www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(1):e120118
doi: 10.7363/120118
Received: 2021 Jan 30; revised: 2021 Feb 18; accepted: 2021 Feb 21; published online: 2023 Jan 16

Original article

Intraventricular hemorrhage in preterm infants: risk factors and neurodevelopmental outcomes

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Abstract

Introduction: Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) is the most common form of intracranial hemorrhage in preterm infants. We evaluated risk factors for GMH-IVH in preterm infants born before 32 weeks of gestational age. Secondary outcomes included the characterization of neurodevelopmental (ND) prognosis at 24-36 months of corrected age.

Methods: We included infants admitted to our Neonatal Intensive Care Unit between May 2011 and January 2017. A total of 161 infants were enrolled, divided into the GMH-IVH group (n = 40) and control group (n = 121). A secondary cohort included the follow-up group (n = 124) at 24-36 months of corrected age. The association of GMH-IVH with risk factors and ND outcomes was investigated.

Results: The incidence of GMH-IVH was 24.8%. Significant risk factors for GMH-IVH were exposure to any resuscitation in the Delivery Room (adjusted odds ratio [aOR]: 34.1; 95% confidence interval [CI] 1.8-657.5) and a low Apgar score at 5 minutes of life (aOR: 0.4; 95% CI: 0.2-

0.9). The incidence of retinopathy of prematurity was significantly higher in the grade I GMH-IVH ($p < 0.001$) group. Gross motor and locomotion dysfunction were significantly more frequent in the GMH-IVH group (24.1% vs. 4.4%; $p = 0.004$) as was auditory and language dysfunction (24.1% vs. 7.8%; $p = 0.040$). GMH-IVH was independently associated with visual impairment (aOR: 21.6; 95% CI: 3.2-145.0).

Conclusions: Lower Apgar score at 5 minutes of life and any resuscitation were independent risk factors for GMH-IVH. GMH-IVH was associated with higher ND morbidity. ND prognosis of grade II GMH-IVH was comparable to grade III GMH-IVH.

Keywords

Diagnostic imaging, intraventricular hemorrhage, neonate, infant, premature, neurodevelopmental disorders, risk factors, ultrasonography.

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How to cite

Soares Reis J, Ayres Pereira I, Lira J, Silva J, Gonçalves M, Torres J, Grenha J. Intraventricular hemorrhage in preterm infants: risk factors and neurodevelopmental outcomes. J Pediatr Neonat Individual Med. 2023;12(1):e120118. doi: 10.7363/120118.

Introduction

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) results from rupture of the small blood vessels within the germinal matrix tissue into the ventricular system. It is the most common form of intracranial hemorrhage in neonates, particularly in preterm infants [1].

The germinal matrix starts to involute by 28 weeks and is generally absent in term infants [2]. The characteristic immaturity of the preterm brain support tissues and cerebral autoregulation mechanisms make the germinal matrix sensitive to hemodynamic fluctuations. Intraparenchymal hemorrhage may result in white matter lesions affecting the myelination and organization of the cerebral cortex [3-6].

The incidence and severity of GMH-IVH increase with decreasing gestational age (GA). It is estimated to occur in about 20% of premature infants born before 32 weeks of GA, and severe GMH-IVH affects approximately 6-9.7% of infants [4, 7].

Despite advances in neonatal and obstetric care in the last decade, GMH-IVH still remains a significant problem due to a greater number of survivors. Long-term sequels such as cerebral palsy (CP), seizures, cognitive or learning disabilities have been implicated, especially for the most severe grades [6].

The aim of this study was to evaluate risk factors for GMH-IVH in preterm infants born before 32 weeks of GA. Secondary outcomes included the characterization of neurodevelopmental (ND) prognosis at 24-36 months of corrected age.

Methods

A retrospective longitudinal cohort study was conducted at the Neonatology Department of Vila Nova de Gaia/Espinho Hospital Center.

Inclusion criteria were preterm infants born before 32 weeks of GA between May 2011 and January 2017; exclusion criteria included major malformation or syndromes at birth and death without cranial ultrasound (cUS).

According to national guidelines and the clinical protocol of our Neonatal Intensive Care Unit (NICU), cUS was performed as soon as possible after birth, repeated on the 7th and 14th day of life and weekly or every 2 weeks depending on the findings.

It was repeated at discharge or at 40 weeks of post-menstrual age (PMA).

The classification of intraventricular bleeding was based on the Volpe GMH-IVH grading system [3], and each case was graded upon the worst GMH-IVH classification during the first 7 days of life.

Baseline demographics – maternal and neonatal characteristics

Demographics, as well as maternal and neonatal characteristics, were collected from medical charts.

