Prediction of Short- and Long-term Outcomes Using Pre-Operative Ventricular Size in Infants with Post-Hemorrhagic Ventricular Dilation

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Abstract

Purpose

Post-hemorrhagic ventricular dilation (PHVD) leads to developmental delays in premature infants, yet the optimal timing for neurosurgical interventions is unknown. Neuroimaging modalities have emerged to delineate injury and follow the progression of PHVD. Fronto-temporal horn ratio (FTHR) is used as a marker of ventricular dilation and can be a standardized tool to direct the timing of neurosurgical intervention. Our study determined the pre-operative FTHR measurement threshold to predict short- and long-term outcomes.

Methods

This is a retrospective cohort study of premature infants with severe intraventricular hemorrhage (IVH) treated in a level IV NICU that developed PHVD and required neurosurgical intervention between 2012 and 2019. A receiver operating characteristic (ROC) curve was performed to evaluate the pre-operative FTHR predictability for developmental delay. An area under the curve (AUC) measured the accuracy of FTHR. In-hospital outcomes and developmental assessments were analyzed.

Results

We reviewed 121 charts of infants with IVH and identified 43 infants with PHVD who required neurosurgical intervention. We found FTHR measurements were an excellent measure of cognitive and motor delay with an AUC of 0.89 and 0.88, respectively. An average pre-operative FTHR of ≥ 0.67 was associated with worse lung and feeding outcomes. There was excellent inter-observer reliability of individual components of FTHR measurements.

Conclusions

Early intervention for PHVD is ideal but not always practical. Identifying ventricular size thresholds associated with better outcomes are needed to direct neurosurgical intervention timing.

Introduction

Post-hemorrhagic ventricular dilation (PHVD) is a common sequela of intraventricular hemorrhage (IVH) in extremely preterm infants and is an important cause of morbidity, mortality, and neurodevelopmental delay. PHVD can lead to elevated intracranial pressure (ICP), termed post-hemorrhagic hydrocephalus (PHH), and is managed by neurosurgical diversion of cerebrospinal fluid (CSF) [1–4]. Several recent studies have demonstrated better outcomes with an early intervention approach. Infants with PHH who

undergo early neurosurgical intervention have less brain injury and better neurodevelopmental outcomes than those who undergo intervention later [4–8].

PHH management has traditionally relied heavily upon clinical factors rather than neuroimaging ventricular size measurements [5]. Clinical factors such as increasing head circumference and splaying of sutures have been shown to be unreliable and trail behind ventricular dilation [9, 10]. Several radiographic measurements have been used to objectively assess ventricular dilation and progression of PHH, including the fronto-temporal horn ratio (FTHR). Both ultrasound- and MRI-derived FTHRs have high inter-observer reliability, excellent correlation with measured ventricular volumes, and relative ease of use [11, 12]. These favorable characteristics give FTHR the potential to be a valuable tool for tracking PHH progression.

Given the risks of early surgery for very low birth weight infants, understanding when harm occurs in PHH is important for determining the optimal threshold for intervention. Various FTHR thresholds for predicting symptomatic progression of ventricular dilation and moderate-to-severe white matter injury have been calculated [11–13]. However, an FTHR threshold for predicting adverse outcomes in childhood has yet to be established and is critical in directing neurosurgical intervention and counseling families. We aimed to determine FTHR cutoffs for predicting short- and long-term outcomes. We hypothesized that an FTHR threshold of 0.6, indicating moderate hydrocephalus, prior to neurosurgical intervention would be predictive of worse outcomes.

Methods

Study Design

We conducted a retrospective cohort study of the neonatal intensive care unit (NICU) and neurosurgical care received by patients with severe IVH and PHH. Approval was granted through the Children's Wisconsin (CW) Institutional Review Board with a waiver of informed consent.

Study Population

Charts were reviewed for patients born at 21 6/7 weeks to 32 6/7 weeks gestation between December 1, 2012 and December 31, 2019 who had a diagnosis of grade III or IV IVH and were admitted to a Level IV NICU in Milwaukee, WI. Patients born at an outside hospital before transfer to our NICU (i.e., "outborn" patients) were included in addition to patients born at our co-located birth center.

