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Germinal Matrix-intraventricular hemorrhage in very preterm infants: Frequency, associated factors, and the role of postnatal clinical course

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ABSTRACT

Objective: Germinal matrix-intraventricular hemorrhage (GMH-IVH) remains one of the most important complications associated with prematurity and is a major cause of neonatal morbidity and mortality. This study aimed to determine the frequency of GMH-IVH and to evaluate prenatal, natal, and postnatal factors associated with its development in preterm infants.

Materials and Methods: This retrospective study included preterm infants with a gestational age between 24 and 32 weeks and a birth weight ≤1500 g who were followed in the neonatal intensive care unit of a tertiary referral center. Cranial ultrasonography, performed within the first 72 hours of life and repeated at the end of the first week, was used to diagnose and grade GMH-IVH according to the Volpe classification. Demographic characteristics, maternal factors, delivery characteristics, and early postnatal clinical and laboratory parameters were analyzed. Infants were grouped according to the presence of GMH-IVH and the severity of hemorrhage.

Results: A total of 312 preterm infants were included in the study. GMH-IVH was detected in 49.7% of the infants. Among these, 83 (53.5%) had mild hemorrhage (Grade 1–2) and 72 (46.5%) had severe hemorrhage (Grade 3–4). Lower gestational age, lower birth weight, absence of antenatal steroid use, lower Apgar scores, requirement for invasive mechanical ventilation, presence of patent ductus arteriosus, and abnormalities in coagulation parameters were significantly associated with GMH-IVH.

Conclusion: GMH-IVH in preterm infants is a multifactorial condition associated with several prenatal and postnatal factors. However, the retrospective design precludes establishing causality. Our findings highlight the strong association with postnatal clinical instability, particularly invasive mechanical ventilation and PDA treatment, suggesting that these are critical markers of illness severity. Identification of modifiable factors and optimization of perinatal and neonatal care may contribute to reducing the incidence and severity of GMH-IVH in this vulnerable population.

Keywords: Associated factors, germinal matrix hemorrhage, neonatal intensive care prematurity, intraventricular hemorrhage

Introduction

Prematurity is defined by the World Health Organization (WHO) as birth occurring before 37 weeks of gestation (1). Of the approximately 135 million live births worldwide each year, nearly 15 million are preterm births (2). Prematurity is considered one of the leading causes of neonatal morbidity and mortality globally (1).

In recent years, a significant increase in preterm birth rates has been observed. A substantial portion of this increase is attributed to the rise in late preterm births due to medically indicated early deliveries and increasing cesarean section rates. In addition, maternal risk factors, the widespread use of assisted reproductive technologies, and the increase in multiple pregnancies have contributed particularly to the growing number of preterm infants born with a birth weight below 1500 grams (3).

Advances in perinatal care, the expansion of neonatal intensive care units, antenatal steroid administration, surfactant therapy, and mechanical ventilation have played major roles in improving survival rates among preterm infants. Although mortality among preterm infants monitored in neonatal intensive care units has decreased, prematurity-related complications remain a significant concern. These complications include sepsis, respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), intraventricular

hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). Germinal matrix--intraventricular hemorrhage (GMH-IVH), one of the major complications observed in preterm infants, may lead to adverse long-term neurodevelopmental outcomes (4,5). The incidence of GMH-IVH increases as gestational age decreases. In particular, the frequency of GMH-IVH may reach approximately 45% in preterm neonates born at or below 26 weeks of gestation, whereas this rate has been reported to range between 5% and 10% in preterm infants born before 32 weeks of gestation (5). One of the principal mechanisms involved in the development of GMH-IVH in preterm neonates is fluctuation in cerebral blood flow accompanied by impaired cerebral autoregulation. Due to the structurally fragile and highly vascular nature of the germinal matrix region, hemorrhages most commonly originate from this area. Approximately 50% of cases are detected within the first 24 hours of life, and 90% within the first 72 hours (4,6).

The aim of this study was to determine the frequency of GMH-IVH in preterm infants born between 24 and 32 weeks of gestation with a birth weight of 1500 grams or less and to evaluate the prenatal, natal, and postnatal clinical characteristics of infants who developed GMH-IVH. Since GMH-IVH in preterm infants is a serious cause of mortality and morbidity, identifying the factors associated with this condition is of great importance. Determination of these factors will contribute to increasing opportunities for early intervention, eliminating preventable factors, and improving both survival rates and long-term quality of life in these infants.

Materials and Methods

Study design and population

This retrospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of Ankara Bilkent City Hospital, a tertiary referral center, between September 2019 and March 2023. The study included preterm infants born at 24–32 weeks of gestation with a birth weight ≤1500 g who were either delivered at the study center and admitted to the NICU within the first 24 hours of life or transferred from another center within the same time frame. To clarify the study population's baseline risk, we have added stratified data on gestational age and birth weight in the Results section. Infants who underwent transfontanel cranial ultrasonography within the first 72 hours of life and whose complete medical records were accessible were included. Exclusion criteria were discharge or death within the first 72 hours, presence of major congenital anomalies, congenital-metabolic diseases, chromosomal abnormalities, or incomplete medical records.

