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Publication Date

2018-04-01

DOI

10.1016/j.jpeds.2017.11.036

Peer reviewed

Antecedents and Outcomes of Abnormal Cranial Imaging in Moderately Preterm Infants

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Abstract

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Objectives—To describe the frequency and findings of cranial imaging in moderately preterm (MPT) infants (born at 29 0/7–33 6/7 weeks of gestation) across centers, and to examine the association between abnormal imaging and clinical characteristics.

Study design—We used data from the Neonatal Research Network MPT Registry, including the most severe early (28 days) and late (>28 days) cranial imaging. Stepwise logistic regression and CART analysis were performed after adjustment for gestational age (GA), antenatal steroids and center.

Results—Among 7,021 infants, 4,184 (60%) underwent cranial imaging. These infants had lower GAs and birth weights and higher rates of birth weight small-for-gestation, outborn birth, cesarean delivery; neonatal resuscitation and treatment with surfactant, compared with those without imaging (*P* < .0001). Imaging abnormalities noted in 15% of the infants included any intracranial hemorrhage (13.2%), grades 3–4 intracranial hemorrhage (1.7%), cystic periventricular leukomalacia (2.6%) and ventriculomegaly (6.6%). Histological chorioamnionitis [OR 1.47; 95% C.I.:1.19–1.83], GA [0.95; 95% C.I.: 0.94–0.97], antenatal steroids [OR 0.55; 95% C.I.: 0.41–0.74] and cesarean delivery [OR 0.66; 95% C.I.: 0.53–0.81] were associated with abnormal imaging. The center with the highest rate of cranial imaging, compared with the lowest, had a higher risk of abnormal imaging [OR 2.08; 95% CI: 1.10–3.92]. On the CART model, cesarean delivery, center, antenatal steroids and chorioamnionitis, in that order, predicted abnormal imaging.

Conclusions—Among the 60% of MPT infants with cranial imaging, 15% had intracranial hemorrhage, cystic periventricular leukomalacia or late ventriculomegaly. Further correlation of imaging and long-term neurodevelopmental outcomes in MPT infants is needed.

In 2014, 9.6% of United States births were preterm (<37 weeks of gestation), including 1.2% at 32–33 weeks and 0.9% at 28–31 weeks (1,2). Despite their substantial numbers, these moderately preterm (MPT) infants, born at 29–33 weeks of gestation, are a largely unstudied population (3, 4). MPT infants have significant neonatal morbidities and frequently require respiratory support and intravenous nutrition. Up to 19% of MPT infants are discharged home with continuing medical needs (5, 6). Compared with full term children, MPT children have increased risks of cerebral palsy (8–14 fold increase), mental retardation or developmental delays (2–fold), seizures (4-fold) and other neurodevelopmental disabilities (2-fold) (7, 8). Despite the increased risk of long-term neurodevelopmental problems in MPT infants, there is relatively little information about early neurologic injury in this group of patients. This may be related to the lack of consistent cranial imaging practices. The American Academy of Neurology guidelines recommend routine head ultrasound (US) screening in preterm infants born at < 30 weeks of gestation (9). Whether and how often MPT infants are evaluated is unclear.

The purpose of this study was to describe the rates of cranial imaging in MPT infants and the frequency of abnormal findings across centers in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

(NRN) MPT Registry (10). We also examined the association between abnormal findings on cranial imaging and baseline characteristics as well as neonatal morbidities prior to initial hospital discharge. We hypothesized that abnormal cranial imaging in MPT infants would be uncommon and would vary with center, antepartum and birth characteristics, similar to extremely preterm infants (11). We hypothesized further that death and morbidities among survivors would be more common in MPT infants with abnormal cranial imaging compared with infants with normal imaging.

Methods

This was a secondary analysis of prospectively collected data from the NICHD NRN MPT Registry (10). The MPT Registry included all live born infants from 29 0/7 through 33 6/7 weeks of gestation cared for at an NRN site between 3/1/ 2012–10/31/2013. Infants were excluded if there was a prenatal diagnosis that influenced the decision to withdraw or limit intensive care. All participating NRN sites obtained institutional review board approval for the study and either parental consent or approval for waiver of parental consent.

The MPT Registry included data on a) maternal characteristics, such as age, marital status, highest level of education, insurance, ethnicity and race; b) pregnancy complications: multiple birth, prenatal care, hypertension, clinical and histological chorioamnionitis; c) labor and delivery: antenatal steroids (ANS) and mode of delivery; and d) neonatal information: birth location (outborn or inborn), sex, gestational age (GA), birth weight small-for-GA (SGA) status, Apgar scores, birth resuscitation and stabilization, and birth weight.

