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Article

A web-based calculator for prediction of severe neurodevelopmental impairment in preterm infants using clinical and imaging characteristics

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Abstract: Although the most common forms of brain injury in preterm infants have been associated with adverse neurodevelopmental outcomes, existing MRI scoring systems lack specificity, do not incorporate clinical factors, and are technically challenging to perform. The objective of this study was to develop a web-based, clinically-focused prediction system which differentiates severe from normal-moderate neurodevelopmental outcomes at two years. Infants were retrospectively identified as those who were born ≤30 weeks gestation, had MR imaging at term-equivalent age, and neurodevelopmental testing at 18-24 months. Each MRI was scored on injury in three domains (intraventricular hemorrhage, white matter injury, and cerebellar hemorrhage) and clinical factors strongly predictive of outcome were investigated. A binary logistic regression model was then generated from the composite of clinical and imaging components. A total of 154 infants were included (mean GA = 26.1±1.8 weeks, BW = 889.1±226.2 grams). The final model (imaging score + ventilator days + delivery mode + antenatal steroids + ROP requiring surgery) had strong discriminatory power for severe disability (AUC=0.850), with a PPV of 76% and NPV of 90%. Available as a web-based tool, it can be useful for prognostication and targeting early intervention services to infants who may benefit most from such services.

Keywords: cerebellar hemorrhage; intraventricular hemorrhage; preterm; MRI; neurodevelopment; outcome prediction; white matter injury

1. Introduction

Brain injury is a common and consequential outcome of prematurity. Preterm infants are affected by three forms of brain injury: intraventricular hemorrhage (IVH), white matter injury (WMI), and cerebellar hemorrhage (CH) [1], all of which have been associated with an increased risk of adverse neurodevelopmental outcomes [2–4]. Although the routine cranial ultrasound is ideal for the detection of intraventricular hemorrhage [5], and may have utility at term-equivalent age for the detection of WMI [6], the brain MRI remains the gold standard, with significantly greater sensitivity for the detection of injury [7].

However, for any imaging modality to have value it must first meet two criteria – ease of use, and reliable prediction of neurodevelopmental outcomes. Four major MRI scoring systems have been developed for preterm infants by Woodward et al. [3] Kidokoro et al. [8], Chau et al. [9], and Brouwer et al [10]. All four systems have strong correlations with adverse outcome, but are complex to perform, requiring precise measurements, *qualitative assessment* by experienced radiologists, brain segmentation, and/or measurement of diffusion or fractional anisotropy. Furthermore, all of the systems are based on imaging alone and do no incorporate clinical factors which may be separately predictive of adverse outcomes.

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Although these approaches have a high negative predictive value (NPV) for infants without evidence of injury [3,11], they have very poor positive predictive value (PPV) for those with injury, ranging between 10 and 50% [3,12]. Not surprisingly, considerable opposition from families has developed as to the utility of the term-equivalent MRI due to the lack of precision in predicting outcome of infants with injury [13]. This ultimately led to an AAP recommendation against routine use of term-equivalent MRI in preterm infants [14].

To overcome these challenges, an ideal scoring system would be user-friendly, account for supratentorial and cerebellar injury, incorporate clinical factors linked to adverse outcomes, and differentiate infants with severe neurodevelopmental delay from those with normal-moderate outcomes with a maximal degree of precision. The objective of this study was to develop a scoring system using a cross-sectional cohort of preterm infants with term-equivalent MRI, accounting for clinical risk factors, and validate the system against formal neurodevelopmental testing at 18-24 months of age. This model was then incorporated into a web-based calculator, which will be useful for prognostication and targeting early intervention services to infants who may benefit most from such services.

2. Materials and Methods

2.1. Patient selection

Infants included in this study represent a cross-sectional population of all preterm infants admitted to the NICU at St. Louis Children's Hospital. Inclusion criteria for the cohort were preterm birth (≤ 30 weeks estimated gestational age [EGA]) and admission to the NICU at our institution between 1 January 2007 and 31 December 2016. Infants were excluded if there was a known congenital anomaly, if the infant died before term-equivalent age, or if he/she was lost to follow-up prior to neurodevelopmental testing. Term-equivalent brain MRI and formal neurodevelopmental testing between 18- and 24-months corrected age using the Bayley Scales of Infant Development, 3rd edition (BSID-III) were performed in all infants as a part of standard clinical care.