Patient demographics, neonatal comorbidities, and neurosurgical data were collected from the electronic medical record. Neonatal comorbidities included the need for surgery (non-neurosurgical) during NICU admission, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), unprovoked electrographic seizures, the requirement of high-frequency oscillatory ventilation (HFOV), duration of intubation, oxygen requirement at NICU discharge, route of feeds at NICU discharge,

and death. Neurosurgical data included type of neurosurgical (NS) intervention and day of life (DOL) at the first NS intervention.

Measurements of Ventricular Size

FTHR was used as the measure of ventricular size in this study. FTHR is calculated by adding the widest distance across the frontal horns and the widest distance across the temporal horns and dividing the sum by two times the widest skull diameter (Fig. 1). All measures are obtained from a single image in the coronal plane at the level of the Foramen of Monro. Two pediatric neuroradiologists independently calculated an FTHR value from head ultrasounds performed immediately before the initial neurosurgical intervention. MRI was used when a head ultrasound was unavailable. Normative FTHR thresholds for mild, moderate, and severe ventricular dilation are 0.55, 0.6, and 0.7, respectively[14]. The area of parenchymal hemorrhage and subsequent periventricular cystic change, when present, was included in the measurement of frontal horn width (Fig. 2). This approach was intended to yield more reliable FTHR measurements than could be obtained if a border was estimated between the area of the lateral ventricle and the area of cystic change.

Outcome Measures

Outcome measures in this study were supplemental oxygen use at 36 weeks CGA, need for a surgically placed feeding tube at NICU discharge, need for an antiepileptic drug (AED) for three or more months and diagnosis of epilepsy within the first two years of life, and developmental delay at 24-months CGA according to Bayley Scales of Infant and Toddler Development scores. Developmental delay in a particular domain was defined as a composite score < 85 in motor, language, and cognitive domains. During the study period, the 4th edition of the Bayley Scales of Infant and Toddler Development (Bayley-IV) was published and replaced the use of the 3rd edition (Bayley-III) at our institution. Bayley-III and Bayley-IV scores will be referred to collectively at Bayley scores[15].

Statistical Analysis

Inter-observer reliability of pre-operative FTHR was assessed using Lin's concordance correlation coefficient (CCC) which is used for measuring the agreement between two observers on continuous variables. Lin's CCC measures both precision and accuracy [16]. We individually performed Lin's CCC for FTHR and for the frontal, temporal, and broadest skull diameter measurements. There are various interpretations for Lin's CCC. We used the interpretation methodology of Pearson's Correlation Coefficient, with < 0.2 as poor and > 0.8 as excellent [17, 18].

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of pre-op FTHR for predicting need for neurodevelopmental delay at 24-months CGA. Neurodevelopmental delay assessments using the Bayley score for motor, language, and cognitive domains were analyzed for these ROC curves. Area under the curve (AUC) analysis was performed to assess the accuracy of the FTHR.

Based on the results of our ROC curve from our neurodevelopmental assessments, we categorized the patients into two groups based on their pre-operative FTHR values using the determined cut-off. Patient demographics, comorbidities, and outcomes prior to discharge and characteristics and comorbidities of patients surviving to discharge were compared between the groups using the Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

SAS 9.4 and IBM SPSS Statistics 28 were used for the analyses. A p-value of < 0.05 was considered statistically significant. Our analyses assumed that data is missing at random (unbiased sample).

Results

We reviewed 121 charts of premature patients with documented grade III or IV IVH (Fig. 3). We excluded a total of 24 patients due to congenital or chromosomal anomalies (n = 8), death before day of life (DOL) 10 (n = 9), discharge home before NS intervention (n = 6), and GA at birth greater than two standard deviations from the cohort mean (n = 1). Our cohort included 43 patients (44%) who received NS intervention and 54 who did not. Of the 43 patients who received NS intervention, 37 survived through NICU discharge and 35 survived to two years of life. Of the two years survivors, 22.9% were diagnosed with epilepsy and 27% required anti-epileptic medication for more than three months. Approximately 40% of these patients had developmental testing at 24-months CGA age (n = 14 for motor, n = 15 for language and cognitive). The median composite score for the motor domain was 79 (IQR 60–101), language domain was 79 (IQR 68–100), and cognitive domain was 80 (IQR 60–105).