The MPT Registry included information on whether or not cranial imaging was performed on or before 28 days of age, defined as early imaging, or after 28 days of age and closest to 36 weeks of postmenstrual age (PMA), defined as late imaging. Results of imaging as reported by the local reader were recorded and included the presence and severity of intracranial hemorrhage (ICH), the presence and location of periventricular leukomalacia (PVL), ventricular dilation and porencephalic cysts. Results of late imaging included cranial US, computed tomography or magnetic resonance imaging (MRI). Cystic PVL (cPVL) was defined as presence of cysts (echolucencies) in the periventricular white matter, whether single or multiple, bilateral or unilateral, diffuse or focal, and irrespective of size. A porencephalic cyst was defined as a single cyst within the cerebral hemisphere, whether congenital or evolving over time at the site of a previous parenchymal hemorrhage. Choroid plexus cysts were not recorded. For the current study, abnormal cranial imaging was defined as any ICH, cPVL, ventricular dilation or porencephalic cyst, according to the interpretation of the local reader.

Data were abstracted for death, type of feeding and respiratory support at 36 weeks PMA, morbidities and length of stay. Age at which full oral feedings were attained was recorded (defined as oral intake of 120 ml/kg/day). Respiratory support was defined as assisted ventilation (high frequency or conventional), nasal intermittent mandatory ventilation, continuous positive airway pressure, nasal cannula or supplemental oxygen by any delivery system. Patent ductus arteriosus (PDA) was defined as clinical evidence of left to right

ductal shunt or ECHO evidence of PDA with documentation of left to right ductal shunting. Medical or surgical treatment for PDA was noted. Other morbidities included early-onset and late-onset sepsis and necrotizing enterocolitis (NEC), defined as modified Bell staging 2 or 3 and therapies such as surfactant and the type of respiratory support at 28 days. Infants who were transferred to another hospital before discharge home had cranial imaging data available, if performed clinically, but did not have available outcomes at discharge.

Statistical Analyses

Descriptive data were presented as means and standard deviations (SD) or medians and interquartile range (IQR) for continuous measures and numbers and proportions for categorical data. Comparisons between groups were conducted using t-tests and chi-square tests, as appropriate. Stepwise logistic regression analysis and classification and regression-tree (CART) analysis were used to evaluate the adjusted association between clinical characteristics and abnormal cranial imaging. Factors previously associated with ICH or cPVL in extremely preterm infants including GA, SGA, sex, race, center, ANS, mode of delivery, birth resuscitation and histological chorioamnionitis were adjusted for in the regression and CART analyses. Variables were allowed to enter the model at p<0.1 and allowed to stay at p<0.05. ORs and 95% confidence intervals (CIs) were generated for each included factor. The CART analysis was performed using Salford Predictive Modeler software V7.0 (Salford Systems, San Diego, California) to determine risk factors for abnormal cranial imaging and important patterns and relationships in data. The development of a classification tree with a series of binary splits was done by recursive partitioning and automatic selection of optimal cut-points of variables. The decision tree was pruned to achieve best fit. Each binary split in a classification tree yielded two subgroups, one with a higher proportion of cases (abnormal cranial imaging) and the other with a higher proportion of controls. The optimal cut-point for each variable was determined by the software using the available data. Also, the more closely associated a variable was in relation to outcome, the higher it was on the decision tree. CART models are designed to handle a large number of predictor variables without making assumptions about their relative importance, does not assume that data are linearly related and the results are resistant to the influence of outlier data. Assuming a range of prevalence rates between 10 and 20% of neonatal morbidities (any of: respiratory support at 28 days, prolonged duration of hospitalization and delayed attainment of oral feeds) in the normal imaging group, a 2-tailed test with 5% type 1 error, and about 500 cases with abnormal imaging, we calculated that we would be able to detect effect sizes or ORs between 1.36 and 1.50 and relative risks between 1.25 and 1.40, with 80% power. P-values <.05 were taken as statistically significant, without correction for multiple comparisons.

Results

A total of 7,057 infants were enrolled in the time-limited observational MPT Registry. Of these, 36 were excluded due to a prenatal diagnosis with subsequent limitation of care (n=34) or missing information on imaging (n=2). Of the remaining 7,021 infants, 4,184 (59.6%) underwent cranial imaging either early (<28 days) or late (>28 days) or both (Figure 1; available at www.jpeds.com). Clinical characteristics differed between MPT

infants who did (n=4,184) and did not (n=2,837) undergo cranial imaging (Table 1). A greater proportion of infants with cranial imaging were born to mothers with hypertension and who underwent cesarean delivery. Infants who underwent imaging had significantly lower mean birth weights and gestational ages, and had higher rates of low 5 minute Apgar scores (<5), birth weights SGA, outborn deliveries, and requirements for intubation, chest compressions and resuscitation medications in the delivery room. They were also more likely to receive surfactant therapy.

