Preterm Neuroimaging and School-Age Cognitive Outcomes

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abstract

BACKGROUND AND OBJECTIVES: Children born extremely preterm are at risk for cognitive difficulties and disability. The relative prognostic value of neonatal brain MRI and cranial ultrasound (CUS) for school-age outcomes remains unclear. Our objectives were to relate near-term conventional brain MRI and early and late CUS to cognitive impairment and disability at 6 to 7 years among children born extremely preterm and assess prognostic value.

METHODS: A prospective study of adverse early and late CUS and near-term conventional MRI findings to predict outcomes at 6 to 7 years including a full-scale IQ (FSIQ) <70 and disability (FSIQ <70, moderate-to-severe cerebral palsy, or severe vision or hearing impairment) in a subgroup of Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial enrollees. Stepwise logistic regression evaluated associations of neuroimaging with outcomes, adjusting for perinatal-neonatal factors.

RESULTS: A total of 386 children had follow-up. In unadjusted analyses, severity of white matter abnormality and cerebellar lesions on MRI and adverse CUS findings were associated with outcomes. In full regression models, both adverse late CUS findings (odds ratio [OR] 27.9; 95% confidence interval [CI] 6.0–129) and significant cerebellar lesions on MRI (OR 2.71; 95% CI 1.1–6.7) remained associated with disability, but only adverse late CUS findings (OR 20.1; 95% CI 3.6–111) were associated with FSIQ <70. Predictive accuracy of stepwise models was not substantially improved with the addition of neuroimaging.

CONCLUSIONS: Severe but rare adverse late CUS findings were most strongly associated with cognitive impairment and disability at school age, and significant cerebellar lesions on MRI were associated with disability. Near-term conventional MRI did not substantively enhance prediction of severe early school-age outcomes.

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WHAT'S KNOWN ON THIS SUBJECT: Adverse neonatal neuroimaging findings among extremely preterm infants are associated with neurologic and developmental challenges in later childhood. But, the relative prognostic value of near-term brain MRI and cranial ultrasound for severe school-age outcomes remains unclear.

WHAT THIS STUDY ADDS: Severe but rare adverse late cranial ultrasound findings were most strongly associated with a full-scale IQ <70 and moderate-to-severe disability at school age. Near-term conventional MRI did not substantively enhance prediction. Prognostic uncertainty remains even with serial brain imaging.

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Children born extremely preterm (EPT) (born <28 weeks' gestation) are at increased risk for global cognitive delays, motor challenges including cerebral palsy (CP), and functional disabilities in childhood. At 8 years, half of the children born EPT in the Victoria Infant Collaborative had some cognitive delay, and 15% had major cognitive delay compared with term-born children.[1] Moderate or severe motor impairment was reported in more than one-quarter of children born at <30 weeks' gestation at 5 years.[2] In a population-based Swedish study of infants born <27 weeks' gestation at 6 years, nearly 30% had moderate or severe cognitive delay compared with 2.5% of term children.[3] A 10-fold greater risk for intellectual or learning disability was seen at 11 years of age among children born <26 weeks' gestation compared with term-born children in the EPICure cohort.[4] With increasing survival of infants born EPT,[5] an enhanced understanding of neonatal predictors of childhood outcomes is important for accurate counseling and informing future interventions to ameliorate later impairments.

Numerous studies have revealed that adverse neonatal neuroimaging findings among infants born EPT are associated with neurologic and developmental challenges in later childhood. Cranial ultrasound (CUS) is the routine neuroimaging modality for this patient population and allows for serial bedside imaging. However, conventional brain MRI performed at near-term equivalent age is more sensitive to white matter abnormalities (WMAs)[6,7] and other findings including cerebellar injury.[8] Links between WMA on neonatal brain MRI and later childhood cognitive, motor, and psychiatric challenges have also been shown.[2,9,10] Adverse neonatal CUS findings among children born EPT have been similarly shown to be strongly associated with outcomes at 2 and 8 years of age, particularly when markers of white matter injury are considered.[11,12] Some authors have emphasized the imprecision of qualitative neonatal neuroimaging in outcomes prediction,[13] whereas others advocate the value of CUS as a screening and serial imaging tool but suggest term-equivalent brain MRI may be used to more accurately predict cognitive outcomes.[14]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) developed the Neuroimaging and Neurodevelopmental Outcomes (NEURO) study, a prospective study of early- and near-term CUS, near-term brain MRI among infants born EPT, and neurodevelopmental outcomes at 18 to 22 months' corrected age[15] and school age. Our objectives were to relate early and late neonatal CUS adverse findings, WMAs, and cerebellar lesions by near-term brain MRI to outcomes at 6 to 7 years, including cognitive impairment and moderate-to-severe disability; our objective was to also assess the relative value of neonatal neuroimaging, in combination with other perinatal and neonatal risk factors, to predict these adverse outcomes.