The study protocol was reviewed and approved by the Washington University Human Research Protection Office.

2.2. Data collection

Demographic and perinatal factors collected included gestational age at birth, birth weight, sex, race, intrauterine growth restriction, pre-eclampsia, chorioamnionitis (diagnosed by histopathology), mode of delivery, emergent delivery, administration of antenatal steroids and/or magnesium sulfate, and the Apgar score at 5 minutes. Clinical characteristics included diagnosis of bronchopulmonary dysplasia (BPD, defined as need for supplemental oxygen after 36 weeks corrected gestational age), ventilator days, inotropic medication administration, sepsis (positive blood culture), necrotizing enterocolitis, presence of clinically apparent seizures, and severe retinopathy of prematurity (defined as stage III disease with need for laser ablative surgery).

2.3. *Imaging scoring system*

All infants underwent standardized cranial ultrasound screening consisting of scans performed at least once in the first three days of life, again between 7 and 10 days of life, and again at 30 days of life. Of note, infants with grade III/IV IVH frequently received more cranial ultrasound exams as a result of weekly surveillance for post-hemorrhagic hydrocephalus.

All infants in the study underwent a non-sedated, non-contrast MRI scan at term equivalent age, including T1, T2 and susceptibility-weighted imaging (SWI) sequences. Magnetic resonance images were acquired by using a 3-T TIM Trio system (Siemens, Erlangen, Germany). MRI scanning included anatomic images obtained with an axial magnetization–prepared rapid gradient echo T1-weighted

sequence (TR/TE 1500/3 milliseconds; voxel size: 1 × 0.7 × 1 mm^3) and a turbo spin echo T2-weighted sequence (TR/TE 8600/160 milliseconds; voxel size: 1 × 1 × 1 mm^3; echo train length: 17).

Cerebellar hemorrhage was identified as a hypointensity in the cerebellum on T2 sequences with corresponding lesion on SWI. Intraventricular hemorrhage was classified using the Papile system [5]. White matter injury was identified as hyperintensity on T1 sequences with corresponding hypointensity on T2 sequences. Diffusion-weighted imaging was not used in the scoring system. All imaging was interpreted by a clinical neuroradiologist at the time of scan, who was blinded to the clinical course of the infant, and later reviewed by one author (ZAV) to confirm findings.

The proposed scoring system consists of three components: IVH score, WMI score and CH score. IVH was classified as none, low-grade (grade I/II), and high-grade (grade III/IV). WMI was classified as none, isolated punctate (≤ 2 lesions), or multiple punctate or cystic. CH was classified as none, punctate/small (<50% of cerebellar hemisphere), or large (>50% of cerebellar hemisphere) with additional points given for bilateral CH.

Table 1. MRI Scoring System

Cerebellar hemorrhage size	• > 50% of cerebellar hemisphere – 3 points • Punctate up to <50% of cerebellar hemisphere – 1 point • None – 0 points
Cerebellar hemorrhage laterality	• Bilateral – 1 point • Unilateral – 0 points
Intraventricular hemorrhage	• Grade III/IV – 5 points • Grade I/II – 2 points • No IVH – 0 points
White matter injury	• Multiple punctate (> 2 lesions) or Cystic – 5 points • Isolated punctate (≤ 2 lesions) – 2 points • None – 1 point

In order to develop the scoring system, infants were first sorted by neurodevelopment outcome. Infants were divided into two groups, those with severe neurodevelopmental impairment (any one BSID-III component greater than 2 standard deviations below the mean [<70]) and those with normal-moderate outcomes (all BSID-III components >70). An iterative score-weighting process was conducted, starting with "baseline" scoring system where all injury components had equal weight (e.g. 0 points for absent, 1 point for present). Using the difference in distribution of radiographic features in the severe group vs. normal-moderate group, the weight of each individual feature was adjusted (by increasing point values) until the sensitivity and specificity were maximized. The scoring system is shown in **Table 1**.

