISS, injury severity score; SDH, subdural hemorrhage; EDH, epidural hemorrhage; SAH, subarachnoid Hemorrhage; IVH, intraventricular Hemorrhage; DAI, diffuse axonal injury; Hb, Hemoglobin.

admission HB, nadir HB, and higher percentage of poor neurologic outcomes.

**DISCUSSION**

Low HB is a common complication in patients with intracranial hemorrhage (13). In adults with ICH, low HB levels and initial levels of consciousness may be associated with poor functional outcome (7, 14, 15). Initial GCS scores related to poor functional outcome have been reported in some studies (16, 17), but few related studies focused on this field in pediatric cases. We believe that our study is the first to analyze and report the role of nadir HB in predicting neurologic outcomes in infants with traumatic ICH, and to identify how low HB levels may be used as a predictor for poor neurologic outcome in infants. In this study, we found that nadir HB was a more powerful...
AHT

Initial GCS 0.910 (0.721–1.126) 0.361 (0.653–0.994) 0.044*

Injury severity score 1.058 (0.908–1.232) 0.47 (0.877–1.238) 0.642

Nadir HB (g/dl) 0.332 (0.156–0.707) 0.004* (0.205–0.709) 0.002*

Rotterdam CT score 2.351 (0.872–7.391) 0.13 (0.639–4.475) 0.29

Accidental head injury

Initial GCS 0.532 (0.249–1.138) 0.104 (0.257–1.211) 0.14

Injury severity score 1.122 (0.869–1.448) 0.376 (0.288–2.703) 0.827

Nadir HB (g/dl) 0.078 (0.007–0.884) 0.039* (0.008–0.874) 0.038*

Rotterdam CT score 22.13 (0.063–77.29) 0.3 (0.349–81.42) 0.147

The adjusted odds ratios were obtained from a multivariate logistic model which included sex, initial GCS, ISS, image findings, retinal hemorrhage, neurosurgery, skull bone fracture, nadir HB; * p < 0.05 statistic significant; AHT, abusive head trauma; GCS, Glasgow Coma Scale; ISS, injury severity score; HB, hemoglobin.

TABLE 4 | Univariate analysis of factors associated with in-hospital mortality.

| Variables | Survivor | Mortality | P-value |
|-----------|----------|-----------|---------|
| Patient number | 112 | 12 | 0.069 |
| Age (month) | 6 ± 3.6 | 4.2 ± 3.2 | 0.069 |
| Sex (male, n, %) | 72 (63.7) | 6 (54.5) | 0.78 |
| Initial GCS | 12.2 ± 3.2 | 4.7 ± 2.6 | <0.01* |
| Admission HB (g/dl) | 9.6 (8.7–10.8) | 9.6 (6.4–10.4) | 0.338 |
| Mean HB (g/dl) | 10.2 (9.5–11.1) | 10.3 (9.3–11) | 0.577 |
| Nadir HB (g/dl) | 8.8 (7.9–10.3) | 7.3 (6.3–8.5) | 0.014* |
| RBC transfusion (n, %) | 53 (46.9) | 8 (72.7) | 0.187 |
| Rotterdam CT score | 2 (2–3) | 4 (3–5) | <0.01* |

(*) p < 0.05.

In the acute phase of an injured brain, but impaired global cerebrovascular autoregulation develops in patients with ICH causing compensatory mechanisms to fail (9, 13, 20). The results indicate that although the CBF increases in patients with an injured brain, it is still insufficient to conquer the reduced \( \text{CaO}_2 \) induced by the low HB. Consequently, decreased levels of cerebral \( \text{DO}_2 \) develop and result in hypoxic damage to the brain.

Previous studies have demonstrated that admission HB, mean HB, and nadir HB are all the predictors for poor prognosis in adults with ICH (7, 8, 21, 22), but they did not report which one was the most useful. In our study, according to the results of the final logistic mode, nadir HB appeared to be the best predictor of poor neurologic outcomes in infants with ICH. We hypothesize nadir HB may reflect the proportion of primary blood loss and the lowest \( \text{CaO}_2 \) level indicating the severity of cerebral hypoxia. Therefore, once nadir HB develops within the 1st day after admission, it may indicate that nadir HB could play a feasible and practical role in predicting poor neurologic outcome. However, in infants with traumatic brain injury, we noticed that no related studies mentioned the issue in detail, so we determined the cutoff value of nadir HB as 9.35 g/dl to predict poor neurologic outcomes in infants with ICH, based on the ROC analysis, which may provide an indicator for primary clinicians to perform early interventions for infants with ICH. Moreover, we determined the cutoff value of nadir HB in predicting poor neurologic outcomes in infants with traumatic ICH caused by AHT and accidental head injury as 9.36 and 8.75 g/dl, respectively.

