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Canadian Preterm Brain Injury Consensus Classification for Cranial Ultrasound and Prediction of Neurodevelopmental Outcome in Preterm Infants

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Abstract

Objective

To determine whether classification of severe preterm brain injury using the Canadian cranial ultrasound (cUS) consensus improves prediction of adverse neurodevelopmental outcomes.

Study Design

Infants born < 29 weeks' gestation (2010–2018) with ≥ 3 cUS examinations, any brain injury, and neurodevelopmental assessment at 18–24 months were studied. Brain injury was assessed from serial cUS using the Canadian consensus classification. Severe injury comprised high-grade intraventricular hemorrhage, severe post-hemorrhagic ventricular dilatation, cystic white matter injury, and/or moderate-large cerebellar hemorrhage. Associations with death and/or significant neurodevelopmental impairment were analyzed and compared with historical reporting.

Results

Among 231 infants, 45% had severe brain injury and 39% experienced adverse outcome. Severe injury was independently associated with adverse outcome (OR 5.44, 95% CI 2.85–10.74). Sensitivity was similar to historical reporting, but specificity for cerebral palsy and severe cognitive delay was higher.

Conclusions

The Canadian cUS consensus classification improves neurodevelopmental outcome prediction and may inform early intervention and neuroprotective strategies.

INTRODUCTION

Brain injury remains a frequent and clinically relevant complication in extremely preterm infants (< 29 weeks' gestation). The most common preterm brain injury types are hemorrhagic or ischemic in origin, including germinal matrix-intraventricular hemorrhage (GMH-IVH), cerebellar hemorrhage (CBH) and white matter injury, and can result in secondary periventricular hemorrhagic infarction (PVHI), post-hemorrhagic ventricular dilatation (PHVD) and brain dysmaturation. Severe brain injury is a major risk factor for adverse neurodevelopmental outcomes in preterm-born children [1–3].

Magnetic resonance imaging (MRI) in the neonatal period offers great sensitivity to detect and characterize preterm brain injury, assess progress of brain maturation, and differentiate injury from normal maturational phenomena, thereby contributing to early prognostication [4–8]. However, MRI is impractical as a routine tool, particularly in critically ill, unstable preterm infants. Cranial ultrasound (cUS) is an easily accessible bedside tool for detecting and monitoring preterm brain injury throughout the neonatal period [1]. While MRI is superior to cUS for visualizing more diffuse and subtle injury types and predicting mildly abnormal neurodevelopmental outcomes in preterm infants, serial neonatal cUS accurately identifies most preterm brain injury types and predicts moderately to severely abnormal

outcomes [1]. Therefore, cUS remains the universally preferred and widely used screening tool for brain injury in the preterm population.

In most neonatal intensive care units, it is routine practice to perform serial cUS throughout the neonatal period in all extremely preterm infants. However, variability in the interpretation and classification of preterm brain injury using cUS may lead to variations in outcome prediction and intervention decisions (such as for PHVD), and limit the comparability of injury prevalence and quality of care [9]. A national Quality Improvement initiative, driven by the Canadian Neonatal Network and Canadian Preterm Birth Network, established a consensus recommendation describing a systematic approach to the classification of preterm brain injury from cUS [9]. Through standardization of preterm brain injury reporting across affiliated centers, the overarching goals of the cUS consensus classification were to facilitate injury comparison across centers, identify modifiable risk factors and inform neuroprotective strategies. While the Canadian consensus classification enhances consistency in cUS-based injury diagnosis and grading in extremely preterm infants (*unpublished data*), whether it improves the predictive accuracy for neurodevelopmental outcomes has yet to be investigated. The primary objectives of this study in extremely preterm infants were to: 1) assess associations between preterm brain injury as per the Canadian cUS consensus classification *and* composite outcome of death and/or severe neurodevelopmental impairment (NDI) at 18–24 months' corrected age, and 2) compare sensitivity and specificity for composite outcome of brain injury classified as per consensus versus historical clinical reporting prior to consensus implementation. Secondary objectives were to explore objectives 1 and 2 separately for neurodevelopmental outcome domains.

SUBJECTS AND METHODS

Study Design

This was a retrospective population-based observational cohort study.

Participants

Preterm infants born between January 2010 and March 2018 at a gestational age of 23^{+0}-28^{+6} weeks and admitted to any of the five neonatal units in Calgary, Canada, serving central and southern Alberta, were eligible for the study if they underwent at least three cUS scans throughout the neonatal period and had any type of acquired brain injury on serial cUS. Infants with antenatal brain injury, congenital brain anomalies or infections, chromosomal or metabolic disorders, fetal alcohol syndrome, and those born at less than 23 weeks' gestation or not residing in central or southern Alberta were excluded. Extremely preterm infants born after March 2018 were not included in this study to limit the chance of selection bias related to restricted in-person neurodevelopmental assessments during the COVID-19 pandemic.

For all included infants, relevant clinical variables were retrospectively extracted from electronic medical records and paper medical charts. Collected variables included pregnancy and birth characteristics and

details on perinatal and neonatal morbidity and mortality.

Ethical approval

for this study was obtained from the Conjoint Health Research Ethics Board of the University of Calgary. A waiver of consent was granted due to the non-invasive, retrospective and observational nature of the study and the risk of causing undue distress to parents.

Cranial Ultrasound

All cUS scans of included infants performed throughout the neonatal period and stored electronically on the local diagnostic image viewing system were reviewed. Throughout the study period, cUS examinations were performed by trained sonographers in all extremely preterm infants according to the standard cUS protocol, including at least six coronal and five sagittal planes via the anterior fontanel. In 2014, acquisition of coronal and axial planes through the mastoid window was added to the standard cUS protocol. Serial cUS were performed at least three times during the neonatal period, i.e., postnatal day 5 to 7, day 14 and 36 weeks' postmenstrual age. In case of (suspected) brain injury, the frequency of cUS was increased. All scans were acquired using a General Electric LOQIC E9 ultrasound machine (GE Healthcare, US).