2.4. Statistical approach

Characteristics of infants with and without severe neurodevelopmental impairment were compared using Fisher's Exact Test for categorical variables and the Mann-Whitney U-test for continuous variables. Comparisons were considered significant where $p < 0.05$. Two variations of the base clinical risk score were created. The first variation ("full model") was generated as a multivariate binary logistic regression model using parameters where $p<0.10$ in univariate analysis and factors known to be associated with adverse neurodevelopmental outcomes in previous studies.

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The second variation ("slim model") was created by entering all collected clinical variables into backwards stepwise logistic regression by Akaike Information Criterion (AIC) to generate the most parsimonious model, maximizing discriminatory power while minimizing risk of over-fitting.

A composite multivariate logistic regression model was then constructed by adding the imaging score to the base clinical score. The variance inflation factor (VIF) was calculated for all covariates in each model to assess for excessive collinearity (defined as VIF > 5). The area under the curve (AUC) was then calculated for both models and variations to assess the degree of improvement in discrimination with the addition of the imaging score. DeLong's test for correlated ROCs was then performed to evaluate if the improvement in AUC was statistically significant.

All statistical testing was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). ROC testing and plots were performed using the pROC package for R [15]. The online calculator was developed using the Shiny package for R.

3. Results

3.1. Sample characteristics

A total of 374 eligible infants were admitted during the study period. Of those, 328/374 (88%) survived to term-equivalent age and 250/328 (76%) underwent a brain MRI. At two years, 8/250 (3%) of infants had died and 3/250 (1%) had such severe neurodevelopmental disability that they were not able to complete the BSID-III. The BSID-III was successfully completed in 154/239 (64%) of the remaining infants (**Figure 1**).

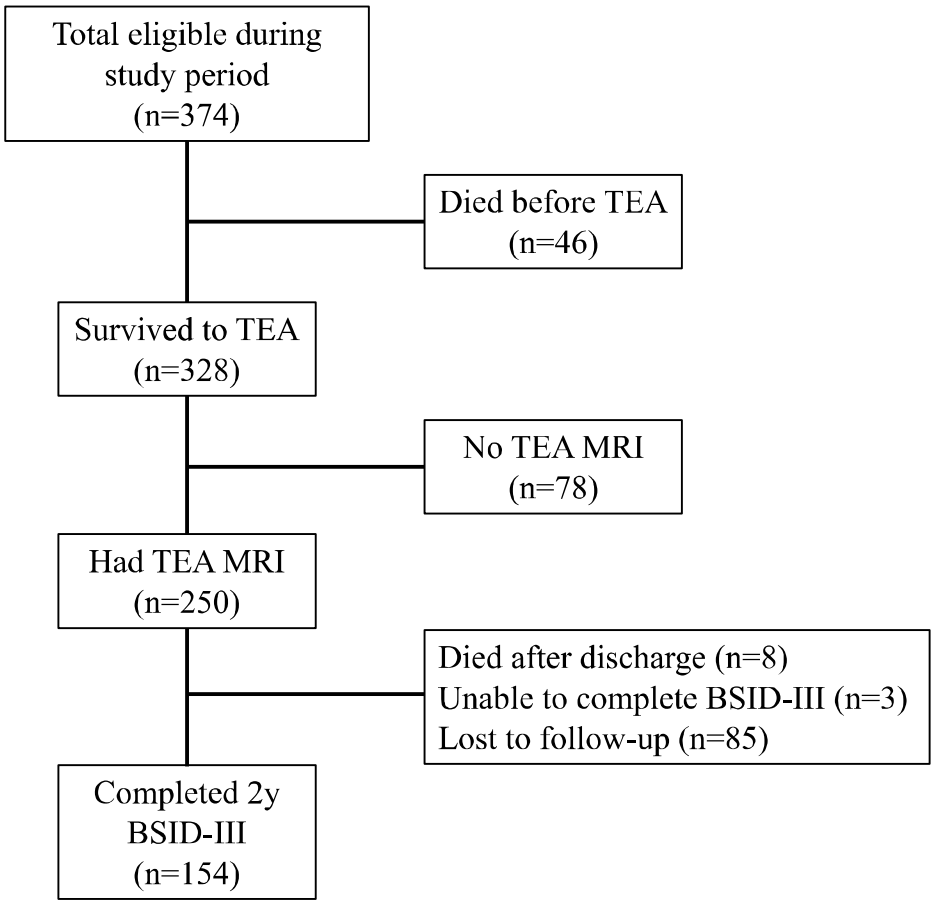

Figure 1. Flow diagram of patient selection.

