ORIGINAL ARTICLES

Predictors of Severe Neurologic Injury on Ultrasound Scan of the Head and Risk Factor-based Screening for Infants Born Preterm

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Objective To identify risk factors for severe neurologic injury (intraventricular hemorrhage grade 3 or greater and/or periventricular leukomalacia) diagnosed by ultrasound scan of the head among infants born at 30^0-32^6 weeks of gestation and compare different screening strategies.

Study design This was a retrospective cohort study of infants born at 30^0-32^6 weeks or >32^6 weeks of gestation with a birth weight <1500 g admitted to neonatal intensive care units in the Canadian Neonatal Network from 2011 to 2016. Stepwise logistic regression analysis was used to identify significant risk factors and calculate aORs and 95% CIs. Risk factor-based screening strategies were compared.

Results The rate of severe neurologic injury was 3.1% among infants screened (285/9221). Significant risk factors included singleton birth (aOR 1.96, 95% CI 1.35-2.85), 5-minute Apgar <7 (aOR 1.81, 95% CI 1.30-2.50), mechanical ventilation on day 1 (aOR 2.65, 95% CI 1.88-3.71), and treatment with vasopressors on day 1 (aOR 3.23, 95% CI 2.19-4.75). Risk categories were low (no risk factor, 1.2%, 25/2137), moderate (singleton with no other risk factor: 1.8%, 68/3678), and high (≥1 risk factor among 5-minute Apgar <7, receipt of vasopressors or mechanical ventilation on day 1: 5.6%, 192/3408). Screening moderate- to high-risk infants identified 91% (260/285) of infants with severe neurologic injury and would require screening fewer infants (1647 infants per year) than screening all infants <33 weeks of gestation (2064 infants screened per year, 93% [265/285] of cases identified).

Conclusions Risk factor-based ultrasound scan of the head screening among infants born at 30-32 weeks of gestation could help optimize resources better than gestational age based screening. *(J Pediatr 2019;214:27-33)*.

Infants born preterm at <33 weeks of gestation are at risk of severe neurologic injury, defined as intraventricular hemorrhage (IVH) grade 3 or greater and/or periventricular leukomalacia (PVL).[1] The risk of severe neurologic injury is associated with a high odds of long-term neurodevelopmental impairment and can be detected by ultrasound scan of the head screening.[2,3] Important risk factors for severe neurologic injury among infants born at <33 weeks include low gestational age, low birth weight, birth in nontertiary units, use of vasopressors, mechanical ventilation, and other types of acute clinical deterioration.[4-6] Recent studies have reiterated that infants born at <30 weeks remain at high risk of severe neurologic injury and warrant ultrasound scan of the head screening.[3,7] However, infants born at 30-32 weeks of gestation represent approximately 50% of all infants born preterm at <33 weeks in Canada,[1] and early identification of severe neurologic injury by ultrasound scan of the head in this population can help refer infants to specialized neonatal follow-up clinics.[8-10] Indeed, a majority of Canadian follow-up clinics do not systematically follow all infants born at >29 weeks and use risk factors, including severe neurologic injury on cranial imaging, for entry criteria.[11] Children born at >29 weeks are followed by their community pediatrician and are referred only if they find an abnormality. However, cost containment and ultrasound scan of the head resource limitations require a targeted screening approach for infants born preterm at risk of severe neurologic injury.

There are significant variations in ultrasound scan of the head screening criteria among infants born at ≥30 weeks of gestation. The Canadian Pediatric Society recommends screening infants born at <32 weeks, yet some neonatal intensive care units (NICUs) continue to screen infants born at <33 weeks and other countries use birth weight (cut-offs ranging from 1000 to 1500 g) or gestational age criteria (cut-offs ranging from 30 to 33 weeks of gestation) to determine which infants to screen.[12-14] Recent studies that have tried to stratify infants born at

CNN	Canadian Neonatal Network
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
NNM	Number needed to misdiagnose
PVL	Periventricular leukomalacia

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≥30 weeks according to risk factors have been limited by the small number of infants who developed severe neurologic injury in their cohorts.[15,16] Consequently, there is a need to explore incidence, risk factors, and predictors of severe neurologic injury in a large number of infants to develop robust estimates and predictors of severe neurologic injury along with a risk factor−stratified approach for screening infants. We aimed to identify risk factors for severe neurologic injury and compare the diagnostic performance of different clinical risk factor-based ultrasound scan of the head screening strategies among infants born at 30^0-32^6 weeks of gestation.