During the study period, 312 eligible preterm infants were identified. Of these, 155 infants with GMH-IVH constituted the study group, and 157 infants without hemorrhage formed the control group. The hemorrhage group was further stratified according to hemorrhage severity.

Data collection

Clinical data were obtained retrospectively from electronic medical records. Prenatal variables included maternal age, multiple pregnancy, antenatal magnesium sulfate administration, antenatal steroid use, smoking during pregnancy, gestational hypertension, gestational diabetes, thyroid dysfunction, preeclampsia, placental anomalies, oligohydramnios or polyhydramnios, prolonged premature rupture of membranes (PPROM), urinary tract infection, other maternal infections, chronic maternal diseases, medication use during pregnancy, and chorioamnionitis. Natal and postnatal variables included mode of delivery, gestational age, birth weight, sex, 1st- and 5th-minute APGAR scores, need for resuscitation, presence of respiratory distress syndrome (RDS), early neonatal sepsis (ENS), development and treatment of patent ductus arteriosus (PDA), surfactant administration within the first 24 hours, invasive or non-invasive mechanical ventilation in the first 24 hours, cardiopulmonary resuscitation (CPR), inotropic support, blood product transfusion, daily fluid intake, first-day body weight, and weight change. The timing of PDA treatment relative to GMH-IVH diagnosis was not consistently documented, a limitation that is addressed in the discussion.

Laboratory and clinical definitions

Cord blood gas parameters (pH, PCO_2, HCO_3, base excess [BE], and lactate) were evaluated, and perinatal asphyxia was defined as cord pH <7.0 or BE <–12 (7). Hemoglobin (HGB), hematocrit (HCT), and platelet (PLT) levels measured within the first 24 hours were recorded, and thrombocytopenia was defined as PLT <150.000/mm^3 (8). Coagulation parameters (INR, APTT, PT) measured within the first 72 hours were analyzed. Acid–base disturbances were defined as pH <7.35 for acidosis and pH >7.45 for alkalosis. Hypoglycemia was defined as blood glucose <50 mg/dL, hyperglycemia as >150 mg/dL, hyponatremia as sodium <135 mEq/L, and hypernatremia as sodium >145 mEq/L (9). Blood culture results obtained within the first 24 hours were recorded. Clinical diagnoses including RDS, PDA, GMH-IVH, and transfusion indications were defined according to Turkish Neonatology Society (TNS) guidelines (7,8). Maternal infection was defined as any infection occurring during pregnancy. Preeclampsia was defined as hypertension and proteinuria occurring after mid-gestation (1). Chorioamnionitis was diagnosed based on clinical criteria including maternal fever >37.5°C, uterine tenderness, foul-smelling vaginal discharge, maternal or fetal tachycardia, and leukocytosis >15.000/mm^3 (1). Prolonged membrane rupture ≥18 hours was accepted as PPROM. Antenatal steroid exposure was defined as administration of at least one dose between $23^0/_7$ and $34^6/_7$ weeks of gestation. Inotropic support was defined as administration of dopamine, dobutamine, adrenaline, or noradrenaline within the first 24 hours (10). Early neonatal sepsis was defined as clinically and/or microbiologically confirmed infection within the first three days of life.

Neuroimaging and hemorrhage classification

The diagnosis of GMH-IVH was established through cranial ultrasonography performed via the anterior fontanelle. Imaging procedures were conducted by experienced pediatric radiologists; however, they were not blinded to the infants' clinical status, and interobserver variability was not assessed—a limitation inherent to the retrospective design. Cranial ultrasonography was performed within the first

72 hours of life and repeated at the end of the first week. The highest grade of hemorrhage recorded during the first week of life was used for analysis. The presence and grade of germinal matrix--intraventricular hemorrhage (GMH-IVH) were recorded. Hemorrhages were classified according to the Volpe classification system (4,5). Grades I–II were considered mild hemorrhage, whereas Grades III–IV or periventricular hemorrhagic infarction (PVHI) were classified as severe hemorrhage. Infants were analyzed both according to the presence or absence of hemorrhage and according to hemorrhage severity.

Statistical analysis

Descriptive statistics were presented as mean and standard deviation, median (min-max), and frequency (percentage). The Shapiro–Wilk test was used to assess the normality of continuous variables. Categorical variables were compared using the chi-square test. For continuous variables, the Independent Samples t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Multivariate logistic regression analysis was performed to identify factors independently associated with GMH-IVH, with results presented as odds ratios (OR) and 95% confidence intervals. Statistical analyses were conducted using IBM SPSS Statistics 21.0, and a p-value <0.050 was considered statistically significant. A post-hoc power analysis was performed using G*Power software (version 3.1.9.7). With a sample size of 312 patients (155 with GMH-IVH, 157 without), an effect size of 0.3, and α=0.05, the study achieved a statistical power of 0.94 (94%). For subgroup analyses comparing Grade 1-2 (n=83) vs. Grade 3-4 (n=72) GMH-IVH, the power was 0.82 (82%). These results indicate that the sample size was adequate to detect clinically meaningful differences.

