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Predictive Risk Factors for Mild and Severe Germinal Matrix Hemorrhage and Associated Neurodevelopmental Prognosis: A Retrospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors WA, HA, ZA and MA did the conceptualization, wrote methodology, formal analysis, investigation, wrote-reviewed-edited and visualized the original draft of the manuscript. Author AA did conceptualization, performed methodology, formal analysis, investigation, provision of resources, reviewed and edited original draft, supervised the study and help in project administration. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To compare commonly mentioned risk factors between mild germinal matrix hemorrhage-Intraventricular hemorrhage (GMH-IVH) (grade I & II) and severe GMH-IVH (grade III & IV) and to study the long-term neurodevelopmental outcomes in relation to severe GMH-IVH.
Study Design: Retrospective cohort study.
Place and Duration of Study: Neonatal intensive care unit, King Fahad University Hospital, between 2000 and 2020.
Methodology: We included 54 premature infants at ≤36 weeks of gestation and with birth weight

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<2500g admitted to our neonatal intensive care unit. Premature neonates were divided into two subgroups: mild GMH-IVH (grade I and II) and severe (grade III and IV). We investigated the risk factors and neurodevelopmental outcomes in association with GMH-IVH.
Results: Amnionitis (OR: 1.190, 95% CI 0.515-2.749), lower genital tract infection (OR: 1.190, 95% CI 0.515-2.749), antenatal infection (OR: 1.406, 95% CI 0.866-2.283), gestational diabetes mellitus (OR: 1.815, 95% CI 1.410-2.337), usage of inotropes (OR: 1.731, 95% CI 1.348-2.222), APGAR score <7 (OR: 0.806, 95% CI 0.493-1.316), birth trauma (OR: 1.767, 95% CI 1.396-2.236), catecholamines (OR: 1.470, 95% CI 0.903-2.393), intubation (OR: 1.300, 95% CI 0.686-2.464), asphyxia (OR: 1.135, 95% CI 0.718-1.794), Abnormal coagulation (OR: 1.197, 95% CI 0.756-1.896), congenital heart disease (OR: 1.727, 95% CI 1.124-2.653), low hematocrit (OR: 1.140, 95% CI 0.688-1.889), resuscitation (OR: 1,193, 95% CI 0.748- 1.904) and ventriculoperitoneal (VP) shunt as a prognosis of hydrocephalus (P-value: 0.005) all showed a higher incidence with severe GMH-IVH
Conclusion: Amnionitis, lower genital tract infection, antenatal infections, GDM, usage of inotropes, APGAR score <7, birth trauma, catecholamines, intubation, asphyxia, resuscitation, abnormal coagulation parameters, congenital heart disease, low hematocrit and hydrocephalus with VP shunt were higher in severe GMH-IVH.

Keywords: Germinal matrix hemorrhage; intraventricular hemorrhagel preterm neonates; risk factors; neurodevelopmental outcomes.

ABBREVIATIONS

GMH-IVH : Germinal matrix hemorrhage-intraventricular hemorrhage;
IVH : intraventricular hemorrhage;
PDA : patent ductus arteriosus;
PROM : Premature rupture of membrane;
GDM : gestational diabetes;
RDS : respiratory distress syndrome;
CS : cesarean section;
GA : gestational age;
CHD : congenital heart disease;
VP : Ventriculoperitoneal;
CI : confidence interval;
OR : odd ratio.

1. INTRODUCTION

Germinal matrix hemorrhage - intraventricular hemorrhage (GMH-IVH) is a significant complication that might affect preterm infants born with less than 32 weeks of gestation. The hemorrhage arises due to rupture of fragile micro-vessels located at the periventricular germinal matrix; bleeding then might reach the ventricular system causing intraventricular hemorrhage or further extends into the intraparenchymal area [1].

Germinal matrix hemorrhage - intraventricular hemorrhage (GMH-IVH) exhibits a vital health issue since it is a leading cause of death in preterm infants as well as its high incidence among them, mainly before 27 weeks of gestation [2]. Among preterm infants born in Saudi Arabia, the incidence of GMH-IVH is between 13% to 27%. Hence, it is valuable to detect and control the factors that might contribute to its development [3].

It is established that GMH-IVH is strongly associated with a broad spectrum of neurological consequences such as hydrocephalus, cerebral palsy, seizures, cognitive or learning disabilities. Preterm infants with severe GMH-IVH (grade III & IV) are more prone to neurological consequences [3].