Cranial US was performed by 28 days of life in 4,062 (57.9%) MPT infants, rates varied from 42.1–80.8% across centers. Abnormalities were detected in 570 infants (14.0%; range across centers 7.9–27.0%). Any ICH occurred in 537 infants (13.2% of those imaged) and Grade 3–4 ICH was demonstrated in 70 infants (1.7%). Late imaging after 28 days of age was performed in 2,022 (28.8%) infants; the majority [1,808 (89.4%)] underwent cranial US, and computed tomography was done in 5 infants (0.3%) and MRI in 209 infants (10.3%). Rates of late imaging across centers varied from 10.7 to 65.3%. Late imaging was preceded by early imaging in all but 2.9% of those who underwent imaging. Abnormalities on late imaging were noted in 171 infants (8.5%; range across centers 3.3–16.3%), and included cPVL in 52 (2.6%), ventricular dilation in 134 (6.6%) and porencephalic cyst in 11 (0.5%) infants. Abnormal cranial imaging, at any time, was noted in 641 (15.3%) infants and varied between centers from 8.2 to 21.4%.

Rates of any cranial imaging, early imaging and late imaging varied significantly across centers (all $p < 0.0001$) as did rates of abnormal cranial imaging ($p<0.0001$). Figure 2, A and B shows rates of early and late cranial imaging and rates of abnormalities across centers. The centers in the tertiles of imaging rates (47.5–52.1%; 55.4–67.6% and 68–81.2%) had abnormal findings ranging from 8.2–16%, 9.4–26.9% and 12.5–19.6% respectively. The overall rate of cranial imaging at 29 weeks was 96.1% (range across centers 93.3–100%); corresponding percentages at 30 weeks: 89.7% (75.7–100%), at 31 weeks: 79.1% (48.5–100%), at 32 weeks: 49.4% (27.2–78.7%) and at 33 weeks: 28.5% (13.2–61.2%).

Among the 1,900 infants who underwent both early and late imaging, 245 (12.9%) had abnormalities on early imaging alone, 64 (3.4%) had abnormal imaging after 28 days only and 100 (5.3%) had abnormalities on both early and late imaging. Among the 570 infants with any abnormality on early cranial imaging, 345 (60.5%) underwent late imaging. The rates of late imaging were 57.6% (269/467) for ICH grades 1 and 2, 77.1% (54/70) for ICH grades 3–4 and 70% (42/60) for PVL on early imaging. Cystic PVL persisted in late imaging in 20 of the 60 infants with early PVL. Among the 209 infants in whom an MRI was performed after 28 days of life, 19 (9.1%) had abnormalities undetected on early cranial US and 16 (7.7%) infants had abnormalities on both the early cranial US and late MRI. Abnormalities on MRI included cPVL (16), ventricular enlargement (25), porencephalic cyst (1) and >1 abnormality (7).

Clinical characteristics of groups of infants with (n=641) and without (n=3,518) abnormal cranial imaging are compared (Table II). Mothers of infants with abnormal cranial imaging were younger, fewer were married or had college degrees, fewer had hypertension, and more had histological chorioamnionitis. A greater proportion of infants with abnormal imaging

were outborn, had a 5-minute Apgar score <5, and required resuscitation in the delivery room or surfactant therapy, and fewer were born via cesarean delivery and exposed to ANS, compared with those with normal imaging. Histologic chorioamnionitis was associated with an increased odds of abnormal neuroimaging (OR 1.47; 95% C.I.: 1.19–1.83) whereas cesarean delivery (OR 0.66; 95% C.I.: 0.53–0.81), ANS exposure (OR 0.55; 95% C.I.: 0.41–0.74) and each increasing week of GA (OR 0.95; 95% C.I.: 0.94–0.97) were associated with decreased odds. The center with the highest rate of cranial imaging (81.2%) had higher odds of abnormal imaging [OR 2.08; 95% CI: 1.10–3.92] than the center with the lowest rate of cranial imaging (47.5%).