A neonatologist and neuroradiologist (LML and JNS, both with over 20 years of experience with cUS) reviewed all cUS images of eligible infants, blinded to the infant's clinical course. For each cUS, the presence and, if applicable, grade of injury was assessed by consensus, according to the Canadian consensus classification, as previously described [9]. Subsequently, for each infant, the presence and type of brain injury and, if applicable, most severe grade of injury across all cUS scans were recorded. The presence of severe preterm brain injury was defined as presence of any of the following: IVH grade 3, PVHI, severe PHVD (defined as anterior horn width > 10 mm), cystic white matter injury, and/or moderate to large CBH [9]. Brain injury other than severe was categorized as mild-moderate. Additionally, for each infant, the presence and characteristics of preterm brain injury as noted in the clinical cUS reports ('historical' reporting) were retrospectively abstracted from their medical charts. The cUS consensus classification was implemented in our local practice and used for cUS reporting in 2021, after the study period.

Neurodevelopmental Assessments

As per local standard practice, all surviving preterm infants born at less than 29 weeks' gestation are eligible to be seen in the Calgary Neonatal Follow-up Clinic at the Alberta Children's Hospital at 18–24 months' corrected age for assessment of evidence of neurodevelopmental or behavioral impairment. The in-person neurodevelopmental assessment during the study period included history taking, a physical and neurological examination, and Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III), to assess cognitive, motor and speech-language development [10]. For all children, BSID-III composite

scores for cognitive, motor and speech-language development, presence of cerebral palsy (CP) and, if applicable, Gross Motor Functional Classification System (GMFCS) classification were recorded [11, 12]. In addition, presence of hearing and/or vision impairment, and need for neurosensory aid, were noted.

For further analysis, children were divided into different groups based on presence and severity of neurodevelopmental impairment (NDI): 1) no NDI; 2) any NDI, defined as one or more of the following: CP of any severity, significant visual impairment (defined as ≥ 1 of: corrected visual acuity < 20/60 and > 20/200 but not bilaterally blind; unilateral blindness; nystagmus; registered with CNIB but not legally blind) or bilateral blindness, mild-moderate neurosensory hearing loss/deafness (defined as any neurosensory hearing loss not requiring amplification/cochlear implants or unilateral deafness requiring amplification) or bilateral deafness, or any BSID-III composite score < 85; 3) significant NDI, defined as one or more of the following: CP with GMFCS 3–5, bilateral blindness (defined as ≥ 1 of: corrected visual acuity < 20/200 in the better eye, light perception or less in the better eye, cortical blindness or atrophy, legally blind with clinical diagnosis), bilateral deafness (defined as bilateral neurosensory hearing loss or auditory neuropathy requiring amplification/cochlear implant), or any BSID-III composite score < 70 [13].

Outcome Measures

The primary outcome was defined as composite of death and/or significant NDI at assessment at 18–24 months' corrected age. Secondary outcomes included mortality, presence and severity of any NDI, presence of any CP, and any BSID-III composite score < 70 at 18–24 months' corrected age.

Statistical Analysis

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, US). For descriptive statistics, categorical variables are presented as number and percentage (%), and continuous variables as mean and standard deviation (SD) for normally distributed variables or median and interquartile ranges (IQR) for non-normally distributed variables. Baseline infant characteristics were compared between infants with and without severe preterm brain injury using the Chi-square or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for continuous variables.

Associations between cUS findings as per the consensus classification (mild-moderate brain injury versus severe brain injury) and neurodevelopmental outcomes were assessed using logistic regression models, with and without adjustment for gestational age at birth, antenatal corticosteroid administration, 5-minute Apgar score < 5, being outborn, presence of bronchopulmonary dysplasia, persistent ductus arteriosus requiring treatment and sex. Covariates were selected based on univariate results and clinical significance. Logistic regression models adjusted for covariates were repeated for the secondary neurodevelopmental outcomes. Results of regression analysis are reported as odds ratios (OR) and 95% confidence intervals (CI). In addition, exact McNemar tests were used to compare sensitivity and specificity for predicting neurodevelopmental outcomes of cUS-based injury diagnosis and grading as per

consensus classification versus historical reporting prior to consensus implementation. All tests were two-sided, with level of significance set as $P < 0.05$.

RESULTS

Infant Characteristics

A total of 1,015 extremely preterm infants were born during the study period, of whom 284 (28%) met the inclusion criteria of ≥ 3 cUS scans and presence of any preterm brain injury. Twenty-eight (10%) infants were subsequently excluded, of whom 22 for congenital anomalies, one for birth at < 23 weeks, and five for poor quality cUS scans. Of the remaining 256 infants, 25 (10%) were lost to follow-up prior to the 18–24 month developmental assessment. A total of 231 (90%) infants were included in the final analysis, of whom 15 (6%) died before the 18–24 month assessment (Fig. 1). Mean gestational age and birthweight were 26.1 weeks (SD ± 1.6 weeks) and 852 grams (SD ± 235 grams), respectively, and just over half (56.3%) were male. Baseline characteristics and cUS findings of eligible infants are shown in Table 1.

Table 1
Baseline characteristics and cranial ultrasound findings for all eligible infants.

Infant and cUS findings	Eligible infants (n = 256)
Pregnancy and perinatal factors	
Gestational age at birth (weeks)	26.1 (1.6)
Birthweight (grams)	852 (235)
Small for gestational age < 10th percentile (Fenton curves)	18 (7.0%)
Maternal age (years)	30 (5)
Multiple birth	77 (30.1%)
Outborn	33 (12.9%)
Antenatal corticosteroids	230 (89.8%)
C-section delivery	130 (50.8%)
5-minute Apgar < 5	42 (16.4%)
Male	144 (56.3%)
Clinical chorio-amnionitis	86/250 (34.4%)
Cord pH < 7.0	8/181 (4.4%)
Hypotension requiring inotropes (dopamine/dobutamine/epinephrine/other)	135 (52.7%)
Patent ductus arteriosus	193 (75.4%)
- Requiring medical/surgical treatment	156 (60.9%)
Invasive ventilation	239 (93.4%)
- Requirement	14 (28)
- Duration (days), median (IQR)	
Blood culture proven sepsis	64 (25.0%)
Cerebrospinal fluid culture proven meningitis	3 (1.2%)
Necrotizing enterocolitis ≥ Stage 2	35 (13.7%)
Bronchopulmonary dysplasia	177/249 (71.1%)
Postnatal steroids (dexamethasone/hydrocortisone)	83 (32.4%)

Characteristics are presented as mean (and standard deviation [SD]), median (and interquartile range [IQR]).or number (and percentage of total [%]).