The severity of GMH-IVH is detected by cranial ultrasonography. The image reflects the degree of hemorrhage that has been classified into four grades. In grade I, hemorrhage is confined into the germinal matrix. In grade II, hemorrhage is extended into the ventricle without causing ventricular dilation. When ventricular dilatation is identified; this is considered as grade III. In grade IV, hemorrhage progresses to occupy the intraparenchymal area (Fig.1) [1].

Several published studies have discussed and analysed sets of factors that potentially increase the risk of developing GMH-IVH in preterm infants. These factors include maternal factors, such as lower gestational age (GA), infection of the lower genital tract, and antenatal infections as well as neonatal factors, such as low birth weight, presence of patent ductus arteriosus (PDA), being male, white race, low APGAR score, and respiratory distress syndrome (RDS)

[4,5,6,7]. However, there is no obvious association between the risk factors and the severity of GMH-IVH and whether the presence of some risk factors can predict later neurological complications.

In this study, we aimed to identify the association between some risk factors and the severity of GMH-IVH and to study long-term neurodevelopmental outcomes in relation with severe GMH-IVH.

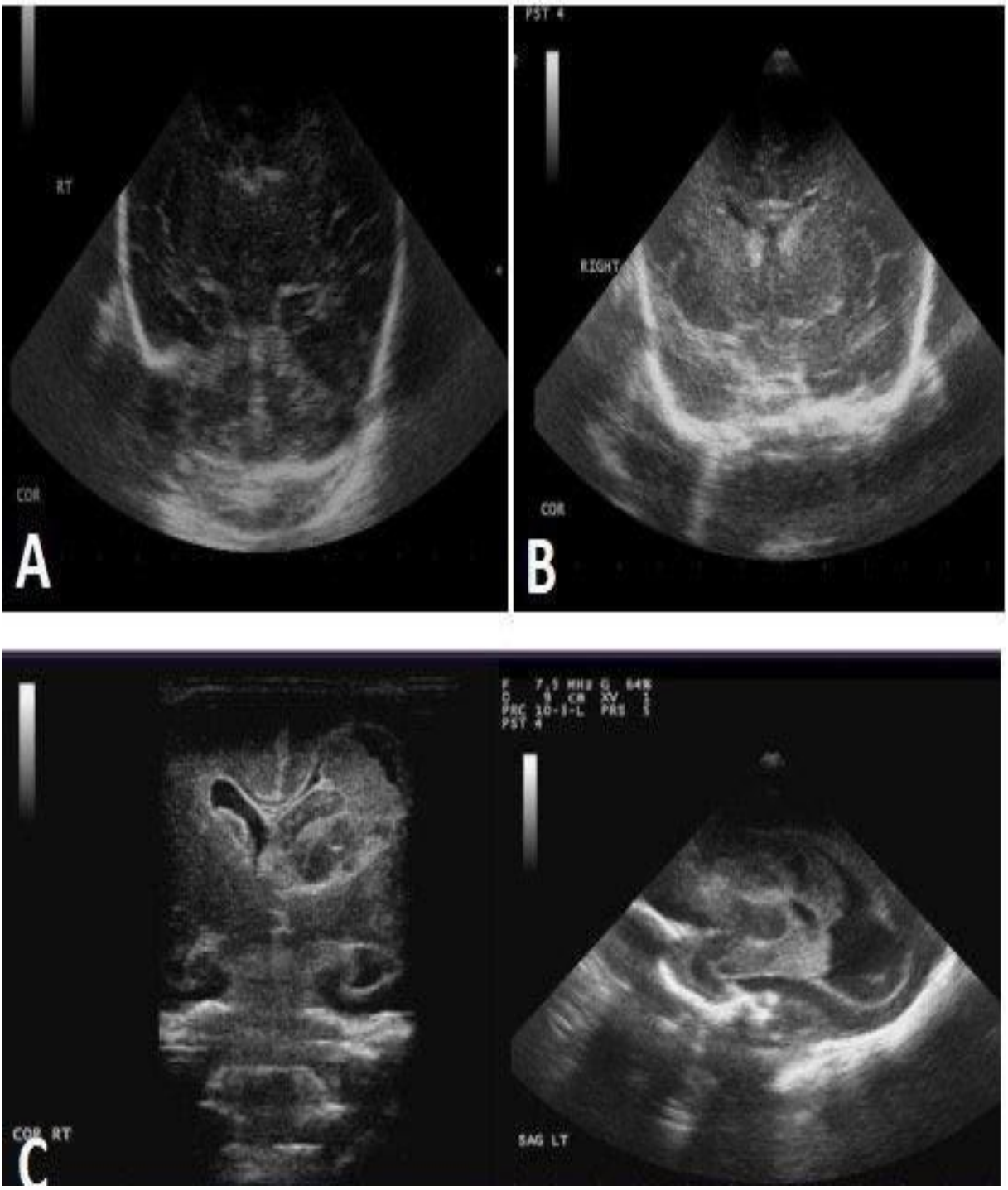

Fig. 1. Germinal matrix hemorrhage - Intraventricular hemorrhage grades. (a) Grade I (b) Grade II (c) Grade IV. Courtesy of Dr. Hanadi Althani, pediatric neuroradiology