Results

Infants with GMH-IVH constituted the study group, while those without GMH-IVH formed the control group. Of the participating infants, 50.3% (n=157) had no GMH-IVH, while 49.7% (n=155) were diagnosed with GMH-IVH. Among the 155 infants with GMH-IVH, grade distribution was as follows: Grade 1: 43 (27.7%), Grade 2: 40 (25.8%), Grade 3: 35 (22.6%), Grade 4: 37 (23.9%). This sums to 155, consistent with the subgroup counts (Grade 1–2: n=83; Grade 3–4: n=72). Stratified data on gestational age and birth weight are as follows: In the entire cohort, 28.2% (n=88) of infants were <26 weeks GA, and 71.8% (n=224) were 26-32 weeks GA. In the <26 weeks GA subgroup, the incidence of GMH-IVH was 68.2% (60/88), compared to 42.4% (95/224) in the 26-32 weeks GA subgroup. Regarding birth weight, 58.3% (n=182) of infants had a birth weight <1000 g, and 41.7% (n=130) had a birth weight between 1000-1500 g. The incidence of GMH-IVH was 62.1% (113/182) in the <1000 g subgroup and 32.3% (42/130) in the 1000-1500 g subgroup. Furthermore, 31.1% (n=97) of the infants were outborn (transferred from another center).

Maternal and Pregnancy Characteristics were shown in Table I. Infants with GMH-IVH had significantly lower mean gestational age (26.48±2.22 vs. 27.36±2.39 weeks, p=0.001) and lower maternal age (28.68±6.26 vs. 29.82±5.09 years, p=0.031). Although the maternal age difference was statistically significant, it is likely not clinically meaningful and should not be overemphasized. Gestational age decreased as hemorrhage grade increased (Grade 3-4: 25.68±1.57 vs. Grade 1-2: 27.18±2.45 weeks, p<0.001). Multiple pregnancy rate was significantly associated with GMH-IVH presence (p=0.034) and severity, with higher rates in Grade 3-4 group (p=0.046). Antenatal steroid use was associated with lower GMH-IVH frequency (p=0.020) and lower grade (p=0.018). Polyhydramnios was associated with reduced GMH-IVH occurrence (p=0.019) but not with grade (p=0.535). No significant associations were found with magnesium sulfate treatment, smoking, gestational diabetes, hypothyroidism, hypertension, preeclampsia, infections, PPROM, chorioamnionitis, amniotic fluid abnormalities, or placental anomalies (all p>0.050). These non-significant variables are presented in the tables for transparency.

Table II represents Perinatal and Early Neonatal Characteristics. Cesarean delivery rate was lower in the GMH-IVH group (84.5%

Table I: Maternal and pregnancy characteristics according to GMH-IVH presence and severity

Variable	No GMH-IVH	GMH-IVH	p	Grade 1–2	Grade 3–4	p
Total number of patients	157	155	-	83	72	-
Gestational age weeks*	27.36±2.39	26.48±2.22	0.001	27.18±2.45	25.68±1.57	<0.001
Maternal age years*	29.82±5.09	28.68±6.26	0.031	29.30±6.75	27.96±5.61	0.254
Multiple pregnancy†	58 (36.9)	40 (25.8)	0.034	16 (19.3)	24 (33.3)	0.046
Antenatal steroid use†	145 (92.4)	130 (83.9)	0.020	75 (90.4)	55 (76.4)	0.018
Polyhydramnios†	8 (5.1)	1 (0.6)	0.019	1 (1.2)	0 (0.0)	0.535
Antenatal magnesium sulfate†	35 (22.3)	32 (20.6)	0.720	18 (21.7)	14 (19.4)	0.739
Smoking during pregnancy†	12 (7.6)	10 (6.5)	0.683	5 (6.0)	5 (6.9)	0.822
Gestational diabetes†	18 (11.5)	15 (9.7)	0.599	8 (9.6)	7 (9.7)	0.986
Hypothyroidism†	11 (7.0)	13 (8.4)	0.649	7 (8.4)	6 (8.3)	0.984
Gestational hypertension†	9 (5.7)	11 (7.1)	0.621	6 (7.2)	5 (6.9)	0.949
Preeclampsia†	15 (9.6)	12 (7.7)	0.558	7 (8.4)	5 (6.9)	0.731
PPROM†	24 (15.3)	20 (12.9)	0.545	11 (13.3)	9 (12.5)	0.887
Chorioamnionitis†	6 (3.8)	5 (3.2)	0.777	3 (3.6)	2 (2.8)	0.775
Urinary tract infection†	14 (8.9)	12 (7.7)	0.704	6 (7.2)	6 (8.3)	0.796

**: mean±SD, †: n(%), Although maternal age difference was statistically significant, it is likely not clinically meaningful. Non-significant variables are included here for transparency as recommended by reviewer.*