When comparing infants with and without severe neurodevelopmental disability, those affected were of lower EGA (25.6 vs 26.2 weeks, p=0.08), lower birthweight (821.5 vs. 911.2 g, p=0.07), less likely to have received antenatal steroids (71% vs 88%, p=0.02), had lower median 5-minute Apgar scores (5.5 vs 6, p=0.09), received more postnatal steroids (50% vs 31%, p=0.05), had greater median ventilator days (31.5 vs. 4 days, p<0.01), received more inotropic medications (50% vs. 32%, p=0.05), and were more likely to have ROP requiring surgical intervention (34% vs. 18%, p=0.04). See **Table 2** for complete details.

Table 2. Sample Characteristics

	No severe disability (n=116)	Severe disability (n=38)	P value
Gestational age, mean (SD), weeks	26.2 (1.9)	25.6 (1.6)	0.08
Birth weight, mean (SD), grams	911.2 (271.4)	821.5 (240.9)	0.07
SGA[a], n (%)	8 (7)	5 (13)	0.31
Male sex, n (%)	53 (46)	19 (50)	0.71
Pre-eclampsia, n (%)	26 (22)	10 (26)	0.66
Chorioamnionitis, n (%)	40 (34)	11 (29)	0.56
Vaginal delivery, n (%)	30 (26)	11 (29)	0.83
Any antenatal steroids, n (%)	102 (88)	27 (71)	0.02*
Complete antenatal steroids, n (%)	57 (49)	16 (42)	0.46
Antenatal magnesium sulfate, n (%)	75 (65)	20 (52)	0.25
5-min Apgar score, median (range)	6 (0-9)	5.5 (0-9)	0.09
Postnatal steroids, n (%)	36 (31)	19 (50)	0.05
Ventilator days, median (range)	4 (0-106)	31.5 (1-251)	<0.01*
BPD[b] diagnosis, n (%)	70 (60)	27 (71)	0.25
Inotropic medication administration, n (%)	37 (32)	19 (50)	0.05
Culture-positive sepsis, n (%)	17 (15)	10 (26)	0.14
Necrotizing enterocolitis, n (%)	13 (11)	6 (16)	0.57
PDA ligation, n (%)	19 (16)	10 (26)	0.23
Clinically apparent seizures, n (%)	4 (3)	3 (8)	0.36
Severe ROP, n (%)	21 (18)	13 (34)	0.04*
BSID-III cognitive score, mean (SD)	91.5 (9.8)	73.3 (10.7)	<0.01*
BSID-III motor score, mean (SD)	89.7 (12.3)	65.5 (12.3)	<0.01*
BSID-III language score, mean (SD)	89.7 (10.2)	69.9 (13.3)	<0.01*

[a]Defined as BW < 10th centile. [b]Defined as need for supplemental oxygen past 36 weeks PMA.

3.2. *Imaging characteristics*

There was a statistically significant, but clinically irrelevant, difference in PMA at MRI between the severe outcome and no severe outcome (40.4 vs 38.2 weeks, p=0.02). Infants with severe outcomes had a greater median number of cranial ultrasounds (8 vs. 4, p<0.01), and a higher overall incidence of brain injury of any type (90% vs. 66%, p<0.01).

Overall, IVH of any grade was more common in infants with severe disability (82% vs. 47%, p<0.01) as was high-grade IVH (61% vs 14%, p<0.01). Cerebellar hemorrhage was more common in the severe disability group, although this difference was not statistically significant (40% vs. 22%, p=0.06). Of those with cerebellar hemorrhage, infants with severe outcome more often had large hemorrhages (21% vs. 5%, p=0.03) and more often had bilateral hemorrhages, although this was not significant (24% vs 13%, p=0.12). Infants with severe outcomes more often had WMI (68% vs 32%) and was more often multiple punctate/cystic (63% vs.13, p<0.01) (**Table 3**). Examples of CH and WMI are shown in **Figure 2**.