Methods

We conducted a retrospective cohort study including infants born at 30^0-32^6 weeks of gestation and at >32^6 weeks with birth weights <1500 g who were admitted to tertiary-level NICUs participating in the Canadian Neonatal Network (CNN) from January 1, 2011, to December 31, 2016. We excluded infants with major congenital anomalies, infants for whom palliative care was provided at birth because of imminent mortality, infants with missing data (gestational age or birth weight), and infants with no neuroimaging results. The 29 participating NICUs represent all tertiary NICUs in Canada[17] and care for approximately 75% of eligible infants.[1]

Data Collection

At each participating site, trained abstractors collected data according to a standard protocol for each infant during their NICU stay. The information from patient charts was entered electronically into a data-entry program with built-in error checking. The CNN database includes information on maternal pregnancy and delivery, infant characteristics, resource use, and outcomes and has high reliability and internal consistency.[18] Approval for CNN data collection was granted at each participating site by either the research ethics board or institutional quality improvement committees. For the current study, approval was obtained from the CNN Executive Committee and the research ethics board at the Montreal Children's Hospital-MUHC.

Variable Definitions

Potential risk factors for severe neurologic injury were selected on the basis of data from previous studies and were divided into 3 categories: prenatal, infant, and postnatal variables.[15,16] Prenatal variables included use of antenatal steroids (1 dose ≥12 hours before delivery), multiple births, mode of delivery, and delivery outside a hospital with a tertiary NICU (outborn). Infant characteristics included gestational age category (30, 31, 32 and >32 weeks), birth weight category (<1000 g, 1000-1249 g, 1250-1499 g, ≥1500 g), and sex. Postnatal variables included 5-minute Apgar score <7, use of mechanical ventilation on day 1, use of surfactant on day 1, and use of vasopressors on day 1.

Outcomes

The primary outcome was severe neurologic injury on ultrasound scan of the head defined as grade 3 or greater IVH according to Papile et al and/or PVL (defined as persistent periventricular echogenicity) according to ultrasound findings.[19] Information regarding the exact timing of diagnosis of severe neurologic injury and number of imaging studies was not available. Abstractors recorded the neuroimaging report performed during hospitalization, and when there was more than 1 report, or report of bilateral IVH, the highest grade was used. Neurosurgery for hydrocephaly included placement of internal and external shunts. All other intracranial bleeds such as subarachnoid, subdural, and tentorial bleeds were not included in the primary outcome. Image interpretation was based on the final radiologic report in each center, and no central adjudication was done because of logistical difficulties.

Statistical Analyses

Descriptive statistics were used to compare characteristics of infants with severe neurologic injury with those without. Unadjusted comparisons were made with the Pearson χ^2 test. A multivariable logistic regression model to identify risk factors for severe neurologic injury was derived with a stepwise variable selection procedure and a significance level of <.2 for entering and <.05 for staying in the model. OR estimates and 95% CIs were calculated for each variable. Using the risk factors identified in the multivariable analysis, we then grouped infants according to exposure to risk factors. Using the probability of severe neurologic injury from each risk group, we classified infants into tertiles of risk (low, moderate, and high).

Three screening strategies were developed: screening only high-risk infants, screening moderate-to-high risk infants, and screening all infants. To evaluate screening strategies, we calculated sensitivity, specificity, number needed to screen (total number of infants that would need to be screened to detect one infant with severe neurologic injury), and the number needed to misdiagnose (NNM). The NNM corresponds to the number of infants that would be screened before one is misdiagnosed (either a false positive or false negative) and is calculated using the following equation: $NNM = 1/(1 - accuracy)$.[20] For example, a NNM of 5 for a specific ultrasound scan of the head screening strategy would mean that 1 of 5 infants would be misclassified (ie, either getting a ultrasound scan of the head when patient does not have severe neurologic injury, or not getting a ultrasound scan of the head despite having severe neurologic injury).

