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“Intraventricular” Hemorrhage and Cystic Periventricular Leukomalacia in Preterm Infants: How Are They Related?

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Abstract

Intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (cPVL) are often co-occurring characteristics of brain damage in preterm infants. Using data from 1016 infants born before 30 completed weeks’ gestational age, we sought to clarify the relationship between severe IVH and cPVL, with special emphasis on common antecedents and potential confounding. After comparing risk factors for IVH grades I through IV and cPVL, it appears the risk patterns for IVH III, IVH IV, and cPVL differ. The association between IVH III and cPVL differs appreciably from the association between IVH IV and cPVL, supporting the notion that IVH III and IVH IV are different entities. The presence of IVH III and IVH IV increases the risk of cPVL, even after adjusting for potential confounders. This raises the possibility that IVH III and IVH IV cause cPVL.

Keywords

preterm; intraventricular hemorrhage; cystic periventricular leukomalacia; risk pattern; association

Introduction

Ultrasound-defined white matter damage, such as cystic periventricular leukomalacia (cPVL) and “intraventricular” hemorrhage (IVH),* is a strong predictor for cerebral palsy and neurodevelopmental disorders among preterm infants.^{1–8} Often, “severe IVH” (defined as grades III or IV, according to Papile⁹) and “white matter damage” (defined as IVH IV or cPVL) are used as joint outcome variables. What if these characteristics are actually different entities with different etiologies? Should they still be joined into one group? We explored whether different grades of IVH (with or without cPVL) and cPVL have different etiologic risk factor patterns. In doing so, we hoped to clarify whether these characteristics should be combined. In addition, we explored the association between different grades of IVH and cPVL to analyze whether their relationship is more likely to be coincidental than causal.

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*Here and in the title, we have placed “intraventricular” in quotes to indicate that not all IVH is truly intraventricular, but includes hemorrhage outside the ventricular system (IVH IV).

Methods

Between January 1997 and January 2008, the Division of the Newborn Medicine at Floating Hospital for Children/Tufts Medical Center (Boston, Massachusetts) collected data from 1646 newborns for report to the Vermont Oxford Network (VON). VON annually published clinical definitions of demographics, treatment, and outcome measures in manuals of operations.¹⁰ The analyses were approved by the Institutional Review Board of Tufts Medical Center.

The VON includes all newborns less than 30 completed weeks' gestational age or with a birthweight of <1500 grams. Including infants based on their birthweight can result in selection bias because of an overrepresentation of small-for-gestational age newborns in such populations.¹¹ Therefore, we excluded infants born after 30 completed weeks' gestational age (n = 484). Other exclusion criteria were death in the delivery room or within 12 hours after admission (n = 53), major birth defects (n = 24), and infants with no cranial imaging on or before day 28 after birth (n = 44). The total number of infants included in our analyses was 1016 (Figure 1).

At Floating Hospital for Children the usual practice is to obtain the first head ultrasound within 1 day to 4 days after birth, the second at around the 28th postnatal day, and the last at a corrected gestational age of 36 weeks. If a child is discharged before 36 weeks postmenstrual age, a head ultrasound is performed at discharge. In case abnormalities are found, multiple head ultrasounds are obtained during the hospital stay at the attending physician's request.

Indicators for brain damage were recorded per VON protocol as cPVL and/or IVH, graded according to Papile.⁹ If a difference between hemispheres was identified or if IVH worsened over time, the highest grade was recorded. We defined white matter damage as the presence of either IVH IV or cPVL.

Cystic PVL was diagnosed when multiple small cysts were identified on neonatal cranial ultrasound in the white matter adjacent to the lateral ventricles. If a porencephalic cyst in the area of a previously identified intraparenchymal hemorrhage was found as the only abnormality, no cPVL was diagnosed. We defined "late sepsis" as sepsis or meningitis diagnosed after 3 days with a blood or cerebral spinal fluid culture positive for bacterial or fungal pathogens. Coagulase negative staphylococcus infection was included if signs of a generalized infection were present and antibiotic treatment was administered for 5 or more days. We defined bronchopulmonary dysplasia as the need for oxygen at 36 weeks postmenstrual age or oxygen use at discharge home before 36 weeks' postmenstrual age. According to the National Institute of Child Health and Human Development (NICHD), our definition of bronchopulmonary dysplasia includes the moderate and severe forms of bronchopulmonary dysplasia. The variable "oxygen use at the 28th day of life" in our dataset includes the mild form of bronchopulmonary dysplasia according to the NICHD definition.^{12,13} Because of missing data, we created 2 additional categories for bronchopulmonary dysplasia, (beyond present/absent) to include (1) unknown bronchopulmonary dysplasia status in infants transferred before 36 weeks' postmenstrual age or transferred home without oxygen and (2) unknown due to death before 36 weeks' postmenstrual age. The same categories were created for the variable "oxygen use at the 28th day of postnatal life."

We used Statistical Analysis Software (SAS 9.1, SAS Institute Inc., Cary, NC, USA) for the analyses. In the exploratory stage, we noted differences in risk patterns for various brain damage indicators with the use of column percentages. The control group was defined as "neither IVH of any grade nor cPVL." We analyzed the association between the 4 grades of

IVH and cPVL using multivariable logistic regression, adjusting for gestational age (less than 26 weeks; 26 or 27 weeks; and more than 27 weeks) and confounders as defined below.