The CART model for prediction of abnormal cranial imaging is shown in Figure 3 (available at www.jpeds.com). The relative importance of the predictors of abnormal cranial imaging based on a summary of a variable's contribution to the overall tree showed that cesarean delivery had the highest score (100.00), followed by center (78.65), ANS (38.03) and histologic chorioamnionitis (15.07) and resuscitation at birth seemed to have the least relative importance (1.31) in predicting abnormal cranial imaging. Center, cesarean delivery, and histologic chorioamnionitis each led to an approximately 1% increase in the positive predictive value. The area under the curve for the CART analysis was 0.578, lower than the C-statistic of the regression analysis at 0.64.

Compared with infants with normal neuroimaging, infants with abnormal neuroimaging had an increased duration of respiratory support at 28 days, an increased rate of early-onset sepsis, longer time to attain full oral feedings (120 ml/kg/day), a longer length of NICU stay, and increased risk of death (Table 3). After adjusting for center, GA, and ANS exposure, the need for respiratory support at 28 days of age was significantly associated with abnormal imaging [OR 1.97; 95% C.I.:1.46–2.65]. The other morbidities did not demonstrate an association with abnormal imaging: treated PDA [OR 0.83; 95% C.I.: 0.47–1.46], NEC [OR 0.69; 95% C.I.: 0.32–1.48], prolonged hospital stay [OR 1.04; 95% C.I.: 0.77–1.40], prolonged attainment of oral feeds [OR 1.08; 95% C.I.: 1.08; 0.82–1.43], and sepsis [OR 1.09; 95% C.I.: 0.67–1.75].

Discussion

Approximately 60% of this cohort of MPT infants cared for at NICHD NRN centers underwent cranial imaging, and 15% showed abnormalities. Our analysis revealed that histological chorioamnionitis and lower GA group were independently associated with abnormalities on cranial imaging, and ANS and cesarean delivery were associated with lower risk. Center was significantly associated with abnormal brain imaging. We also found a 2–fold higher requirement for respiratory support at 28 days of age among those with abnormal cranial imaging.

Neonatologists appeared to use a selective approach to cranial imaging, restricting it to smaller, less mature infants who received interventions in the delivery room or surfactant therapy or who were sicker. In a previous retrospective study, screening for ICH by cranial US was performed in 38% of preterm infants born between 30 and 34 weeks GA (12). Screening US was performed in 89% of infants born at 30 weeks but the screening rate

decreased to 35% for those born at 33 weeks GA (12). Similarly, in the NICHD NRN cohort of MPT infants from which the current study is derived, the frequency of cranial imaging increased with decreasing gestational age (10). We found that the inter-center variation in imaging rates increased at higher GAs.

Among infants who underwent neuroimaging in our MPT cohort, rates of any ICH and grade 3–4 ICH were 13.2% and 1.7%. Previous studies found somewhat lower rates of ICH among MPT infants (5,12). Most studies, including ours, are biased by inconsistent US screening; our cohort included infants born at 29 weeks of gestation, and cranial imaging was targeted to higher risk infants. Altman et al evaluated the Swedish Perinatal Quality Register for MPT births (30–34 weeks GA, n=6,674) between 2001 and 2008. Infants born at 30–32 weeks were screened for ICH (5). Reported rates of any ICH were 8.3%, 6.2%, 3.5%, and 0.2% for 30, 31, 32, and 33 weeks, respectively; corresponding rates for grade 3 or 4 ICH were 1.6%, 1.1%, 1.1%, and <0.1%, respectively (5). In other studies that included infants born at 30–34 weeks GA with inconsistent rates of screening cranial imaging, rates of any ICH varied from 1.1–6.3% and higher grades of ICH from 0–2%. In these studies, ICH was poorly predicted by clinical criteria (3, 6, 12–15).

In the current data set, we found that histologic chorioamnionitis, lack of ANS, and vaginal delivery were independently associated with abnormal cranial imaging, predominantly ICH. The Cochrane meta-analysis of ANS for women at risk of preterm birth showed a reduction in ICH among infants born before 32 weeks (RR 0.52, 95%CI 0.28 to 0.99, 277 infants) and before 34 weeks GA (RR 0.53, 95% CI 0.29 to 0.95, 515 infants), based only on a study conducted by Liggins et al in 1972 (16,17). The demonstration of a protective effect in this population with a low ICH disease burden supports recent data on the benefits of ANS in MPT infants.

The association of histologic chorioamnionitis with abnormal cranial imaging in the MPT population is consistent with previous studies that have addressed this issue in broader cohorts of preterm infants (18). Among very low birth weight infants or infants born at < 32 weeks GA, histological chorioamnionitis was found to be a risk factor for ICH in many, although not all, studies (19–22). One study included infants born at 32–33 weeks GA and showed histological chorioamnionitis to be significantly associated with abnormal early cranial imaging (23).

