The impact of intraventricular hemorrhage and periventricular leukomalacia on mortality and neurodevelopmental outcome in very preterm and very low birthweight infants : a prospective population-based cohort study

The impact of intraventricular hemorrhage and periventricular leukomalacia on mortality and neurodevelopmental outcome in very preterm and very-low-birthweight infants: a prospective population-based cohort study

Short title: Mortality and neurodevelopment in very-preterm and very-low-birthweight infants

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ABSTRACT

OBJECTIVES

To survey the incidence of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) by gestational age (GA) and to report the impact on mortality and neurodevelopmental outcome in very preterm (VPT)/very low birthweight (VLBW) infants.

STUDY DESIGN

This was a population-based cohort study of 1927 VPT/VLBW infants born in 2014-2016 and admitted to Flemish neonatal intensive care units (NICU's). Infants underwent standard follow-up assessment until two years corrected age (CA) with the Bayley-III and neurological assessments.

RESULTS

No brain lesion was present in 31% of infants born <26 weeks GA and in 75.8% of infants born 29-32 weeks GA. Prevalence of low-grade IVH/PVL (grade I and II) was 16.8% and 12.7%, respectively. Low-grade IVH/PVL was not significantly related to increased likelihood for mortality, motor or cognitive delay, except for PVL grade II which was associated with a fourfold increase in developing cerebral palsy (CP) (OR=4.1; 95%CI=1.2-14.6).

High-grade lesions (III-IV) were present in 22.0% of the infants born with <26 weeks GA and decreased to 3.1% at 29-32 weeks GA, and odds of death was ≥14.0 (IVH OR=14.0; 95%CI=9.0-21.9; PVL OR=14.1; 95%CI=6.6-29.9). PVL grade III-IV showed increased odds of 17.2 for motor delay and 12.3 for CP , but was not increased significantly for cognitive delay (OR=2.9; 95%CI: 0.5-17.5; p=0.24).

CONCLUSIONS

Both prevalence and severity decreased significantly with increasing GA. More than 75% of all infants with low-grades IVH/PVL showed normal motor and cognitive outcome at two years CA. High grades PVL/IVH have become very rare and were associated with adverse outcome.

List of abbreviations:

Bayley-III-NL	Bayley Scales of Infant and Toddler Development
BW	Birth weight
CA	Corrected age
CI	Confidence interval
CP	Cerebral palsy
EPIBEL	Extremely preterm infants in Belgium
GA	Gestational age
GMH	Germinal matrix hemorrhage
IVH	Intraventricular hemorrhage
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
OR	Odds ratio
PVHI	Periventricular hemorrhagic infarction
PVL	Periventricular leukomalacia
VLBW	Very low birth weight
VPT	Very preterm

INTRODUCTION

Very preterm (VPT) and very low birth weight (VLBW) infants are at high risk of injury to the developing and immature brain [1]. Independent of the presence of any brain lesions, previous research by our group has shown mild neurodevelopmental impairments (NDIs) in 25.2% of preterm infants and moderate to severe NDIs in 10.9% [2]. Other research suggests an even higher prevalence of mortality and morbidity related to specific brain lesions [3-5]. The main brain lesion patterns affecting preterm infants are 1) hemorrhages, including germinal matrix hemorrhage (GMH) and intraventricular hemorrhage (IVH) and 2) white matter injury or periventricular leukomalacia (PVL) [6-8].

IVH typically initiates in the germinal matrix, and may extend into the ventricle and lead to ventricular dilatation [9]. The prevalence of IVH has been reported to range between 15% and 45% in VPT/VLBW infants, with a higher occurrence in infants born before 28 weeks gestational age (GA) [12-14]..

Incidence of PVL lesions also varies due to GA, ranging from 39.6% of infants born before 28 weeks to 7.3% of infants born before 37 weeks [24]. Notably, the incidence of moderate to severe PVL lesions has decreased from 29-3.2% of VPT infants in 1990-2001 to only 9-1.3% in 2001-2009[25,26]. Several studies have shown the negative impact of IVH and PVL on neurodevelopmental outcomes [14, 18-22 27-29].

The increased neonatal survival rate of VPT/VLBW infants and the continuous improvement of neonatal care require up-to-date information about the incidence and impact of the most frequent brain lesions in preterm infants. Moreover, few large cohort studies have reported the impact of both IVH and PVL on mortality risk and neurodevelopmental outcome in a population-based cohort of VPT/VLBW infants. Therefore, the aim of our study was to survey

cerebral injury by GA and to report the impact of IVH and PVL on mortality and neurodevelopmental outcome at two years corrected age (CA) in VPT/VLBW infants.

METHODS

Participants

This study presents additional analyses on the population-based cohort study that was published earlier [32], including all VPT (defined as <31 weeks GA) and/or VLBW (<1500 g) infants born between January 1, 2014 and December 31, 2016 and admitted to one of the eight Flemish neonatal intensive care units (NICUs). This database was a result of a Royal decree named the 'Belgian follow-up convention'. Stillbirths or infants who died in the delivery room were not included. In this convention, VPT (<31 weeks GA) and/or VLBW (<1500g) infants, are eligible for standardised assessments, hence the cut-off for VPT births does not match the definition of the World Health Organization [33].