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Table 3. Imaging Characteristics

	No severe disability (n=116)	Severe disability (n=38)	P value
Any IVH, n (%)	55 (47)	31 (82)	<0.01*
Grade III/IV IVH, n (%)	16 (14)	23 (61)	<0.01*
Any cerebellar hemorrhage, n (%)	26 (22)	15 (40)	0.06
Cerebellar hemorrhage size			
Large, n (%)	6 (5)	8 (21)	0.03*
Small, n (%)	12 (10)	5 (13)	
Punctate, n (%)	8 (7)	2 (5)	
None, n (%)	90 (78)	23 (61)	
Bilateral cerebellar hemorrhage, n (%)	15 (13)	9 (24)	0.12
WMI			
Multiple punctate or cystic, n (%)	15 (13)	24 (63)	<0.01*
Isolated punctate, n (%)	22 (19)	2 (5)	
None, n (%)	79 (68)	12 (32)	
Any brain injury, n (%)	77 (66)	34 (90)	<0.01*
Number of HUS, median (range)	4 (0-28)	8 (2-38)	<0.01*
PMA at MRI	38.2 (2.6)	40.4 (5.7)	0.02*

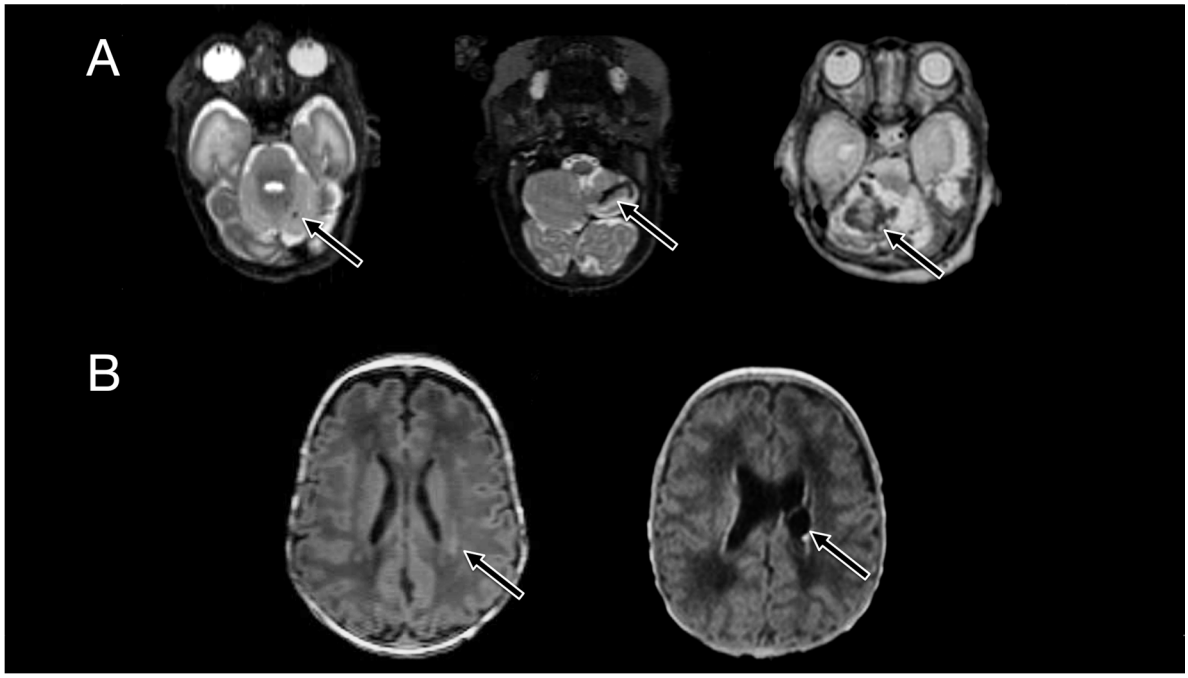

Figure 2. Cerebellar hemorrhage examples are shown in row A: punctate injury is shown in left column, small in the middle, and large in right column. All images are from T2 axial sequences. Primary focus of injury shown by arrow. White matter injury examples are shown in row B: punctate injury is shown at left while a cystic lesion in shown on the right.