Table II: Perinatal and early clinical characteristics according to GMH-IVH presence and severity

Variable	No GMH-IVH	GMH-IVH	p	Grade 1–2	Grade 3–4	p
Total number of patients	157	155	-	83	72	-
Mode of delivery (C/S*)	144 (91.7)	131 (84.5)	0.049	70 (84.3)	61 (84.7)	0.947
1-min Apgar score†	4.33±1.70	3.75±1.75	0.002	4.08±1.84	3.38±1.56	0.014
5-min Apgar score†	6.27±1.59	5.82±1.58	0.004	6.17±1.58	5.42±1.51	0.003
Birth weight g†	990.4±320.6	895.4±267.4	0.016	959.5±298.1	821.5±205.4	0.003
Day 1 weight g†	966.9±315.1	882.1±258.2	0.028	941.4±286.6	813.7±202.2	0.004
Weight change day 1 g†	−28.7±33.8	−17.7±39.6	0.006	−22.3±42.5	−11.9±35.2	0.131
Invasive ventilation*	89 (56.7)	115 (74.2)	0.001	48 (57.8)	67 (93.1)	<0.001
Surfactant therapy*	121 (77.1)	137 (88.4)	0.008	65 (78.3)	72 (100)	<0.001
PDA*	88 (58.3)	110 (73.8)	0.004	53 (65.4)	57 (83.8)	0.011
PDA treatment*	53 (35.1)	90 (60.4)	<0.001	42 (51.9)	48 (70.6)	0.020
Inotrope support*	34 (21.7)	44 (28.4)	0.170	17 (20.5)	27 (37.5)	0.019
RDS*	148 (94.3)	149 (96.1)	0.442	77 (92.8)	72 (100)	0.022

***:** *n(%),* **†:** *mean±SD*

Table III: Comparison of hematological and biochemical parameters according to the presence and severity of GMH-IVH

Variable	No GMH-IVH*	GMH-IVH* *	p	Grade 1–2*	Grade 3–4*	p
Total number of patients	157	155	-	83	72	-
Hemoglobin (g/dL)	16.29 ± 2.38	15.29 ± 2.20	<0.001	15.90 ± 2.12	14.59 ± 2.10	<0.001
Hematocrit (%)	52.37 ± 7.67	48.99 ± 7.01	<0.001	50.79 ± 6.63	46.91 ± 6.89	<0.001
INR	1.61 ± 0.73	2.09 ± 1.20	0.002	1.99 ± 1.68	2.14 ± 0.87	0.042
PT (sec)	18.12 ± 7.79	23.67 ± 15.10	0.002	23.34 ± 22.65	23.85 ± 9.18	0.039
APTT (sec)	44.23 ± 17.21	53.87 ± 23.95	0.032	44.40 ± 18.80	58.96 ± 25.05	0.014
First sodium (mEq/L)	141.76 ± 6.07	141.29 ± 7.26	0.435	142.27 ± 6.80	140.14 ± 7.65	0.018
Cord blood PCO_2 (mmHg)	42.56 ± 9.78	39.23 ± 12.34	0.003	40.39 ± 13.86	37.45 ± 9.42	0.185
Cord blood HCO_3 (mmol/L)	21.79 ± 3.22	20.35 ± 4.05	0.010	20.03 ± 4.44	20.84 ± 3.36	0.704
Cord lactate (mmol/L)	3.59 ± 1.95	3.79 ± 2.76	0.888	4.25 ± 3.14	3.09 ± 1.86	0.010

***:** *mean±SD, Although a statistical difference was observed between severity groups, the mean value was higher in Grade 1–2 than in Grade 3–4. This finding should not be overinterpreted as higher lactate being associated with more severe hemorrhage; it merely indicates a difference between groups.*

Table IV: Comparison of GMH-IVH according to maternal chronic diseases

Maternal Disease	No GMH-IVH*	GMH-IVH*	Grade 1–2*	Grade 3–4*
Hypothyroidism	11 (45.8)	13 (54.2)	7 (53.8)	6 (46.2)
Hypertension	8 (47.1)	9 (52.9)	4 (44.4)	5 (55.6)
Hypertension + Hypothyroidism	5 (71.4)	2 (28.6)	1 (50.0)	1 (50.0)
Asthma	1 (25.0)	3 (75.0)	3 (100.0)	0 (0.0)
Other	12 (60.0)	8 (40.0)	4 (50.0)	4 (50.0)