In a population-based database of very low birth neonates born at 24–34 weeks GA in Israel over a 10-year period, the rate of severe ICH was 7.7% for infants born by cesarean delivery, compared with 13.6% in those born via vaginal delivery (24). However, in a multivariable regression analysis, cesarean delivery had no significant effect on the risk of severe ICH (24). Our results suggest that histological chorioamnionitis, lack of ANS exposure, and need for respiratory support at 28 days should be considerations for early and late cranial imaging in MPT infants. Center was noted to be an independent predictor of abnormal imaging, possibly due to inter-center variation in imaging practices.

The rates of ventriculomegaly and cPVL on late imaging were 6.6% and 2.6% in our data set. In the population-based Swedish study, cPVL occurred in 1.6%, 1.1%, 1% and 0.3% of

infants at 30, 31, 32 and 33 weeks' GA, respectively (5). Reported rates of PVL in other studies of infants born at 30–33 week GA cohorts were approximately 1.5% (12, 14). Townsend et al also reported the occurrence of cPVL in infants between 30 and 32 weeks and concluded that clinical characteristics were not helpful in predicting the need for imaging (25). In a review article on MPT infants, Laptook noted the superiority of MRI in the detection of diffuse PVL, which accounts for approximately 90% of non-cystic PVL (26). Abnormal MRI in MPT and late preterm (32–36 6/7 weeks GA) infants, compared with term-born controls have been described in previous studies (27, 28). In our cohort, only 10% of MPT infants underwent MRI. Therefore, conclusions about the necessity and yield of this technique are not possible. The final gestational weeks are critical for brain development in general and, specifically, for a rapid increase in myelinated white matter volume, which continues after birth (29). Whether any imaging abnormalities in this population correlate with later neurodevelopmental outcome remains unknown because most studies (including ours) lack follow-up data.

There are some limitations to our study. We collected data on cranial imaging acquired at the discretion of the provider. There was no consistent protocol for imaging MPT infants across NRN centers; therefore ascertainment bias was inevitable. Although data were based on the interpretation of cranial US by local readers, diagnosis of higher grades of ICH, cPVL and ventriculomegaly is likely to be reliable. Previous multicenter studies have found good agreement in the interpretation of ventriculomegaly and higher grades of ICH (30, 31). Another limitation was the lack of neurodevelopmental correlation with abnormal imaging. Our CART and logistic regression analyses were exploratory, limited by inconsistent imaging practices and had relatively low areas under the curve.

The strengths of our study were that we were able to prospectively collect data on neuroradiologic findings in a large contemporary cohort of a relatively understudied population across the multiple centers of the NRN. This allowed us to provide insights into current imaging practices, which may be used to formulate recommendations on early cranial imaging in the MPT population. We confirmed that important abnormalities such as severe ICH, ventriculomegaly and cPVL are detected in MPT infants, albeit rarely.

There was wide inter-center variation in cranial imaging among MPT infants, more so at older GAs. Other antenatal and intrapartum characteristics such as chorioamnionitis, ANS and mode of delivery were identified as risk factors for abnormal imaging. Given the frequency of abnormal cranial imaging, universal screening with cranial ultrasounds should be considered in infants born MPT. The current data may be useful in the design of prospective studies for targeted prevention and treatment of neurodevelopmental morbidities in the MPT population.

Acknowledgments

University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo (U10 HD68263, UL1 TR42) – Satyan Lakshminrusimha, MD; Ann Marie Scorsone, MS; Julianne Hunn, BS; Rosemary Jensen; Holly I.M. Wadkins, MA; Stephanie Guilford, BS; Ashley Williams, M.S. Ed.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689) – Myra Wyckoff, MD; Luc P. Brion, MD; Diana M. Vasil, RNC-NIC; Lijun Chen, PhD RN; Lizette E. Torres, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) –Jon E. Tyson, MD MPH; Julie Arldt-McAlister, RN BSN; Carmen Garcia, RN CCRP; Karen Martin, RN; Georgia E. McDavid, RN; Sharon L. Wright, MT (ASCP).

Wayne State University, University of Michigan, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Athina Pappas, MD; John Barks, MD; Rebecca Bara, RN BSN; Shelley Handel, AD; Diane F White, RT; Mary Christensen, RT; Stephanie A. Wiggins, MS.