3.3. *Base Clinical Logistic Regression Model*

The first variation of the base clinical model was constructed from biologically plausible and statistically-likely (defined as $p<0.10$) factors including gestational age, birth weight, antenatal steroids, 5-minute Apgar scores, postnatal steroids, ventilator days, inotrope use, and ROP requiring surgical treatment. The model R^2 was 0.146, with a modest AUC of 0.694, and an AIC of 132.1. The second "slim" variation was generated by backwards stepwise multivariate logistic regression by AIC (ventilator days, delivery mode, antenatal steroids, and ROP requiring surgery). The model R^2

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was 0.140, an improved AUC of 0.727, and an AIC 127.8. The VIF for covariates was < 5 in both variations.

3.4. Image scoring system

After the iterative weighting process of individual injury components, the mean MRI score in the severe impairment group was 8.1±3.6 while the infants with normal-moderate outcomes had a mean score of 3.5 ± 2.5 ($p<0.01$). A score threshold of > 8 was 83% sensitive and 89% specific for prediction of severe delay.

3.5. Combined clinical and imaging logistic regression model

The final scoring system demonstrates the value of incorporating all aspects of preterm brain injury in an additive model in conjunction with key clinical factors. When the imaging score (CH score + IVH score + WMI score) was added to the "slim" clinical model, the composite model was strongly predictive of severe neurodevelopmental outcome. The model R^2 was 0.458 with an excellent AUC of 0.850. The VIF for all covariates was < 5. The final composite model had a PPV of 76% and an NPV of 90%. ROC curves for all models and variations is shown in **Figure 3**.

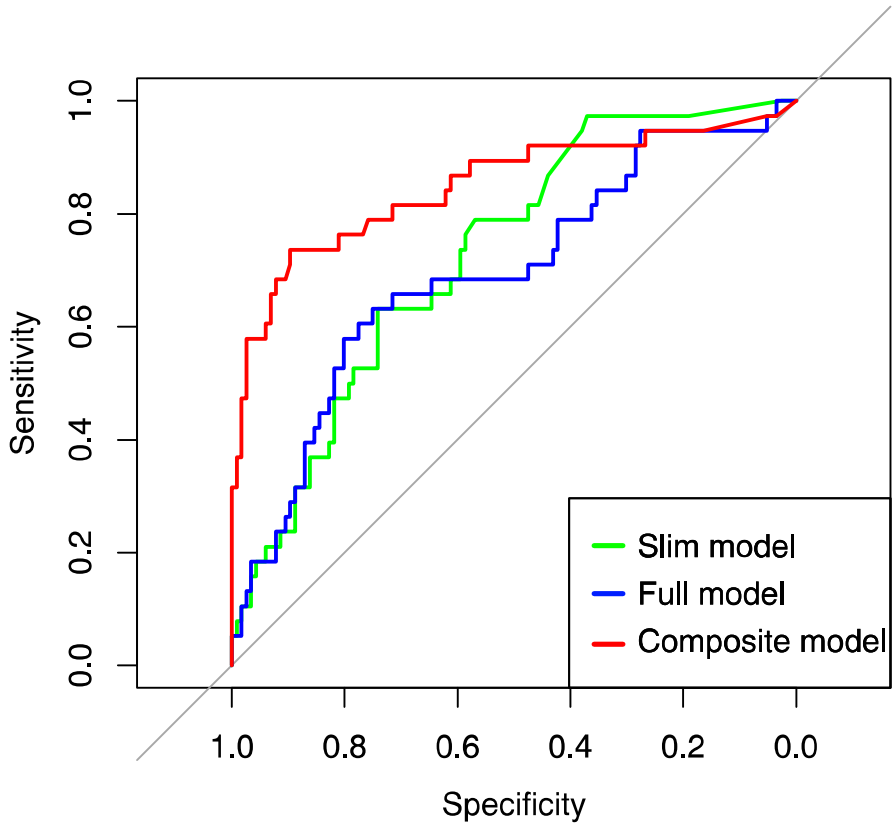

Figure 3. ROC curves for the "full" clinical factor model (blue), "slim" clinical factor model (green), and the composite imaging and "slim" clinical model.

4. Discussion

In this single-center study, we have successfully developed and described a composite clinical and MRI-based scoring system, which is highly predictive of severe neurodevelopmental impairment. Novel features of this scoring system are the inclusion of clinical factors in the predictive model, the use of supratentorial and cerebellar injury, and an interactive web-based risk calculator. This scoring system is pragmatic, clinically focused, and can be accomplished by any center which utilizes term-equivalent MRI scanning in preterm infants.