To further explore the association of IVH III with cPVL and the association of IVH IV with cPVL, we report 2 separate analyses for IVH III and IVH IV predicting cPVL. To analyze the association for IVH III and cPVL, we created a separate dataset, from which infants with IVH IV were omitted. Similarly, for the analyses of IVH IV predicting cPVL, we omitted infants with IVH III to prevent dilution of the control group by infants with IVH III.

We started with univariable logistic regression analyses modeling the relationship between IVH III (or IV) and cPVL. To identify potential confounders, effect-modifiers, and mediators, we divided the pre- and postnatal characteristics into 4 groups according to the occurrence of the variable in relationship to the presumed “occurrence” of IVH and PVL (Figure 2). Unfortunately, the time of occurrence for the characteristics had not been recorded. Therefore, we had to make several assumptions. Because 90% of all cases of IVH are detected within the first 4 to 5 days,¹⁴ we assumed that IVH “occurs” (= becomes visible on ultrasound images) at some time during the first week of life. Since cPVL becomes visible several weeks after birth,¹⁴ we assumed cPVL to be diagnosed at around 4 weeks to 6 weeks.

We organized groups of variables in a time-oriented fashion. The first group included variables likely to occur before IVH and included prenatal and variables occurring or measured at birth. The second group contained early postnatal variables that potentially occur in the same period as IVH and therefore it is undetermined whether they occur before, simultaneously as, or after IVH. The third group represented postnatal variables likely to occur after IVH, but before cPVL is diagnosed. The fourth group included late postnatal variables occurring in the period that cPVL is diagnosed, and it is therefore unknown whether the characteristics occur before, concomitant with, or after cPVL.

By definition, *confounders* are associated with both IVH and cPVL, and are risk factors for cPVL among infants without IVH. Therefore, they can occur at any time before cPVL is diagnosed. We defined a variable as a *definite confounder* when the beta-coefficient in the multivariable logistic regression changed by more than 10% when adjusted for the variable. A change of more than 5% but less than 10% was considered a *possible confounder*. Confounders occurring before or concurrently with IVH can be a common antecedent. Variables occurring after the diagnoses of IVH but prior to the cPVL can be confounders by being associated with an unknown common antecedent occurring before the IVH. After identifying the confounders in our population, we created a logistic regression model for IVH III predicting cPVL while adjusting for all the definite confounders. We created a second model predicting all definite and possible confounders to test if the confounders can explain the association between IVH III and cPVL. The same analyses were done for the association between IVH IV and cPVL.

Effect modifiers are characteristics that modify the strength of the association between IVH and cPVL. Thus, they should be present before both IVH and cPVL occur. To identify such effect modifiers, we stratified the prenatal and variables measured at birth and compared the differences in odds ratio (OR) for the IVH/cPVL relationship between strata defined by the presence or absence of the potential effect modifier. In addition, we created interaction-terms and used multivariable logistic regression to test for significance of the effect modification terms while keeping raw effects in the model.

Lastly, we tried to identify potential *mediators* in the association between IVH and cPVL. These are confounders that occur after IVH but before cPVL. Such variables cannot cause IVH (retrospectively), but could cause cPVL, and are therefore potential causal mediators of

the relationship between IVH and cPVL. Therefore, we analyzed early, intermediate, and late postnatal variables. We defined mediators as variables with an appreciable difference in the OR between the strata defined by the presence or absence of the potential mediator.

Results

In our sample, gestational age ranged from 23 + 0 weeks to 29 + 6 weeks, with 25% of the infants born before 26 weeks' completed gestation. Birthweight ranged from 406 grams to 1683 grams (median = 961 grams). Forty-seven percent of the infants were male. Seventy-nine percent of infants had a Caucasian mother and 13% an African-American mother. Seventeen percent of infants' mothers were Hispanic. Virtually all infants had received prenatal care. Almost two-thirds (59%) of the infants were delivered by Caesarean section. One-hundred-sixteen (11.4%) infants died after 12 hours of admission (Table 2).

Head ultrasound revealed cPVL in 44 infants (4.3%), white matter damage in 92 (9.1%), and IVH grade III or grade IV in 151 infants (14.9%). Forty-three percent of the patients with cPVL also had IVH III or IVH IV and 13% of patients with an IVH III or IVH IV also had cPVL. The number of infants with a combination of cPVL and IVH III or IVH IV (observed $n = 19$) was larger than expected if the 2 conditions were unrelated (expected $n = 7$), calculated by multiplying the prevalence of cPVL and IVH III and IVH IV found in our population ($14.9\% * 4.3\% = 0.6\%$).

Risk Patterns for IVH and/or cPVL

A “dose-response relationship” is visible for most characteristics in relationship to “no IVH” vs IVH I/II vs IVH III (Table 2 and Table 3). This suggests that the characteristics are not only risk factors for IVH but also for the severity of IVH I through IVH III. IVH IV appeared to be on the dose-response curve for characteristics that occur postnatally, but not for characteristics representing the child's immaturity or illness severity.

When looking at the risk pattern for cPVL (Table 2 and Table 3), the number of infants is small because of the overlap with IVH. However, even with small numbers, cPVL without IVH appears to have a risk pattern different from the control group or any of the IVH groups. By definition, infants with white matter damage (cPVL or IVH IV) have a risk pattern that reflects the joint risk patterns of infants with IVH IV and/or cPVL.