Infant and cUS findings	Eligible infants (n = 256)
Pregnancy and perinatal factors	
Retinopathy of prematurity ≥ Stage 3 or treated	47/219 (21.5%)
Seizures	12/255 (4.7%)
cUS findings	
Highest germinal matrix-intraventricular hemorrhage	73 (28.5%)
- Grade 1	113 (44.1%)
- Grade 2	70 (27.3%)
- Grade 3	
Periventricular hemorrhagic infarction	72 (28.1%)
Post-hemorrhagic ventricular dilatation	53 (20.7%)
Cystic white matter injury	14/246 (5.7%)
Cerebellar hemorrhage	13 (5.1%)
- Grade 1	6/13 (46.2%)
- Grade 2	1/13 (7.7%)
- Grade 3	6/13 (46.2%)
Other lesions	89/216 (41.2%)
Characteristics are presented as mean (and standard deviation [SD]), median (and interquartile range [IQR]).or number (and percentage of total [%]).	

cUS Findings

Of the 231 included infants, 103 (45%) showed severe and 128 (55%) showed mild-moderate brain injury on serial cUS. Baseline characteristics for the infants with mild-moderate and with severe brain injury are shown in Table 2. Severe brain injury was significantly more common in younger preterm infants, males and infants with 5-minute Apgar score < 5. In addition, they experienced more hypotension requiring inotropes and seizures compared to infants with mild-moderate brain injury ($P < 0.05$ for all).

Table 2
Comparison of baseline characteristics between infants with mild-moderate and with severe preterm brain injury.

Infant parameters	**Mild-Moderate Brain Injury (n = 128)**	**Severe Brain Injury (n = 103)**	***P* value**
Gestational age at birth (weeks)	26.3 (1.5)	25.8 (1.6)	**0.028***
Birthweight (grams)	861 (240)	836 (223)	0.416
SGA < 10th percentile (Fenton curves)	10 (7.8%)	7 (6.8%)	0.769
Maternal age (years)	31 (6)	30 (5)	0.180
Multiple Birth	38 (29.7%)	29 (28.2%)	0.799
Outborn	16 (12.5%)	17 (16.5%)	0.387
Antenatal corticosteroids	119 (93.0%)	90 (87.4%)	0.150
C-section	59 (46.1%)	55 (53.4%)	0.270
5-minute Apgar < 5	14 (10.9%)	24 (23.3%)	**0.012***
Male	65 (50.8%)	67 (65.0%)	**0.029***
Clinical chorio-amnionitis	48/125 (38.4%)	31/100 (31.0%)	0.248
Cord pH < 7.0	3/87 (3.4%)	4/77 (5.2%)	0.707
Hypotension requiring inotropes (dopamine/dobutamine/epinephrine/other)	56 (43.8%)	67 (65.0%)	**0.001***
Patent ductus arteriosus	95 (74.2%)	81 (78.6%)	0.433
- Requiring medical/surgical treatment	84 (65.6%)	59 (57.3%)	0.194
Invasive ventilation	117 (91.4%)	98 (95.1%)	0.266
- Requirement	11 (26)	16 (25)	0.119
- Duration (days), median (IQR)			
Blood culture proven sepsis	29 (22.7%)	30 (29.1%)	0.262
CSF culture proven sepsis	2 (1.6%)	1 (1.0%)	> 0.999
Necrotizing enterocolitis ≥ Stage 2	15 (11.7%)	17 (16.5%)	0.295

Characteristics are presented as mean (and standard deviation [SD]) or number (and percentage of total [%]). *, significant *P* values. SGA, small for gestational age; CSF, cerebrospinal fluid; ROP, retinopathy of prematurity.

Infant parameters	Mild-Moderate Brain Injury (n = 128)	Severe Brain Injury (n = 103)	*P* value
Bronchopulmonary dysplasia	92/126 (73.0%)	69/99 (69.7%)	0.584
Postnatal corticosteroids	41 (32.0%)	32 (31.1%)	0.876
ROP ≥ Stage 3 or treated	24/114 (21.1%)	18/85 (21.2%)	0.983
Seizures	1 (0.8%)	11/102 (10.8%)	**< 0.001***

Characteristics are presented as mean (and standard deviation [SD]) or number (and percentage of total [%]). *, significant *P* values. SGA, small for gestational age; CSF, cerebrospinal fluid; ROP, retinopathy of prematurity.

Neurodevelopmental Outcomes

Data on neurodevelopmental assessment were available for 216 out of the 231 included infants (94%); 15 infants (6%) died prior to the 18–24 month assessment (Fig. 1). Mean age at assessment was 21 months (range 18–29 months) corrected age. Of the 179 children with primary outcome data, 70 (39%) had primary outcome of death and/or significant NDI. A total of 40 out of 216 children (19%) with available motor development data were diagnosed with CP, of whom 10 (25%) were classified as severe (GMFCS 3–5). Details on neurodevelopmental outcomes are shown in Table 3.

Table 3

Neurodevelopmental outcomes at mean of 21 months (range 18–29 months) corrected age for all included children and divided by severity of brain injury on neonatal cUS, and comparison of outcomes between children with mild-moderate versus severe brain injury.