Inter-observer reliability

There was excellent agreement between the two blinded neuroradiologists for frontal (CCC = 0.97), temporal (CCC = 0.93) and broadest skull diameter (CCC = 0.94, Table 3). For the calculated FTHR, there was modest agreement between the two blinded neuroradiologists (CCC = 0.80).

ROC analysis for two-year outcomes

FTHR is an *excellent* measure for predicting cognitive (AUC = 0.89,) and motor (AUC = 0.88,) delay at two years of life (Fig. 4). A pre-operative FTHR of ≥ 0.67 predicts cognitive delay with 77.8% sensitivity and 83.3% specificity and motor delay with 75% sensitivity and 83.3% specificity. FTHR is also a *good* measure for predicting language delay (AUC = 0.82,), with pre-op FTHR ≥ 0.67 predicting language delay with 70% sensitivity and 80% specificity.

In hospital outcomes of patients requiring NS

Of the 43 infants who received NS intervention, the median pre-operative FTHR of the lower threshold group was 0.62 (IQR 0.60–0.64) and the higher threshold group was 0.72 (IQR 0.70–0.75). There were no significant differences in patient demographics and comorbidities prior to discharge between the two

groups (Table 1). There was twice as many infants who were outborn in the higher threshold group compared to the lower threshold group, although this difference did not reach statistical significance.

There was a significant difference in median days intubated between the groups in those patients who survived to discharge, where patients in the higher threshold group were intubated ~ 20 days longer (Table 2). Patients in the higher threshold group were more likely to go home with gastric tube feeds and less likely to be orally fed. There was a trend towards longer length of hospital stay and having more bronchopulmonary dysplasia (BPD) in patients in the higher threshold group.

Discussion

We assessed the relationship between pre-operative FTHR and short- and long-term outcomes infants with a history of PHH. As the use of ventricular measurements in the management of PHVD becomes more widespread, evidence-based thresholds treatment are needed. The novel finding of this study is that an FTHR threshold of ≥ 0.67 at time of intervention can predict cognitive and motor delays in premature infants at 24-months CGA with significant sensitivity and specificity. This higher FTHR threshold was also associated with worse lung and feeding outcomes in this high-risk population. These findings add to the growing body of evidence supporting the value of ventricular measurements in guiding the timing of intervention for PHH.

Several studies have determined that earlier interventions for PHH lead to better outcomes [4–8]. The most recent example is the ELVIS trial, which compared infants who received NS intervention at a low threshold of ventricular dilation to those who received intervention at a high threshold [6, 7]. In this study, a ventricular index (VI) of > 97th percentile and anterior horn width (AHW) of > 6mm was considered a low threshold measure and a VI of > 97th percentile + 4mm and AHW of > 10mm was considered a high threshold measure. This study demonstrated that infants in the low-threshold group had normal or mild injury on MRI compared to the high-threshold group. Furthermore, they found that smaller ventricular size at time of neurosurgical intervention for PHH was positively associated with better Bayley cognitive and motor scores at two years of life [6, 7]. However, the benefits of early intervention must be weighed against the risks of earlier surgery. Preterm infants are at increased risk of post-operative morbidity, including infection, sepsis, and bleeding, and major surgery is independently associated with increased risk of death among VLBW infants [19–21]. Neurosurgery for PHH also carries the risks associated with an implanted device, such as need for revision [22]. Preterm infants have a high burden of comorbidities that can increase surgical risk and delay neurosurgical intervention [23]. In our cohort, most infants had BPD, PDA, and required surgery for an indication other than PHH (Tables 1 and 2). Moreover, since PHVD can resolve without intervention in greater than 30% of patients, early neurosurgery poses the risk of exposing infants to unnecessary surgery [4, 5, 24]. Given the risks and challenges of surgery for preterm infants with PHH, understanding how long surgery can be delayed before harm occurs is a critical step in determining the optimal timing of intervention.