2. METHODOLOGY

2.1 Subject

Our retrospective study was conducted at the NICU of King Fahad University Hospital between 2000 and 2020. Out of 1614 Premature neonates born at ≤36 weeks of gestation, with birth weight <2500 g and admitted in NICU, 54 neonates were qualified for inclusion in our study. We excluded neonates with congenital anomalies rather than congenital heart disease (CHD) and unspecified GMH-IVH grade. We divided neonates with GMH-IVH into two subgroups: mild GMH-IVH (grade I and II) and severe (grade III and IV). Our study was approved by Imam Abdulrahman Bin Faisal University Institutional Review Board (IRB-UGS-2020-01-381).

2.2 Diagnosis of Intraventricular Hemorrhage

GMH-IVH is diagnosed based on the routine cranial ultrasound, which was done between the first 3-7 days. If there were abnormal findings, further follow-up once a week for at least four weeks was needed. Any additional studies were preformed depending on the patient status and GA.

2.3 Data Collection

The data was collected from an electronic database (Quadramed) in King Fahad University hospital. We studied the relationship between the GMH-IVH grading and gestational age, specific maternal and neonatal variables. The maternal variables were: premature rupture of membrane, amnionitis, placental abruption, preeclampsia, lower genital tract infection, antenatal infection, gestational diabetes mellitus, and usage of inotropes. The neonatal variables were: APGAR score <7, birth trauma, respiratory distress syndrome, catecholamines, intubation, asphyxia, resuscitation, abnormal coagulation parameters, congenital heart disease, cesarean section as a mode of delivery, and low hematocrit.

For the prognosis, we explored the relation of hydrocephalus, presence of VP shunt, and death in neonates with severe GMH-IVH groups.

2.4 Statistical Analysis

Primary data were entered into Microsoft Excel, and further statistical analysis was performed using IBM SPSS statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Comparison of variables between the two subgroups of presence and absence of associated factors was performed using t-test and Chi-square test. T-test applied on gestational age as an independent sample. The odd ratio (OR) and 95% confidence intervals (95% CI) were calculated. A P-value below 0.05 was judged to be statistically significant.

3. RESULTS

3.1 Gestational age and GMH-IVH Grades

(Table 1) shows a comparison between mild and severe GMH-IVH in relation to gestational age. Our study showed that there is an insignificant relationship between gestational age and GMH-IVH grades (P-value: 0.547).

3.2 Risk Factors of GMH-IVH

3.2.1 Maternal risk factors

(Table 2) presents the relation between maternal risk factors with mild and severe GMH-IVH. In premature neonates with mild GMH-IVH, the incidence of PROM (OR: 1.348, 95% CI 0.702-2.587), placental abruption (OR: 2.364, 95% CI 1.721-3.247), and preeclampsia (OR: 1.175, 95% CI 0.494-2.794) was higher in comparison with severe GMH-IVH.

On the other hand, the incidence of amnionitis (OR: 1.190, 95% CI 0.515-2.749), lower genital tract infection (OR: 1.190, 95% CI 0.515-2.749), antenatal infection (OR: 1.406, 95% CI 0.866-2.283), GDM (OR: 1.815, 95% CI 1.410-2.337) and usage of inotropes (OR: 1.731, 95% CI 1.348-2.222) was higher in severe GMH-IVH.

3.2.2 Neonatal risk factors

(Table 3) presents the relation between neonatal risk factors with severe and mild GMH-IVH. In total of 54 patients whose birth weights were documented, number of patients with birth weight <2500g were 31 and 23 in severe and mild GMH-IVH respectively. APGAR score <7 (OR: 0.806, 95% CI 0.493-1.316), birth trauma (OR: 1.767, 95% CI 1.396-2.236),catecholamines (OR: 1.470, 95% CI 0.903-2.393), intubation (OR: 1.300, 95% CI 0.686-2.464), asphyxia (OR: 1.135, 95% CI 0.718-1.794), and resuscitation (OR: 1,193, 95% CI 0.748-1.904) all showed a higher incidence with severe GMH-IVH in comparison with mild GMH-IVH.