Neurodevelopmental outcomes	**All Included Children (n = 231)**	**Mild-Moderate Brain Injury (n = 128)**	**Severe Brain Injury (n = 103)**	**Crude OR (95% CI) Severe versus mild-moderate brain injury**
Primary outcome				
Death or significant NDI	70/179 (39.1%)	19/92 (20.7%)	51/87 (58.6%)	**5.44 (2.85–10.74)***
Secondary outcomes				
Death or any NDI	138/195 (70.8%)	60/104 (57.7%)	78/91 (85.7%)	**4.40 (2.23–9.19)***
Any NDI	123/180 (68.3%)	59/103 (57.3%)	64/77 (83.1%)	**3.67 (1.84–7.72)***
Significant NDI	55/164 (33.5%)	18/91 (19.8%)	37/73 (50.7%)	**4.17 (2.12–8.46)***
Cerebral Palsy (any severity)	40/216 (18.5%)	2/127 (1.6%)	38/89 (42.7%)	**46.57 (13.57–292.9)***
BSID-III cognitive score < 70	20/208 (9.6%)	1/123 (0.8%)	19/85 (22.4%)	**35.12 (7.05–638.1)***
Death	15/231 (6.5%)	1/128 (0.8%)	14/103 (13.6%)	**19.98 (3.91–365.3)***
Other individual outcomes				
Cerebral palsy GMFCS 3–5	10/216 (4.6%)	0/127 (0.0%)	10/89 (11.2%)	NA
Significant visual impairment or bilateral blindness	13/215 (6.0%)	0/126 (0.0%)	13/89 (14.6%)	NA
Bilateral blindness	3/215 (1.4%)	0/126 (0.0%)	3/89 (3.4%)	NA
Any neurosensory hearing loss	4/214 (1.9%)	2/126 (1.6%)	2/88 (2.3%)	1.44 (0.17–12.20)
Bilateral deafness	4/214 (1.9%)	2/126 (1.6%)	2/88 (2.3%)	1.44 (0.17–12.20)

Outcomes are presented as number (and percentage of total [%]). *, significant crude OR. OR, odds ratio; CI, confidence interval; NDI, neurodevelopmental impairment; BSID-III, Bayley Scales of Infant and Toddler Development, 3rd edition; GMFCS, Gross Motor Functional Classification System; NA, not applicable.

Neurodevelopmental outcomes	All Included Children (n = 231)	Mild-Moderate Brain Injury (n = 128)	Severe Brain Injury (n = 103)	Crude OR (95% CI) Severe versus mild-moderate brain injury
Primary outcome				
BSID-III cognitive score < 85	56/208 (26.9%)	19/123 (15.4%)	37/85 (43.5%)	**4.22 (2.23–8.22)***
BSID-III language score < 85	82/179 (45.8%)	40/101 (39.6%)	42/78 (53.8%)	1.78 (0.98–3.25)
BSID-III language score < 70	40/179 (22.3%)	16/101 (15.8%)	24/78 (30.8%)	**2.36 (1.16–4.92)***
BSID-III motor score < 85	77/169 (45.6%)	29/101 (28.7%)	48/68 (70.6%)	**5.96 (3.07–11.94)***
BSID-III motor score < 70	26/169 (15.4%)	2/101 (2.0%)	24/68 (35.3%)	**27.00 (7.57–172.7)***

Outcomes are presented as number (and percentage of total [%]). *, significant crude OR. OR, odds ratio; CI, confidence interval; NDI, neurodevelopmental impairment; BSID-III, Bayley Scales of Infant and Toddler Development, 3rd edition; GMFCS, Gross Motor Functional Classification System; NA, not applicable.

Associations between Severe Brain Injury and Neurodevelopmental Outcomes

Severe preterm brain injury was associated with significantly increased risk of composite of death and/or significant NDI and secondary outcomes of death, any and significant NDI, any CP, BSID-III composite cognitive score < 85 and < 70, composite language score < 70, and composite motor score < 85 and < 70 (Table 3). No associations were found for neurosensory impairments.

After adjustment for covariates, children with severe preterm brain injury still had significantly higher odds of a composite of death and/or significant NDI (adjusted OR 4.29, 95% CI 2.10–9.05), death and/or any NDI (adjusted OR 4.06, 95% CI 1.96–8.91), any NDI (adjusted OR 3.85, 95% CI 1.83–8.35), significant NDI (adjusted OR 3.85, 95% CI 1.83–8.35), any CP (adjusted OR 51.2, 95% CI 14.1–335), BSID-III composite cognitive score < 70 (adjusted OR 31.7, 95% CI 6.18–180), and death (adjusted OR 8.93, 95% CI 1.32–180).

Accuracy of cUS Findings as per Consensus Classification versus Historical Reporting for Neurodevelopmental Outcome Prediction

Comparison of sensitivity of cUS-based injury diagnosis as per consensus classification versus historical reporting for predicting neurodevelopmental outcomes showed no differences for the children with

adverse neurodevelopmental outcomes, with generally high sensitivity for outcomes for both cUS injury classifications (Table 4). However, absence of severe preterm brain injury and IVH grade 3 as per consensus classification showed significantly higher specificity for the absence of CP and significantly abnormal cognitive outcome (BSID-III composite score < 70) than historical reporting. No significant difference in specificity was found for other brain injury types or neurodevelopmental domains (Table 4).

Table 4

Predictive values of cUS findings as per consensus scoring versus historical reporting prior to consensus implementation for adverse outcomes at 18–29 months corrected age.