Association Between IVH and cPVL

The risk for cPVL increased with the severity of IVH (Table 4). Infants with IVH I or IVH II were not at increased risk for cPVL. The crude OR for IVH III predicting cPVL in the entire dataset was 3.7 (95% confidence interval [CI], 1.6 – 8.6) and 7.1 (3.1 – 16.6) for IVH IV. Adjustment for gestational age yielded 3.6 (1.5 – 8.7) for IVH III and 6.6 (2.6 – 16.4) for IVH IV.

The dataset created for analyses of IVH III and cPVL relationship consisted of 958 infants, with 93 infants diagnosed with IVH III and 34 infants diagnosed with cPVL (Table 5, left column). The crude OR for IVH III in this dataset was 3.6 (1.6 – 8.0). Confounders were high-frequency ventilation, continuous positive airway pressure, persistent ductus arteriosus, postnatal glucocorticoids, and bronchopulmonary dysplasia. Possible confounders were birthweight < 1000 grams and gestational age. When all *definite confounders* (including potential mediators) were combined in one model, the association between IVH III and cPVL yielded an OR of 2.6 (1.1 – 6.3). When also including the *possible confounders*, the OR remained virtually unchanged at 2.8 (1.1 – 7.0).

The dataset used for the analyses of IVH IV and cPVL contained information on 923 infants, of which 58 were diagnosed with IVH IV and 35 with cPVL (Table 5, right column). The crude OR for the IVH IV in this database was 7.0 (95% CI, 3.2 – 15.4). Continuous positive airway pressure, oxygen at the 28th day of postnatal life, and late sepsis appeared to be confounders for the association between IVH IV and cPVL. Possible confounders were race, birthweight < 1000 grams, persistent ductus arteriosus, bronchopulmonary dysplasia, and retinopathy of prematurity. All definite confounders combined in one model yielded an OR of 11.3 (4.4 – 29.3). Including the possible confounders, the OR increased to 15.1 (5.0 – 45.4).

Effect Modification

By means of stratified analysis, we identified gestational age, birthweight <1000 grams, respiratory distress syndrome, and high-frequency ventilation as effect modifiers of the association between IVH III and cPVL (Table 6A). The effect modifiers of the association between IVH IV and cPVL were maternal race, gestational age, gender, a Hispanic mother, antenatal corticoids, multiple gestation, birthweight <1000 grams, birth outside our hospital, Apgar < 5 after 1 minute and persistent ductus arteriosus (Table 6B). Small numbers limited our ability to test for significance using interaction terms in logistic regression models. The only interaction term that achieved formal statistical significance was birthweight <1000 grams ($P = .03$) * IVH IV predicting cPVL.

Mediator Variables

We identified high-frequency ventilation, necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity as potential mediators of the association between IVH III and cPVL (Table 7A). Only high-frequency ventilation could plausibly cause IVH and cause cPVL, while causation by IVH of necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity are less plausible.

For the association between IVH IV and cPVL, mediators were persistent ductus arteriosus, postnatal glucocorticoids, late sepsis, and retinopathy of prematurity (Table 7B). In this scenario, postnatal glucocorticoids seem to be the most plausible mediator.

Discussion

In controls, in infants with IVH I/II, and in those with IVH III, most risk factors increased or decreased almost in a “dose-response” fashion. IVH IV did not follow this pattern, especially when looking at characteristics that occur early in the postnatal period. One explanation might be that IVH IV is etiologically different from IVH I–III.

Most patients with cPVL have some degree of IVH. The risk pattern of the infants diagnosed with cPVL and IVH closely resembles the risk pattern of the IVH grade they were diagnosed with. Infants with cPVL without IVH showed a different risk pattern compared with controls or with the groups of infants with cPVL and IVH. This suggests that cPVL with IVH and cPVL without IVH are etiologically different entities. However, numbers in our database are too small to come to a solid conclusion regarding what exactly the characteristics of this difference might be.

Others have found a similar risk pattern for infants with IVH grade III and infants with PVL.¹⁵ In this study, IVH was classified according to Volpe¹⁶ and PVL according to De Vries' classification system.¹⁷ Their finding no difference in risk pattern might have been due to overlap, because infants with both IVH and PVL were assigned to either one, depending on which was considered the predominant lesion, depending on highest grade. Moreover, PVL was not restricted to cPVL but also included echodense lesions persisting

more than 15 days and cases of symmetrical or asymmetrical ventricular dilatation in the absence of hydrocephaly or IVH.

The group of patients with IVH III is heterogeneous since ventriculomegaly is one major component of both IVH III and IV, and can be caused by different mechanisms. The entities that could lead to ventriculomegaly include diffuse white matter damage with white matter loss, periventricular cystic white matter damage, congenital ventriculomegaly, isolated large-volume IVH, or posthemorrhagic hydrocephalus.¹⁸ While hemorrhage could be the cause of the ventriculomegaly, the hemorrhage can also be co-occurring with nonpressure ventriculomegaly due to white matter loss.

Our results suggest a strong association between IVH III or IVH IV and cPVL that we could not “explain away” by confounders or common antecedents for cPVL. Moreover, our data suggest that both are associated with an increased cPVL risk, albeit at different levels. Since in our database only the highest grade of IVH is recorded for each individual child, we cannot speak to the issue of IVH IV being a mediator between IVH III and cPVL.