Abbreviations

MPT   moderately preterm

MPR   Moderate Preterm Registry

GA   gestational age

NICHD   *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NRN   Neonatal Research Network

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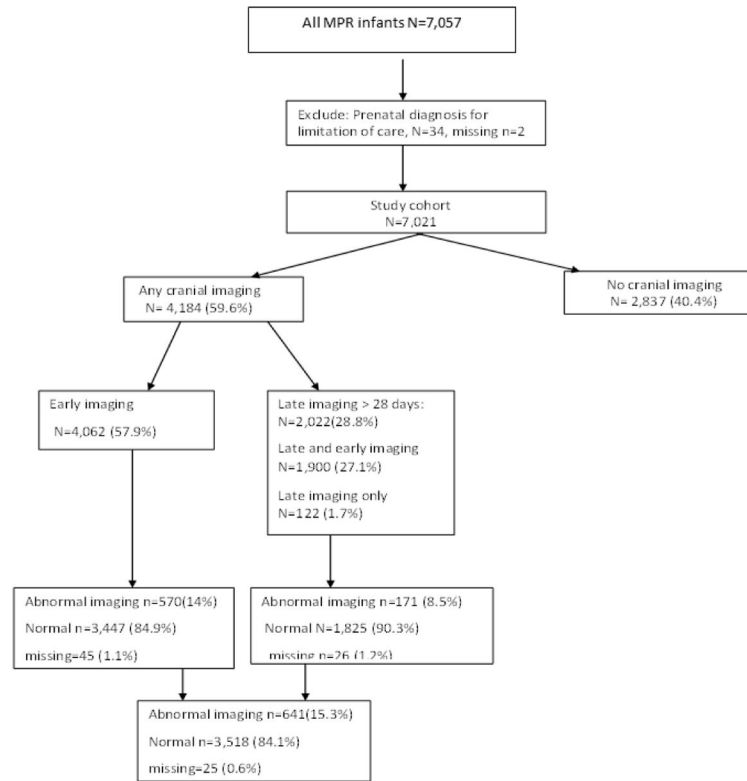
Figure 1 online.
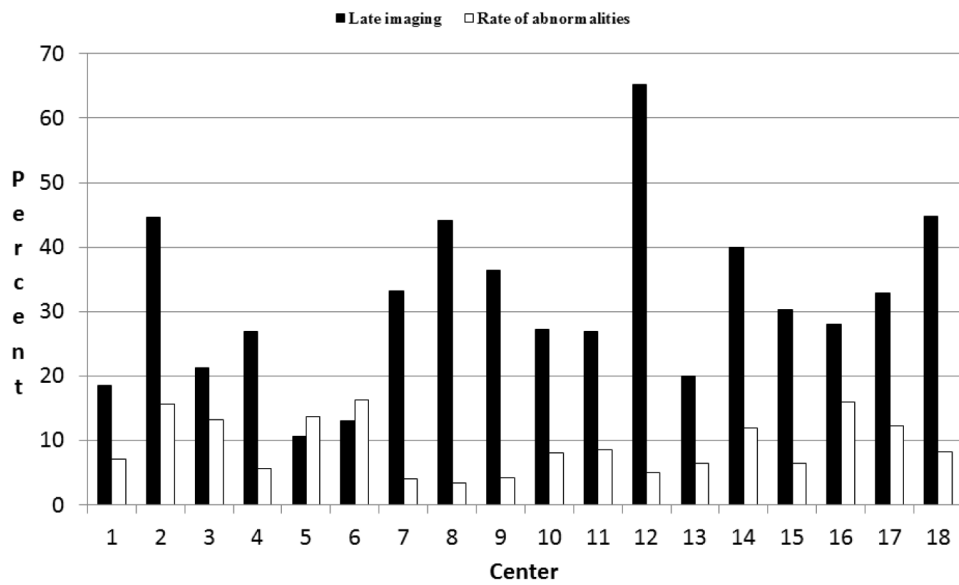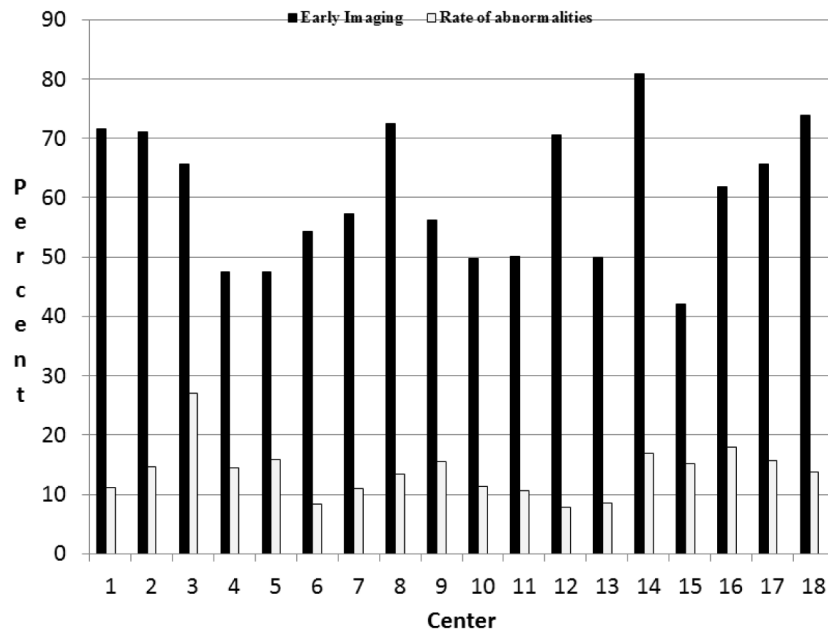Flowchart of study cohort