Neurodevelopmental outcomes	Sensitivity		*P* value	Specificity		*P* value
	Consensus Classification	Historical Reporting		Consensus Classification	Historical Reporting	
Death or Significant NDI						
Severe brain injury	51/70 (72.9%)	54/70 (64.3%)	0.070	73/109 (67.0%)	67/109 (61.5%)	0.210
IVH Grade 3	35/70 (50.0%)	36/70 (51.4%)	> 0.999	86/109 (78.9%)	84/109 (77.1%)	0.791
PVHI	35/70 (50.0%)	30/70 (42.9%)	0.302	86/109 (78.9%)	81/109 (74.3%)	0.180
PHVD	30/70 (42.9%)	31/70 (44.3%)	> 0.999	96/109 (88.1%)	94/109 (86.2%)	0.625
Death or Any NDI						
Severe brain injury	78/138 (56.5%)	79/138 (57.2%)	> 0.999	44/57 (77.2%)	41/57 (71.9%)	0.549
IVH Grade 3	53/138 (38.4%)	56/138 (40.6%)	0.648	49/57 (86.0%)	48/57 (84.2%)	> 0.999
PVHI	57/138 (41.3%)	56/138 (40.6%)	> 0.999	52/57 (91.2%)	49/57 (86.0%)	0.375
PHVD	42/138 (30.4%)	44/138 (31.9%)	0.754	54/57 (94.7%)	54/57 (94.7%)	NA
Any NDI						
Severe brain injury	64/123 (52.0%)	66/123 (53.7%)	0.804	44/57 (77.2%)	41/57 (71.9%)	0.549
IVH Grade 3	43/123 (35.0%)	46/123 (37.4%)	0.607	49/57 (86.0%)	48/57 (84.2%)	> 0.999
PVHI	45/123 (36.6%)	49/123 (39.8%)	0.424	52/57 (91.2%)	49/57 (86.0%)	0.375
PHVD	32/123 (26.0%)	35/123 (28.5%)	0.508	54/57 (94.7%)	53/57 (94.7%)	NA
Significant NDI						

Outcomes are presented as number (and percentage of total [%]). *, significant *P* values. NDI, neurodevelopmental impairment; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; PHVD, post-hemorrhagic ventricular dilatation; NA, not applicable as there were no discordant pairs; BSID-III, 3rd edition, Bayley Scales of Infant and Toddler Development.

Neurodevelopmental outcomes	Sensitivity		*P* value	Specificity		*P* value
	Consensus Classification	Historical Reporting		Consensus Classification	Historical Reporting	
Death or Significant NDI						
Severe brain injury	37/55 (67.3%)	32/55 (58.2%)	0.125	73/109 (67.0%)	67/109 (61.5%)	0.210
IVH Grade 3	25/55 (45.5%)	26/55 (47.3%)	> 0.999	86/109 (78.9%)	84/109 (77.1%)	0.791
PVHI	23/55 (41.8%)	23/55 (41.8%)	> 0.999	86/109 (78.9%)	81/109 (74.3%)	0.180
PHVD	20/55 (36.4%)	22/55 (40.0%)	0.625	96/109 (88.1%)	94/109 (86.2%)	0.625
Cerebral Palsy (any)						
Severe brain injury	38/40 (95.0%)	37/40 (92.5%)	> 0.999	125/176 (71.0%)	113/176 (64.2%)	**0.043***
IVH Grade 3	30/40 (75.0%)	29/40 (72.5%)	> 0.999	152/176 (86.4%)	140/176 (79.5%)	**0.036***
PVHI	32/40 (80.0%)	32/40 (80.0%)	> 0.999	152/176 (86.4%)	144/176 (81.8%)	0.115
PHVD	21/40 (52.5%)	22/40 (55.0%)	> 0.999	157/176 (89.2%)	155/176 (88.1%)	0.625
BSID-III cognitive score < 70						
Severe brain injury	19/20 (95.0%)	16/20 (80.0%)	0.250	122/188 (64.9%)	107/188 (56.9%)	**0.008***
IVH Grade 3	14/20 (70.0%)	12/20 (60.0%)	0.625	149/188 (79.3%)	137/188 (72.9%)	**0.036***
PVHI	12/20 (60.0%)	12/20 (60.0%)	> 0.999	146/188 (77.7%)	137/188 (72.9%)	0.064
PHVD	12/20 (60.0%)	13/20 (65.0%)	> 0.999	162/188 (86.2%)	160/188 (85.1%)	0.727

Outcomes are presented as number (and percentage of total [%]). *, significant *P* values. NDI, neurodevelopmental impairment; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; PHVD, post-hemorrhagic ventricular dilatation; NA, not applicable as there were no discordant pairs; BSID-III, 3rd edition, Bayley Scales of Infant and Toddler Development.

DISCUSSION

In this study, the presence of severe brain injury on cUS as defined by the Canadian preterm brain injury consensus classification accurately and independently predicted adverse neurodevelopmental outcomes

at 18–24 months' corrected age in extremely preterm infants. Comparing severe brain injury as per the consensus classification with historical reporting, we found that, while the sensitivity for adverse outcomes was comparable, the consensus classification yielded significantly higher specificity for predicting the absence of CP and significant cognitive delay. This suggests that the standardized approach to diagnoses and grading of preterm brain injury using cUS contributes to reliable identification of infants at the highest risk for death or significant NDI, while offering greater certainty in predicting favorable outcomes in absence of severe brain injury.

The predictive value of preterm brain injury diagnosed from cUS in our study aligns with existing literature on cUS-based prognostication. Previous studies have consistently shown that severe brain injury on cUS is highly predictive of moderate-to-severe NDI, while prediction of milder impairments is often more variable, probably in part related to the limited sensitivity of cUS to detect more diffuse and subtle lesions [14–20]. The high sensitivity of the consensus classification observed across all outcomes, comparable to historical reporting and consistent with prior studies, was expected as severe injury is typically identified on cUS. However, a key advantage of the injury consensus classification over local historical reporting is the enhanced specificity. By providing standardized criteria, such as for differentiating grade 2 from grade 3 IVH by quantifying ventricular size and for distinguishing PVHI from transient periventricular echodensities, the consensus framework may reduce misclassification of milder or transient injury as severe injury from cUS [9, 21, 22]. As a result, when a cUS does not show severe brain injury according to the consensus classification, clinicians can predict the absence of CP and significant cognitive delays with greater confidence.