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The weighting of this scoring system reveals the importance of both cerebellar and supratentorial injury in the development of severe neurodevelopmental impairment. While the impact of all three forms of brain injury has been previously described [3,5,7,16–19], a composite system using imaging and clinical factors, validated against neurodevelopmental outcomes, has not been previously developed. While cerebellar hemorrhage has long been linked to adverse outcomes, the relationship between specific radiographic features was not known. Given that cerebellar hemorrhage is tightly linked with both IVH [20] and white matter injury [21,22], it is impossible to ever untangle the magnitude of developmental impairment caused by each discrete form of injury. As a result of under diagnosis [23], CH is not well understood and no standardized imaging scoring system exists, although it is clear that MRI is the superior radiographic approach for detection [7]. Although other authors have reported imaging findings of CH in relationship to neurodevelopmental outcomes, there is no standardized method for radiographic diagnosis of cerebellar hemorrhage. Correspondingly, this scoring system captures the composite impact of all three types of injury, enabling, neurologists and neonatologists to provide informed prognostic detail to families, beyond what had previously been available.

There are several important limitations of this study which should be considered. Despite a relatively large initial cohort, the final group of infants was smaller. For the 220 infants excluded, three primary factors drove this exclusion – mortality (25%), no term-equivalent MRI (35%), and lost to hospital follow-up (38%). Given that the mortality rate of infants diagnosed with CH may be as high as 67% [7], mortality is a notable limitation. However, as most preterm infant who die, do so in the first 48 hours of life [24,25], this period is far too short for accurate assessment of other forms of brain injury (IVH, WMI) which evolve over longer periods of time. The ambiguous clinical utility of the term-equivalanet MRI was the predominant driving factor behind the lack of MR imaging, both a limitation of the study and further evidence of the vital need for a more predictive scoring system. Given the scope of the underlying cohort (nearly 400 infants over nearly 10 years), and characteristics of infants at greatest risk for brain injury (very preterm, severe lung disease, high mortality rates) it is challenging to identify, scan, and follow-up infants in large numbers, avoiding bias as infants are excluded at each stage. However, it is reassuring that there was no difference in basic clinical characteristics between those with and without MRI (EGA 26.1 vs. 26.4 weeks, p=0.41; BW 845 vs. 948 grams, p=0.21; antenatal steroids 83% vs. 85%, p=0.65) or those with and without two-year neurodevelopmental follow-up (EGA 26.3 vs. 26.8 weeks, p=0.21; BW 919 vs. 992 grams, p=0.53; antenatal steroids 85% vs 84%, p=1.00)

A possible future line of inquiry includes whether this system can be adapted to earlier MRI or non-MRI imaging. While the sum total of injury by the IVH mechanism is typically well established by the first 7-10 days of life, WMI takes much longer evolve, with many experts recommending ultrasound surveillance at 30 days of life. While all infants in this study were term-equivalent age at the time of the scan, it is possible that this system could be used at an earlier PMA. Further investigation will be needed to validate this at early gestational ages. An alternative approach could be taken with ultrasound imaging. While this methodology is simpler and less expensive, it lacks the resolution to detect punctate cerebellar and white matter lesions [23,26], essentially eliminating the bottom end of the imaging scale. Significant adaptation would be needed to overcome these challenges.

5. Conclusions

In conclusion, this practical, clinically-focused predictive score, which takes cerebellar and supratentorial injury into account with clinical factors, can reliably differentiate infants with normal-moderate outcomes from those with severe delay. This approach has a substantially improved PPV compared to previous systems. Available as a web-based tool, it can be useful for prognostication and targeting early intervention services to infants who may benefit most from such services.

Supplementary Materials: An interactive web-based calculator, which displays the probability ± SE of severe outcome given clinical and MRI factors, can be accessed at: https://wustl-neo.shinyapps.io/mri-calc/.

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Conflicts of Interest: Declare conflicts of interest or state "The authors declare no conflict of interest." Authors must identify and declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. Any role of the funders in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript, or in the decision to publish the results must be declared in this section. If there is no role, please state "The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results".

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