METHODS

Study Design and Population

The NEURO study was a secondary study to the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT), a randomized, multicenter trial of ventilation and oxygenation management strategies among infants at 24 to 27 + 6/7 weeks' gestation.[16,17] The NEURO study cohort represents a subgroup of the SUPPORT cohort, in that it was approved and began recruitment after SUPPORT began enrollment, and not all centers participated nor did they launch simultaneously.[15]

The study was approved by the institutional review boards of all participating centers and by the International Review Board of Research Triangle Institute (RTI) International, the data coordinating center (DCC) for the NICHD NRN.

Neonatal Neuroimaging: CUS and Brain MRI

CUS

An "early" CUS at 4 to 14 days of age and a "late" CUS at 35 to 42 weeks' postmenstrual age (PMA) were obtained for NEURO study participants. CUS imaging was obtained per local center clinical protocol and did not specify views. Central reader interpretations were used for all study analyses. Two masked central readers (D.B. and Thomas L. Slovis, MD [see acknowledgments]) reviewed all study CUS independently by using a modified central reading form used in previous NICHD NRN studies.[18] A composite adverse finding on early CUS was defined as the presence of grade III or IV intracranial hemorrhage (ICH)[19] or cystic periventricular leukomalacia (cPVL) on either or both sides. A composite adverse finding on late CUS was defined as having cPVL or porencephalic cyst, moderate-to-severe ventricular enlargement (VE) on either or both sides, or a shunt. For all CUS, assessment of interobserver reliability between central readers revealed $\kappa = 0.75$ for the early CUS composite adverse finding and a $\kappa = 0.88$ for the late CUS composite adverse finding. Mastoid views were included in only 48.2% of early CUS and 46.1% of late CUS.[15]

Brain MRI

A conventional brain MRI was obtained at 35 to 42 weeks' PMA and within 2 weeks of late CUS. Minimum requirements have been previously described,[15] and it was advised that neonatal brain MRIs be obtained without the use of sedation.

Central reader interpretations were used for study analyses. Copies of MRIs were sent to RTI International by sites in digital or film format. A masked central reader (P.D.B.) reviewed all brain MRIs by using a central reader form that included WMA scoring according to a widely used classification system used to evaluate 5 areas of white matter assessment.[6,20] Interrater agreement for moderate or severe WMA by using this classification system has been reported to be >95%.[20] Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or ≥4 mm in size. Adverse findings on brain MRI were defined as moderate or severe WMA or significant cerebellar lesions.

Neurodevelopmental Follow-up Assessments at Early School Age

The school-age visit occurred at 6 years 4 months to 7 years 2 months of age and included a battery of assessments and questionnaires. For this analysis, general intellectual, motor, and neurosensory function were the focus. General intellectual functioning was assessed by using the full-scale IQ (FSIQ) of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)[21] (age standardized scores for FSIQ are mean = 100 and SD = 15). Neurologic examination included assessment for CP,[22] with severity assigned according to the Gross Motor Function Classification System (GMFCS) level.[23,24] Determination of vision and hearing was established by both assessment and parent report at visit. Severe vision impairment was defined as blind or able to perceive only light in both eyes or only perceive light in 1 eye, with the other eye with impairment not correctable with glasses or lenses. Severe hearing impairment was defined as having no useful hearing even with hearing aid(s), implant(s), or other amplification device or if hearing impairment is profound and considered not responsive to amplification. Examiners and coordinators from all study sites were required to attend a 2-day training session. For both the WISC-IV and neurologic examination, site examiners were then required to be certified before their first study visit including submission of a video of study assessments with an age-appropriate child. Site examiners were recertified at the midpoint of the study follow-up period.

The prospectively defined outcomes were (1) significant cognitive impairment defined as an FSIQ <70 and (2) moderate-to-severe disability defined as an FSIQ <70, CP with a GMFCS level ≥2, severe hearing impairment, or severe vision impairment. Other outcomes were evaluated including an FSIQ <85; minimal or no disability, which was defined as having all of the following: an FSIQ >85, no CP, and no hearing or vision impairment or impairments that were completely correctable; and severe disability, which was defined as an FSIQ <55, CP with a GMFCS level of 4 or 5, or severe hearing or severe vision impairment.