In addition, we compared the diagnostic performance of the 3 screening strategies we developed with the following 3 gestational age−based screening recommendations: all infants born at <32 weeks of gestation, all infants <33 weeks, and all infants <33 weeks or birth weight <1500 g. We calculated the incremental number needed to screen ratio, which corresponds to the additional number of ultrasound scans of the head required (by each respective screening strategy) to detect each additional case of severe neurologic injury compared with only screening infants born at <32 weeks (the current reference standard in Canada). The following equation was used: (Number of infants screened with strategy B – Number of infants screened with strategy A)/(Number of infants with severe neurologic injury detected using strategy B – Number of infants with severe neurologic injury detected using strategy A).[21] The annual number of infants that would meet screening criteria for each screening strategy was estimated by applying the criteria to all infants with and without neuroimaging results (N = 13 276). A 2-sided P value of < .05 was considered statistically significant. All statistical analyses were performed with SAS, version 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

In total, 13 935 infants born at 30^0-32^6 weeks of gestation or both born at ≥30 weeks and a birth weight <1500 g were admitted to the 29 tertiary-level NICUs in the CNN during the study period. A total of 561 infants were excluded (**Figure**; available at www.jpeds.com). Among 13 276 eligible infants born at 30, 31, and 32 weeks, the screening rates were 84%, 76%, and 52%, respectively. The final study population included 9221 infants; 285 (3.1%; 95% CI 2.7-3.4) had severe neurologic injury. Overall, 63 infants (0.6%) had grade 3 IVH, 126 infants (1.3%) had grade 4 IVH, and 141 infants (1.5%) had PVL. Infants who were excluded because of a lack of neuroimaging were born at a greater gestational age and birth weight and less likely to have a 5-minute Apgar score <7 or receive surfactant, mechanical ventilation, or vasopressors on day 1 than infants who had a neuroimaging report (**Table I**; available at www.jpeds.com).

Characteristics and outcomes of infants with and without severe neurologic injury are compared in **Table II**. Unadjusted comparison revealed that lack of antenatal steroids, singleton birth, outborn birth, low birth weight group, male sex, 5-minute Apgar <7, mechanical ventilation on day 1, use of surfactant, and use of vasopressors on day 1 were associated with severe neurologic injury. Of these, only 4 variables remained significantly associated with severe neurologic injury after stepwise selection of risk factors: singleton birth, 5-minute Apgar <7, mechanical ventilation on day 1, and use of vasopressors on day 1 (**Table III**). The probability of severe neurologic injury increased with cumulative exposure to risk factors (**Table IV**; available at www.jpeds.com).

Among infants without any other risk factors, singletons had a greater incidence of severe neurologic injury (1.8% [68/3676]) than multiples (1.2% [25/2137]). Among both singletons and multiples, exposure to at least 1 postnatal risk factor (5-minute Apgar <7, mechanical ventilation, or use of vasopressors on day 1) increased the probability of severe neurologic injury. Among the 14 infants who were treated with a neurosurgical intervention for hydrocephalus, all had at least 1 of the aforementioned postnatal risk factors, and all survived to NICU discharge.

Three categories of risk were developed on the basis of the probability of severe neurologic injury (risk tertile) and grouping of risk factors: low risk (multiple with no postnatal risk factor), moderate risk (singleton with no postnatal risk factor), and high risk (any infant with ≥1 postnatal risk factor) (**Table V**).

The diagnostic performance of the various screening strategies is presented in **Table VI**. The sensitivity of screening only high-risk infants was similar to screening all infants born at <32 weeks of gestation (67% vs 66%) but misclassified fewer infants (NNM 2.78 vs 1.56). In contrast,

Table II. Characteristics and outcomes of infants with severe neurologic injury compared with those without severe neurologic injury

Variables	Infants with severe neurologic injury (N = 285)	Infants without severe neurologic injury (N = 8936)	P value*
Prenatal variables, n (%)			
Antenatal steroids	213 (75)	7595 (85)	<.001
Multiple births	57 (20)	3128 (35)	<.001
Caesarean birth	177 (62)	5897 (66)	.17
Outborn	77 (27)	1161 (13)	<.001
Infant characteristics			
Gestational age group, wk, n (%)			
30	100 (35)	2770 (31)	.52
31	91 (32)	3038 (34)	
32	74 (26)	2502 (28)	
>32	20 (7)	626 (7)	
Birth weight group, g, n (%)			
<1000	11 (4)	447 (5)	.002
1000-1249	37 (13)	1161 (13)	
1250-1499	51 (18)	2412 (27)	
≥1500, n	186 (65)	4916 (55)	
Male sex, n (%)	171 (60)	4825 (54)	.04
Postnatal variables			
5-min Apgar score <7, n (%)	114 (40)	1573 (18)	<.001
Mechanical ventilation on day 1, n (%)	179 (62)	2503 (28)	<.001
Use of surfactant, n (%)	125 (44)	2287 (25)	<.001
Use of vasopressors on day 1, n (%)	73 (25)	383 (4)	<.001
Outcomes			
Seizures, n (%)	56 (20)	86 (1)	<.001
Length of stay, d, median (IQR)	34 (18-51)	26 (14-40)	<.001
Mortality before NICU discharge, n (%)	41 (14)	91 (1)	<.001

*Significance assessed using the Pearson χ^2 test for categorical data and Wilcoxon rank-sum test for continuous variables.