Prolonged rupture of membranes (PROM) was defined as rupture more than 18 hours before delivery. Clinical chorioamnionitis was determined by maternal fever (axillary

temperature > 38ºC) and at least 1 of the following criteria: maternal leukocytosis (> 15,000 cells/µl), maternal or fetal tachycardia, uterine tenderness and/or foul odor of the amniotic fluid. Histological chorioamnionitis included inflammation of the placental membranes and chorionic plate with polymorphonuclear leucocyte infiltration. Antenatal corticosteroids exposure was defined as the mother receiving at least 1 dose of dexamethasone or betamethasone. Off-peak delivery was defined as occurring between midnight and 8 o'clock am.

Estimated GA was determined by the best obstetric estimate. Cardiopulmonary resuscitation (CPR) during the delivery period was defined as the need for chest compressions, epinephrine or endotracheal intubation. Any resuscitation was considered when positive pressure ventilation or CPR was administered. Significant patent ductus arteriosus (PDA) was defined as PDA lasting for > 72 h needing medical or surgical treatment. Neonatal sepsis was defined as a clinical course suggestive of sepsis prior to GMH-IVH diagnosis. Volume expansion was considered when crystalloids and/or blood transfusion components were administered before a GMH-IVH diagnosis was made, and hypotension was defined as mean blood pressure below value corresponding to neonate's GA with signs of poor systemic perfusion. Seizures were only included as a possible risk factor if they occurred before the diagnosis of GMH-IVH. Pulmonary hemorrhage was defined as nontraumatic bloody secretion from the endotracheal tube associated with clinical deterioration. Respiratory distress syndrome was diagnosed based on the onset of progressive respiratory failure shortly after birth and a characteristic chest radiograph. Exposure to sedatives or analgesics included administration of morphine, fentanyl or midazolam. Periventricular leukomalacia (PVL) was defined as evidence of cystic or other lesions in the periventricular area on cUS or magnetic resonance imaging (MRI). Hydrocephalus was defined as clinical signs of increased intracranial pressure and/or progressive ventricular dilation on serial cUS. Ototoxic medication exposure was considered when ototoxic drugs were given for at least 5 days.

Neurodevelopment assessment

CP was defined as abnormal tone or reflexes in at least 1 extremity and abnormal control of movement or posture that interferes with age-appropriate activity. The presence of any auditory deficit was defined as auditory threshold > 20 dB on brainstem evoked response audiometry and characterized as uni/bilateral. The presence of visual impairment included any refraction error, retinopathy of prematurity (ROP) and strabismus or blindness on ophthalmological evaluation. The presence of developmental delay was categorized as any delay above 2 standard deviations (SD) for age in 1 of the 8 development areas evaluated with Schedules of Growing Skills (SGS) assessment tool at that age (gross motor/locomotor, manipulative, visual, hearing and language, speech and language, interactive social, autonomy and cognition areas). Autism spectrum disorder alert signs were assessed with Modified Checklist for Autism in Toddlers (M-CHAT) at 16-30 months and considered positive if the child failed 2 critical items or a total of 3 items.

Outcome definitions

The aim of this study was to evaluate possible risk factors for GMH-IVH in preterm infants born before 32 weeks of gestation.

Secondary outcomes included the characterization of ND outcomes at 24-36 months of corrected age.

This study was approved by the local Ethics Committee.

Statistical analysis

Categorical variables are described as frequencies and percentages, and continuous variables as means and SD or medians and interquartile ranges (IQR), accordingly. Differences between case and control groups were tested using Chi-squared test or Fisher exact test for categorical variables and Student's t-test or Mann-Whitney test for independent samples, as appropriate. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with GMH-IVH and ND outcomes. Only significant factors were plotted in a multivariate logistic regression model for the dichotomous outcome. All data analyses were performed using the SPSS®, version 24.0. Statistical significance was determined at the level of $p < 0.05$. Confidence intervals (CI) were set at 95%.

Results

A total of 178 infants aged less than 32 weeks GA were identified during the study period; 16 were excluded because of death within a few hours of birth and 1 for major congenital malformation. A total of 161 were eligible for the primary study. Of these, 17 patients died, and 20 patients were lost to follow-up or had an incomplete ND evaluation at 24-36 months of corrected age (**Fig. 1**).