Perinatal data definitions

Cranial ultrasound is the gold standard in Belgium and performed according to standard of care in each VPT/VLBW infant multiple times during a NICU stay up until discharge.IVH was graded according to the modified Papile classification criteria [10, 11] and PVL was classified using the four-grade classification by de Vries et al [23].

IVH and PVL grades I-II were defined as low-grade, while grades III-IV were defined as high-grade. PVL and IVH grade I were considered as mild, PVL/IVH grade II as moderate and III to IV as severe.

When magnetic resonance imaging was carried out, the results were classified based on the Surveillance of Cerebral Palsy in Europe classification criteria [34]. Lesions classified as 'other

haemorrhages' were located in brain regions other than intraventricular, such as subarachnoidal, thalamoventricular or cerebellar.

Neurodevelopmental outcome

At two years CA (range 22-26 months CA) routine clinical follow-ups were performed at clinics linked to the different NICU's. The neurological examinations were performed by experienced paediatricians or paediatric neurologists. Motor and cognitive outcomes were assessed by trained paediatric physiotherapists and (educational) psychologists, respectively, and reported using the Bayley Scales of Infant and Toddler Development (Bayley-III-NL; Dutch version with norm values based on Flemish [Belgian] infants) [35]. Finally, cerebral palsy (CP) was defined by the European Cerebral Palsy Network definition [34].

The definition of NDI is based on motor, cognitive, hearing, and vision impairments and is reported in Table 1; online.

Ethical approval

Ethical approval for this study was obtained by the authors' institutional review board or equivalent committee.

Statistics

Descriptive statistics are reported with proportions and percentages for categorical variables and mean and standard deviations for continuous data. Between-group comparisons of perinatal characteristics were investigated using t-test or Mann-Whitney U Test and Fisher exact test for normally and non-normally distributed data, respectively. Further, Chi-Square test was used to investigate rates of impairment in relation to GA and BW. Between-group differences were assessed for infants who died before discharge and those who survived to

discharge from NICU. Prevalence of different brain lesions based on GA was calculated for four age categories: <26 weeks, 26-28 weeks, 29-32 weeks, and >32 weeks GA.

Finally, univariate logistic regression analysis was performed to investigate the odds ratio (OR) compared to a term born typical developing infants for motor, cognitive and neurodevelopmental delays, mortality and CP related to specific brain lesions, independent of GA. ORs and 95% confidence intervals (CI) were reported and $p<0.05$ was defined as statistically significant. Analyses were performed using SPSS Statistics for Windows (v24; IBM Corp., Armonk, N.Y., USA) and were performed on a subpopulation of children that survived to discharge from NICU.

RESULTS

Patients' characteristics

A total of 1942 VPT/VLBW infants were admitted to the NICUs. For 15 infants, the data about brain lesions were not completely entered into the database, therefore they were excluded from the study. This led to a final cohort of 1927 VPT/VLBW infants. Of these, 78 infants showed combined IVH and PVL lesions and thus were included in both analyses. For 47 infants, data about possible presence of PVL lesions were not available. Consequently, it was not clear whether these infants had only IVH or combined lesions. Therefore, these infants were not included in prevalence analysis concerning PVL lesions.

Out of 1927 included infants, 158 (8.2%) died before discharge. Mortality decreased from 31.0% in VPT at <26 weeks GA to 7.2% at 26-29 weeks GA, and decreased further to 2.5% at 30-32 weeks GA. A small increase towards 8.9% was seen for VLBW (<1500gr, GA>32w). The mean GA and BW of those infants who died was significantly lower than those of infants who survived to discharge, with 26.47±2.7 weeks versus 28.86±2.4 weeks and 863.04±323.4 grams versus 1181.05±313.7grams, respectively. Other differences between infants who died

before discharge and survivors are reported in Table 2. Follow-up data at two years CA were available for 1089 infants.

Prevalence of brain lesions based on GA

The number of VPT/VLBW infants admitted to the NICU having no brain lesions ranged from 31.0% at <26 weeks to 75.8% at 29-32 weeks. High-grade lesions (grades III-IV) were present in one in five infants born before 26 weeks and this prevalence was lower (three in 100) in infants born at 29-32 weeks GA. The presence of PVL III-IV was lower (3.9-0.6%) than IVH III/PVHI (18.1-2.5%). The prevalence of low-grade lesions (grades I-II) was16.4%, 4.7% and 29.3% for PVL I, PVL II and IVH I-II, respectively, in infants born at GA <26 weeks. Also, the prevalence of PVL I, PVL II and IVH I-II were lower in infants born 29-32 weeks GA (7.3; 1.5 and 11.9%, respectively). For VLBW infants with >32weeks GA, brain lesions were present in less than 10%, with the majority consisting of low-grade lesions (5.5% IVH I-II and 2.8% PVL I, Figure 1).

Prevalence and neurodevelopmental outcomes of PVL

Altogether, PVL grades I-IV were observed in 14.3% of the VPT/VLBW infants. Prevalence ranged from 28.1% in infants born <26 weeks GA to 4.7% of infants born >32 weeks GA and BW <1500g (Figure 1B). All GA together, the prevalence of low-grade PVL was higher (12.7%) than high-grade PVL (1.5%). (Table 2) A decreasing trend in prevalence was seen with increasing GA across all grades of PVL. (see Figure 1D and Table 3; online).