Accurate prognostication is essential for providing evidence-based family counseling and facilitating timely and targeted enrollment of high-risk infants into neuroprotective and development-promoting interventions. The implementation of neuroprotection bundles in the care of extremely preterm infants during admission to the neonatal unit has proven to effectively reduce acute brain injury and improve long-term neurodevelopmental outcomes [23, 24]. In addition, post-discharge intervention programs initiated early in the window of brain development plasticity show promise for improving the functioning of children born extremely preterm anticipated to have significantly abnormal outcomes [25]. Equally important as accurate prognostication is the reliability and practicality of the classification system used as a prognostic marker, particularly in view of multicenter studies and Quality Improvement initiatives [26]. While highly detailed quantitative scoring systems for cUS offer high predictive capabilities, their clinical utility is often limited by their complexity and the time required for image analysis [27–29]. The Canadian cUS consensus classification addresses this limitation by maintaining simplicity while standardizing diagnostic thresholds [9].

The presence of severe brain injury in our cohort was primarily accounted for by high-grade IVH, i.e., grade 3 IVH and PVHI, with their absence driving more favorable motor and cognitive outcomes. This is consistent with recent reviews demonstrating that high-grade IVH, and secondary PHVD and brain dysmaturation, are independent predictors of developmental delays across multiple domains [30, 31]. The predictive value of PHVD as per the consensus classification for outcomes was similar to historical

reporting and prior studies [32, 33]. While the cUS consensus classification includes definitions for CBH grades, derived from Boswinkel et al. [34], the overall number of infants with isolated CBH was too small to be analyzed as an independent predictor of outcomes. Nevertheless, accurate identification of PHVD and CBH remains crucial. Evidence demonstrates that larger CBH and progressive PHVD, even in the absence of clinical symptoms, predispose affected preterm infants to NDI, and augment the risk for NDI associated with high-grade IVH [31, 35–37].

This study has several limitations. The retrospective design and eight-year-long study period may have introduced potential unmeasured confounding factors, influencing neurodevelopmental trajectories, related to evolution of clinical care, imaging protocols, and follow-up practices. Routine assessment of the posterior fossa via the mastoid window was introduced as standard practice halfway through the study period. Although the prevalence of CBH did not differ before and after this practice implementation (5% and 4%, respectively), CBH may have remained underdiagnosed in the earlier cohort, limiting our ability to evaluate its independent impact on adverse outcomes. As the study was aimed at assessing associations between consensus-derived brain injury classification and neurodevelopmental outcomes, we did not include infants without brain injury on cUS, limiting our ability to explore increases in risk from baseline in extremely preterm infants. Finally, the exclusion of infants who did not have at least three cUS scans and those who were lost to follow-up prior to the Neonatal Follow-up Clinic visit may have introduced bias into our prediction models. However, no significant differences in clinical course and cUS-based injury were present between included and excluded infants. In addition, study limitations are partly mitigated by the use of adjusted multivariate regression models and blinded review of all serial cUS scans by an experienced neonatologist and neuroradiologist.

In conclusion, the standardized Canadian preterm brain injury consensus classification is a reliable, systematic and clinically practical tool for prognosticating neurodevelopmental outcomes in extremely preterm infants. By improving accuracy for ruling out significant motor and cognitive impairment as compared to our non-standardized pre-consensus implementation cUS reporting, the consensus classification may give clinicians greater confidence in counseling families about favorable outcomes in the absence of severe brain injury, particularly high-grade IVH. Broader institutional adoption of these standardized diagnostic cUS criteria has the potential to reduce diagnostic variability, improve the reliability of international benchmarking and multicenter studies, and facilitate the early identification of infants requiring intensive neurodevelopmental support.

Declarations

Conflict of interest:

The authors declare no competing financial interests.

Ethics approval and consent to participate:

Ethical approval for this study was obtained from the Conjoint Health Research Ethics Board of the University of Calgary (REB21-1127). A waiver of consent was granted due to the non-invasive, retrospective and observational nature of the study and the risk of causing undue distress to parents. This study was performed in accordance with the Declaration of Helsinki.

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Author Contributions:

LML and KM: major contributions to conception and design, acquisition of data, analysis and interpretation of data, and writing and revising the manuscript; LH and AB: substantial contributions to acquisition of data, interpretation of data, and revising the manuscript; ST: substantial contributions to acquisition of data, analysis interpretation of data, and revising the manuscript; JNS and SM: substantial contributions to acquisition of data and revising the manuscript; all authors provided final approval of the version to be published.

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Data availability statement:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. van Wezel-Meijler G, Mohammad K, editors. Neonatal brain injury: an illustrated guide for clinicians counselling parents and caregivers. Springer Cham, 2025. doi: 10.1007/978-3-031-55972-3
2. Ybarra M, Miller SP. Advances in preterm brain injury. Pediatr Clin North Am 2025;72(5):919–937. doi: 10.1016/j.pcl.2025.05.009
3. Burnett A, Axford SB, Seid AM, Anderson PJ, Waterland JL, Gilchrist CP, et al. Predicting long-term neurodevelopmental outcomes for children born very preterm: a systematic review. Arch Dis Child Fetal Neonatal Ed 2026;111(2):F169-F176. doi: 10.1136/archdischild-2025-328891