Statistical Analyses

The unadjusted associations between neonatal neuroimaging findings and school-age outcomes were examined by χ^2 tests, Fisher's exact tests, or analysis of variance. We determined test characteristics of neonatal adverse findings for school-age outcomes by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). To evaluate the relative predictive value of early CUS, late CUS, and MRI findings, we developed a series of generalized linear mixed models to predict the binary outcomes of FSIQs <70 and moderate-to-severe disability by neuroimaging findings, controlling for NRN center and perinatal or neonatal risk factors. Risk factors were selected for inclusion as control variables in each model on the basis of backward stepwise regression with a retention criterion of $P < .10$. Potential risk factors included the following: estimated gestational age (EGA) (24–25 + 6/7 weeks vs 26–27 + 6/7 weeks), race, male sex, multiple gestation, maternal education less than high school, late-onset sepsis, bronchopulmonary dysplasia (BPD), postnatal steroids (PNS), and surgery for patent ductus arteriosus, necrotizing enterocolitis (NEC), or retinopathy of prematurity (ROP). Neuroimaging findings included (1) early CUS composite adverse finding, (2) late CUS composite adverse finding, (3) moderate or severe WMA based on MRI, and (4) significant cerebellar lesions based on MRI. Results of the models were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We then conducted receiver operating characteristic (ROC) curve analyses from these models and compared the predictive capabilities on the basis of the area under the curve (AUC) of the ROC curves.

RESULTS

A total of 480 infants had complete neuroimaging with late CUS and brain MRI within 2 weeks of each other, of whom 17 were known to have died after all neuroimaging was obtained and before 6 to 7 years of age. Seventy-seven children were lost to follow-up for the school-age visit (36 lost without further information, families of 35 declined, 3 were adopted, and 3 were out of state or country and travel could not be arranged within the visit window). Therefore, 386 children had school-age visit data (83.3% follow-up among survivors), for whom determination of an FSIQ <70 could be made in 373 and moderate-to-severe disability in 379 (96% and 98%, respectively, of those with

TABLE 1 Baseline Perinatal, Demographic, and Neonatal Characteristics and Selected Outcomes at 6–7 Years for Participants at School-Age Follow-up and Those Lost to Follow-up

Characteristic	Participants (*N* = 386), *n* (%)	Lost to Follow-up (*N* = 77), *n* (%)	*P*
BW, mean ± SD	861.8 ± 190.1	823.6 ± 182.8	.105
EGA, mean ± SD	25.9 ± 1.0	25.7 ± 1.0	.044
24–25 wk	137 (35)	34 (44)	.150
Multiple gestation	89 (23)	16 (21)	.663
Race			.385
Non-Hispanic African American	128 (33)	18 (23)	
Non-Hispanic white	162 (42)	38 (49)	
Hispanic	85 (22)	18 (23)	
Other	11 (3)	3 (4)	
Male sex	209 (54)	45 (58)	.489
Any antenatal steroids	371 (96)	75 (97)	.583
Cesarean delivery	260 (67)	57 (74)	.250
Maternal education less than high school	96 of 379 (25)	22 of 74 (30)	.430
Late sepsis[a]	119 (31)	28 (36)	.341
NEC (stage 2 or greater)	29 (8)	4 (5)	.470
Severe ROP[b]	40 of 359 (11)	11 of 70 (16)	.280
Surgery for PDA, NEC, or ROP	72 (19)	16 (21)	.664
PNSs[c]	27 of 383 (7)	11 of 76 (14)	.032
BPD[d]	142 (37)	34 (44)	.224
Neonatal neuroimaging			
Early CUS adverse finding	35 (9)	9 (12)	.478
Late CUS adverse finding	24 (6)	2 (3)	.208
Moderate or severe WMA on MRI	72 (19)	16 (21)	.664
Any cerebellar lesions on MRI	60 (16)	15 (19)	.392
Significant cerebellar lesions on MRI	42 (11)	7 (9)	.641
6–7 y major outcomes			
FSIQ (*n* = 373), mean ± SD	85.6 ± 17.4	—	—
FSIQ <70	47 of 373 (13)	—	—
FSIQ <85	169 of 373 (45)	—	—
Moderate-to-severe disability	57 of 379 (15)	—	—
Minimal or no disability	234 of 379 (62)	—	—

BW, birth weight; PDA, patent ductus arteriosus; —, not applicable.

[a] Late sepsis is defined as culture-proven sepsis from 7 d of age to discharge and treated with antibiotics for at least 5 d.

[b] Severe ROP: threshold ROP, ophthalmologic surgery, or the use of bevacizumab treatment of retinopathy.

[c] PNSs are defined as any corticosteroid given for the prevention or treatment of BPD.

[d] BPD: oxygen use at 36 wk PMA.

study visit data). The presence or absence of CP was determined in all 386 children. The mean ± SD age at visit was 6.35 ± 0.54 years.