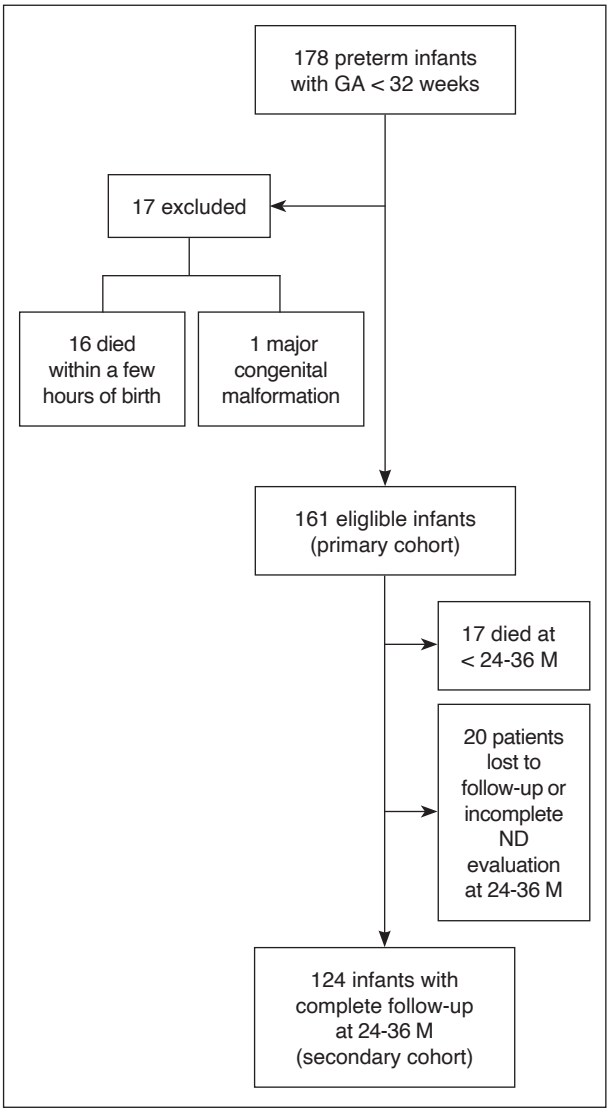

Figure 1. Study enrolment flow.
GA: gestational age; M: months of corrected age; ND: neurodevelopmental.

Risk factors for germinal matrix hemorrhage-intraventricular hemorrhage

The GMH-IVH group included 40 neonates, and 121 infants were included in the control group, with a total incidence for GMH-IVH of 24.8%. Hemorrhage classification according to Volpe's criteria included 15 (9.3%) grade I GMH-IVH, 10 (6.2%) grade II GMH-IVH, and 15 (9.3%) grade III GMH-IVH. Venous periventricular hemorrhagic infarction presented in 15 newborns (of these, 93.3% were grade III GMH-IVH). At presentation, 30 (75%) were asymptomatic, 4 (10%) had decreased spontaneous movements, 3 (7.5%) presented with hypotonia, 3 (7.5%) had hemodynamic instability, 2 (5%) presented with apnea and 1 (2.5%) showed a bulging anterior fontanelle.

Demographic as well as maternal and neonatal characteristics are reported in **Tab. 1**. Histological evidence of chorioamnionitis was significantly higher in the hemorrhage group ($p < 0.005$), although clinical chorioamnionitis, maternal fever or PROM were not significantly different ($p = 1.000$, $p = 0.682$, $p = 0.554$, respectively). Antenatal steroid therapy was similar in both major groups, although less frequent in grade III GMH-IVH. Vaginal ($p = 0.033$) and off-peak delivery ($p = 0.003$) were more common in the GMH-IVH group.

Median GA was significantly lower in cases vs. controls (27.5 [IQR 4] vs. 30 [IQR 2] weeks, $p < 0.001$) and also birth weight (960 g [IQR 560] vs. 1,260 g [IQR 440], $p = 0.011$).

Infants with GMH-IVH were more likely to be exposed to cardiopulmonary resuscitation ($p < 0.001$) or any resuscitation ($p = 0.019$) in the Delivery Room, mechanical ventilation ($p < 0.001$), volume expansion ($p = 0.001$), pulmonary hemorrhage ($p < 0.001$) and sedatives/analgesics ($p < 0.001$). PDA and hypotension were higher in the GMH-IVH group ($p < 0.001$ and $p = 0.001$, respectively). PVL was significantly higher in cases ($p = 0.007$), as was hydrocephalus ($p = 0.015$), particularly in the grade III GMH-IVH group ($p = 0.001$).

The multivariate logistic regression analysis included all the maternal, neonatal and demographic variables that differ between the 2 major groups in the univariate analysis ($p < 0.05$). Results are described in **Tab. 2**. Exposure to any resuscitation in the Delivery Room (adjusted odds ratio [aOR]: 34.124; 95% CI: 1.771-657.485) was found to be an independent risk factor for any GMH-IVH, as well as a low Apgar score at 5 minutes of life (aOR: 0.422; 95% CI: 0.209-0.850).

Table 1. Maternal and neonatal characteristics for germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) cases and controls and severity of GMH-IVH (n = 161).