Measuring trajectories of ventricular dilation using a standard guideline is optimal, but not always possible or practical when caring for infants between different hospitals. In the United States, many different neonatal centers can serve a single catchment area, meaning that an infant requiring a higher level of care may be treated at multiple centers during the neonatal period. In our cohort, 88% of patients were born at outside hospitals and received care at these facilities prior to transfer to our NICU. In the absence of national guidelines, care for infants with PHH is often driven by available resources, resulting in significant practice variation between centers. Our hospital uses FTHR to measure ventricular size and we found that FTHR $\geq$ 0.67 is both sensitive and specific for predicting motor and cognitive delay (Fig. 2). Despite small sample sizes, the AUC above 0.8 provides confidence that our threshold measurement has high predictive performance. Optimal transfer timing for neurosurgical intervention remains unknown and PHVD thresholds can guide these conversations between centers. Neonatologists at smaller NICUs can start communicating with neurosurgical sites when FTHR exceeds 0.55 (the normative value for mild PHVD). A clear-cut measurement threshold may help balance need for neurosurgical intervention and management of other comorbidities.

FTHR is one of several ventricular size measurements in use. Other frequently used measurements include the AHW, VI, and thalamo-occipital distance (TOD). All measurements demonstrate substantial inter-observer reliability and good sensitivity and specificity for predicting need for intervention, with no measurement showing consistently superior results across studies [11, 13, 25]. One of the most common approaches to ventricular size measurement is the use of VI in conjunction with AHW. This approach benefits from the fact that AHW best reflects rounding of the frontal horns, which is one of the first signs of increased ICP [25, 26]. However, VI is dependent on gestational age at the time of measurement and the percentile charts against which it is validated are restricted to 24–42 weeks GA, limiting its use [13]. TOD, like AHW, is also thought to reflect some of the earliest signs of increased ICP, as the occipital horns are often the first to enlarge [26, 27]. However, visualizing this angle can be challenging, making TOD more prone to errors in measurement [28]. FTHR is independent of gestational age, can be captured from a single image, and demonstrates high inter-observer reliability [11, 13]. In the present study, we found excellent agreement between the components of the FTHR obtained by our two observers. In addition, a distinct advantage of FTHR is that MRI and US-derived values have excellent concordance, and both have high correlation with measured ventricular volumes [12]. FTHR is reliable, quick to obtain, and conveys clinically relevant information from a single image, making it a valuable tool for communicating patient status between facilities and teams.

The limitations of this study include the retrospective nature, small sample size, and low rate of neurodevelopmental follow-up. Attendance at high-risk infant (NICU) follow-up clinics is a well-documented challenge across the United States [29–31]. For example, Patra et al. observed a 52–62% attendance rate among VLBW infants at the first follow-up appointment but found that this rate dropped to 27–30% by the final two-year follow-up visit [31]. A 62% loss to follow-up rate by 24 months CA among preterm infants referred for NICU follow-up has previously been observed at our own institution [30]. The attendance rates in our current cohort are consistent with these findings. Despite our low follow-up rate, the data has strong predictive performance suggesting a larger multi-center study would be the natural

next step to confirm our findings. Despite these limitations, the primary strength of this study is the identification of a clear-cut threshold for intervention that may be associated with better short- and long-term outcomes. Furthermore, we confirm that FTHR measurements are reliable between observers.

Since this study period, we have significantly increased our high-risk infant follow attendance through a multi-disciplinary clinic model[32]. We have also formalized our neuroimaging and neurocritical care practice guidelines in the NICU to promote earlier interventions and promote consistent practice among regional NICUs. Therefore, future studies to further examine the potential benefits of earlier neurosurgical interventions are possible.