Perinatal, neonatal, and demographic variables for participants in school-age follow-up and for those lost to follow-up are shown in Table 1. The participants and groups lost to follow-up were similar overall with the exception of a slightly higher mean EGA at delivery and lower rates of PNS use among those who returned for the study visit. For participants in the school-age visit, ~62% had no or minimal disability and 55% had a WISC-IV FSIQ ≥85. Only 5 children had severe visual impairment (1.3%), and 1 had severe hearing impairment.

Brain MRI findings in relation to cognitive impairment and disability are shown in Tables 2 and 3. Increasing severity of WMA (Table 2) and the presence of cerebellar lesions (Table 3) were associated with a significantly lower mean FSIQ, higher rates of FSIQs <70 and <85, higher rates of moderate-to-severe disability, and lower rates of minimal or no disability. Among those with moderate and severe WMA combined, the rate of an FSIQ <70 was 23%, and moderate-to-severe disability was 31%. Early and late neonatal CUS findings in relation to outcomes are shown in Tables 4 and 5. Both adverse early and late CUS findings were associated with a lower mean FSIQ, higher rates of FSIQs <70 and <85, and moderate-to-severe disability, but the strength of the association was more substantial for late CUS (Table 5). Of note, the numbers of children with adverse early CUS findings (*n* = 33) or adverse late CUS findings (*n* = 22) were low. Diagnostic validity of adverse neuroimaging findings for selected school-age outcomes reveal overall poor sensitivity of adverse neonatal neuroimaging for school-age outcomes, with good to excellent specificity (Table 6). The PPVs of adverse early CUS or

TABLE 2 Brain MRI Findings in Relation to Cognitive Impairment and Disability Outcomes at Early School Age: Relation of WMA Severity on Near-Term Brain MRI to Outcomes

Outcome at Early School Age	Severity of WMA				
	Normal, *N* = 84	Mild, *N* = 223	Moderate, *N* = 51	Severe, *N* = 15	*P*
FSIQ, mean ± SD	90.1 ± 15.5	85.9 ± 16.8	84.0 ± 17.0	62.7 ± 19.6	<.0001
FSIQ <70	7 of 84 (8)	25 of 223 (11)	6 of 51 (12)	9 of 15 (60)	<.0001
FSIQ <85	27 of 84 (32)	100 of 223 (45)	29 of 51 (57)	13 of 15 (87)	<.0001
FSIQ ≥85	57 of 84 (68)	123 of 223 (55)	22 of 51 (43)	2 of 15 (13)	<.0001
Any CP	2 of 87 (2)	6 of 227 (3)	4 of 55 (7)	10 of 17 (59)	<.0001
CP with GMFCS level ≥2	0 of 87 (0)	1 of 227 (0)	1 of 55 (2)	4 of 17 (24)	<.0001
Moderate-to-severe disability	8 of 85 (9)	27 of 224 (12)	8 of 53 (15)	14 of 17 (82)	<.0001
Minimal or no disability	47 of 85 (55)	88 of 224 (39)	15 of 53 (28)	0 of 17 (0)	<.0001
FSIQ <70 or death	9 of 86 (10)	34 of 232 (15)	10 of 55 (18)	11 of 17 (65)	<.0001
Moderate-to-severe disability or death	10 of 87 (11)	36 of 233 (15)	12 of 57 (21)	16 of 19 (84)	<.0001

Data shown as *n*/*N* (%) unless otherwise specified.

TABLE 3 Brain MRI Findings in Relation to Cognitive Impairment and Disability Outcomes at Early School Age: Cerebellar Lesions on Near-Term Brain MRI and Outcomes

Outcome at Early School Age	Cerebellar Lesions			
	No Cerebellar Lesions, *N* = 316	Any Cerebellar Lesions, *N* = 57	*P*[a]	Significant Cerebellar Lesions,[b] *N* = 39
Cognition				
FSIQ, mean ± SD	87.0 ± 16.5	78.4 ± 20.0	.001	76.8 ± 20.4
FSIQ <70	32 of 316 (10)	15 of 57 (26)	.001	10 of 39 (26)
FSIQ <85	136 of 316 (43)	33 of 57 (58)	.038	22 of 39 (56)
FSIQ ≥85	180 of 316 (57)	24 of 57 (42)	.038	17 of 39 (44)
Any CP	13 of 326 (4)	9 of 60 (15)	.001	9 of 42 (21)
CP with GMFCS level ≥2	3 of 326 (1)	3 of 60 (5)	.019	3 of 42 (7)
Moderate-to-severe disability	37 of 319 (12)	20 of 60 (33)	<.0001	15 of 42 (36)
Minimal or no disability	135 of 319 (42)	15 of 60 (25)	<.0001	10 of 42 (24)
FSIQ <70 or death	45 of 329 (14)	19 of 61 (31)	.001	14 of 43 (33)
Moderate-to-severe disability or death	50 of 332 (15)	24 of 64 (38)	<.0001	19 of 46 (41)

Data shown as *n*/*N* (%) unless otherwise specified.