***:** *n(%), p-value (GMH-IVH presence): 0.501; p-value (grade comparison): 0.394**

vs. 91.7%, p=0.049) but not associated with grade (p=0.947). Both 1-minute and 5-minute Apgar scores were significantly lower in infants with GMH-IVH (p=0.002 and p=0.004), with the lowest scores in Grade 3-4 GMH-IVH (p=0.014 and p=0.003). Birth weight was significantly lower in the GMH-IVH group (895.4±267.4 g vs. 990.4±320.6 g, p=0.016), particularly in Grade 3-4 GMH-IVH (821.5±205.4 g vs. 959.5±298.1 g, p=0.003). A similar pattern was observed for postnatal day 1 weight (p=0.028 for GMH-IVH presence; p=0.004 for grade). Early weight loss differed between groups (p=0.006) but was not associated with grade (p=0.131). Invasive mechanical ventilation was more frequent in the GMH-IVH group (74.2% vs. 56.7%, p=0.001), especially in Grade 3-4 GMH-IVH (93.1% vs. 57.8%, p<0.001). Surfactant therapy was more common in the GMH-IVH group (88.4% vs. 77.1%, p=0.008), and all infants with severe GMH-IVH received surfactant (100% vs. 78.3%, p<0.001). PDA was more frequent in the GMH-IVH group (73.8% vs. 58.3%, p=0.004), with higher rates in Grade 3-4 GMH-IVH (83.8% vs. 65.4%, p=0.011). PDA treatment was also more common in the GMH-IVH group (60.4% vs. 35.1%, p<0.001) and in severe GMH-IVH (70.6% vs. 51.9%, p=0.020). Inotrope support was not associated with overall GMH-IVH (p=0.170) but was more frequent in severe GMH-IVH (37.5% vs. 20.5%, p=0.019). RDS was associated with severe GMH-IVH (100% vs. 92.8%, p=0.022) but not with overall GMH-IVH presence (p=0.442).

Laboratory Parameters were summarized in Table III. Hemoglobin and hematocrit levels were significantly lower in the GMH-IVH group (p<0.001 for both), with further decreases in Grade 3-4 GMH-IVH (p<0.001). INR, PT, and APTT were significantly higher in the GMH-IVH group (p=0.002, p=0.002, and p=0.032, respectively) and in severe GMH-IVH (p=0.042, p=0.039, and p=0.014). Acidosis was not associated with overall GMH-IVH (p=0.587) but was significantly related to grade (p=0.004). Initial sodium level was lower in severe GMH-IVH (p=0.018) but not associated with GMH-IVH presence (p=0.435). Cord blood PCO_2 and HCO_3 were significantly lower in the GMH-IVH group (p=0.003 and p=0.010) but not associated with grade. Cord lactate was significantly different only in severe GMH-IVH (p=0.010). Of note, cord lactate values appeared higher in the Grade 1–2 group than in the Grade 3–4 group; therefore, we do not conclude that higher lactate is associated with more severe hemorrhage, but merely that a difference exists. No significant

Table V: Comparison of GMH-IVH presence and grade according to medications used during pregnancy

Medication Used During Pregnancy	GMH-IVH Absent*	GMH-IVH Present*	p	Grade 1-2*	Grade 3-4	p
Total number of patients	56	61	-	35	26	-
Alphamed	12 (63.2)	7 (36.8)	-	5 (71.4)	2 (28.6)	-
Antibiotics	8 (38.1)	13 (61.9)	-	9 (69.2)	4 (30.8)	-
Coraspin	4 (50.0)	4 (50.0)	-	2 (50.0)	2 (50.0)	-
LT4	9 (40.9)	13 (59.1)	0.694	6 (46.2)	7 (53.8)	0.448
Oxapar	2 (40.0)	3 (60.0)	-	3 (100.0)	0 (0.0)	-
Alphamed + Coraspin	4 (44.4)	5 (55.6)	-	2 (40.0)	3 (60.0)	-
Insulin	1 (25.0)	3 (75.0)	-	1 (33.3)	2 (66.7)	-
Other	16 (55.2)	13 (44.8)	-	7 (53.8)	6 (46.2)	-

***:** *n(%)*

Table VI: Univariate and multivariate logistic regression analysis of factors associated with GMH-IVH

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Gestational week	0.849 (0.768-0.937)	0.001	1.365 (0.712-2.617)	0.349
Maternal age	0.965 (0.928-1.004)	0.080	0.877 (0.721-1.068)	0.192
Multiple pregnancy	0.594 (0.366-0.964)	0.035	0.485 (0.051-4.619)	0.530
Antenatal steroid	0.430 (0.208-0.891)	0.023	1.059 (0.044-25.735)	0.972
Polyhydramnios	0.121 (0.015-0.979)	0.048	0.033 (0.000-11.071)	0.250
Apgar 1st minute	0.824 (0.723-0.940)	0.004	0.501 (0.139-1.806)	0.291
Apgar 5th minute	0.837 (0.726-0.965)	0.014	1.436 (0.386-5.350)	0.589
Birth weight	0.999 (0.998-1.000)	0.005	0.992 (0.923-1.066)	0.830
Postnatal day 1 body weight	0.999 (0.998-1.000)	0.010	1.010 (0.940-1.085)	0.782
Day 1 body weight change	1.008 (1.001-1.015)	0.023	0.961 (0.888-1.039)	0.314
Invasive mechanical ventilation	2.197 (1.361-3.545)	0.001	32.451 (1.095-961.402)	0.044
Surfactant administration	2.264 (1.223-4.194)	0.009	1.315 (0.050-34.737)	0.870
PDA presence	2.019 (1.240-3.289)	0.005	0.098 (0.005-1.753)	0.114
PDA treatment	2.821 (1.766-4.506)	<0.001	35.366 (1.837-680.798)	0.018
Hemoglobin	0.824 (0.744-0.913)	<0.001	0.807 (0.233-2.788)	0.734
Hematocrit	0.939 (0.909-0.969)	<0.001	0.902 (0.593-1.372)	0.631
INR	1.992 (1.128-3.518)	0.018	0.001 (0.001-253.458)	0.234
PT	1.067 (1.011-1.127)	0.018	2.399 (0.600-9.596)	0.216
APTT	1.024 (1.003-1.046)	0.024	0.918 (0.817-1.030)	0.146
Umbilical cord blood PCO_2	0.973 (0.949-0.997)	0.026	1.042 (0.941-1.154)	0.431
Umbilical cord blood HCO_3	0.894 (0.827-0.965)	0.004	0.729 (0.511-1.038)	0.080