Previous studies have reported relationships between IVH (of various grades) and PVL. One group of investigators found an OR of 1.6 (95 CI, 1.0 – 2.4) for infants with a grade I/II IVH to develop cPVL and an OR of 5.3 (95% CI, 3.0 – 9.5) for infants with a grade III IVH. This association was higher for infants born at a gestation of 30 weeks to 32 weeks.¹⁹ Our results are similar when taking into account that we excluded babies born after 30 weeks of gestation. Another group found an OR predicting white matter echolucency, corrected for gestational age, of 4.9 (2.5 – 9.5) for IVH and 18.4 (9.4 – 35.8) for IVH with ventriculomegaly.²⁰ These colleagues decided to look at white matter “echolucency,” a definition that does not allow for the distinction between IVH grade IV and PVL we wanted to make in our present study.

Several possible explanations exist for the relationship between IVH and cPVL. When a patient is diagnosed with IVH III or IVH IV, cPVL may be overlooked and misinterpreted as atrophy due to high-grade IVH. It can be difficult to differentiate between IVH IV and cPVL based on ultrasound characteristics.²¹ A large proportion of infants with white matter disease share the characteristics of both periventricular leukomalacia and periventricular hemorrhagic infarction. Kuban and colleagues, therefore, suggest using the descriptive term “white matter disease of prematurity” when white matter abnormalities are found on ultrasound imaging.

Ultrasound has proved to be very successful in diagnosing IVH III or IVH IV. However, diagnosing IVH I or IVH II, or diagnosing cPVL by ultrasound, can be more difficult.^{14, 22–24} By obtaining several head ultrasounds by radiologists with experience in neonatal brain imaging, we tried to achieve the optimal quality of the diagnosis. The prevalence of the various grades of IVH and cPVL found in our research is similar to earlier reports.¹⁴ Therefore, we have no reason to believe that the quality of ultrasound screening in our study is inferior to similar studies.

One biological theory for the association between IVH and cPVL is that iron released in an intraventricular hemorrhage enhances oxidative stress, thereby causing damage to pre-oligodendrocytes.^{25,26} A simulation of intraventricular hemorrhage in rodents showed that blood injected into the ventricular system led to white matter apoptosis and damage in 2-day-old rodents. Injecting thrombin caused similar brain damage, while a thrombin inhibitor prevented damage. Hence, thrombin might play a significant role in neonatal periventricular brain damage after periventricular hemorrhage.²⁷ However, if iron and/or thrombin were causes of brain damage, one would expect finding an effect by any IVH grade (including IVH I and IVH II) on the prevalence of cPVL. The fact that we were unable to find an

association between IVH I or IVH II and cPVL could be due to a threshold effect of the amount of blood or a location effect of the intraventricular bleeding leading to cPVL. In a separate but related biological explanation for an association between intraventricular hemorrhage and cPVL, the role attributed to iron is played by pro-inflammatory cytokines.²⁸ In essence, proteins that can damage developing neurons and glia cells might gain access to the brain parenchyma via blood in the ventricular system.

Another hypothesis for the association between IVH III and IVH IV and cPVL is that IVH and cPVL might be caused by common antecedents and cPVL is not visible at the time IVH becomes apparent. We have tested this hypothesis by identifying potential confounders as a common antecedent. However, we have not been able to find evidence for antecedents or a combination of antecedents that could explain the association.

We excluded infants who died within 12 hours of birth since it was not standard practice to obtain a head ultrasound this early. Therefore, early IVH and cPVL would not have been ascertained in the majority of these infants. In our population, 116 infants died later and were included. Most of them died within days after birth, 38% within the first 3 days of life. Had we excluded the infants who died, we would have created a selection bias, because high grades of IVH and/or cPVL are strong predictors for death.^{6, 29} However, including these infants also influences the association. Preterm infants tend to develop IVH within days and cPVL within weeks. Therefore, infants who die within the first few days of postnatal life have a certain likelihood of developing IVH, but a much smaller chance of developing cPVL. This might have led to our finding being an underestimation of the true association. In additional analyses along these lines, we found that in survivors the association between IVH III and cPVL was 2.9 (1.1 – 7.9) and 11.9 (4.3 – 32.9) for IVH IV and cPVL.

Unfortunately, we did not record the number of head ultrasounds made per patient. The normal practice would be at least 3 studies per child: one within the first few days of life, one after one month, and one at 36 weeks' postmenstrual age or at discharge. However, we can not be entirely sure this was done for all patients in our database.

We considered the possibility of false-negative cPVL due to early discharge. In our population only 23 infants left our hospital within 6 weeks after birth. These infants had a higher gestational age and birthweight, and there were no abnormalities visible on the ultrasound before discharge. These 23 infants had a very low risk of subsequently developing cPVL. Consequently, the risk of having a (false-negative) undiagnosed cPVL due to early discharge is negligible in this population.