	Controls (n = 121)	GMH-IVH (n = 40)	p-value (GMH-IVH vs. controls)	Grade I GMH-IVH (n = 15)	p-value (grade I GMH-IVH vs. controls)	Grade II GMH-IVH (n = 10)	p-value (grade II GMH-IVH vs. controls)	Grade III GMH-IVH (n = 15)	p-value (grade III GMH-IVH vs. controls)	p-value (grade II GMH-IVH vs. grade III GMH-IVH)
Maternal age, median (IQR)	32 (9)	33 (8)	NS	32.5 (6)	NS	33 (11)	NS	33 (10)	NS	NS
Gemelarity	56 (46.3)	8 (20)	**0.003**	2 (13.3)	**0.015**	1 (10)	**0.042**	5 (33.3)	NS	NS
PROM	20/119[a] (16.8)	5/39[a] (12.8)	NS	2 (13.3)	NS	2/9[a] (22.2)	NS	1 (6.7)	NS	NS
Maternal fever	6 (5)	1 (2.5)	NS	1 (6.7)	NS	0 (0)	NA	0 (0)	NS	NS
Histological chorioamnionitis	28/106[a] (26.4)	17/32[a] (53.1)	**0.005**	7/14[a] (50)	NS	4/7[a] (57.1)	NS	6/11[a] (54.5)	NS	NS
Clinical chorioamnionitis	8 (6.6)	3 (7.5)	NS	1 (6.7)	NS	0 (0)	NA	2 (13.3)	NS	NS
Antenatal corticosteroids	97/120[a] (80.2)	32 (80)	NS	12 (80)	NS	9 (90)	NS	11 (73.3)	NS	NS
Vaginal delivery	30 (24.8)	17 (42.5)	**0.033**	7 (46.7)	NS	4 (40)	NS	6 (40)	NS	NS
Off-peak delivery	21/120[a] (17.5)	16 (40)	**0.003**	7 (46.7)	**0.016**	2 (20)	NS	7 (46.7)	**0.016**	NS
Male gender	64 (52.9)	22 (55)	NS	7 (46.7)	NS	6 (60)	NS	9 (60)	NS	NS
GA, median (IQR)	30 (2)	27.5 (4)	**< 0.001**	28.5 (5)	NS	27.5 ± 4	**0.04**	26 (3)	**0.001**	NS
Birth weight, g, median (IQR)	1.260 (440)	960 (560)	**0.011**	1.200 (635)	NS	990 (555)	NS	920 (380)	**0.003**	NS
Apgar score at 5 min, mean ± SD	8.5 ± 1.5	7.0 ± 1.9	**< 0.001**	7.7 ± 1.5	**0.025**	7 ± 1.5	**0.003**	6.4 ± 2.2	**< 0.001**	NS
Cardiopulmonary resuscitation	28 (23.1)	27 (67.5)	**< 0.001**	6 (40)	NS	8 (80)	**0.001**	13 (86.7)	**< 0.001**	NS
Any resuscitation (including positive pressure)	62 (51.2)	29 (72.5)	**0.019**	8 (53.3)	NS	8 (80)	NS	13 (87.6)	**0.009**	NS
Mechanical ventilation	34 (28.1)	32 (80)	**< 0.001**	10 (66.7)	**0.006**	9 (90)	**< 0.001**	13 (86.7)	**< 0.001**	NS
Maximum FiO_2, %, median (IQR)	30 (18)	60 (66)	**< 0.001**	45 (36)	**0.043**	80 (60)	**0.001**	73 (66)	**< 0.001**	NS
PDA	32 (26.4)	22/38[a] (57.9)	**< 0.001**	9 (60)	**0.014**	6 (60)	**0.034**	7 (53.8)	NS	NS
Neonatal sepsis	47 (38.8)	20 (50)	NS	9 (60)	**0.116**	5 (50)	NS	6 (40)	NS	NS
Volume expansion	37 (30.6)	30 (75)	**0.001**	8 (53.3)	NS	10 (100)	**< 0.001**	12 (80)	**< 0.001**	NS
Hypotension	36 (29.8)	24 (60)	**0.001**	6 (40)	NS	6 (60)	NS	12 (80)	**< 0.001**	NS
Seizures	0 (0)	2 (5)	NS	0 (0)	NA	1 (10)	NS	1 (6.7)	NS	NS
Pulmonary hemorrhage	3 (2.5)	11 (27.5)	**< 0.001**	1 (6.7)	NS	4 (40)	**0.001**	6 (40)	**< 0.001**	NS
Respiratory distress syndrome	58 (47.9)	26 (65)	NS	9 (60)	NS	7 (70)	NS	10 (66.7)	NS	NS
Sedoanalgesia	18 (14.9)	23 (57.5)	**< 0.001**	6 (40)	**0.027**	6 (60)	**0.003**	11 (73.3)	**< 0.001**	NS
PVL	6/120[a] (5)	8 (20)	**0.007**	3 (20)	NS	3 (30)	**0.022**	2 (13.3)	NS	NS
Hydrocephalus	0 (0)	3 (7.5)	**0.015**	0 (0)	NA	0 (0)	NA	3 (20)	**0.001**	NS
Ototoxic medication exposure	95 (82.6)	37 (92.5)	NS	14 (93.3)	NS	9 (90)	NS	14 (93.3)	NS	NS

Data are presented as n (%) if not otherwise stated.
[a] Missing values.
FiO_2: fraction of inspired O_2; GA: gestational age; GMH-IVH: germinal matrix hemorrhage-intraventricular hemorrhage; IQR: interquartile range; NS: not significant; PDA: persistent ductus arteriosus; PROM: prolonged rupture of membranes; PVL: periventricular leukomalacia; SD: standard deviation.