Table III. aOR estimates for factors selected in the prediction model for severe neurologic injury

Variables	Multivariable OR (95% CI)
Singleton births	1.96 (1.35-2.85)
5-min Apgar score <7	1.81 (1.30-2.50)
Mechanical ventilation on day 1	2.65 (1.88-3.71)
Use of vasopressors on day 1	3.23 (2.19-4.75)

Model metrics: area under the curve with 95% CI = 0.73 (0.69-0.77), *P* value for Hosmer–Lemeshow goodness-of-fit test = 0.22.

screening only moderate-to-high risk infants was associated with the greatest sensitivity of all the risk factor–based strategies (correctly identifying 91% [260/285] of infants with severe neurologic injury) but misclassified more infants (NNM 1.35). When compared with screening all infants <32 weeks, the moderate-to-high risk strategy would require screening 54 infants for each additional case of severe neurologic injury diagnosed but would only miss 6 cases of severe neurologic injury per year (compared with 23 missed cases with the <32 weeks screening strategy). Screening all moderate-to-high risk infants had similar sensitivity to screening all infants born <33 weeks but required screening fewer infants per year.

Discussion

In this large contemporary cohort of infants born preterm at 30^0-32^6 weeks of gestation or born at ≥30 weeks with a birth weight <1500 g, we found that 3.1% of infants screened had severe neurologic injury. We identified that singleton birth, 5-minute Apgar <7, use of mechanical ventilation on day 1, and use of vasopressors on day 1 were significant risk factors for severe neurologic injury in this population. We propose 3 severe neurologic injury risk categories, defined using clinical variables that are available on day 1 of NICU admission, to help tailor ultrasound scan of the head screening guidelines.

Approximately 80% of infants born at <32 weeks of gestation in this cohort had a ultrasound scan of the head, suggesting neonatologists have deviated from guidelines that recommend screening all infants born at <32 weeks. Neonatologists also have extended screening to infants born at 32^1 to 32^6 weeks of gestation. These changes in practice may represent selection bias, as infants who underwent ultrasound scan of the head may have other risk factors or characteristics that were the reason for ultrasound scan of the head. The ultrasound scan of the head screening rates among infants born at 30-32 weeks reported here are similar to those recently reported by the Neonatal Research Network, despite recommendations from the American Academy of Neurology to only systematically screen infants born at <30 weeks of gestation.[12,13,22]

Among infants who had ultrasound scan of the head, after adjustment for clinical risk factors, gestational age was not associated with risk of severe neurologic injury among infants born at 30-32 weeks of gestation. The lack of association may be a selection bias resulting from screening more sick infants in the high gestational age groups. However, in a large population study from Sweden, where the majority of infants born at 30, 31, and 32 weeks of gestation had ultrasound scan of the head, gestational age also was not associated with risk of severe neurologic injury.[23] Together, these results suggest that perinatal and postnatal risk factors are more significant contributors to severe neurologic injury than gestational age among infants born at ≥30 weeks of gestation. Differentiating which factors contribute to risk of severe neurologic injury is important because identifying at-risk infants using gestational age criteria may not be optimal, whereas using clinical risk factors may require screening infants born at 33-34 weeks with clinical risk factors of severe neurologic injury.[15]

We identified that singleton birth, 5-minute Apgar <7, use of mechanical ventilation on day 1, and use of vasopressors on day 1 were associated independently with the risk of severe neurologic injury. This observed high risk among singleton infants is consistent with a previous CNN report showing that singletons born preterm at 24-32 weeks had greater rates of severe neurologic injury than multiples of the same gestational age.[24] This result is likely because of greater rates of antenatal steroids,

Table V. Probability of severe neurologic injury by risk tertile with corresponding gestational age subgroups