One major limitation is that the timing of the occurrence of a potential confounder, effect modifier, or mediator as well as the time of the diagnoses of IVH and cPVL were not recorded. Therefore, we had to make several assumptions based on literature. We assumed that IVH occurred during the first week and cPVL would become visible after 4 weeks to 6 weeks. However, severe IVH can occur as late as 3 weeks postnatal and cPVL is sometimes not diagnosed until several months after birth. Similarly, cPVL can be present during the first days of postnatal life.¹⁴ It is difficult to distinguish confounders (causes of cPVL not caused by IVH) from mediators (causes of cPVL caused by IVH) without prior knowledge, especially when these variables tend to occur after IVH but prior to cPVL. Moreover, unknown or unmeasured variables that occur in the pre- or early postnatal periods could be causes of both the confounder/mediator as well as IVH and cPVL. Given these caveats, high-frequency ventilation might be a mediator in the association between IVH III and cPVL if IVH III contributes to the necessity to use high-frequency ventilation, which in turn contributes to cPVL via increased oxidative³⁰ and/or pro-inflammatory stress.³¹ Similarly,

postnatal glucocorticoids could be a mediator between IVH IV and cPVL,³² if glucocorticoids were prescribed despite the presence of IVH and before cPVL occurred.

We offer 3 conclusions based on our findings. First, the difference in risk patterns between IVH grade III and grade IV suggests they might be different entities due to different etiologies. Based on their different risk patterns, we conclude that IVH III and IVH IV should not be combined as brain damage characteristics in research on neonatal brain damage.

Second, the risk pattern of cPVL without IVH is different from the risk pattern of the controls and from infants with cPVL who also were diagnosed with IVH. This suggests there might be etiologic differences between cPVL with IVH on the one hand, and cPVL without IVH on the other. This issue deserves further study.

Third, patients with IVH III or IVH IV (but not I or II) are at increased risk for cPVL. This association could not be explained by confounders or common antecedents. Although we hesitate to draw causal inferences from observational data, we feel rather confident that IVH III and IVH IV are likely causes of cPVL.

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Figure 1.
Derivation of study sample

Figure 2.

Time-oriented classification of variables considered for potential confounders/common antecedents, effect modifiers, and mediators in the association between IVH grade III or IV and cPVL. Abbreviations: BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; DOL = day of life; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = persistent ductus arteriosus; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.

Table 1

Prevalence of Characteristics in the Study Population (n = 1016)

	n	%
Indicators cerebral damage/death		
CPVL	44	4.3
WMD	92	9.1
IVH		
Grade I	214	21.1
Grade II	87	8.6
Grade III	93	9.2
Grade IV	58	5.7
Death	116	11.4
Infant characteristics		
Birthweight <1000 g	556	54.7
Gestational age		
<26 weeks	256	25.2
26 or 27 weeks	350	34.5
>27 weeks	410	40.4
Gender		
Male	541	53.3
Female	475	46.8
Multiple gestation	335	33.0
Birth in other hospital	170	16.7
Hispanic	174	17.1
Race (n = 968)		
Black	122	12.6
Caucasian	764	78.9
Other	82	8.5
Prenatal care	1001	98.5
Vaginal delivery	419	41.2
Respiratory and other characteristics		
Antenatal corticoids (n = 1014)	905	89.3

	n	%
Postnatal corticoids (n = 1012)	136	13.4
Mechanical ventilation	918	90.4
High-frequency ventilation	320	31.5
CPAP	904	89.0
Oxygen at 28th DOL		
Yes	523	51.5
Unknown	209	20.6
unknown due to death	102	10.0
No	182	17.9
BPD		
Yes	170	16.7
Unknown	478	47.1
unknown due to death	113	11.1
No	255	25.1
Oxygen at discharge	365	35.9
RDS	942	92.7
Surfactant therapy	907	89.3
Apgar <5, 1 min (n = 646)	367	56.8
Apgar <5, 5 min (n = 1013)	68	6.7
Early sepsis (n = 1015)	13	1.3
Late sepsis (n = 973)	232	23.8
NEC	84	8.3
PDA	371	36.5
Any ROP (n = 604)	285	47.2
ROP grade III/IV (n = 604)	87	14.4

Abbreviations: BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; DOL = day of life; NEC = necrotizing enterocolitis; PDA = persistent ductus arteriosus; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; WMD = white matter damage.

Table 2

Prevalence of Infant Characteristics in Different Subgroups of IVH and/or cPVL

IVH grade	No		I/II		III		IV		I – IV		No or I-IV		WMD *	Total
	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes			
Cystic PVL	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes		
n	548	292	84	48	16	28	44	92	1016					
<hr/>														
Birthweight <1000 g	48	55	73	90	63	71	68	79	55					
Gestational age <26 weeks	18	25	44	65	19	54	41	53	25					
Gender														
Male	53	54	54	50	44	54	50	50	53					
Female	47	46	46	50	56	46	50	50	47					
Multiple gestation	35	30	37	27	19	36	30	28	33					
Birth in other hospital	14	17	21	31	13	25	20	26	17					
Hispanic	15	16	21	31	31	18	23	27	17					
Maternal race														
Black	9	16	18	19	6	16	12	15	13					
Caucasian	81	77	74	81	81	72	76	79	79					
Other	10	6	8	0	13	12	12	6	9					
Prenatal care	99	98	98	100	100	96	98	99	99					
Vaginal delivery	37	44	51	48	50	57	55	51	41					

Numbers in the body of the table are column percents.

*WMD = IVH grade IV and/or cPVL.

Abbreviations: cPVL = cystic periventricular leukomalacia; IVH = intraventricular hemorrhage; WMD = white matter damage.