***MV:** Mechanical ventilation, **PDA:** Patent ductus arteriosus, **GMH-IVH:** Germinal matrix–intraventricular hemorrhage, Bold ORs and p-values indicate statistical significance (p<0.05). These associations should be interpreted with extreme caution due to the risk of reverse causality inherent to the retrospective design, as well as the very wide confidence intervals suggesting model instability.*

associations were found with thrombocytopenia, platelet count, admission blood gas parameters (pH, PCO_2, HCO_3, BE, lactate), initial glucose, or cord blood pH (all p>0.050).

Maternal Chronic Diseases and Medication Use are Tables IV-V. No significant associations were found between GMH-IVH presence or grade and maternal chronic diseases (hypothyroidism, hypertension, asthma, etc.) (p=0.501 and p=0.394) or medications used during pregnancy (alphamed, antibiotics, coraspin, LT4, oxapar, insulin, etc.) (p=0.694 and p=0.448).

Table VI presents univariate and multivariate logistic regression analyses of factors associated with GMH-IVH in preterm infants. In univariate analysis, significant factors included lower gestational week (OR: 0.849), absence of antenatal steroids (OR: 0.430), lower Apgar scores, lower birth weight, invasive mechanical ventilation (OR: 2.197), surfactant administration (OR: 2.264), PDA presence (OR: 2.019), PDA treatment (OR: 2.821), lower hemoglobin/hematocrit, and elevated INR, PT, and APTT (all p<0.05). In multivariate analysis, invasive mechanical ventilation (OR: 32.451, p=0.044) and PDA treatment (OR: 35.366, p=0.018) remained independently associated with GMH-IVH. However, the very wide confidence intervals (e.g., 1.095–961.402 for mechanical ventilation) suggest model instability and possible collinearity; these findings should be interpreted with caution and do not imply causation.

Discussion

In this study, the frequency of GMH-IVH and the prenatal, natal, and postnatal factors affecting its development were evaluated in premature infants with a gestational age of 24–32 weeks and a birth weight ≤1500 g. In our study population, the incidence of GMH-IVH was found to be 49.7%. Approximately half of the infants with hemorrhage

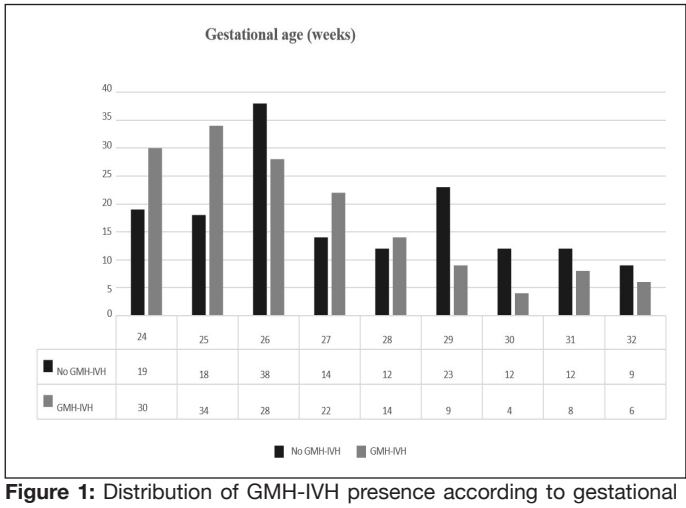

Figure 1: Distribution of GMH-IVH presence according to gestational week. A statistically significant difference was observed between gestational weeks and GMH-IVH presence (p=0.004). The frequency of GMH-IVH decreased as gestational week increased.