Risk groups	IVH grade III, n (%)	IVH grade IV, n (%)	PVL, n (%)	Severe neurologic injury,* n (%)	Total, N
Low risk: multiple with no postnatal risk factor†	5 (0.2)	12 (0.6)	12 (0.6)	25 (1.2)	2137
Gestational age 30 wk	NA (<1.0)	NA (<0.6)	NA (<1.2)	8 (1.7)	484
Gestational age 31 wk	NA (<0.6)	5 (0.7)	5 (<0.6)	10 (1.3)	758
Gestational age 32 wk	0	NA (<0.5)	5 (0.7)	7 (1.0)	738
Gestational age >32 wk and <1500 g	0	0	0	0	157
Moderate risk: singleton with no postnatal risk factor†	11 (0.3)	29 (0.8)	36 (1.0)	68 (1.8)	3676
Gestational age 30 wk	8 (0.7)	8 (0.7)	14 (1.3)	25 (2.2)	1120
Gestational age 31 wk	NA (<0.4)	9 (0.7)	12 (1.0)	20 (1.6)	1221
Gestational age 32 wk	NA (<0.4)	8 (0.8)	6 (0.6)	14 (1.4)	998
Gestational age >32 wk and <1500 g	NA (<0.4)	NA (<1.2)	NA (<1.2)	9 (2.7)	337
High risk: singleton or multiple with ≥1 postnatal risk factor†	47 (1.4)	85 (2.5)	93 (2.8)	192 (5.6)	3408
Gestational age 30 wk	15 (1.2)	31 (2.4)	33 (2.6)	65 (5.1)	1271
Gestational age 31 wk	16 (1.4)	25 (2.2)	27 (2.4)	61 (5.3)	1150
Gestational age 32 wk	14 (1.6)	23 (2.7)	27 (3.1)	55 (6.4)	863
Gestational age >32 wk and <1500 g	NA (<2.0)	6 (4.8)	6 (5.0)	11 (8.9)	124

Severe neurologic injury defined as IVH grade 3 or greater and/or PVL.
*Infants counted in several categories of IVH3, IVH4, or PVL on the basis of the ultrasound scan of the head report were only counted as 1 case of severe neurologic injury.
†Postnatal risk factors include the following: 5-min Apgar <7, mechanical ventilation on day 1, and use of vasopressors on day 1.

Table VI. Comparison of different severe neurologic injury screening strategies

Screening strategy	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Number of infants required to diagnose 1 case	NNM*	Incremental number needed to screen†	Estimated number of infants screened/per year‡	Estimated number of missed cases of severe neurologic injury/year‡
All infants <32 wk of gestation	66 (61-72)	35 (34-36)	31	1.56	Reference	1241	23
Only infants at high risk	67 (62-73)	64 (63-65)	18	2.78	NA§	698	22
Only infants at moderate or high risk	91 (87-94)	24 (23-25)	27	1.35	54	1647	6
All infants <33 wk of gestation or birth weight <1500 g	100 (99-100)	0 (0-1)	32	1.03	62	2212	0
All infants <33 wk of gestation (no birth weight)	93 (89-96)	7 (6-8)	32	1.11	70	2064	5

*NNM = 1/(1 − accuracy).
†Incremental number needed to screen ratio = (Number of infants screened with strategy B – Number of infants screened with only criteria <32 weeks of gestational age) / (Number of infants with severe neurologic injury detected using strategy B – Number of infants with severe neurologic injury detected screening only infants <32 weeks of gestational age).
‡Estimated number of infants screened and missed cases were estimated using average yearly number of infants that met those criteria between 2011 and 2016.
§Incremental number needed to screen cannot be calculated if strategy B (screening high-risk infants only) requires screening less infants and detects more infants than strategy A (screening infants <32 weeks of gestational age).

cesarean births, and prenatal care in multiple births than singletons. Low Apgar scores, early respiratory distress requiring mechanical ventilation, and hemodynamic instability consistently have been reported as significant risk factors for severe neurologic injury among infants born preterm,[22,23,25] likely because of the fluctuations in cerebral blood flow and interference with cerebrovascular autoregulation.[26,27]

Contrary to previous studies, mode of delivery, treatment with antenatal steroids, sex, and outborn status were not associated with severe neurologic injury after adjustment for covariates.[22,25] The absence of association of these prenatal factors with severe neurologic injury may be because of the integration of postnatal variables (use of mechanical ventilation and vasopressors on day 1) in our model that may better predict severe neurologic injury in infants born between 30^0 and 32^6 weeks of gestation. Alternatively, it could be that the prenatal variables are of less importance in this gestational age group.