Table 2. Multivariate analysis of any germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH).

Risk factors	aOR for any GMH-IVH (95% CI)
Gemelarity	0.526 (0.118-2.343)
Histological chorioamnionitis	2.535 (0.628-10.236)
Vaginal delivery	2.967 (0.590-14.931)
Off-peak delivery	1.192 (0.229-6.200)
Male gender	0.882 (0.223-3.497)
GA	1.084 (0.605-1.943)
Birth weight	1.001 (0.997-1.004)
Apgar score at 5 min	**0.422 (0.209-0.850)** [a]
Cardiopulmonary resuscitation	2.966 (0.219-40.271)
Any resuscitation (including positive pressure)	**34.124 (1.771-657.485)** [a]
Mechanical ventilation	3.845 (0.527-28.050)
Maximum FiO_2	0.993 (0.958-1.030)
PDA	3.532 (0.865-14.420)
Volume expansion	24.348 (0.213-277.872)
Hypotension	16.717 (0.410-681.452)
Pulmonary hemorrhage	9.925 (0.843-116.820)
Sedoanalgesia	3.444 (0.473-25.067)

[a] Indicates significant differences.
aOR: adjusted odds ratio; CI: confidence interval; FiO_2: fraction of inspired O_2; GA: gestational age; GMH-IVH: germinal matrix hemorrhage-intraventricular hemorrhage; PDA: persistent ductus arteriosus.

Neurodevelopmental outcomes

Mortality was higher in the GMH-IVH group when compared to the control group (58.8% vs. 41.2%, p = 0.001).

Of the 124 neonates who were evaluated for ND outcomes at 24-36 months of corrected age, 95 (76.6%) belonged to the controls group and 29 (23.4%) to the GMH-IVH group (n = 14 grade I GMH-IVH, n = 9 grade II GMH-IVH, and n = 6 grade III GMH-IVH). Results are presented in **Tab. 3**.

CP affected 9 children, of whom 8 (88.9%) were spastic, and 6 (66.7%) were bilateral. CP was more frequent in the GMH-IVH group (p = 0.005). Compared with controls, only grade II GMH-IVH (p = 0.008) and grade III GMH-IVH (p = 0.027) were associated with an increased risk of CP.

Auditory deficits affected 7 children and were more prevalent in the GMH-IVH group (p = 0.007). This difference was significant for grade II GMH-IVH (p = 0.031) and grade III GMH-IVH (p = 0.016).

Visual impairment was also more prevalent in the GMH-IVH group (p = 0.001), showing a higher prevalence of refraction errors (p = 0.011), strabismus (p = 0.024) and ROP (p = 0.001). There was no blindness reported in the control group in contrast to 7.4% in the GMH-IVH group. When comparing each GMH-IVH subgroup with controls, grade I GMH-IVH had more ROP (28.6%, p < 0.001) while grades II and III GMH-IVH had more refraction errors (42.9%, p = 0.016) and strabismus (33.3%, p = 0.038), respectively.

On global development assessment by SGS, gross motor and locomotion dysfunction was more prevalent in the GMH-IVH group (p = 0.004), particularly for grade II GMH-IVH (55.6%, p < 0.001) and grade III GMH-IVH (33.3%, p = 0.044). Auditory and language dysfunction was also more frequent in the GMH-IVH group (p = 0.040), particularly for higher grades (grade II GMH-IVH 33.3%, p = 0.046; grade III GMH-IVH 16.7%, p > 0.050) with no inter-group differences.

Multivariate binary logistic regression was used to adjust for confounding factors that may influence ND outcomes, and that showed inter-group differences in the main analysis, such as sex, gemelarity, GA, Apgar score at 5 minutes, PVL and hydrocephalus. For auditory deficits we also adjusted for ototoxic medication, and for visual impairment we adjusted for the higher oxygen concentration administered during admission (FiO_2) (**Tab. 4**). Results revealed that GMH-IVH was an independent risk factor for visual impairment (aOR: 21.57; 95% CI: 3.21-145.04). Despite the higher mortality risk associated with GMH-IVH, GA was detected as a confounding factor. PVL and hydrocephalus were confounding factors for CP and gross motor/locomotion developmental delay, as was gemelarity for the former and Apgar score at 5 minutes for the latter. Hydrocephalus, ototoxic medication and GA were confounding factors for auditory deficits and auditory and language developmental delay, and PVL was also a risk factor for the latter.