Mortality rates by brain lesions are reported in Table 4. In infants with low-grade PVL, 6.1 to 9.8% died before NICU discharge, while nearly half (48.3%) of infants with high-grade PVL did not survive. Intensive care was withheld or withdrawn in 85.7% of infants with high grade PVL. Infants with severe brain lesions were 14.1 times more likely to die before discharge.

Differences between high and low-grade PVL lesions were also reflected in the neurodevelopmental outcomes. Only 6 out of 15 infants with high-grade PVL had follow-up

data available. These infants had considerably lower scores on the motor index (65.8±17.9) compared to infants with other or no brain lesions (motor index mean scores between 88.4 and 94.6, respectively). Additionally, infants with severe PVL lesions were 17.2 times more likely to experience motor delay and 12.3 times more likely to experience CP. The average cognitive index for high-grade PVL was considerably lower (81.0) compared to all other brain lesions(low-grade PVL or all kinds of IVH) or no brain lesion (raging from 89.5 to 95.0). However, no significant relationship between cognitive impairment and high grade PVL was found (ORcogn=2.9; 95%CI=0.5-17.5; p=0.24). Infants with PVL grade I lesions did not have increased odds for motor or cognitive Impairment. Infants with PVL II lesions had a significantly increased likelihood of developing CP (ORcp=4.1; 95%CI=1.2-14.6; p=0.03). An overview of all neurodevelopmental outcome scores and ORs can be found in Tables 4 and 5.

Prevalence and neurodevelopmental outcome of IVH

The prevalence of any intracranial hemorrhage was inversely related with GA, ranging from 77.8% in infants born with 22-23 weeks GA to 8.2% in infants with ≥32 weeks GA (and BW <1500g)(figure 1B). Low-grade IVH lesions were observed in 16.8% and high grade IVH were present in 94 of the 1927 (4.9%) VPT/VLBW infants included in the study. The infants with 24-25 weeks GA had the highest prevalence of IVH grade III and PVHI (18.4%), followed by the infants with GA of 22-23 weeks (11.1%). Otherwise, the prevalence of low and high-grade IVH was inversely related to GA (Figure 1C, Table 3).

Mortality rates for infants with IVH ranged from nearly 10% for IVH grades I-II to nearly 50% for IVH grades III/PVHI. While low-grade IVH was not significantly associated with increased odds of death, IVH grade III/PVHI was associated with 14.0 times higher odds of death before NICU discharge. In 73.3% of the infants with IVH III/PVHI who died, intensive care was withheld or withdrawn.

The presence of IVH lesions were also related to neurodevelopmental outcomes at two years CA. Infants with low-grade lesions had motor (93.3±17.8) and cognitive (94.3±14.5) indices within normal range and no increased odds for motor or cognitive delays, nor CP

(ORmotor=1.1; 95%CI=0.7-1.6; ORcogn=1.32, 95%CI=0.9-2.0 and ORcp=1.0, 95%CI=0.4-2.1). Infants with high-grade IVH lesions had a 2.6- and 3.0-times higher likelihood of developing a motor or cognitive delay, respectively, and a 15.6 times higher likelihood of developing CP (See Tables 4 and 5).

DISCUSSION

While the majority of papers discussing outcomes in VPT/VLBW focus on adverse neurodevelopmental disorders, we would like to focus on the bright side. We found that the majority (62.7%) of VPT/VLBW infants had no neonatal brain lesions detected by routine neuroimaging. While neurocognitive problems may also exist in infants without brain lesions, possibly due to abnormal brain connectivity [36], our data support that the absence of overt brain injury is generally associated with improved outcomes. Most of the brain lesions observed in this study were comprised of low-grade IVH and PVL, having no or mild impact on mortality and favorable motor and cognitive outcomes, with the exception of infants with PVL grade II who were four times more likely to develop CP. On the other hand, infants with high-grade PVL and IVH (grades III/PVHI), though fortunately rare and representing only 3% of the whole sample, had a 14-fold higher likelihood of dying before NICU discharge and higher rates of adverse neurodevelopmental outcomes at two years CA among survivors.

A decrease of both overall prevalence and severity of brain lesions was observed with increasing GA, with IVH being the most common variety of neonatal brain lesion, and with mild lesions more prevalent than moderate or severe lesion, as in other literature [27, 37 26] . Compared to other international studies, severe IVH was found to be less prevalent in our cohort of infants who survived to discharge [38] . This may be explained by the fact that half of the

children with severe IVH did not survive to discharge. Moreover, compared to some other high-income countries, our cohort included only a small number of infants admitted to the NICU at GA of 22-23 weeks [39] [40-42] .

For PVL lesions, previously reported to be the second most common brain lesion in preterm infants, prevalence ranged from 10.5% to only 3% for grade I and grades II-IV lesions, respectively [38, 43, 44]. The prevalence of high-grade PVL (grade III-IV) observed in our study (overall 1.5%, up to 4.4% in infants 24-25 weeks GA) is comparable, and perhaps lower, with respect to another large cohort study in VPT/VLBW infants that reported an incidence between 2% and 6% [38].