4. Miller SP, Ferriero DM, Leonard C, Piecuch R, Glidden DV, Partridge JC, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Pediatr 2005;147:609–616. doi: 10.1016/j.jpeds.2005.06.033
5. Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics 2014;134:e444-453. doi: 10.1542/peds.2013-2336
6. Cayam-Rand D, Guo T, Grunau RE, Benavente-Fernández I, Synnes A, Chau V, et al. Predicting developmental outcomes in preterm infants: a simple white matter injury imaging rule. Neurology 2019;93:e1231-1240. doi: 10.1212/WNL.0000000000008172
7. Martinez-Biarge M, Arnaez J, Arca G, Valverde E, Llorens-Salvador R, García-Alix A; en representación del Grupo Cerebro Neonatal Español. Recommendations for the use of brain MRI in the neonatal period. An Pediatr 2025;103(3):503935. doi: 10.1016/j.anpede.2025.503935
8. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685–694. doi: 10.1056/NEJMoa053792
9. Mohammad K, Scott JN, Leijser LM, Zein H, Afifi J, Piedboeuf B, et al. Consensus approach for standardizing the screening and classification of preterm brain injury diagnosed with cranial ultrasound: a Canadian perspective. Front Pediatr 2021;11;9:607684. doi: 10.3389/fped.2021.618236
10. Bayley N. Bayley scales of infant and toddler development, third edition: technical manual, 3rd ed. Harcourt: San Antonio, TX, 2006
11. Russman BS, Gage JR. Cerebral palsy. Curr Probl Pediatr 1989;19:65–111. doi: 10.1016/0045-9380(89)90010-8
12. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–223. doi: 10.1111/j.1469-8749.1997.tb07414.x
13. Synnes A, Luu TM, Moddemann D, Church P, Lee D, Vincer M, et al; Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network. Determinants of developmental outcomes in a very preterm Canadian cohort. Arch Dis Child Fetal Neonatal Ed 2017;102:F235–F234. doi: 10.1136/archdischild-2016-311228
14. Leijser LM, de Bruïne FT, van der Grond J, Steggerda SJ, Walther FJ, van Wezel-Meijler G. Is sequential cranial ultrasound reliable for detection of white matter injury in very preterm infants? Neuroradiology 2010;52(5):397–406. doi: 10.1007/s00234-010-0668-7
15. Tréluyer L, Chevallier M, Jarreau PH, Baud O, Benhammou V, Gire C, et al. Intraventricular hemorrhage in very preterm children: mortality and neurodevelopment at age 5. Pediatrics 2023;151(4):e2022059138. doi: 10.1542/peds.2022-059138
16. Rees P, Callan C, Chadda KR, Vaal M, Diviney J, Sabti S, et al. Preterm brain injury and neurodevelopmental outcomes: a meta-analysis. Pediatrics 2022;150(6):e2022057442. doi: 10.1542/peds.2022-057442

17. Franckx H, Hasaerts D, Huysentruyt K, Cools F. Cranial ultrasound and neurophysiological testing to predict neurological outcome in infants born very preterm. Dev Med Child Neurol. 2018;60(12):1232–1238. doi: 10.1111/dmcn.13961
18. Hintz SR, Bann CM, Vohr BR, McGowan EC, Vaucher YE, Fuller MG, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal neuroimaging among children born extremely preterm and motor coordination impairment at school-age. J Pediatr 2025;285:114704. doi: 10.1016/j.jpeds.2025.114704
19. Campbell H, Check J, Kuban KCK, Leviton A, Joseph RM, Frazier JA, et al. Neonatal cranial ultrasound findings among infants born extremely preterm: associations with neurodevelopmental outcomes at 10 years of age. J Pediatr 2021;237:197–205.e4. doi: 10.1016/j.jpeds.2021.05.059
20. Hintz SR, Barnes PD, Bulas D, Slovis TL, Finer NN, Wrage LA, et al; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. Pediatrics 2015;135(1):e32-42. doi: 10.1542/peds.2014-0898
21. Hand IL, Shellhaas RA, Milla SS; committee on fetus and newborn, section on neurology, section on radiology. Routine neuroimaging of the preterm brain. Pediatrics 2020;146(5):e2020029082. doi: 10.1542/peds.2020-029082
22. Parodi A, Govaert P, Horsch S, Bravo MC, Ramenghi LA; eurUS.brain group. Cranial ultrasound findings in preterm germinal matrix haemorrhage, sequelae and outcome. Pediatr Res 2020;87(Suppl 1):13–24. doi: 10.1038/s41390-020-0780-2
23. Murthy P, Zein H, Thomas S, Scott JN, Abou Mehrem A, Esser MJ, et al. Neuroprotection care bundle implementation to decrease acute brain injury in preterm infants. Pediatr Neurol 2020;110:42–48. doi: 10.1016/j.pediatrneurol.2020.04.016
24. Benlamri A, Murthy P, Zein H, Thomas S, Scott JN, Abou Mehrem A, et al. Neuroprotection care bundle implementation is associated with improved long-term neurodevelopmental outcomes in extremely premature infants. J Perinatol 2022;42(10):1380–1384. doi: 10.1038/s41372-022-01443-0
25. Orton J, Doyle LW, Tripathi T, Boyd R, Anderson PJ, Spittle A. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane Database Syst Rev 2024;2(2):CD005495. doi: 10.1002/14651858.CD005495.pub5
26. Shukla VV, Klinger A, Yazdi S, Rahman AKMF, Wright S, Barganier A, et al. Prevention of severe brain injury in very preterm neonates: A quality improvement initiative. J Perinatol 2022;42(10):1417–1423. doi: 10.1038/s41372-022-01437-y
27. Skiöld B, Hallberg B, Vollmer B, Ådén U, Blennow M, Horsch S. A novel scoring system for term-equivalent age cranial ultrasound in extremely preterm infants. Ultrasound Med Biol 2019;45(3):786–794. doi: 10.1016/j.ultrasmedbio.2018.11.005
28. Agut T, Alarcon A, Cabañas F, Bartocci M, Martinez-Biarge M, Horsch S; eurUS.brain group. Preterm white matter injury: ultrasound diagnosis and classification. Pediatr Res 2020;87(Suppl 1):37–49. doi: 10.1038/s41390-020-0781-1