Table 3. Prevalence of neurodevelopmental (ND) outcomes for controls, germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH), and for each GMH-IVH grade (n = 124).

	Controls (n = 95)	GMH-IVH (n = 29)	p-value (GMH-IVH vs. controls)	Grade I GMH-IVH (n = 14)	p-value (grade I GMH-IVH vs. controls)	Grade II GMH-IVH (n = 9)	p-value (grade II GMH-IVH vs. controls)	Grade III GMH-IVH (n = 6)	p-value (grade III GMH-IVH vs. controls)	p-value (grade II GMH-IVH vs. grade III GMH-IVH)
CP	3 (3.2)	6 (20.7)	**0.005**	1 (7.1)	NS	3 (33.3)	**0.008**	2 (33.3)	**0.027**	NS
	Controls (n = 80)	**GMH-IVH (n = 24)**	**p-value (GMH-IVH vs. controls)**	**Grade I GMH-IVH (n = 12)**	**p-value (grade I GMH-IVH vs. controls)**	**Grade II GMH-IVH (n = 7)**	**p-value (grade II GMH-IVH vs. controls)**	**Grade III GMH-IVH (n = 5)**	**p-value (grade III GMH-IVH vs. controls)**	**p-value (grade II GMH-IVH vs. grade III GMH-IVH)**
Auditory deficit	2 (2.5)	5 (20.8)	**0.007**	1 (8.3)	NS	2 (28.6)	**0.031**	2 (40)	**0.016**	NS
	Controls (n = 79)	**GMH-IVH (n = 27)**	**p-value (GMH-IVH vs. controls)**	**Grade I GMH-IVH (n = 14)**	**p-value (grade I GMH-IVH vs. controls)**	**Grade II GMH-IVH (n = 7)**	**p-value (grade II GMH-IVH vs. controls)**	**Grade III GMH-IVH (n = 6)**	**p-value (grade III GMH-IVH vs. controls)**	**p-value (grade II GMH-IVH vs. grade III GMH-IVH)**
Any visual disfunction	9 (11.4)	12 (44.4)	**0.001**	6 (42.9)	**0.009**	3 (42.9)	**0.053**	3 (50)	**0.034**	NS
Refraction error	5 (6.3)	7 (25.9)	**0.011**	2 (14.3)	NS	3 (42.9)	**0.016**	2 (33.3)	NS	NS
Strabismus	3 (3.8)	5 (18.5)	**0.024**	1 (7.1)	NS	2 (28.6)	**0.051**	2 (33.3)	**0.038**	NS
ROP	0 (0)	5 (18.5)	**0.001**	4 (28.6)	**< 0.001**	0 (0)	NA	1 (16.7)	NS	NS
Blindness	0 (0)	2 (7.4)	NA	0 (0)	NA	1 (14.3)	NS	1 (16.7)	NS	NS
	Controls (n = 90)	**GMH-IVH (n = 29)**	**p-value (GMH-IVH vs. controls)**	**Grade I GMH-IVH (n = 14)**	**p-value (grade I GMH-IVH vs. controls)**	**Grade II GMH-IVH (n = 9)**	**p-value (grade II GMH-IVH vs. controls)**	**Grade III GMH-IVH (n = 6)**	**p-value (grade III GMH-IVH vs. controls)**	**p-value (grade II GMH-IVH vs. grade III GMH-IVH)**
Gross motor/locomotion	4 (4.4)	7 (24.1)	**0.004**	0 (0)	NS	5 (55.6)	**< 0.001**	2 (33.3)	**0.044**	NS
Manipulation	8 (8.9)	5 (17.2)	NS	0 (0)	NS	3 (33.3)	NS	2 (33.3)	NS	NS
Hearing/language	7 (7.8)	7 (24.1)	**0.040**	2 (14.3)	NS	3 (33.3)	**0.046**	1 (16.7)	NS	NS
Speech/language	16 (17.8)	8 (27.6)	NS	4 (28.6)	NS	2 (22.2)	NS	2 (33.3)	NS	NS
Visual	4 (4.4)	3 (10.3)	NS	0 (0)	NS	2 (22.2)	NS	2 (33.3)	NS	NS
Social interaction	3 (3.3)	3 (19.3)	NS	1 (7.1)	NS	1 (11.1)	NS	1 (16.7)	NS	NS
Autonomy	7 (7.8)	5 (17.2)	NS	1 (7.1)	NS	2 (22.2)	NS	2 (33.3)	NS	NS
Cognition	6 (6.7)	3 (10.7)	NS	0 (0)	NS	2/8 [a] (25)	NS	1 (16.7)	NS	NS
	Controls (n = 93)	**GMH-IVH (n = 28)**	**p-value (GMH-IVH vs. controls)**	**Grade I GMH-IVH (n = 14)**	**p-value (grade I GMH-IVH vs. controls)**	**Grade II GMH-IVH (n = 8)**	**p-value (grade II GMH-IVH vs. controls)**	**Grade III GMH-IVH (n = 6)**	**p-value (grade III GMH-IVH vs. controls)**	**p-value (grade II GMH-IVH vs. grade III GMH-IVH)**
M-CHAT positive score	2 (2.2)	1 (3.6)	NS	1 (7.1)	NS	0 (0)	NS	0 (0)	NS	NS