[a] *P* values reflect comparisons between no cerebellar lesions and any cerebellar lesions groups.

[b] Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or ≥4 mm in size.

TABLE 4 Major Neonatal CUS Findings in Relation to Cognitive Impairment and Disability Outcomes at Early School Age: Major Early CUS Findings and Outcomes

Outcome at School Age	Early CUS			
	All Without ICH Grade III or IV or cPVL on Early CUS, *N* = 341	ICH Grade III or IV or cPVL, *N* = 32	*P*[a]	Normal,[b] *N* = 277
Cognition				
FSIQ, mean ± SD	86.4 ± 17.0	77.9 ± 19.1	.008	86.0 ± 16.7
FSIQ <70	38 of 341 (11)	9 of 32 (28)	.006	31 of 277 (11)
FSIQ <85	149 of 341 (44)	20 of 32 (63)	.041	123 of 277 (44)
FSIQ ≥85	192 of 341 (56)	12 of 32 (38)	.041	154 of 277 (56)
Any CP	11 of 350 (3)	10 of 35 (29)	<.0001	10 of 284 (4)
CP with GMFCS level ≥2	3 of 350 (1)	3 of 35 (9)	<.0001	2 of 284 (1)
Moderate-to-severe disability	43 of 345 (12)	14 of 33 (42)	<.0001	35 of 282 (12)
Minimal or no disability	143 of 345 (41)	7 of 33 (21)	<.0001	120 of 282 (43)
Death or FSIQ <70	52 of 355 (15)	11 of 34 (32)	.007	41 of 287 (14)
Death or moderate-to-severe disability	57 of 359 (16)	16 of 35 (46)	<.0001	45 of 292 (15)

Data shown as *n*/*N* (%) unless otherwise specified.

[a] *P* values reflect comparisons between those with and without early CUS composite adverse findings (ICH grade III or IV or cPVL).

[b] "Normal" CUS were interpreted and coded as such by central reader neuroradiologists and thus are a subset of all without adverse findings.

TABLE 5 Major Neonatal CUS Findings in Relation to Cognitive Impairment and Disability Outcomes at Early School Age: Major Late CUS Findings and Outcomes

Outcome at School Age	Late CUS			
	All Without Porencephalic Cyst, cPVL, Moderate-to-Severe VE, or Shunt, *N* = 354	Porencephalic Cyst, cPVL, Moderate-to-Severe VE, or Shunt, *N* = 19	*P*[a]	Normal[b] *N* = 284
Cognition				
FSIQ, mean ± SD	86.7 ± 16.7	65.9 ± 18.7	<.0001	87.0 ± 16.1
FSIQ <70	36 of 354 (10)	11 of 19 (58)	<.0001	24 of 274 (9)
FSIQ <85	153 of 354 (43)	16 of 19 (84)	<.0001	118 of 274 (43)
FSIQ ≥85	201 of 354 (57)	3 of 19 (16)	<.0001	156 of 274 (57)
Any CP	10 of 362 (3)	12 of 24 (50)	<.0001	6 of 278 (2)
CP with GMFCS level ≥2	2 of 362 (1)	4 of 24 (17)	<.0001	1 of 278 (0)
Moderate-to-severe disability	40 of 357 (11)	17 of 22 (77)	<.0001	27 of 275 (10)
Minimal or none disability	149 of 357 (42)	1 of 22 (5)	<.0001	117 of 275 (43)
Death or FSIQ <70	51 of 369 (14)	13 of 21 (62)	<.0001	30 of 280 (11)
Death or moderate-to-severe disability	55 of 372 (15)	19 of 24 (79)	<.0001	33 of 281 (12)

Shown as *n*/*N* (%) unless otherwise specified.

[a] *P* values reflect comparisons between those with and without early CUS composite adverse findings (ICH grade III or IV or cPVL).

[b] "Normal" CUS were interpreted and coded as such by central reader neuroradiologists and thus are a subset of all without adverse findings.