Using the identified risk factors, we proposed 3 risk categories to guide clinicians and policy makers in deciding ultrasound scan of the head criteria for infants born preterm between 30^0 and 32^6 weeks of gestation, if ultrasound scan of the head is available. All 3 risk-based screening strategies had either similar or superior sensitivity to screening all infants born at <32 weeks. Screening only high-risk infants would reduce the use of ultrasound scan of the head, would miss an average of 22 cases of severe neurologic injury per year, and was associated with the greatest NNM, suggesting less misclassification. However, the NNM assumes the consequences of misclassification (cost and social impacts of false negative and false positive) are similar, but no data are available on the impact of not detecting infants with severe neurologic injury. Indeed, to the authors' knowledge, no studies have assessed the trajectory of care of infants with severe neurologic injury who were not diagnosed during the neonatal period. Screening infants at moderate-to-high risk would miss approximately 6 infants with severe neurologic injury per year and would require less ultrasound scan of the head per year than expanding ultrasound scan of the head screening to all infants born at <33 weeks. Despite being at low risk, 9% (25/285) of severe neurologic injury occurred in infants with no risk factors, which reflects the moderate accuracy of our prediction model for severe neurologic injury and is similar to model performance in other studies.[22,25]

Challenges remain for clinicians and policy makers when determining which infants to screen for severe neurologic injury. If the objective of ultrasound scan of the head is to identify all infants with severe neurologic injury, then the best option is to screen >2000 infants per year born between 30 and 32 weeks of gestation in Canada to identify the approximately 68 infants per year with severe neurologic injury. Also, if identifying all infants with severe neurologic injury is a priority, expanding ultrasound scan of the head to infants born at >32 weeks of gestation would be required. However, if optimizing short-term resource use is the priority, screening infants at moderate-to-high-risk would not significantly increase the number of ultrasound scans of the head (1647 per year) over what was reported by Canadian NICUs during the study period (1536 infants screened per year).

Infants born at 30-32 weeks of gestation are at greater risk of long-term neurodevelopment impairment than infants born at term, yet most neonatal follow-up clinics do not systematically follow-up these infants due to lack of resources.[11] Instead, risk factors such as severe neurologic injury on ultrasound scan of the head are used as an entry criteria by most neonatal follow-up clinics. This approach has limitations due to the complexity of outcome prediction, and careful explanations of the limitations of neonatal neuroimaging for predicting for long-term outcome should be provided to families.[3]

The strengths of our study include the large sample size and the use of a validated contemporary dataset, which allowed us to generate new insights into current imaging practices in Canada and formulate guidelines on ultrasound scan of the head imaging in infants born at ≥30 weeks of gestation. However, we acknowledge the limitations of our study. First, we did not have data on the timing and number of ultrasound scans of the head done, but we report the worst ultrasound scan of the head findings. Second, several prenatal and perinatal factors that may contribute to the risk of severe neurologic injury are not systematically collected in the CNN and not included in our model. For example, further studies are required to determine whether maternal chorioamnionitis, cord pH, postnatal hypotension, or use of fluid resuscitation could better identify infants at risk of severe neurologic injury. Third, some infants born at 30-32 weeks were not screened for severe neurologic injury, and these infants had fewer risk factors than infants undergoing an ultrasound scan of the head. It is likely that clinicians screened the sickest infants, which would overestimate the prevalence of severe neurologic injury and make our results conservative.[28] Fourth, we did not collect data on clinical findings suggestive of severe neurologic injury, including changes in clinical status (apneas, lethargy, or falling hematocrit), that may help identify additional infants with severe neurologic injury. Fifth, ultrasound scan of the head has low sensitivity for detecting white matter injury compared with magnetic resonance imaging, and white matter injury is a better predictor of long-term neurodevelopment impairment[29,30]; however, magnetic resonance imaging of the brain in infants born at a gestational age of 30-32 weeks is not the current standard. Sixth, we did not assess long-term neurodevelopment of these neonates, which would be ideal but too labor-intensive for the current follow-up programs.[8] Seventh, inter-reader agreement was not assessed due to the retrospective nature of our study; however, inter-rater reliability is reasonable (>0.75) for significant brain lesions using ultrasound scan of the head.[31-33] There is a tendency to over-read PVL, but this would bias interpretation by increasing the false-positive rate without affecting the negative predictive value of the examination.[28]