Data are presented as n (%) if not otherwise stated.
[a] Missing value.
CP: cerebral palsy; GMH-IVH: germinal matrix hemorrhage-intraventricular hemorrhage; M-CHAT: Modified Checklist for Autism in Toddlers; NS: not significant; ROP: retinopathy of prematurity.

Table 4. Binary regression models for neurodevelopmental (ND) outcomes.

ND outcomes	Crude OR (95% CI)	aOR (95% CI) Model 1	aOR (95% CI) Model 2	aOR (95% CI) Model 3	aOR (95% CI) Model 4	aOR (95% CI) Model 5
Mortality [a]	**5.43 (1.9-15.45)** [g]	**4.91 (1.48-16.28)** [g]	1.61 (0.44-5.84)	-	-	-
CP [b]	**8 (1.86-34.42)** [g]	**5.47 (1.15-26.14)** [g]	4.0 (0.77-20.64)	3.98 (0.75-21.00)	5.53 (0.99-30.78)	-
Visual impairment [c]	**6.22 (2.22-17.40)** [g]	**9.76 (1.85-51.4)** [g]	-	-	-	-
Auditory deficit [d]	**10.26 (1.84-57.029)** [g]	**10.86 (1.4-84.18)** [g]	5.9 (0.54-65.03	7.55 (0.953-59.79)	4.35 (0.42-44.59)	-
Auditory and language domain [e]	**3.77 (1.20-11.89)** [g]	**3.91 (1.16-13.26)** [g]	2.75 (0.712-10.61)	2.80 (0.767-10.26)	3.10 (0.89-10.80)	3.075 (0.83-11.45)
Locomotion/ gross motor function [f]	**6.84 (1.84-25.47)** [g]	**4.63 (1.097-19.55)** [g]	4.08 (0.92-18.09)	3.78 (0.823-17.37)	4.139 (0.90-19.00)	-

[a] Model 1 – Adjusted for sex, 5' Apgar score, PVL, hydrocephaly and gemelarity; Model 2 – Adjusted for GA.
[b] Model 1 – Adjusted for GA, sex and 5´Apgar score; Model 2 – Adjusted for model 1 + adjusted for PVL; Model 3 – Model 1 + adjusted for hydrocephaly; Model 4 – Model 1 + adjusted for gemelarity.
[c] Model 1 – Adjusted for sex, GA, 5' Apgar score, PVL, hydrocephaly, gemelarity and max FiO_2.
[d] Model 1 – Adjusted for sex, gemelarity, 5' Apgar score and PVL; Model 2 – Model 1 + adjusted for GA; Model 3 – Model 1 + adjusted for ototoxic medication > 5 days; Model 4 – Model 1 + adjusted for hydrocephaly.
[e] Model 1 – Adjusted for sex; Model 2 – Model 1 + adjusted for GA; Model 3 – Model 1 + adjusted for PVL; Model 4 – Model 1 + adjusted for ototoxic medication > 5 days; Model 5 – Model 1 + adjusted for hydrocephaly.
[f] Model 1 – Adjusted for sex, gemelarity and GA; Model 2 – Model 1 + adjusted for 5' Apgar score; Model 3 – Model 1 + adjusted for PVL; Model 4 – Model 1 + adjusted for hydrocephaly.
[g] Indicates significance.
aOR: adjusted odds ratio; CI: confidence interval; FiO_2: fraction of inspired O_2; GA: gestational age; ND: neurodevelopmental; OR: odds ratio; PVL: periventricular leukomalacia.

Discussion

In this study, the total incidence of GMH-IVH and severe GMH-IVH is similar to those previously reported in the literature [4, 7-9], suggesting an overall improvement in the quality of neonatal intensive care when compared to prior studies [10, 11].

The fragile geminal matrix is vulnerable to fluctuations in systemic blood pressure with associated risk for hemorrhage. Hypotension, anemia and respiratory distress can cause hypoxia, hypercapnia and acidemia, also leading to fluctuations in cerebral blood flow [1, 12, 13].