Abnormal coagulation (OR: 1.197, 95% CI 0.756-1.896), congenital heart disease (OR: 1.727, 95% CI 1.124-2.653), and low hematocrit (OR: 1.140, 95% CI 0.688-1.889) also showed a higher incidence in severe GMH-IVH. On the other hand, the incidence of mild GMH-IVH was higher in premature infants with RDS (OR: 1.193, 95% CI 0.578-2.462) and in infants delivered by CS (OR:1.537, 95% CI 0.836-2.826).

3.3 Prognosis and GMH-IVH Grades

(Table 4) presents a variable prognosis in relation to severe GMH-IVH. Our study showed a significant relation between severe GMH-IVH and having a VP shunt as a prognosis of hydrocephalus (P-value: 0.005). Meanwhile, there was insignificant relation with hydrocephalus (P-value: 0.012) and with death (P-value: 0.272).

Table 1. Analysis of gestational age in weeks of mild GMH-IVH and severe GMH-IVH [T-test]

	Grade I & II	Grade III & IV	P-value
Gestational Age (Mean ± SD)	28.09 ± 3.397	27.47 ± 3.893	0.55

Table 2. Maternal variables comparing neonate with mild GMH-IVH and severe GMH-IVH

	Grade I & II (N=54)	Grade III & IV (N=54)	P-value	Odd ratio of Grade I & II	Odd ratio of Grade III & IV
PROM	6 (26.1)	5 (16.7)	.31	1.348	.764
Amnionitis	1 (4.3)	2 (6.7)	.60	.758	1.190
Placental abruption	1 (4.3)	0 (0.00)	.43	2.364	0
Preeclampsia	3 (13)	3 (10)	.53	1.175	.870
Lower genital tract infection	1 (4.3)	2 (6.7)	.60	.758	1.190
Antenatal infection	2 (8.7)	6 (20)	.23	.536	1.406
GDM	0	4 (12.9)	.11	0	1.815
Usage of inotropes	0	2 (7.1)	.35	0	1.731

Table 3. Neonatal variables comparing neonate with mild GMH-IVH and severe GMH-IVH

	Grade I & II (N=54)	Grade III & IV (N=54)	P-value	Odd ratio of Grade I & II	Odd ratio of Grade III & IV
APGAR <7	17 (85.0%)	22 (75.9%)	.34	1.453	.806
Birth trauma	0 (0%)	1 (3.2%)	.57	-	1.767
RDS	17 (31.5%)	21 (38.9%)	.43	1.193	.884
Catecholamines	9 (39.1%)	19 (61.3%)	.09	.597	1.470
Intubation	16 (69.6%)	24 (80%)	.29	.743	1.300
Asphyxia	8 (34.8%)	13 (41.9%)	.40	.838	1.135
Resuscitation	7 (30.4%)	12 (40%)	.34	.783	1.193
Abnormal coagulation parameters	6 (26.1%)	11(35.5%)	.33	.768	1.197
Congenital heart disease	4(17.4%)	15(48.4%)	.02	.388	1.727
CS	12(52.2%)	10(33.3%)	.14	1.537	.705
Low hematocrit	14 (60.9%)	21(67.7%)	.41	.844	1.140

Table 4. Prognosis of mild and severe GMH-IVH

	Grade I & II (N=54)	Grade III & IV (N=54)	P-value	Odd ratio of Grade I & II	Odd ratio of Grade III & IV
Hydrocephalus	1 (4.3%)	10 (32.3%)	.01	.178	1.861
Presence of VP shunt	0 (0.0%)	9 (29.0%)	.01	0	2.045
Death	7 (30.4%)	14(45.2%)	.27	.208	1.294

4. DISCUSSION

Our single-center retrospective study, that included 1614 preterm neonates with GA ≤36 weeks, demonstrated an overall incidence of GMH-IVH in 4.15% of preterm neonates. We aimed to identify multiple neonatal and maternal risk factors associated with GMH-IVH in preterm neonates and the prognosis in severe GMH-IVH preterm neonates.

Our study showed that mothers who had amnionitis were more likely to have a neonate with severe GMH-IVH. In consistent with our findings, previous studies showed that amnionitis could cause low GA and birth weight which they considered them as risk factors for severe GMH-IVH [8,9].

Antenatal infection, including lower genital tract infection during pregnancy, is associated with a higher risk of having severe GMH-IVH as resulted in our study. In other studies, they found that antenatal infection and maternal lower genital tract infection are risk factors for developing and early deterioration of GMH-IVH [10,5]. The study mentioned that infections and inflammatory responses are strongly associated with neonatal brain injury, including GMH-IVH. Early management of lower genital tract infection is essential in preventing GMH-IVH in neonates [5].