We identified that important risk factors for severe neurologic injury among infants born at 30-32 weeks of gestation include singleton birth, 5-minute Apgar <7, use of mechanical ventilation on day 1, and use of vasopressors on day 1. Using these risk factors, we propose modified screening criteria to optimize resource use. More studies are required to validate our findings, identify other contributors to severe neurologic injury to improve risk prediction, and develop preventive interventions in this preterm population. ■

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50 Years Ago in *The Journal of Pediatrics*

The Prevalence of Congenital Heart Disease in United States College Freshmen, 1956–1965

Perry LW, Henikoff LM, Findlan C. J Pediatr 1969;75:876-8

In this study, the authors determined the prevalence of congenital heart disease (CHD) in 767 600 college freshmen using a questionnaire and physical examination. The prevalence of CHD was 0.07%, and the most common type of CHD was "not specified," followed by ventricular septal defects and atrial septal defects. Only 9.5% of the students with CHD had cardiac surgery performed.

We are now much better at diagnosis, medical management, and surgical repair of CHD. Perry et al relied on invasive tests such as cardiac catheterization to determine cardiac anatomy in many patients. Today we use echocardiography to diagnose CHD noninvasively, quickly, and accurately at the bedside. Cardiac magnetic resonance imaging gives great detail about the structure and function of many types of CHD. With fetal echocardiography, many are now diagnosed with CHD before they are even born. A higher proportion of newborns with cyanotic heart disease survive to adulthood with prostaglandin infusions keeping them alive while awaiting surgery, and surgeons perform complex repairs that were not possible 50 years ago.

Fifty years later, more children with CHD are surviving into adulthood. In 2010, there were approximately 1.4 million adults in the US with CHD, including nearly 300 000 adults with severe CHD such as hypoplastic heart syndrome, which was universally fatal in infancy 50 years ago. Fifty years later, there are now more adults than children with CHD,[1] and the median age of patients with severe CHD is now 25 years.[2] Complex CHD has become a college health issue, as these adolescents are often independent for the first time. It is important that adolescents with CHD become educated about their health and have guidance transitioning to medical care as an adult.[3] It is equally important that primary care providers for young adults, particularly those in college, understand the unique healthcare needs of adolescents with complex CHD.

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Appendix

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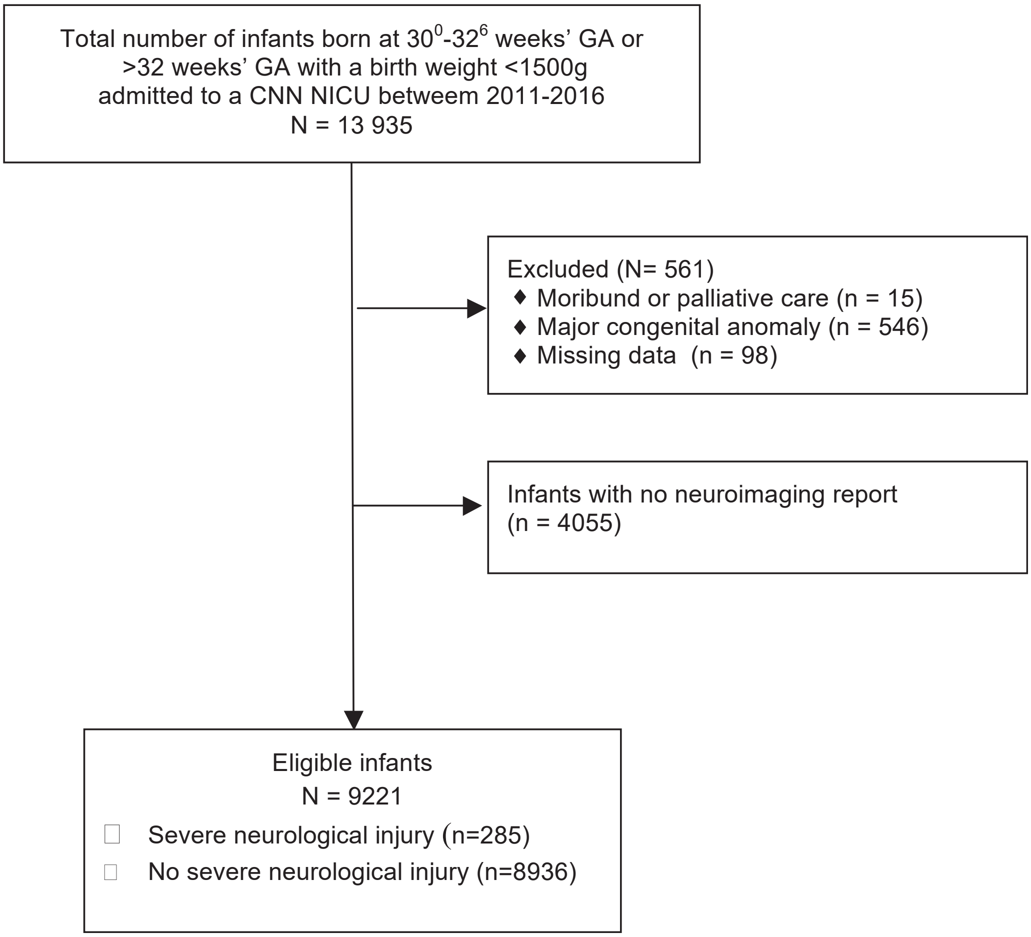