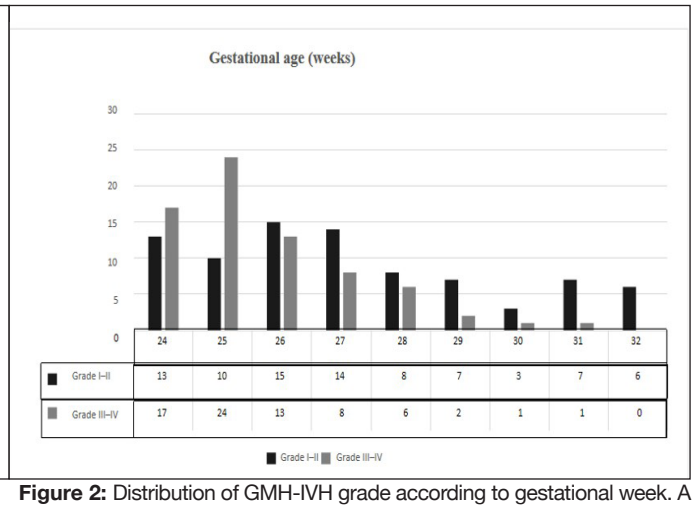

Figure 2: Distribution of GMH-IVH grade according to gestational week. A statistically significant difference was observed between gestational weeks and GMH-IVH grade (p=0.001). The severity of GMH-IVH decreased as gestational week increased.

had mild-stage hemorrhage (Grade 1–2), while the remaining half had severe-stage hemorrhage (Grade 3–4). This high incidence is likely explained by the high-risk nature of our cohort, which included a large proportion of infants <26 weeks GA (28.2%), extremely low birth weight (<1000 g, 58.3%), and outborn neonates (31.1%), all of whom are at increased baseline risk for GMH-IVH. Our findings suggest that the development of GMH-IVH in preterm infants is a multifactorial process and that gestational age, birth weight, antenatal steroid use, postnatal adaptation indicators, the need for respiratory support, the presence of PDA, and certain hematological parameters are associated with this condition.

Gestational age is one of the most important factors associated with the development of GMH-IVH in premature infants. The immature vascular structure of the germinal matrix region and the insufficient development of cerebral autoregulation mechanisms increase the risk of hemorrhage, particularly at lower gestational ages (11,12). As described by Volpe, the germinal matrix contains a dense capillary network, and these vessels are structurally thin-walled and fragile (11). In the classical study conducted by Papile et al. (13), the incidence of GMH-IVH was also reported to increase significantly with decreasing gestational age. In our study, the mean gestational age was significantly lower in infants who developed GMH-IVH, and gestational age was even lower in cases with severe-stage hemorrhage. These findings are consistent with the data reported in the literature.

Birth weight is another important factor closely associated with the development of GMH-IVH. In particular, the fragility of germinal matrix vessels and instability in cerebral blood flow are more pronounced in very low birth weight (<1500 g) and extremely low birth weight (<1000 g) infants. In a comprehensive review conducted by Ballabh, it was demonstrated that the immature structure of germinal matrix vessels and hemodynamic fluctuations play a critical role in the pathogenesis of GMH-IVH in premature infants (14). Recent epidemiological studies have also reported a strong association between low birth weight and the development of GMH-IVH (15). Similarly, in our study, the birth weight of infants with GMH-IVH was significantly lower, and birth weight was even lower in infants with severe-stage hemorrhage.

Antenatal steroid administration is one of the most important obstetric interventions that improves neonatal outcomes in pregnancies at risk for preterm birth. In addition to accelerating fetal lung maturation, antenatal steroids may reduce the risk of GMH-IVH by improving cerebral vascular stability. Recent meta-analyses have shown that antenatal steroid use significantly reduces both mortality and the risk of GMH-IVH in premature infants (16). In our study, a significant association was observed between antenatal steroid use and the development of GMH-IVH, and the rate of hemorrhage was higher in pregnancies that did not receive steroids. These findings further support the importance of antenatal steroid administration in pregnancies at risk of preterm delivery.

Perinatal adaptation indicators also provide important markers for the development of GMH-IVH. In our study, the 1st- and 5th-minute Apgar scores were significantly lower in infants who developed GMH-IVH. Low Apgar scores may indicate hypoxia and hemodynamic instability occurring during delivery. It is known that sudden changes in cerebral blood flow in premature infants may lead to rupture of the fragile vessels within the germinal matrix (11). Therefore, maintaining hemodynamic stability in the early postnatal period may play an important role in reducing the development of GMH-IVH.

The need for respiratory support was another factor associated with GMH-IVH in our study. The requirement for invasive mechanical ventilation was significantly higher among infants with GMH-IVH. Changes in intrathoracic pressure during mechanical ventilation may affect cerebral venous return and lead to fluctuations in cerebral blood flow. Recent studies have suggested that aggressive ventilation

strategies may negatively affect cerebral hemodynamic stability in premature infants (17). In addition, the need for ventilation generally reflects a more severe clinical condition, which may further increase the risk of GMH-IVH.

Patent ductus arteriosus (PDA) is a common cardiovascular condition in premature infants and may have significant effects on systemic circulation and cerebral perfusion. The presence of PDA may contribute to the development of GMH-IVH by causing fluctuations in cerebral blood flow (14). Recent clinical studies have also demonstrated that the presence of PDA may increase the risk of GMH-IVH, particularly in very low birth weight infants (18). In our study, both the presence of PDA and the need for PDA treatment were found to be significantly associated with GMH-IVH.