Figure 2.
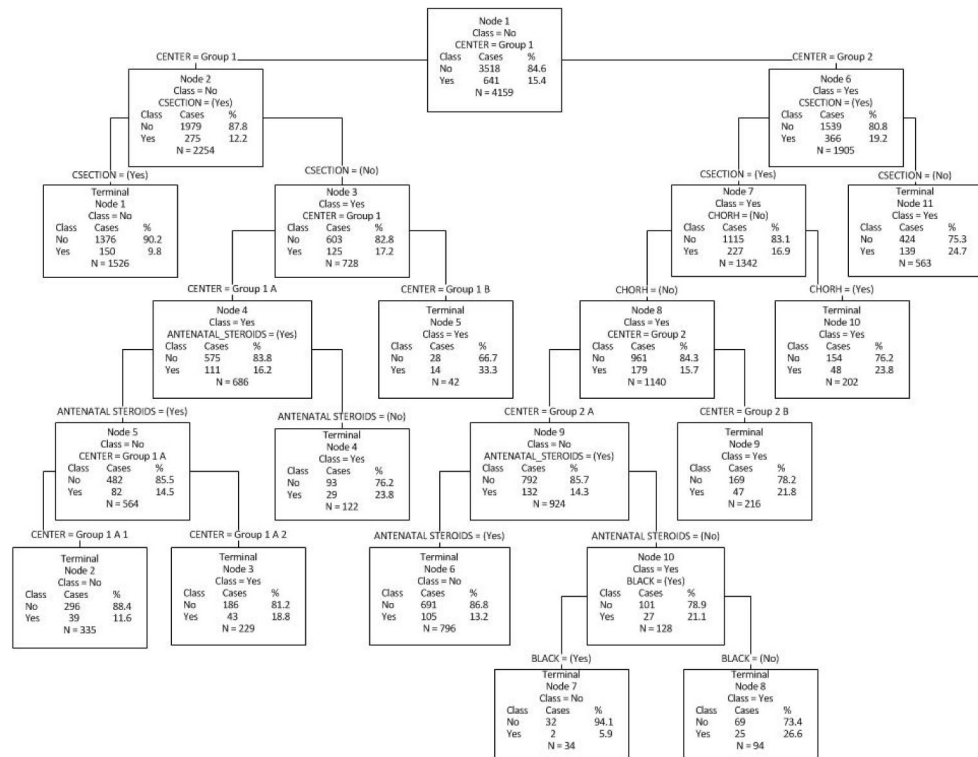Rates of early and late imaging and abnormalities in early and late imaging across centers

Figure 3 (online).
CART analysis of the association between clinical characteristics and abnormal imaging

Table 1

Comparison of clinical characteristics of infants with and without cranial imaging