In previous studies, the initial GCS score and ISS were identified as risk factors for poor prognosis in pediatric cases, (23, 24). However, in our retrospective study, we found that nadir HB, initial GCS, and ISS were all related factors, and nadir HB may be more effective than the initial GCS score and ISS for predicting poor prognosis. The present study found that all of the nadir HB were detected within 12 h after admission (3.6 ± 3.5 h). Therefore, the nadir HB also provided other information: if the initial brain CT and admission HB were not critical to indicate aggressive surgical intervention, the lower nadir HB could be a parameter for monitoring disease progression and the need for further surgical intervention. In our study, we surveyed the related factors for in-hospital mortality, and found that the initial GCS score remained the independent predictor for in-hospital mortality in the

### TABLE 5 | Logistic regression model to predict mortality.

| Logistic regression | Odds ratio | P-value |
|---------------------|------------|---------|
| Univariate          |            |         |
| Initial GCS         | 0.528 (0.389–0.716) | <0.001 |
| Nadir HB (g/dl)     | 0.6 (0.415–0.867) | 0.007 |
| Rotterdam CT score  | 4.493 (2.102–9.603) | <0.01 |
| Multivariate        |            |         |
| Initial GCS         | 0.528 (0.389–0.716) | <0.001 |

(*) p < 0.05 statistic significant.

GCS, Glasgow Coma Scale; HB, hemoglobin.
multivariate mode rather than nadir HB. This may be because 66.6% (8 of 12) of mortalities presented with out-of-hospital cardiac arrest and a GCS score of 3. Considering the brain lesions, 91.7% (11 of 12) of mortalities had diffuse axonal injuries with hypoxia and hypotension, a potential risk for in-hospital mortality (25). In consequence, initial GCS scores are
a powerful predictive value for in-hospital mortality in infants with traumatic ICH.

In our study, we also found why accidental head injury and AHT showed different cutoff value of nadir HB in predicting outcomes and different blood transfusion strategies. We think that the reason may be due to different trauma mechanisms. As we know, the trauma mechanisms are quietly different between the group with accidental head injury and AHT. In the group with accidental head injury, EDH resulting from injured meningeal artery is more common causing by one trauma episode. Repeated shaking head at different time points resulting in acute on chronic SDH, diffuse axonal injury may be common in the group with AHT. EDH may cause more blood loss than SDH potentially. The different blood transfusion strategies and different outcomes may be based on the different trauma mechanisms.

Until now, there is no golden standard for blood transfusion in adult and pediatric TBI (26, 27). Previous studies demonstrated that HB lower than 7 g/dl will cause anemia-induced brain injury. But the optimal transfusion threshold is still controversial. The transfusion threshold from 7 to 10 g/dl is the common transfusion strategy in the clinical practice. There is still no conclusion whether blood transfusion is associated with better or worse outcomes. Some studies demonstrated RBCT is benefit (28, 29) or harmful (30, 31) or no impact (32, 33) for neurologic outcome in patients with TBI. Our multivariate logistic regression analysis was not powered to detect an association between RBC transfusion and poor prognosis. Further randomized controlled trials based on different transfusion thresholds settings are required.

### CONCLUSIONS

We demonstrated the association between nadir HB and poor neurologic outcome in infants with traumatic ICH. We determined the best cutoff value of nadir HB to be 9.35 g/dl for predicting poor neurologic outcomes in infants with traumatic ICH. Furthermore, the cutoff value of nadir HB in predicting poor neurologic outcomes in infants with ICH caused by AHT and accidental head injury were taken as 9.36 and 8.75 g/dl, respectively.

### DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article-supplementary material.
ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institution Review Board and ethics committee of Chang-Gung Memorial hospital. IRB No.: 104-8307B. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

E-PL, L-LZ, and S-HH conceived and designed the study. L-LZ and S-HH participated in data analysis. O-WC and C-YL gathered the data. E-PL, Y-TS, and JL drafted the manuscript. H-PW and J-JL designed and oversaw the study, interpreted the data. H-PW revised the manuscript. All authors have read and approved the final manuscript for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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