Table 3
Prevalence of Respiratory and Other Characteristics in Different Subgroups of IVH and/or cPVL

IVH grade	No		I/II		III		IV		I-IV		No or I-IV		WMD*	Total
	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes		
Cystic PVL	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes		
n	548	292	84	48	16	28	44	92	1016					
Antenatal corticoids	91	90	85	73	88	86	86	86	86	86	86	79	89	
Postnatal corticoids	10	16	23	8	25	27	26	26	26	26	26	17	13	
Mechanical ventilation	88	90	98	94	94	100	98	98	98	98	98	96	90	
High-frequency ventilation	20	36	55	75	31	64	52	52	52	52	52	64	32	
CPAP	93	90	77	50	100	89	93	93	93	93	93	71	89	
Oxygen at 28th DOL														
Yes	50	53	63	33	56	64	61	61	61	61	61	47	52	
Unknown	28	16	5	0	25	4	11	5	11	5	11	5	21	
Unknown due to death	4	10	23	60	6	18	14	14	14	14	14	38	10	
No	19	21	10	6	13	14	14	14	14	14	14	10	18	
BPD														
Yes	15	20	19	10	13	36	27	18	27	18	27	18	17	
Unknown	60	39	23	13	38	11	20	16	20	16	20	16	47	
Unknown due to death	4	11	26	63	13	25	20	42	20	42	20	42	11	
No	21	31	32	15	38	29	32	23	32	23	32	23	25	
Oxygen at discharge	32	33	45	75	38	43	41	59	41	59	41	59	36	
RDS	91	95	95	98	100	93	95	97	95	97	95	97	93	
Surfactant therapy	87	90	96	98	94	93	93	96	93	96	93	96	89	
Apgar <5, 1 min	52	59	61	74	50	68	63	69	63	69	63	69	57	
Apgar <5, 5 min	5	6	14	15	6	7	7	11	7	11	7	11	7	
Early sepsis	1	2	2	4	0	4	2	3	2	3	2	3	1	
Late sepsis	22	23	35	19	44	43	43	33	43	33	43	33	24	
NEC	7	9	12	0	13	21	18	9	18	9	18	9	8	
PDA	28	40	61	50	38	71	59	54	59	54	59	54	37	
Any ROP	43	46	63	72	30	68	55	62	55	62	55	62	47	
ROP grade III/IV	11	14	23	33	20	32	28	30	28	30	28	30	14	

Numbers in the body of the table are column percents.

Abbreviations: BPD = bronchopulmonary dysplasia; DOL = day of life; CPAP = continuous positive airway pressure; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = persistent ductus arteriosus; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.

Prevalence of cPVL Stratified by Grade of IVH and Multivariable Logistic Regression Models Measuring Association Between IVH and cPVL

Table 4

cPVL						
	Cases/total	%	OR	95% CI	OR (adj)*	95% CI
No	16/564	3	Reference		Reference	
IVH grade I	6/214	3	1.0	0.4–2.6	1.0	0.4–2.6
IVH grade II	3/87	3	1.2	0.3–4.3	1.2	0.3–4.2
IVH grade III	9/93	10	3.7	1.6–8.6	3.6	1.5–8.7
IVH grade IV	10/58	17	7.1	3.1–16.6	6.6	2.6–16.4

Multivariable logistic regression model in second column consists of the 4 grades of IVH predicting cPVL.

* Adjusted for gestational age.

Abbreviations: CI = confidence interval; cPVL = cystic periventricular leukomalacia; IVH = intraventricular hemorrhage; OR = odds ratio.

Table 5

Crude and Adjusted Logistic Regression Models Estimating the Association Between IVH III and cPVL and Between IVH IV and cPVL.

	IVH grade III predicting cPVL		IVH grade IV predicting cPVL			
	OR	95% CI	OR	95% CI		
Crude OR	3.6	1.6–8.0	7.0	3.2–15.4		
Change adjusted for potential β-confounder coefficient						
Hispanic	3.5	1.6–7.8	2.2	7.0	3.1–15.5	0.2
Maternal race	3.5	1.6–7.9	1.2	8.2	3.6–18.6	8.3
Prenatal care	3.6	1.6–7.9	0.4	7.2	3.3–15.9	1.4
Antenatal corticoids	3.6	1.6–7.9	0.7	7.0	3.1–15.6	0.3
Gender	3.6	1.6–8.0	0.4	7.0	3.2–15.4	0.1
Multiple gestation	3.7	1.7–8.1	1.2	7.0	3.2–15.4	0.0
Birthweight <1000 g	3.3	1.5–7.3	7.8	6.2	2.7–14.0	6.5
Gestational age	3.3	1.4–7.6	7.1	6.7	2.8–16.0	2.1
Birth in other hospital	3.6	1.6–8.1	0.8	7.0	3.1–15.7	0.1
Vaginal delivery	3.4	1.5–7.5	4.8	6.8	3.1–14.9	1.9
Apgar <5, 1 min	3.6	1.6–8.0	0.9	6.5	2.8–14.9	3.9
Apgar <5, 5 min	3.7	1.6–8.2	1.6	7.2	3.2–15.9	1.3
RDS	3.6	1.6–7.9	0.4	6.8	3.1–14.9	1.8
Surfactant therapy	3.6	1.6–7.9	0.8	6.9	3.1–15.4	0.4
Mechanical ventilation	3.4	1.5–7.5	4.9	6.7	3.1–14.9	2.0
High-frequency ventilation	3.1	1.3–7.1	12.2	6.5	2.7–15.5	4.1
CPAP	4.1	1.8–9.2	10.7	11.2	4.7–26.4	24.1
Early sepsis	3.5	1.6–7.8	1.7	7.4	3.3–16.3	2.8
PDA	3.1	1.3–6.9	12.8	6.1	2.7–13.6	7.4
Postnatal glucocorticoids	2.9	1.2–6.7	17.3	7.7	3.4–17.0	4.6
Oxygen use at 28 th DOL	3.4	1.5–7.9	4.1	10.0	3.9–25.5	18.2
Late sepsis	3.5	1.6–7.8	2.5	10.6	4.6–24.1	21.1
NEC	3.4	1.5–7.6	4.1	7.5	3.4–16.7	3.6
BPD	2.8	1.2–6.5	18.5	6.2	2.4–16.1	6.0
Any ROP	3.7	1.6–8.2	1.4	7.8	3.4–17.8	5.6