Characteristics Mean (SD) or N (%)	Cranial imaging N=4,184	No cranial imaging N=2,837	p value
Birth weight, grams	1531 (390)	1940 (338)	<0.0001
GA, weeks	30.9(1.3)	32.4(0.9)	<0.0001
Male sex	2159/4183(51.6)	1504/2834(53.1)	0.24
Hispanic ethnicity	585/4182 (14.0)	417/2833 (14.7)	0.39
Race:			
Caucasian	2355/4167(56.5)	1649/2825(58.4)	0.12
Black	1344/4167(32.3)	883/2825(31.3)	0.38
Asian/Pacific Islander	181/4167(4.3)	97/2825(3.4)	0.06
Other	287/4167(6.9)	196/2825(6.9)	0.94
5-min Apgar score< 5	275/4148(6.6)	67/2826(2.4)	<0.0001
Birth weight small for GA	873/4182(20.9)	286/2834(10.1)	<0.0001
Maternal Age (years)	28.3(6.5)	28.5(6.5)	0.11
Maternal hypertension	1504/4167(36.1)	861/2833(30.4)	<0.0001
Histologic chorioamnionitis	872/3435(25.4)	599/2349(25.5)	0.92
Outborn	462/4184(11.0)	171/2837(6.0)	<0.0001
Cesarean delivery	2884/4182(69.0)	1558/2837(54.9)	<0.0001
Antenatal steroids	3564/4141(86.1)	2374/2815(84.3)	0.05
Singleton	2949/4184(70.5)	2023/2837(71.3)	0.46
Resuscitation at Birth:			
Intubation	953/4179 (22.4)	232/2837 (8.2)	<0.0001
Chest compressions	140/4178 (3.4)	32/2837 (1.1)	<0.0001
Medications	59/4178 (1.4)	19/2837 (0.7)	0.004
Surfactant use	1449/4184(34.6)	376/2835(13.3)	<0.0001

Table 2

Comparison of characteristics of infants with normal and abnormal cranial imaging

Mean (SD) or N (%)	Normal cranial imaging N=3,518	Abnormal cranial imaging N=641	P value
Birth weight (grams)	1523.7(384.1)	1563.2(422.3)	0.03
GA (weeks)	30.9(1.3)	30.8(1.4)	0.08
Male sex	1793/3517(51.0)	352/641(54.9)	0.07
Hispanic ethnicity	489/3516 (13.9)	91/641 (14.2)	0.85
Race			
Caucasian	1993/3503(56.9)	348/640(54.4)	0.24
Black	1120/3503(32.0)	218/640(34.1)	0.30
Asian/Pacific Islander	151/3503(4.3)	29/640(4.5)	0.80
Other	239/3503(6.8)	45/640(7.0)	0.85
5-min Apgar score < 5	205/3496(5.9)	67/627(10.7)	<0.0001
Birth weight small for GA	756/3516(21.5)	113/641(17.6)	0.03
Maternal Age (years)	28.4(6.5)	27.6(6.4)	0.0051
Married maternal status	1653/3516(47.0)	272/641(42.4)	0.03
Maternal college degree	750/3502(21.4)	110/636(17.3)	0.02
Public insurance	1925/3514(54.8)	361/640(56.4)	0.45
Maternal hypertension	1318/3505(37.6)	181/637(28.4)	<0.0001
Histological chorioamnionitis	697/2909(24.0)	172/504(34.1)	<0.0001
Outborn	357/3518(10.1)	103/641(16.1)	<0.0001
Cesarean delivery	2490/3516(70.8)	377/641(58.8)	<0.0001
Antenatal steroids	3033/3483(87.1)	510/633(80.6)	<0.0001
Singleton	2414/3518(68.6)	516/641(80.5)	<0.0001
Resuscitation at Birth:			
Intubation	751/3514(21.4)	199/640(31.1)	<0.0001
Chest compressions	101/3513(2.9)	37/640(5.8)	0.0002
Medications	41/3513(1.2)	18/640(2.8)	0.0012
Surfactant use	1178/3518(33.5)	263/641(41.0)	0.0002

Table 3

Comparison of in-hospital morbidities in groups of infants with and without neurologic morbidities

In-hospital Morbidities Mean (SD) or N (%)	Normal imaging N=3,518	Abnormal cranial imaging N=641	P value
Respiratory support at 28d [*]	668/3,365(19.9)	187/610(30.7)	<.0001
Ventilator	88/668 (13.2)	36/187 (19.3)	0.0370
Continuous positive airway pressure	60/668 (8.98)	22/187 (11.8)	0.2534
PDA	486 (13.8%)	147 (22.9%)	<0.001
Treated PDA	149/485(30.7)	31/147(21.1)	0.0234
Necrotizing enterocolitis [**]	112/3,515(3.19)	18/639(2.82)	0.6217
Days to oral feeding volume of 120ml/kg/d	31.8(17.0)	34.2 (16.8)	0.0030
Died in NICU	83(2.36)	28 (4.37)	0.0037
Early-onset sepsis	30 (0.85)	15 (2.34)	0.0008
Late-onset sepsis	151/3,512 (4.30)	37/640 (5.78)	0.0973
Oxygen at 28 days [*]	647/3366(19.2)	179/610(29.3)	<.0001
Length of stay (days)	40.0(16.8)	42.1 (17.1)	0.0106

[*] The denominators refer to numbers of infants who survived until 28 days and had data available

[**] Bell's stage 2–3.