Any resuscitation in the Delivery Room was significantly associated with an overall risk of GMH-IVH (aOR: 34.124; 95% CI: 1.771-657.485). Intubation is often accompanied by physiological responses that increase intracranial pressure [14]. In addition, the delivery of high tidal volumes administered during positive pressure ventilation can increase the risk of severe GMH-IVH [15]. Accordingly, a lower Apgar score at 5 minutes was also an independent risk factor for GMH-IVH (aOR: 0.422; 95% CI: 0.209-0.850). This suggests that, although birth weight and GA are significantly different between controls and the GMH-IVH group, the events happening in the Delivery Room might play a more significant role [7, 16, 17]. Fluctuations in pCO_2 have been implicated with loss of cerebral autoregulation and increased risk of GMH-IVH. In a study by Altaany et al., fluctuations in pCO_2 of 10 mmHg in the first 3 days of life were associated with an increased risk of severe GMH-IVH [18].

Although data is lacking regarding the relationship between GMH-IVH and pulmonary hemorrhage, a case series by Pandit et al. demonstrated that pulmonary hemorrhage was associated with major IVH (OR 3.1, CI 1.5-6.4) [19, 20]. Similarly, hypotension, volume expansion, or significant PDA also seem to increase the risk of GMH-IVH due to sudden cerebral blood flow (CBF) alterations [7, 13].

Antenatal steroid treatment has been reported as protective against the development of IVH [21]. Although we did not find statistical significance, the grade III GMH-IVH group received less antenatal steroids than the control group.

Interestingly, administration of any sedatives or analgesics was significantly associated with GMH-IVH. Morphine, fentanyl and midazolam are the most commonly used opioids/sedatives in our NICU. Despite the growing knowledge about the long-term consequences of neonatal pain and discomfort, uncertainty on the long-term effects of these pain management drugs remain. Several studies also reported the occurrence of IVH during opioid sedation [22]. It can be postulated that significant changes in the mean arterial pressure can occur in the presence of these drugs and influence CBF. However, there can be other confounding factors, such as the fact that patients exposed to sedatives or analgesics are critically ill and usually under mechanical ventilation.

Off-peak delivery showed a significant association with GMH-IVH and severe GMH-IVH. In our center, emergency deliveries occur more frequently during the night period and are probably related to complications that may interfere with the risk of hemorrhage [23].

Histological chorioamnionitis was associated with an increased risk of GMH-IVH. Several studies have shown that prenatal exposure to chorioamnionitis can potentially increase the local production of cytokines and damage the blood-brain barrier. Our findings suggest that there may be placental inflammation even without maternal fever, PROM or other clinical findings suggestive of chorioamnionitis [24].

Regarding ND outcomes, preterm neonates with GMH-IVH have a higher risk of mortality, CP, auditory and visual impairment, gross motor function and auditory/language delay. When evaluating ND outcomes of GMH-IVH according to GMH-IVH severity, most studies aggregate grades I and II GMH-IVH, labeling it as "low-grade GMH-IVH". Results vary within studies between those that do not find differences when compared to controls and those finding a worse prognosis [5, 6, 25, 26]. In this study, each GMH-IVH grade was compared with controls, so that its relative contribution to ND outcomes could be adequately studied. We found that for grade I GMH-IVH, only ROP was significantly different. Although some studies do not find this association, the inclusion of grade II GMH-IVH in the "low-grade GMH-IVH" group – for whom we found adverse prognosis comparable to grade III GMH-IVH – may constitute a bias [26]. We detected a greater risk of ND delay and comorbidities in grade III GMH-IVH, with no significant differences from grade II GMH-IVH. As such, the authors question the frequent categorization of grade II GMH-IVH as "low-grade GMH-IVH". Caution must be taken when counseling parents and planning follow-up as other ND disorders may develop later in childhood, even for "low-grade GMH-IVH".

Despite being independently associated with visual impairment, the results from the logistic regression models are consistent with the finding that other factors play a role in ND outcome and mortality, such as PVL, hydrocephaly, GA and ototoxic medication [27].

This study is limited by its retrospective nature and the small sample size. GMH-IVH diagnosis was based on cUS, and classification of GMH-IVH was made according to Volpe grading system, whose definition and pathophysiologic mechanisms of each grade of GMH-IVH differs from GMH-IVH classification applied in other case series. Regarding ND outcomes, one limitation to this study is the absence of long-term follow-up until school age. The SGS assessment tool used, although validated and recommended by national guidelines, is not commonly applied in other case series, limiting the comparison of results.

The adjustment for data for the desired outcomes is a strength of this study, enhancing the validity of the results.

Conclusions

Lower Apgar score at 5 minutes of life and any CPR were independent risk factors for GMH-IVH in preterm infants. GMH-IVH was associated with higher mortality and ND morbidity. ND prognosis of grade II GMH-IVH was comparable to grade III GMH-IVH, questioning the classification as "low-grade GMH-IVH" and reinforcing the importance of long-term surveillance.

Declaration of interest

No potential conflict of interest was reported by the Authors. No funding or other financial support was needed for this study.

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