TABLE 6 Diagnostic Validity of Adverse Neonatal Neuroimaging for Selected School-Age Outcomes

Neonatal Neuroimaging	Sensitivity	Specificity	PPV	NPV
Early CUS adverse findings				
FSIQ <70	19	93	28	89
FSIQ <85	12	94	63	56
Severe disability	17	92	12	94
Moderate or severe disability	25	94	42	88
Late CUS adverse findings				
FSIQ <70	23	98	58	90
FSIQ <85	9	99	84	57
Severe disability	26	96	27	95
Moderate or severe disability	30	98	77	89
MRI adverse findings				
FSIQ <70	38	79	21	90
FSIQ <85	30	83	60	59
Severe disability	52	78	13	96
Moderate or severe disability	46	80	29	89

adverse MRI findings were poor for FSIQs <70 and moderate-to-severe or severe disability and, for adverse late CUS, were only fair to moderate for an FSIQ <85 and moderate-to-severe disability. However, the NPVs for the most severe school-age outcomes were 88% to 96% for all neuroimaging.

Results of stepwise multivariable models are shown in Fig 1. Early CUS adverse findings were not significantly associated with either outcome when any other imaging was taken into account. In full regression models, for the outcome of an FSIQ <70, only late CUS findings remained independently associated among neonatal neuroimaging variables. For moderate-to-severe disability, both late CUS findings and significant cerebellar lesions on MRI remained independently associated with the outcome. The magnitude of the association with late CUS findings was substantial for both outcomes, although the 95% CI was wide. In limited models excluding late CUS, MRI findings were not significantly associated with either outcome; however, for moderate-to-severe disability, the association with both moderate-to-severe WMA ($P = .056$) and significant cerebellar lesions ($P = .058$) approached significance. In limited models excluding MRI, late CUS adverse findings, but not early CUS adverse findings, remained significantly associated with both outcomes. Results of the ROC curve analyses are shown in Table 7. Point estimates of model AUCs improved slightly with the addition of neuroimaging compared with models that included only perinatal-neonatal variables for both outcomes. Importantly, however, the 95% CIs of the AUCs for all models overlapped substantially.

DISCUSSION

We found that adverse findings on neonatal early and late CUS and MRI were associated with 6- to 7-year outcomes in unadjusted analyses. Sensitivity and PPV of adverse neuroimaging findings were poor for FSIQs <70 and moderate-to-severe disability, although NPV was very good to excellent. In multivariable models, severe but rare, late CUS findings remained strongly independently associated with both FSIQs <70 and moderate-to-severe disability but with wide CIs. Significant cerebellar lesions on brain MRI also remained associated with moderate-to-severe disability, but prognostic capabilities as assessed by AUC–point estimates improved only marginally with the addition of neuroimaging, with 95% CIs overlapping broadly. Our findings reveal that the prediction