Conclusions

PHH should be identified early by using neuroimaging measurements that are easy to use and have excellent inter-observer reliability. Early intervention for PHH is ideal, but not always practical. Neuroimaging thresholds that correlate strongly to better short- and long-term outcomes should be used to direct timing for intervention.

Declarations

Author Contribution

M.S., E.C., A.F. and S.C. wrote the main manuscript text, J.Z. and K.Y. performed the statistical analysis, T.D. and M.M. performed all neuroradiologic assessments, and all authors reviewed the manuscript.

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Declaration of Conflicts of Interest (COI): All authors have no disclosures or COI to disclose.

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Tables

Tables 1-3 are available in the Supplementary Files section.

Figures

Figure 1:

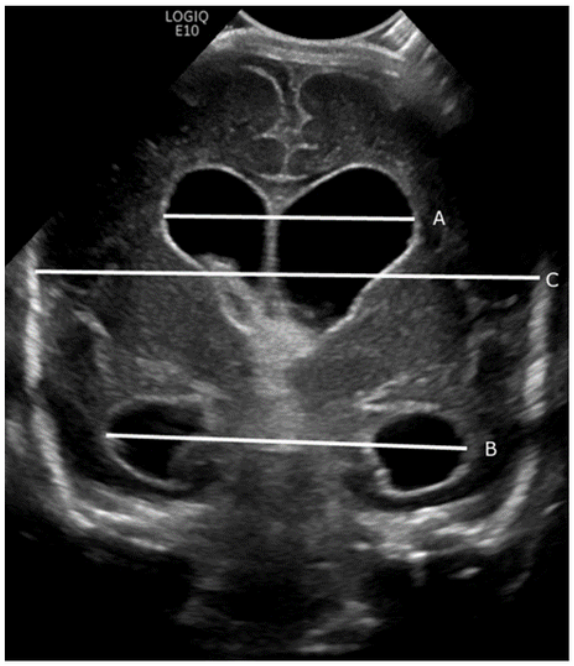

Figure 1

Coronal head ultrasound at the foramen of Monro in a 26-days-old male with PHH, shows measurement of widest distance across frontal horns (A), widest distance across temporal horns (B) and broadest skull diameter (C). FTHR = A+B / 2C.

Figure 2:

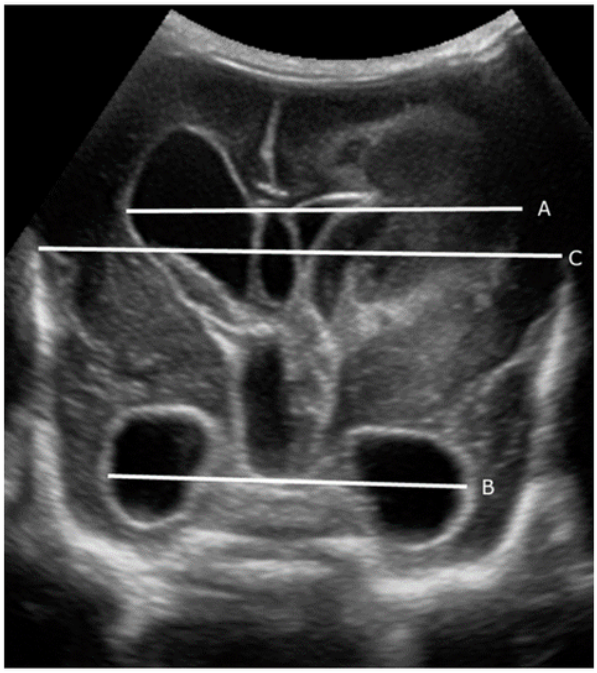

Figure 2

Coronal head ultrasound at the foramen of Monro in a 14-days-old male with PHH including left periventricular intraparenchymal hemorrhage, shows inclusion of the area of parenchymal hemorrhage in the measurement of widest distance across frontal horns (A). Measurements B, C, and FTHR calculation are similar to Figure 1.