It should be noted that mortality rates were closely related to local resuscitation policies and perinatal care, which also have an impact on the follow-up population and make it difficult to generalize current results to other countries or care settings.

The high mortality rate in infants with high-grade IVH/PVL in our sample might indicate a more progressive policy regarding withdrawing or withholding care in our cohort of infants with severe brain lesions, which are known to have poor neurodevelopmental prognoses [7, 19, 29].

Although this stricter resuscitation and treatment policy may have influenced overall survival rates, it is notable that mortality of these groups ranged from 31% in infants with <26 weeks GA to 2.4% in infants with 29-32 weeks GA. Compared to a previously reported mortality rate of 54% in the EPIBEL study (which reported outcomes in VPT infants born <26 weeks GA between 1999 and 2000 in Belgium), survival of these VPT infants in Belgium has improved by 23% [45].

Previously, it was believed that low-grade GMH-IVH was benign and did not increase the likelihood of NDI beyond the risk associated with prematurity alone [20, 46]. Lately, this has been

debated as some studies have reported the association of adverse neurodevelopmental outcomes with low-grade IVH [12, 14, 22]. We found that 83% of all infants with low-grade lesions had normal motor function at two years CA possibly supporting the former hypothesis that low grade brain lesions (i.e., IVH or PVL) are associated with a favorable prognosis. However, PVL grade II lesions were associated with a four-fold increased odds of developing CP, which is consistent with the notion that low grade lesions may be associated with neurodevelopmental risk. Since it is known that the predominant location of damage within the white matter in preterm infants is around the corticospinal tract and their descent into the internal capsule [11, 28, 29, 47], which are the main structures to control motor function, it is not surprising that c-PVL is related to adverse motor outcomes.

On the other hand, the effect of brain lesions on cognitive outcomes is less clear. In total, 80.3% of infants with low-grade IVH and 62.5% of infants with high-grade IVH have normal cognitive outcomes at two years CA, consistent with earlier reported outcomes at school-age [22]. For PVL, 71-76% of infants with low-grade lesions and 60% of infants with high-grade lesions had normal cognitive function. Some studies have reported higher prevalence of cognitive disability in infants with PVL, with increasing rates according to the severity of PVL [31, 48, 49]. Others did not find associations between PVL grade I and adverse cognitive outcomes [50-52]. . The association between PVL and adverse cognitive outcomes might also be confounded by accompanying neural abnormalities affecting not only the cerebral white matter but also the thalamus, basal ganglia, cerebral cortex, brainstem and cerebellum, which together constitute a complex amalgam of 'encephalopathy of prematurity'[11]. Nevertheless, the effect of brain lesions on cognitive function is more ambiguous since redirection of care in the more severely affected cases could at least partly have influenced outcome and cognitive testing is less accurate at this young age [53]. In this study, we assessed cognition using the Bayley-III-NL at

two years CA. However, a more accurate assessment for cognitive function would be the Wechsler Intelligence Scale at a later age, whilst assessments of behavior and executive functions at this later age are also important [54]. Further, children with congenital anomalies were also included in these population-based analyses who may be more prone to have cognitive disabilities. Given that only 8 infants had diagnosed and 12 were suspected to have chromosomal anomalies, we do not expect that inclusion of these infants significantly influenced findings.

It is important is to contextualize the results of our study in the light of the health care system and available support for families of VPT/VLBW infants in Belgium. All VPT/VLBW infants are screened and followed up for risk of neuromotor impairments. Based on the results of the multidisciplinary team, the team provides advice and, if necessary, refers for appropriate assistance. In case of a high risk, or early diagnosis of any neuromotor impairment, the infants and their families are referred to outpatient therapy such as physiotherapists, speech therapists, occupational therapist and/or rehabilitation centers. If the infant needs more specific care due to a disability, he or she can go to special preschool childcare from birth until 4 years, and to special education from the age of 2.5 years. Hence, children with high-risk profiles will have benefited from additional therapy at time of follow-up.

The strength of this study is the large and comprehensive study sample. Starting in 2014, a national follow-up program has been implemented for all infants born VPT in Belgium, and since 2016 all the results have been systematically registered into a database. We note that only children with BW lower than 1500g were included for infants born after 32 weeks GA, since literature has shown that these children are at high risk for developmental disorders [55]. Hence, results of the >32 weeks VLBW group must be interpreted with caution.

We note the potential impact of missing data on prevalence analyses as 47 infants were excluded from PVL prevalence analysis due to missing data about presence of PVL lesions. We also note that 4% of all infants (n=78) had both IVH and PVL lesions and were included in each independent prevalence analysis. Finally, the regression analysis to predict neurodevelopmental outcome at two years CA was only performed on a subset of this sample for whom follow-up data were available. Notably, among the infants with PVL grade III-IV, 14 out of 29 died and of the remaining 15 only six had follow-up data available. Consequently, caution is needed in interpreting follow-up results given the proportionally high attrition (due to mortality and loss to follow-up) in the subset of infants with high-grade lesions who are at highest risk for severe impairment. Nevertheless, the whole subset still contains a large sample of children (n=1089).