When hematological parameters were evaluated, hemoglobin and hematocrit levels were significantly lower in infants with GMH-IVH. In addition, coagulation parameters, including INR, PT, and APTT, were higher in infants who developed GMH-IVH. The immaturity of the coagulation system and incomplete development of platelet function in premature infants may increase the tendency for bleeding. Recent studies have indicated that abnormalities in coagulation parameters may be associated with the development of GMH-IVH (19,20).

When metabolic parameters were evaluated, the presence of acidosis was not directly associated with the development of GMH-IVH; however, it was observed more frequently in severe-stage hemorrhages. Electrolyte disturbances and metabolic instability may adversely affect cerebral circulation in premature infants (21-23).

The multicenter cohort study conducted by Poryo et al. (24) supports the findings of our study. After controlling for maternal factors, the researchers demonstrated that the factors significantly associated with GMH-IVH were predominantly related to the postnatal period. In our study, no significant association was found between GMH-IVH and maternal factors such as gestational diabetes, hypertension, preeclampsia, maternal infections, and PPROM. This finding suggests that the degree of prematurity and the postnatal clinical condition may be more decisive than maternal factors in the development of GMH-IVH.

The most striking finding of our study is that invasive mechanical ventilation (OR: 32.451) and PDA treatment (OR: 35.366) emerged as factors independently associated with GMH-IVH. However, these associations should not be interpreted as causal. The retrospective design introduces a critical risk of reverse causality. Infants with severe prematurity and hemodynamic instability are more likely to require both invasive ventilation and PDA treatment. Furthermore, it is plausible that an infant who develops a severe GMH-IVH may subsequently experience hemodynamic instability, leading to the diagnosis and treatment of a PDA. Without precise documentation of the timing of these events, our multivariate analysis cannot establish whether PDA treatment preceded GMH-IVH or vice versa. In our study, the exact temporal relationship between PDA treatment and the diagnosis of GMH-IVH could not be determined due to the retrospective design. Therefore, it remains unclear whether PDA treatment preceded hemorrhage or occurred as a consequence of hemodynamic instability following hemorrhage. This is a major limitation that must be considered when interpreting our results. Our findings align with recent meta-analyses. Chen et al. (25) identified mechanical ventilation (OR: 2.09) and PDA (OR: 1.86) as significant factors associated with IVH in very low birth weight infants. The substantially higher odds ratios in our study may reflect the severity of illness in our cohort, highlighting that infants requiring invasive ventilation and PDA treatment represent a particularly vulnerable population requiring heightened surveillance to mitigate GMH-IVH risk.

Limitations

Our study has several limitations. The retrospective, single-center design may limit the generalizability of our findings and introduces potential for selection bias. The tertiary referral center setting, with a high proportion of outborn and extremely preterm infants, may not reflect the outcomes of lower-risk populations. Excluding infants who died or were discharged within the first 72 hours may have introduced selection bias, as the sickest and most immature infants at highest risk for severe hemorrhage were not included. The absence of blinding for radiologists, lack of interobserver reliability assessment, and the lack of standardized timing for interventions like PDA treatment relative to GMH-IVH diagnosis are significant limitations. Residual confounding from unmeasured variables (e.g., exact severity of respiratory illness, minute-to-minute hemodynamic fluctuations) is also possible. Furthermore, we did not use MRI for confirmation of hemorrhagic lesions, and long-term neurodevelopmental outcomes were not assessed. The inborn/outborn status was recorded (31.1% outborn), but differences in transport conditions and early stabilization could not be fully controlled for. Several findings, such as those related to multiple pregnancy and polyhydramnios, are based on very small subgroup numbers and should be interpreted cautiously. These points should be considered when interpreting the results.

Conclusion

Our study demonstrates that the development of GMH-IVH in premature infants is a multifactorial process. Lower gestational age, lower birth weight, absence of antenatal steroid use, lower Apgar scores, the need for invasive mechanical ventilation, the presence of PDA, and abnormalities in coagulation parameters were found to be associated with the development of GMH-IVH. However, the associations with mechanical ventilation and PDA treatment should be interpreted with caution due to the risk of reverse causality. Early identification of these factors and the implementation of appropriate clinical management strategies, with careful attention to hemodynamic and respiratory stability, may contribute to reducing the incidence and severity of GMH-IVH in this vulnerable population. Future prospective studies are needed to clarify the temporal relationship between clinical interventions and GMH-IVH.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent

City (01.11.2023, reference number: E2-23-5429).

Contribution of the authors

Study conception and design: İZA, CT; data collection: İZA; analysis and interpretation of results: İZA, CT; draft manuscript preparation: İZA, CT. All authors reviewed the results and approved the final version of the article

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Conflict of interest

The authors declare that there is no conflict of interest.

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