	IVH grade III predicting cPVL		IVH grade IV predicting cPVL	
	OR	95% CI	OR	95% CI
Category of ROP	3.4	1.5–7.7	4.3	3.4–17.6
				5.1

Abbreviations: BPD = bronchopulmonary dysplasia; CI = confidence interval; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; DOL = day of life; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PDA = persistent ductus arteriosus; RDS = respiratory distress syndrome. ROP = retinopathy of prematurity.

Table 6A

Potential Effect Modifiers for the Association Between IVH III and cPVL

Potential effect modifier	OR IVH grade III predicting cPVL			OR IVH grade III predicting cPVL		
	OR	95% CI	n	OR	95% CI	n
Crude OR	3.6	1.6–8.0	958			
Maternal race						
Black	3.4	0.3–39.9	112			
Caucasian	2.3	0.8–7.1	721			
Other	3.0	0.3–30.8	82			
Gestational age						
<26 weeks	4.6	1.4–15.0	219			
26 or 27 weeks	0.9	0.1–7.2	335			
>27 weeks	6.9	1.4–35.4	404			
Gender						
Male	5.0	1.6–15.3	510			
Female	2.7	0.8–8.4	448			
	Yes			No		
Hispanic	4.4	0.96–19.8	157	3.2	1.3–8.3	801
Prenatal care	3.8	1.7–8.4	943	*		15
Antenatal corticoids	3.9	1.7–9.1	862	2.0	0.2–20.5	94
Multiple gestation	3.0	0.6–15.5	317	3.9	1.6–9.7	641
Birthweight <1000 g	2.4	0.9–6.4	506	6.8	1.7–27.4	452
Birth in other hospital	4.7	0.7–30.3	151	3.4	1.4–8.3	807
Vaginal delivery	2.7	0.9–8.0	391	4.5	1.4–14.9	567
Apgar <5, 1 min	3.4	0.99–11.9	327	2.0	0.4–9.6	267
Apgar <5, 5 min	3.8	0.2–65.9	60	3.7	1.6–8.4	895
RDS	3.2	1.4–7.4	885	16.7	0.9–319.9	73
Surfactant therapy	3.7	1.7–8.4	850	*		108
Mechanical ventilation	3.4	1.5–7.6	863	*		95
High-frequency ventilation	5.3	1.8–15.5	276	0.9	0.1–7.0	682

Potential effect modifier	OR IVH grade III predicting cPVL			OR IVH grade III predicting cPVL		
	OR	95% CI	n	OR	95% CI	n
CPAP	3.8	1.7–8.8	872	*		86
Early sepsis	*		11	3.2	1.4–7.4	947
PDA	3.4	1.2–9.1	339	2.5	0.5–11.3	619

* Multivariable logistic regression analyses impossible due to zero cells. Cells contain the OR for IVH III and cPVL, stratified for the potential effect modifier.

Abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; IVH = intraventricular hemorrhage; OR = odds ratio; PDA = persistent ductus arteriosus; RDS = respiratory distress syndrome.

Table 6B

Potential Effect Modifiers for the association between IVH IV and cPVL

Potential effect modifier	OR IVH grade IV predicting cPVL			OR IVH grade IV predicting cPVL		
	OR	95% CI	n	OR	95% CI	n
Crude OR	7.0	3.2–15.4	923			
Maternal race						
Black	11.9	1.5–95.9	107			
Caucasian	7.7	3.2–18.8	702			
Other	*		75			
Gestational age						
<26 weeks	5.5	1.7–18.1	213			
26 or 27 weeks	4.9	0.97–25.2	313			
>27 weeks	19.1	3.1–116.4	397			
Gender						
Male	13.1	4.6–37.5	491			
Female	3.3	0.9–12.0	432			
	Yes			No		
Hispanic	3.5	0.6–19.6	153	8.6	3.5–21.0	770
Prenatal care	7.2	3.3–15.9	910	*		13
Antenatal corticoids	7.9	3.3–19.0	826	3.9	0.6–26.0	95
Multiple gestation	17.8	4.8–66.1	302	4.2	1.5–12.0	621
Birthweight < 1000 g	4.0	1.6–10.3	489	31.4	6.4–154.2	434
Birth in other hospital	11.4	2.3–55.8	150	5.9	2.2–15.5	773
Vaginal delivery	5.1	1.7–15.4	371	9.3	3.0–28.8	552
Apgar <5, 1 min	8.6	3.0–24.5	323	2.3	0.3–20.0	251
Apgar <5, 5 min	6.6	0.4–117.5	55	7.2	3.2–16.6	865
RDS	6.9	3.1–15.2	854	*		69
Surfactant therapy	7.1	3.2–15.9	817	*		106
Mechanical ventilation	6.9	3.1–15.4	827	*		96
High-frequency ventilation	6.8	2.3–20.0	266	5.8	1.2–27.8	657