In summary, the prevalence and severity of IVH/PVL decreased significantly with increasing GA. Low-grade IVH/PVL lesions occur in one out of six to eight VPT/VLBW and are not related to increased odds of mortality or neurodevelopmental impairment. More than 75% of infants with low-grade IVH/PVL showed normal motor and cognitive outcomes at two years CA. High-grade PVL/IVH lesions have become very rare, but are nonetheless still associated with high mortality rates and adverse neurodevelopmental outcomes.

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1. CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

2. **FUNDING**

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3. FIGURE LEGENDS

Figure 1 Top: (A) Prevalence of brain lesions based on gestational age. . (B): Distribution for each brain lesion by gestational age. Distribution of IVH (C) and PVL (D) grade by gestational age. Note that for all figures, infants with multiple lesions were included in the counts of each lesion type..

Abbreviations: IVH: intraventricular haemorrhage, NICU: neonatal intensive care unit, PVHI: periventricular haemorrhagic infarction, PVL: periventricular leukomalacia.

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Fig. 1

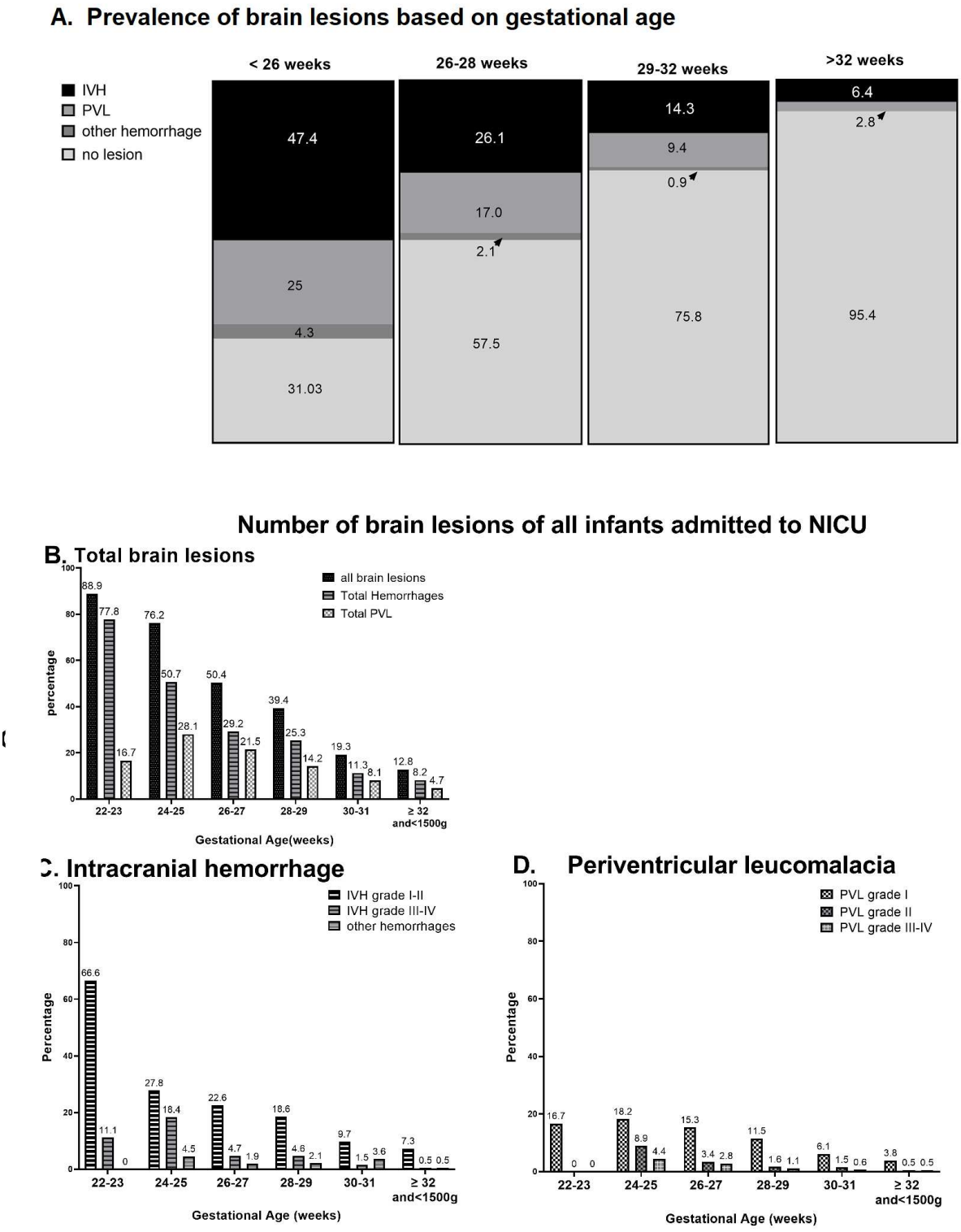

Figure. A, Prevalence of brain lesions based on gestational age. B, Distribution for each brain lesion by gestational age. Distribution
of IVH (C) and PVL (D) grade by gestational age. Note that for all figures, infants with multiple lesions were included in the counts of each lesion type. PVHI: periventricular hemorrhagic infarction, PVL: periventricular leukomalacia.