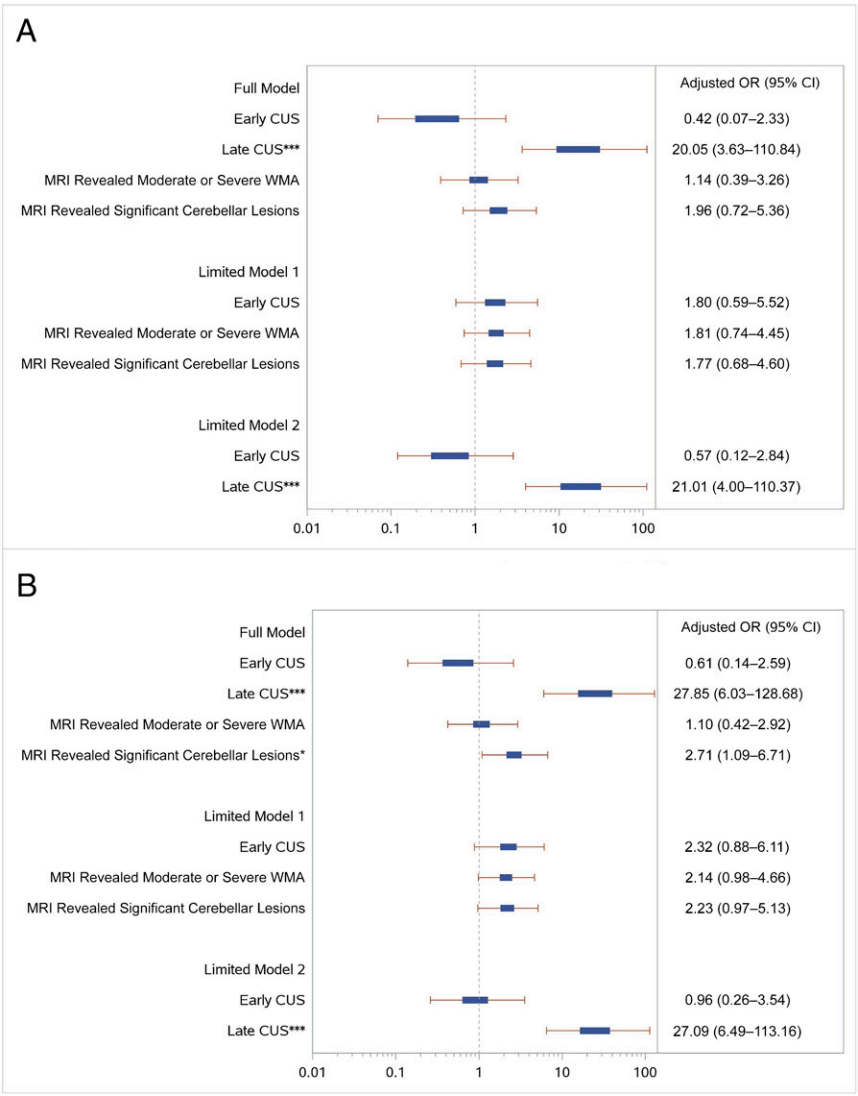

FIGURE 1

Independent associations of neonatal neuroimaging findings with cognitive impairment and moderate-to-severe disability at early school age. A, FSIQ <70. B, Moderate-to-severe disability. Early CUS composite adverse finding was defined as grade III or IV ICH or cPVL. Late CUS composite adverse finding was defined as moderate or severe VE, cPVL, porencephalic cyst, or shunt. The full model included the following perinatal, neonatal, and sociodemographic factors that were associated with $P < .2$ in backward stepwise models: FSIQ <70: male sex (OR: 2.07; 95% CI 1.0–4.28; $P = .049$), maternal education less than high school (OR: 2.05; 95% CI 0.98–4.29; $P = .056$), BPD (OR: 1.59; 95% CI 0.78–3.23; $P = .20$); moderate-severe disability: male sex (OR: 1.93; 95% CI 0.98–3.80; $P = .057$), BPD (OR: 1.30; 95% CI 0.67–2.50; $P = .44$). Limited model 1 includes perinatal and neonatal factors, early CUS, and brain MRI (excludes late CUS); limited model 2 includes perinatal and neonatal factors, early CUS, and late CUS (excludes MRI). * $P < .05$; *** $P < .001$.

of FSIQs <70 and moderate-to-severe disability is not substantively improved over and above CUS by the addition of conventional MRI at near-term. With our findings, we further highlight uncertainty in positive prediction of complex school-age outcomes from perinatal and neonatal factors, including adverse neonatal neuroimaging findings.

Other investigators have shown independent associations of moderate-to-severe WMA on neonatal MRI with early childhood and school-age cognitive outcomes, which would seem to be in contrast with our findings. But those studies have varied in design, with some authors considering only high-grade ICH or cPVL rather than later CUS findings[20] or showing that qualitative conventional-term MRI reveals little additional data in contrast to CUS done on the same day to predict adverse outcomes at 2 or 6 years.[25,26] Some authors of previous school-age studies also focus narrowly on predictive capabilities of MRI findings without a goal of comparison with CUS.[9,27] Others have reported on prognostic validity of severe CUS findings alone for long-term outcomes. Similar to our findings, the Etude éPIdémiologique sur les Petits Ages Gestationnels group reported that significant cognitive impairment and moderate-to-severe disability at 8 years of age were most strongly associated with severe neonatal neuroimaging findings, particularly adverse near-term CUS findings.[13] Nonetheless, the severe findings did not systematically predict poor cognitive outcomes and disability in that cohort. This is consistent with our results, which revealed only moderate PPV of late CUS for moderate-to-severe disability, although better than early CUS or MRI.

Our prospective objective for this analysis of the NEURO study school-age follow-up was to determine the relative value of adverse findings on early and late CUS and near-term brain MRI to predict significant impairments at school age. We acknowledge that the outcomes examined in this study were on the severe end of the spectrum, and prospective prediction from adverse, but in this patient group rare, neuroimaging findings. However, although positive prediction of our main outcomes was generally poor or, at best, moderate, it is important to note that the NPV for adverse findings

TABLE 7 Classification Statistics for ROC Curve Analyses Based on Stepwise Models