29. Cuzzilla R, Cowan FM, Rogerson S, Anderson PJ, Doyle LW, Cheong JLY, Spittle A. Relationships between early postnatal cranial ultrasonography linear measures and neurodevelopment at 2 years in infants born at < 30 weeks' gestational age without major brain injury. Arch Dis Child Fetal Neonatal Ed 2023;108(5):511–516. doi: 10.1136/archdischild-2022-324660
30. Rees P, Dronavalli M, Carter B, Dickson M, Green C, Lawler K, et al. School performance of preterm-born children after intraventricular hemorrhage. JAMA Netw Open 2025;8(12):e2547584. doi: 10.1001/jamanetworkopen.2025.47584
31. Leijser LM, de Vries LS, Cizmeci MN. Long-term neurodevelopmental outcomes and follow-up of germinal matrix-intraventricular hemorrhage in preterm infants. Semin Fetal Neonatal Med 2026:101733, online ahead of print. doi: 10.1016/j.siny.2026.101733
32. Lai GY, Abdelmageed S, DeRegnier RO, Gaebler-Spira D, Dizon MLV, Lam SK. Degree of ventriculomegaly predicts school-aged functional outcomes in preterm infants with intraventricular hemorrhage. Pediatr Res 2022;91(5):1238–1247. doi: 10.1038/s41390-021-01631-2
33. Groulx-Boivin E, Paquette M, Khairy M, Beltempo M, Dudley R, Ferrand A, et al. Spontaneous resolution of post-hemorrhagic ventricular dilatation in preterm newborns and neurodevelopment. Pediatr Res 2023;94(4):1428–1435. doi: 10.1038/s41390-023-02647-6
34. Boswinkel V, Steggerda SJ, Fumagalli M, Parodi A, Ramenghi LA, Groenendaal F, et al. The CHOPIn study: a multicenter study on cerebellar hemorrhage and outcome in preterm infants. Cerebellum 2019;18(6):989–998. doi:10.1007/s12311-019-01053-1.
35. Musiime GM, Mohammad K, Momin S, Kwong GPS, Riva-Cambrin J, Scott J, et al. Prediction of post-hemorrhagic ventricular dilatation trajectory using a growth mixture model in preterm infants. Pediatr Res 2025;97(1):213–221. doi: 10.1038/s41390-024-03396-w
36. Hortensius LM, Dijkshoorn ABC, Ecury-Goossen GM, Steggerda SJ, Hoebeek FE, Benders M, Dudink J. Neurodevelopmental consequences of preterm isolated cerebellar hemorrhage: a systematic review. Pediatrics 2018;142(5):e20180609. doi: 10.1542/peds.2018-0609
37. Villamor-Martinez E, Fumagalli M, Alomar YI, Passera S, Cavallaro G, Mosca F, Villamor E. Cerebellar hemorrhage in preterm infants: a meta-analysis on risk factors and neurodevelopmental outcome. Front Physiol 2019;10:800. doi: 10.3389/fphys.2019.00800

Figures

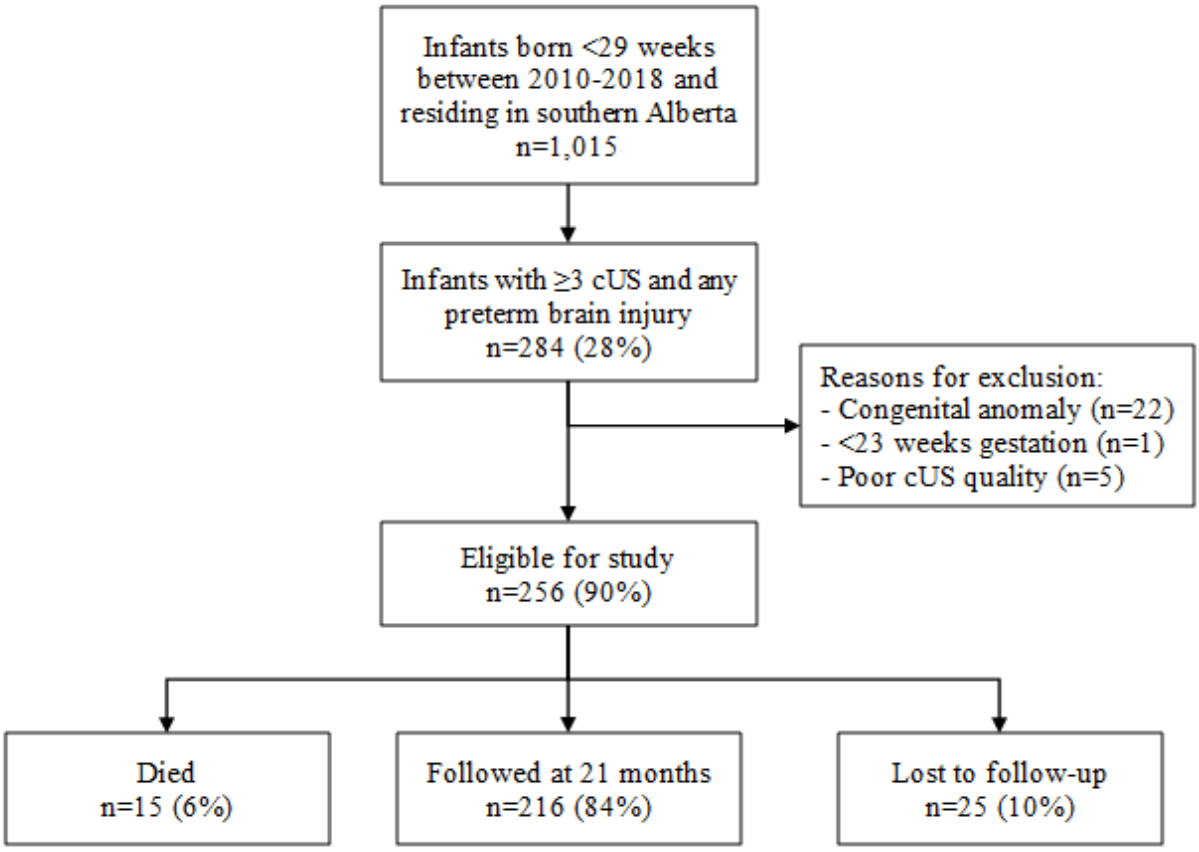


Figure 1

Flow diagram of study population. cUS, cranial ultrasound