Table 1. Definitions of neurodevelopmental impairment

Category	Mild NDI	Moderate NDI	Severe NDI
Motor	Motor composite score of 70-84 on Bayley-III	Motor composite score of <70 on Bayley-III	Motor composite score of <55 on Bayley-III
Cognition	Cognitive composite score 70-84 on Bayley-III	Cognitive composite score of <70 on Bayley-III	Cognitive composite score of <55 on Bayley-III
CP	CP GMFCS I	CP GMFCS II	CP GMFCS III-IV
Hearing	Hearing loss <40dBHL	Hearing loss corrected with aids (40-70dBHL) or some hearing loss but not corrected by aids (70-90dBHL)	Profound >90dBHL (no useful hearing even with aids)
Vision	Vision impaired but appears to have useful vision	Seems to have moderately reduced vision but better than severe impairment or blind in one eye with good vision in the contralateral eye	Blind or can only perceive light or light reflecting objects

Abbreviations: Bayley-III: Bayley Scales of Infant and Toddler Development, third edition; CP: cerebral Palsy; dBHL: Decibels Hearing Level; GMFCS: Gross Motor Function Classification System; NDI: neurodevelopmental impairment.

Table 2. Characteristics of the infants

	Died before discharge NICU (n=158)	**Survived to discharge NICU (n=1769)**	
	N (%) / Mean±SD	**N (%) / Mean±SD**	***p*-value**
Perinatal characteristics			
GA (wks)	26.47±2.65	28.86±2.36	**<0.001**
22-23	4/158 (2.5)	5/1769 (0.2)	
24-25	68/158 (43.0)	155/1769 (8.8)	
26-27	41/158 (25.9)	318/1769 (18.0)	
28-29	26/158 (16.5)	543/1769 (30.7)	
30-31	11/158 (7.0)	537/1769 (30.4)	
≥32 (and <1500g)	8/158 (5.0)	211/1769 (11.9)	
BW (g)	863.04±323.39	1181.05±313.73	**<0.001**
<1000	114/158 (72.2)	532/1769 (30.1)	**<0.001**
1000-1499	38/158 (24.1)	1029/1769 (58.2)	
>1500 (and <31wks)	6/158 (3.8)	208/1769 (11.8)	
Gender (Boys)	84/158 (53.2)	897/1769 (50.7)	0.562
SGA (<10^{th} pc)	32/158 (20.3)	232/1769 (13.1)	**0.016**
Multiple birth	48/158 (30.4)	568/1769 (32.1)	0.722
Apgar score <7 at 5 minutes	65/156 (41.7)	292/1759 (16.6)	**<0.001**
Outborn	24/158 (15.2)	212/1769 (12.0)	0.254
Age at admission (days)	0.40±3.31	0.91±8.36	
Hospital stay (days)	19.07±41.79	45.65±393.7	
Therapy			
Resuscitation	117/158 (74.1)	796/1762 (45.2)	**<0.001**
Nasal CPAP (days)	5.49±12.64	13.99±18.10	
Oxygen therapy (days)	13.15±21.27	23.59±32.65	
Endotracheal ventilation (days)	10.38±12.75	4.67±9.78	
Surfactant	128/158 (81.0)	959/1769 (54.2)	**<0.001**
Systemic corticotherapy	45/158 (28.5)	255/1767 (14.4)	**<0.001**
Number of blood transfusion(s)	2.85±3.00	1.67±2.80	

Thoracic surgery	7/156 (4.5)	50/1764 (2.8)	0.221
Abdominal surgery	18/158 (11.4)	86/1758 (4.9)	**0.002**
Neurosurgery	3/158 (1.9)	32/1768 (1.8)	0.761
Neonatal morbidity			
Intracranial Hemorrhage			
IVH grade I-II	32/158 (20.3)	292/1769 (16.5)	0.223
IVH grade III and PVHI	45/158 (28.5)	49/1769 (2.8)	**<0.001**
Other hemorrhage	12/158 (7.6)	20/1769 (1.1)	**<0.001**
White matter disease			
PVL grade I	12/129 (9.3)	186/1750 (10.6)	0.766
PVL grade II	4/129 (3.1)	36/1750 (2.1)	0.350
PVL grade III-IV	14/129 (10.9)	15/1750 (0.9)	**<0.001**
Airleak syndrome	18/158 (11.4)	58/1767 (3.3)	**<0.001**
BPD at 36wks GA	-	462/1417 (32.6)	-
PDA	58/158 (36.7)	305/1768 (17.3)	**<0.001**
Necrotizing enterocolitis	14/158 (8.9)	66/1769 (3.7)	**0.005**
Infection early onset (≤72hours)	33/134 (24.6)	136/1452 (9.4)	**<0.001**
Infection late onset (>72hours)	53/134 (39.6)	465/1452 (32.0)	0.083
ROP (≥ stadium 3)	-	89/1401 (6.4)	-
Congenital malformations	25/154 (16.2)	103/1756 (5.9)	**<0.001**