Outcome	Model Variables	AUC	95% CI
FSIQ <70			
	Perinatal or neonatal	0.68	0.60–0.77
	Perinatal or neonatal and early CUS	0.73	0.65–0.81
	Perinatal or neonatal, early CUS, and late CUS	0.76	0.68–0.85
	Perinatal or neonatal and late CUS	0.76	0.67–0.84
	Perinatal or neonatal, early CUS, and MRI	0.74	0.67–0.82
	Perinatal or neonatal, early CUS, late CUS, and MRI	0.78	0.70–0.86
Moderate-to-severe disability			
	Perinatal or neonatal	0.64	0.56–0.72
	Perinatal or neonatal and early CUS	0.71	0.63–0.79
	Perinatal or neonatal, early CUS, and late CUS	0.74	0.65–0.82
	Perinatal or neonatal and late CUS	0.73	0.65–0.81
	Perinatal or neonatal, early CUS, and MRI	0.72	0.65–0.80
	Perinatal or neonatal, early CUS, late CUS, and MRI	0.74	0.66–0.82

at early school age was very good to excellent. We will be able to augment our findings in the future analyses given the comprehensive nature of the NEURO school-age visit data. Neonatal MRI WMA has been shown to be associated with non-CP motor outcomes such as developmental coordination disorder, which is prevalent among children born preterm and can significantly affect their school-age functional capabilities and even academic performance.[28] Cerebellar injury among infants born EPT has been associated with both motor and cognitive impairment[29] and with impaired growth of cortical regions that has been linked with cognitive, motor, and neuropsychiatric challenges.[30] Although cerebellar lesions may be visualized by appropriate CUS views, smaller lesions are much more likely to be seen by MRI.[31] Nevertheless, the impact of these smaller lesions on developmental outcomes remains unclear. Some have reported no association of small cerebellar hemorrhages (<4 mm) with 2-year neurodevelopmental outcomes,[32] whereas others have reported associations with later abnormalities on neurologic examination but not with functional ambulation impairments or significant differences in developmental testing at 3 to 6 years of age.[8] With our study, we found an independent association of significant cerebellar lesions with disability but not cognitive delay and no substantive enhancement of predictive capabilities. It is also possible that significant cerebellar lesions could have been better detected by CUS had mastoid and posterior fossa views been required as part of the study protocol[33] and that overall quality of CUS images could have been enhanced with more stringent CUS protocol. With our findings, we highlight the importance of including CUS sequences to optimize cerebellar views.

We also recognize that since the NEURO study was initially launched, an expanded and globally more detailed scoring system for abnormalities on qualitative brain MRI was published,[34] which has subsequently been shown to be associated with lower IQ, math, and motor scores,[35] and poorer memory and learning performance[36] at 7 years of age among very preterm children. However, in a recent Dutch cohort of infants born EPT, the prognostic value of that MRI scoring system for 2-year outcomes was limited.[37] With our study, we also focused on the MRI WMA component of the older classification system and not gray matter. Our large multicenter study called for conventional, qualitative brain MRI at near term with a goal of generalizability based on the recognition that not all institutions have advanced imaging approaches available. Furthermore, our study is differentiated from most others in that we called for both early and late CUS, the modality that continues to be the mainstay of neuroimaging for infants born EPT in the NICU, with the objective of assessing the relative predictive value of conventional neuroimaging tools in this cohort. Nonetheless, advanced and quantitative neuroimaging may hold promise in predicting childhood outcomes for preterm infants at 2 to 3 years of age[38] and in later childhood.[39,40] Continued research of advanced imaging techniques may be used to better connect patterns of neonatal injury with disrupted brain development and identify opportunities to prevent such injury.

CONCLUSIONS

With our findings, we underscore the sustained influence of severe neonatal brain injury but also add to our understanding of prognostic uncertainty for individual preterm infants even with serial brain

imaging. Neonatologists making decisions regarding the need for near-term conventional brain MRI should be cognizant of the complexities of outcomes and limitations to predict them, the incremental benefits relative to increased costs,[41] and the varying perspectives of the meaning of outcomes to patients and families, physicians, and investigators.[42–44] Although near-term MRI did not substantively improve the prediction of school-age outcomes over and above CUS in this study, the outcomes examined were severe, and prospective prediction was from rare and significantly adverse imaging findings. Further analyses from this data set may be used to delineate when and whether the information gained by near-term conventional MRI can provide improved prognostic or supportive capabilities.

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ABBREVIATIONS

AUC: area under the curve
BPD: bronchopulmonary dysplasia
CI: confidence interval
CP: cerebral palsy
cPVL: cystic periventricular leukomalacia
CUS: cranial ultrasound
DCC: data coordinating center
EGA: estimated gestational age
EPT: extremely preterm
FSIQ: full-scale IQ
GMFCS: Gross Motor Function Classification System
ICH: intracranial hemorrhage
NEC: necrotizing enterocolitis
NEURO: Neuroimaging and Neurodevelopmental Outcomes
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NPV: negative predictive value
NRN: Neonatal Research Network
OR: odds ratio
PMA: postmenstrual age
PNS: postnatal steroid
PPV: positive predictive value
ROC: receiver operating characteristic
ROP: retinopathy of prematurity
RTI: Research Triangle Institute
SUPPORT: Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial
VE: ventricular enlargement
WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition
WMA: white matter abnormality

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