Figure. Study patient flow chart.

Table I. Characteristics of infants who underwent neuroimaging compared with those with no neuroimaging results

Variables	Infants with no neuroimaging (N = 4055)	Infants with neuroimaging done (N = 9221)	*P* value*
Prenatal variables			
Antenatal steroids, n (%)	3301 (84)	7837 (85)	.08
Multiple births, n (%)	1422 (35)	3158 (34)	.31
Caesarean birth, n (%)	2186 (54)	6085 (66)	<.01
Outborn, n (%)	560 (14)	1298 (14)	.88
Infant characteristics			
Gestational age group, wk, n (%)			
30	478 (12)	2875 (31)	<.01
31	969 (24)	3129 (34)	
32	2336 (58)	2599 (28)	
>32	272 (7)	618 (7)	
Birth weight group, g, n (%)			
<1000	34 (1)	461 (5)	<.01
1000-1249	167 (4)	1198 (13)	
1250-1499	645 (16)	2489 (27)	
≥1500	3207 (79)	5071 (55)	
Male sex, n (%)	2254 (56)	4979 (54)	.14
Postnatal variables			
5-min Apgar <7, n (%)	480 (12)	1659 (18)	<.01
Mechanical ventilation on day of admission, n (%)	583 (14)	2674 (29)	<.01
Use of surfactant, n (%)	535 (13)	2397 (26)	<.01
Use of vasopressors on day of admission, n (%)	76 (2)	461 (5)	<.01

*Significance assessed using the Pearson χ^2 test.

Table IV. Probability of severe neurologic injury based on exposure to each risk factor*

Risk factors	Severe neurologic injury, n	Total, N	Probability, %
Multiple gestation with use of vasopressors on day of admission	0	0	0
Multiple gestation with 5-min Apgar score <7 and use of vasopressors on day 1	NA	NA	0
Multiple gestation with 5-min Apgar score <7	NA	NA	0.4
Multiple gestation with no other risk factors	25	2137	1.2
Singleton with no other risk factors	68	3676	1.8
Singleton with 5-min Apgar score <7	12	445	2.7
Multiple gestation with mechanical ventilation on day 1	15	492	3.0
Singleton with use of vasopressors on day 1	NA	NA	2.8
Multiple gestation with 5-min Apgar score <7 and mechanical ventilation on day 1	7	196	3.6
Singleton with mechanical ventilation on day 1	38	1010	3.8
Multiple gestation with mechanical ventilation and use of vasopressors on day 1	NA	NA	6.5
Singleton with 5-min Apgar score <7 and mechanical ventilation on day 1	48	593	8.1
Singleton with 5-min Apgar score <7 and use of vasopressors on day 1	NA	NA	10.0
Singleton with mechanical ventilation and use of vasopressors on day 1	22	138	15.9
Singleton with 5-min Apgar score <7, mechanical ventilation, and use of vasopressors on day 1	36	169	21.3
Multiple gestation with 5-min Apgar score <7, mechanical ventilation, and use of vasopressors on day 1	8	36	22.2

NA, not available to maintain patient confidentially because number in box <5.
*Risk factors are mutually exclusive.