Abbreviations: BPD: Bronchopulmonary dysplasia; BW: Birthweight; CPAP: Continuous positive airway pressure; g:grams; GA: Gestational age; IVH: Intraventricular hemorrhage; N: Number; NICU: *Neonatal* intensive care unit; Pc: percentile; PDA: Patent ductus arteriosus; PVHI: periventricular hemorrhagic infarction; PVL: Periventricular leucomalacia; ROP: Retinopathy of Prematurity; SD: Standard deviation; SGA: Small for gestational age; wks: weeks.
Congenital malformations present were: anal imperforation (1), congenital cardiac malformation (36), cleft lip palate (8), diaphragmatic hernia (4), esophageal atresia (15), hydrocephaly (3), intestinal artresia (5), karyotype anomaly (18), limb reduction defects (3), obstructive uropathy (4), omphalocoele (1), other (69).

Table 3. Brain lesions by gestational age of all infants admitted to the NICU and of the survivors to discharge

Brain lesion	22-23 weeks GA	24-25 weeks GA	26-27 weeks GA	28-29 weeks GA	30-31 weeks GA	≥32 weeks GA (and <1500g)	Overall
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
ALL INFANTS ADMITTED TO THE NICU							
Intracranial Hemorrhage							
IVH grade I-II	6/9 (66.6)	62/223 (27.8)	81/359 (22.6)	106/569 (18.6)	53/548 (9.7)	16/219 (7.3)	324/1927 (16.8)
IVH grade III and PVHI	1/9 (11.1)	41/223 (18.4)	17/359 (4.7)	26/569 (4.6)	8/548 (1.5)	1/219 (0.5)	94/1927 (4.9)
Other hemorrhage	0/9 (0.0)	10/223 (4.5)	7/359 (1.9)	12/569 (2.1)	2/548 (0.3)	1/219 (0.5)	32/1927 (1.7)
All Hemorrhages	7/9 (77.8)	113/223 (50.7)	105/359 (29.2)	144/569 (25.3)	62/548 (11.3)	18/219 (8.2)	450/1927 (23.4)
White matter disease							
PVL grade I	1/6 (16.7)	37/203 (18.2)	54/354 (15.3)	65/563 (11.5)	33/541 (6.1)	8/213 (3.8)	198/1880 (10.5)
PVL grade II	0/6 (0.0)	11/203 (5.4)	12/354 (3.4)	9/563 (1.6)	8/541 (1.5)	1/213 (0.5)	41/1880 (2.2)
PVL grade III-IV	0/6 (0.0)	9/203 (4.4)	10/354 (2.8)	6/563 (1.1)	3/541 (0.6)	1/213 (0.5)	29/1880 (1.5)
PVL grade I-IV	1/6 (16.7)	57/203 (28.1)	76/354 (21.5)	80/563 (14.2)	44/541 (8.1)	10/213 (4.7)	268/1880 (14.3)
All brain lesions*	8/9 (88.9)	170/223 (83.7)	181/359 (50.4)	224/569 (39.4)	106/548 (19.3)	28/219 (12.8)	718/1927 (37.3)
ALL SURVIVORS TO DISCHARGE							
Intracranial Hemorrhage							
IVH grade I-II	4/5 (80.0)	44/155 (28.4)	72/318 (22.6)	103/543 (19.0)	53/537 (9.9)	16/211 (7.6)	292/1769 (16.5)
IVH grade III and PVHI	1/5 (20.0)	11/155 (7.1)	9/318 (2.8)	20/543 (3.7)	7/537 (1.3)	1/211 (0.5)	49/1769 (2.8)
Other hemorrhage	0/5 (0.0)	4/155 (2.6)	4/318 (1.3)	10/543 (1.8)	2/537 (3.7)	0/211 (0.0)	20/1769 (1.1)
All Hemorrhages	5/5 (100.0)	59/155 (38.1)	85/318 (26.7)	133/543 (24.5)	62/537 (11.5)	17/211 (8.1)	361/1769 (20.4)
White matter disease							
PVL grade I	1/4 (25.0)	30/151 (19.9)	51/316 (16.1)	64/539 (11.9)	32/533 (6.0)	8/208 (3.8)	186/1751 (10.6)
PVL grade II	0/4 (0.0)	8/151 (5.3)	13/316 (4.1)	8/539 (1.5)	8/533 (1.5)	1/208 (0.5)	37/1751 (2.1)
PVL grade III-IV	0/4 (0.0)	3/151 (2.0)	5/316 (1.6)	3/539 (0.5)	3/533 (5.6)	1/208 (0.5)	15/1751 (0.9)
PVL grade I-IV	1/4 (25.0)	41/151 (27.1)	69/316 (21.8)	75/539 (13.9)	43/533 (8.0)	10/208 (4.8)	238/1751 (13.6)
All brain lesions*	5/5 (100.0)	100/155 (64.5)	154/318 (48.4)	208/543 (38.3)	105/537 (19.6)	27/211 (12.8)	599/1769 (33.9)

*the sum of all lesions, however it is possible that infants have a combination of a hemorrhage and white matter disease; Abbreviations: g: gram; GA: Gestational age; IVH: Intraventricular hemorrhage; N: Number; NICU: *Neonatal* intensive care unit; PVHI: periventricular hemorrhagic infarction; PVL: Periventricular leucomalacia; PVL grade I consists of the presence of periventricular echodense area>7 days.