Figure 3:

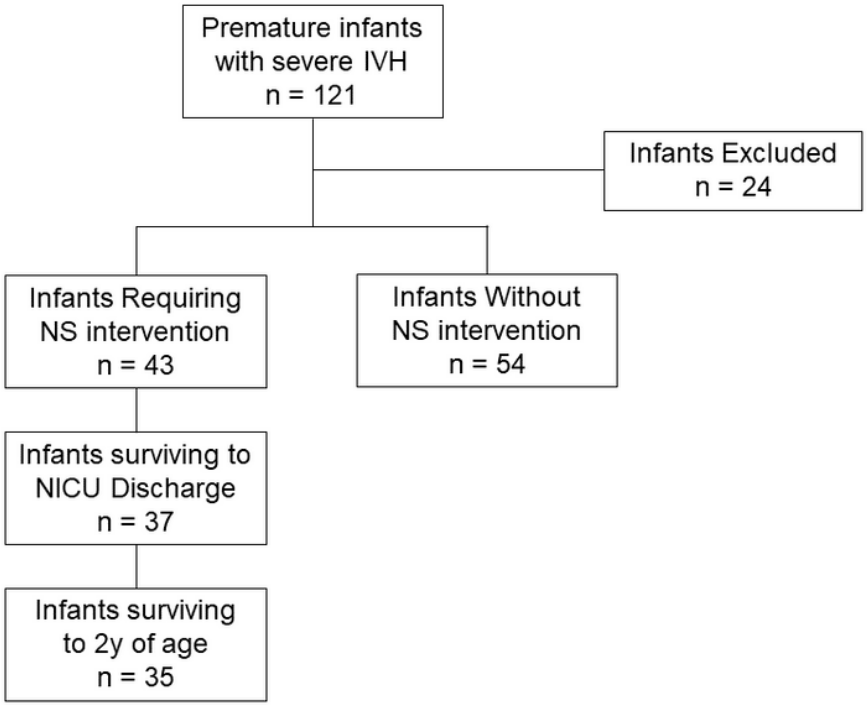

Figure 3

Study Flow Diagram

Figure 4.

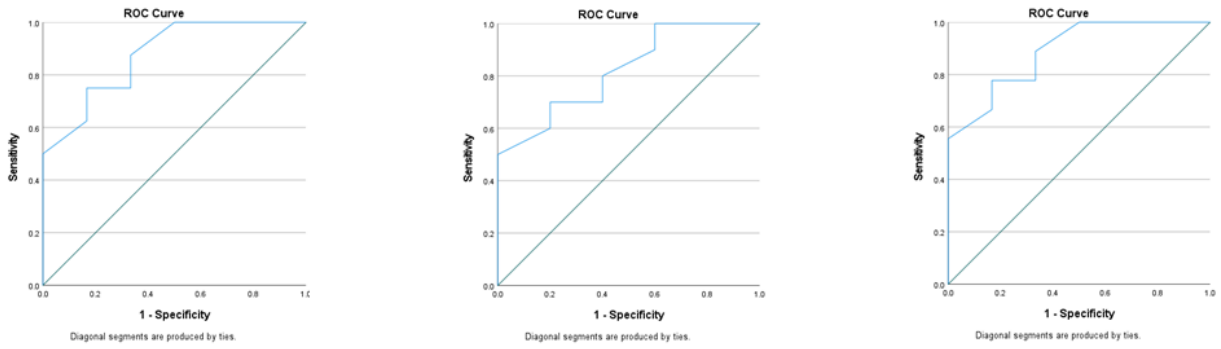

Figure 4

Average Pre-operative FTHR ROC curve analysis for 24-month composite Bayley scores. FTHR is an *excellent* measure for predicting cognitive (AUC = 0.89, p=0.013) and motor (AUC = 0.88, p=0.02) delay at two years of life. A pre-operative FTHR of ≥0.67 predicts cognitive delay with 77.8% sensitivity and 83.3% specificity and motor delay with 75% sensitivity and 83.3% specificity. FTHR is also a *good* measure for predicting language delay (AUC = 0.82, p=0.05), with pre-op FTHR ≥0.67 predicting language delay with 70% sensitivity and 80% specificity.

Supplementary Files

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