Also, we found that gestational diabetes was associated with increased risk of severe GMH-IVH compared with the mild GMH-IVH. However, a study done in the United States showed no relation between GMH-IVH and GDM [11]. We suspected that this difference might be due to variances in the population study.

Our data suggested that administration of inotropes can increase the incidence of severe GMH-IVH. Unfortunately, there were insufficient studies supporting or disproving our result.

Low 1- and 5-minutes APGAR score was described as one of the most important risk factors for developing GMH-IVH in preterm neonates. Similarly, our study showed that the incidence of severe GMH-IVH is higher than the incidence of mild GMH-IVH in neonates with low APGAR score [12].

Etiopathogenesis of birth trauma leading to GMH-IVH still cannot be defined clearly. Birth trauma is a risk factor for GMH-IVH, mainly in full-term neonates. Although we noticed a low incidence of birth trauma in GMH-IVH preterm neonates, yet it was higher in severe GMH-IVH by 3.2% [13].

Catecholamine therapy is used as hypotension therapy in neonates. Unfortunately, the use of catecholamine was identified as a risk factor of GMH-IVH in multiple studies. Similarly, our data revealed a high incidence of using catecholamine therapy in neonates with severe GMH-IVH [14].

Our findings demonstrated a higher incidence of severe GMH-IVH in comparison with mild GMH-IVH in preterm infants who were intubated. This result is supported by published literature that also showed an increased risk of severe GMH-IVH with intubation [15,16].

Asphyxia is considered as an independent risk factor for GMH-IVH in previous studies [17]. In line with these studies, we found that severe GMH-IVH is more likely to occur than mild GMH-IVH in preterm infants who suffered from asphyxia.

One of the frequently cited risk factors that attributed to severe GMH-IVH is delivery room resuscitation [17,18]. Based on our findings, the incidence of severe GMH-IVH was higher than the incidence of mild GMH-IVH with resuscitation.

Coagulation abnormalities are still controversial as a risk factor for GMH-IVH. [4] However,

according to our data, the occurrence of severe GMH-IVH was higher with the presence of coagulation abnormalities.

The majority of infants with CHD develop GMH-IVH as most of them are born preterm. Previous studies showed that the vast majority of preterm infants with CHD had mild grade GMH-IVH. In contrast, our study showed that infant with CHD had a higher risk to develop severe GMH-IVH rather than mild GMH-IVH [19].

Our data revealed that low hematocrit was more associated with severe GMH-IVH. This was also shown in previous studies as they stated that a low hematocrit was associated with severe GMH-IVH in preterm neonates. Moreover, a higher initial hematocrit decreased the incidence of premature GMH-IVH [20,3]. However, it is unclear whether a low hematocrit is considered a risk factor of GMH-IVH or it is low due to bleeding [3].

GMH-IVH may result in injuries to the brain and severe complications, such as hydrocephalus [21]. We found that hydrocephalus with VP shunt was significantly associated with severe GMH-IVH. This implies the importance of discussing the possible prognosis to the families.

5. CONCLUSION

Our study set out that severe GMH-IVH is associated with several maternal and neonatal risk factors. The maternal risk factors that showed association are amnionitis, lower genital tract infection, antenatal infections, GDM, and usage of inotropes. For the neonatal risk factors, APGAR score <7, birth trauma, catecholamines, intubation, asphyxia, resuscitation, abnormal coagulation parameters, congenital heart disease, and low hematocrit were higher in severe GMH-IVH. Regarding the prognosis, hydrocephalus with VP shunt was associated with severe GMH-IVH.

6. APPLICATION

This study highlighted the importance of ultrasonographic grading of GMH-IVH and may help clinicians and healthcare providers to identify the risk factors of severe GMH-IVH that benefits in early prevention and management. Moreover, it might help in prediction of its possible neurodevelopmental outcomes.

7. LIMITATIONS AND RECOMMENDATIONS

The limitations that we met during our research were as follows: (1) since our sample was confined to a single center, it was small; consequently, most of our variables were insignificant. (2) The nature of our study is retrospective; as a result, we faced some difficulties in obtaining data. (3) Long-term neurodevelopmental outcomes were difficult to track. We recommend further studies in a larger sample size including, long-term follow-up for neurodevelopmental outcomes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was approved (reference number: IRB-UGS-2020-01-381) by the institutional review board of the study setting.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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