OR IVH grade IV predicting cPVL					
Potential effect modifier	OR IVH grade IV predicting cPVL		OR IVH grade IV predicting cPVL		
	OR	95% CI	n	OR	95% CI
CPAP	10.3	4.2–25.2	831	*	
Early sepsis	*		10	7.4	3.3–16.3
PDA	8.2	3.0–22.3	313	3.4	0.7–15.8

Cells contain the OR for IVH IV and cPVL, stratified for the potential effect modifier.

* Multivariable logistic regression analyses impossible due to zero cells.

Abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; IVH = intraventricular hemorrhage; OR = odds ratio; PDA = persistent ductus arteriosus; RDS = respiratory distress syndrome.

Table 7A
Multivariable Logistic Regression Analyses to Determine Mediators in the Association Between IVH III and cPVL

Potential mediator	OR IVH grade III predicting cPVL			OR IVH grade III predicting cPVL		
	OR	95% CI	n	OR	95% CI	n
Crude OR	3.6	1.6–8.0	958			
	Yes			No		
Mechanical ventilation	3.4	1.5–7.6	863	*		95
High-frequency ventilation	5.3	1.8–15.5	276	0.9	0.1–7.0	682
CPAP	3.8	1.7–8.8	872	*		86
Early sepsis	*		11	3.2	1.4–7.4	947
PDA	3.4	1.2–9.1	339	2.5	0.5–11.3	619
Postnatal corticoids	3.6	0.9–13.9	131	2.5	0.8–7.7	823
Oxygen use at 28 th DOL						
Yes	3.2	1.2–8.7	501	5.2	0.5–51.6	178
Unknown	*		209			
Unknown due to death	5.1	0.4–59.1	70			
Late sepsis	3.5	1.1–11.0	222	3.5	1.1–10.9	709
Unknown	*					
NEC	6.6	1.2–37.3	82	2.9	1.1–7.3	876
BPD						
Yes	8.6	2.2–32.8	163	0.9	0.1–7.0	244
Unknown	2.9	0.3–24.6	472			
Unknown due to death	1.6	0.2–10.1	79			
Any ROP	9.5	2.5–35.3	266	1.2	0.1–9.8	313
Unknown	2.4	0.5–11.6	379			
Category of ROP						
Grade I–II	14.6	1.3–168.2	186	1.2	0.1–9.8	313
Grade III–IV	6.2	1.2–30.9	80			
Unknown	2.4	0.5–11.6	379			

Cells contain the OR for IVH III and cPVL, stratified for the potential mediator.

* Multivariable logistic regression analyses impossible due to zero cells.

Abbreviations: BPD = bronchopulmonary dysplasia; CI = confidence interval; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; DOL = day of life; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PDA = persistent ductus arteriosus; ROP = retinopathy of prematurity.

Table 7B
Multivariable Logistic Regression Analyses to Determine Mediators in the Association Between IVH IV and cPVL

Potential mediator	OR IVH grade III predicting cPVL			OR IVH grade III predicting cPVL		
	OR	95% CI	n	OR	95% CI	n
Crude OR	3.6	1.6–8.0	923			
	Yes			No		
Mechanical ventilation	6.9	3.1–15.4	827	*		96
High-frequency ventilation	6.8	2.3–20.0	266	5.8	1.2–27.8	657
CPAP	10.3	4.2–25.2	831	*		92
Early sepsis	*		10	7.4	3.3–16.3	912
PDA	8.2	3.0–22.3	313	3.4	0.7–15.8	610
Postnatal corticoids	4.3	0.4–44.2	113	8.4	3.6–19.7	807
Oxygen use at 28 th DOL						
Yes	10.7	3.7–31.1	464	13.8	1.2–162.7	173
Unknown	*		205			
Unknown due to death	5.0	0.5–50.0	81			
Late sepsis	12.1	2.9–49.7	201	9.9	3.5–27.5	688
Unknown	*		34			
NEC	*		71	5.9	2.5–13.9	852
BPD						
Yes	11.0	1.7–70.9	149	13.1	3.2–53.2	227
Unknown	*		458			
Unknown due to death	2.3	0.5–11.0	89			
Any ROP	25.5	6.4–101.7	244	5.1	0.5–47.3	297
Unknown	3.4	0.9–13.0	382			
Category of ROP						
Grade I–II	115.0	11.8–999	174	5.1	0.5–47.3	297
Grade III–IV	3.3	0.3–37.3	70			
Unknown	3.4	0.9–13.0	382			

Cells contain the OR for IVH IV and cPVL, stratified for the potential mediator.

* Multivariable logistic regression analyses impossible due to zero cells.

Abbreviations: BPD = bronchopulmonary dysplasia; CI = confidence interval; CPAP = continuous positive airway pressure; cPVL = cystic periventricular leukomalacia; DOL = day of life; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PDA = persistent ductus arteriosus; ROP = retinopathy of prematurity.