Table 4. Neurodevelopmental outcomes at 2 years corrected age

	No hemorrhage or PVL N(%) / Mean±SD	IVH grade I-II N(%) / Mean±SD	IVH grade III and PVHI N(%) / Mean±SD	Other intracranial hemorrhage N(%) / Mean±SD	PVL grade I N(%) / Mean±SD	PVL grade II N(%) / Mean±SD	PVL grade III-IV N(%) / Mean±SD
Mortality rate	46/1249 (3.7)	32/324 (9.9)	45/94 (47.9)	12/32 (37.5)	12/198 (6.1)	4/41 (9.8)	14/29 (48.3)
Motor							
Mean ± SD	88.42±15.6	93.3±17.8	88.0±20.6	88.0±16.9	94.6±18.4	93.7±17.2	65.8±17.9
<70	31/622 (5.0)	14/168 (8.3)	4/22 (18.2)	1/8 (12.5)	11/112 (9.8)	2/20 (10.0)	2/5 (40.0)
70-84	74/622 (11.9)	25/168 (14.9)	5/22 (22.7)	3/8 (37.5)	15/112 (13.4)	2/20 (10.0)	2/5 (40.0)
≥85	517/622 (83.1)	129/168 (76.8)	13/22 (59.1)	4/8 (50.0)	86/112 (76.8)	16/20 (80.0)	1/5 (20.0)
Cognition							
Mean ± SD	94.24±16.7	94.30±14.5	90.0±22.0	95.0±14.6	92.4±15.0	89.5±16.0	81.0±20.4
<70	24/689 (3.5)	7/188 (3.7)	4/24 (16.7)	0/8 (0.0)	7/124 (5.6)	2/21 (9.5)	2/5 (40.0)
70-84	96/689 (13.4)	30/188 (16.0)	5/24 (20.8)	2/8 (25.0)	23/124 (18.5)	4/21 (19.0)	0/5 (0.0)
≥85	569/689 (82.6)	151/188 (80.3)	15/24 (62.5)	6/8 (75.0)	94/124 (75.8)	15/21 (71.4)	3/5 (60.0)
CP	19/703 (2.7)	8/192 (4.2)	9/25 (36.0)	1/8 (12.5)	9/128 (7.0)	3/21 (14.3)	2/6 (33.3)
NDI	206/626 (32.9)	69/170 (40.6)	17/23 (73.9)	5/8 (62.5)	51/118 (43.2)	9/21 (42.9)	5/6 (83.3)

Abbreviations: CP: cerebral palsy; IVH: intraventricular hemorrhage; N: number; NDI: neurodevelopmental impairment; PVHI: periventricular hemorrhagic infarction; PVL: periventricular leukomalacia, SD: standard deviation.

Table 5. Univariate logistic regression

Brain lesion	Odds ratio	95% CI	p-value
Mortality rate			
IVH I-II	1.285	0.854-1.931	0.229
IVH III-PVHI	13.979	8.938-21.862	**<0.001**
Other hemorrhage	7.188	3.445-14.995	**<0.001**
PVL I	0.862	0.467-1.592	0.636
PVL II	1.524	0.534-4.349	0.431
PVL III-IV	14.081	6.636-29.881	**<0.001**
Cognitive delay (Bayley-III composite score <85)			
IVH I-II	1.065	0.715-1.587	0.757
IVH III-PVHI	2.653	1.144-6.156	**0.023**
Other hemorrhage	1.436	0.288-7.717	0.659
PVL I	1.453	0.931-2.266	0.100
PVL II	1.756	0.672-4.586	0.250
PVL III-IV	2.908	0.482-17.521	0.244
Motor delay (Bayley-III composite score <85)			
IVH I-II	1.323	0.886-1.978	0.171
IVH III-PVHI	2.969	1.249-7.058	**0.014**
Other hemorrhage	4.219	1.045-17.033	**0.043**
PVL I	1.321	0.823-2.119	0.249
PVL II	1.055	0.348-3.194	0.925
PVL III-IV	17.218	1.913-155.009	**0.011**
Cerebral palsy			
IVH I-II	0.978	0.448-2.134	0.955
IVH III-PVHI	15.625	6.470-37.736	**<0.001**
Other hemorrhage	3.276	0.394-27.209	0.272
PVL I	1.980	0.927-4.230	0.078
PVL II	4.129	1.168-14.593	**0.028**
PVL III-IV	12.256	2.182-68.847	**0.004**
Neurodevelopmental impairment			
IVH I-II	1.260	0.897-1.769	0.183
IVH III-PVHI	5.216	2.037-13.358	**0.001**
Other hemorrhage	2.974	0.706-12.523	0.137
PVL I	1.412	0.955-2.088	0.084
PVL II	1.339	0.558-3.211	0.513
PVL III-IV	8.985	1.045-77.227	**0.045**

Abbreviations: CI: confidence interval; IVH: intraventricular hemorrhage; PVHI: periventricular hemorrhagic infarction; PVL: periventricular leukomalacia