Research Square

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Intraventricular Hemorrhage in preterm neonates transported to a Tertiary Care facility: Does distance and transport vehicle effect the occurrence of hemorrhage?

Karen Maldonado Leguizamon
karen.maldonado1@peds.ufl.edu
University Of Florida https://orcid.org/0009-0006-3042-7592
Nikolay Bliznyuk
https://orcid.org/0000-0001-7118-7907
Harman Kaur
University Of Florida
Juan Roig
Frederic Phelps
University Of Florida
Daniel Vargas-Boggiano
University Of Florida
Livia Sura
Dhanashree Rajderkar
https://orcid.org/0000-0002-5962-2854
Michael Weiss
https://orcid.org/0000-0002-4567-9286

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Abstract

Background

Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a major morbidity in premature neonates, with higher incidence in outborn infants requiring transport.

Objective

To identify factors associated with high-grade GMH-IVH in outborn preterm neonates transported to UF Health.

Methods

This retrospective, single-center cohort study included 69 outborn neonates diagnosed with IVH between 2016 and 2021. Logistic regression and ANOVA models (parametric and nonparametric) were used to assess associations between transport-related factors and GMH-IVH severity.

Results

Among neonates born at ≤ 30 weeks' gestation, both transport distance and duration were significantly associated with increased risk of high-grade GMH-IVH ($p = 0.01$). Mode of transport was not significantly associated. Lower gestational age and birth weight were also linked to higher GMH-IVH severity ($p < 0.05$).

Conclusion

Transport distance and duration may contribute to GMH-IVH severity in extremely preterm neonates. Early implementation of GMH-IVH prevention bundles at referring hospitals and use of head ultrasound during transport may help mitigate risk and guide early interventions.

1. INTRODUCTION

Although neonatal care for preterm infants born at less than or equal to 30 weeks' gestation has greatly improved over the past several decades, germinal matrix-intraventricular hemorrhage (GMH-IVH) remains a significant cause of morbidity in this population. The severity of GMH-IVH is inversely correlated with gestational age [1]. Recently, a bundle of nursing interventions applied during the first 72 hours postnatally has been shown to reduce the risk of high-grade GMH-IVH, cystic periventricular leukomalacia, and/or mortality in very preterm infants [2, 3, 4, 5]. These bundles typically include

maintaining the head in a midline position, minimizing stimulation, avoiding elevating the feet above the head, and refraining from abdominal examinations [2].

Despite advances in neonatal care, many infants born at less than or equal to 30 weeks' gestation are not delivered in facilities with tertiary or quaternary neonatal intensive care units (NICUs). Consequently, the referring centers often lack the same level of expertise and experience in initial resuscitation and stabilization. Moreover, these infants must be transported, often by ambulance, helicopter, or fixed-wing aircraft, to higher-level NICUs. Transport environments are frequently chaotic, with loud noise, vibration, and multiple bed transfers. Not surprisingly, outborn neonates who require transport exhibit a higher incidence of GMH-IVH. Consistent with published data, since the implementation of a neuroprotection bundle in our unit, 39% of neonates transferred to our center developed high-grade GMH-IVH (Papille Grade III–IV), compared to 14.6% of inborn neonates.

The UF Health NICU serves as a regional referral center for North Central Florida, the Florida Panhandle, and surrounding areas, including parts of Georgia and, occasionally, South Carolina. Transport distances range from less than 10 miles to over 400 miles, utilizing helicopters, fixed-wing aircraft, and ground ambulances.

This study aims to identify factors that are associated with GMH-IVH in preterm infants born at less than or equal to 30 weeks' gestation who require transport to a quaternary NICU. We hypothesize that, after adjusting for known risk factors associated with GMH-IVH (e.g., clinical acuity and gestational age), the severity of GMH-IVH in outborn infants will be associated with transport characteristics, including distance, duration, and mode. Specifically, we anticipate that greater transport distances, prolonged transport times, and air transport will be associated with an increased risk of severe GMH-IVH.

2. MATERIALS AND METHODS:

This single-center, retrospective, observational cohort study was approved by the University of Florida Institutional Review Board with a waiver of informed consent, prior to any data collection. Our NICU at UF Health Shands Hospital is a Level IV unit. Transport of outborn infants referred to UF Health is provided by a dedicated neonatal transport team, which includes neonatal specialists and offers critical stabilization and intensive care during interhospital transfers.

2.1 Study Population

Data was collected on outborn neonates transferred to our Level IV NICU between January 2016 and December 2021. Inclusion criteria were outborn neonates at ≤ 30 weeks' gestational age who were diagnosed with an IVH after transport to UF Health Shands Hospital. Neonates born at greater than 30 weeks' gestation or older than 7 days at the time of transport were excluded.

2.2 Data Collection

All data were retrospectively gathered through review of electronic health records (EPIC), including transport flowsheets, clinical care notes, and laboratory results. Collected variables related to GMH-IVH included the grade of GMH-IVH and the postnatal age at diagnosis. Grade of GMH-IVH was based on review of medical records of HUS done within the first 7 days of life at UF Health Shand's Hospital.

Transport variables included mode of transport (e.g., ground ambulance, helicopter, fixed-wing aircraft), transport distance, transport duration (minutes), and age of transport (hours or days of life).

Additional data were collected to account for potential confounders or effect modifiers, including gestational age, birth weight, mode of delivery, type of respiratory support, steroid administration, need for pressors, resuscitation at birth (CPR), and maternal pregnancy complications.

2.3 Statistical Analysis

The GMH-IVH grade severity was thresholded to create a binary variable with levels low-grade (GMH-IVH grades 1 and 2) and high-grade (GMH-IVH grades 3 and 4) as in our preceding research [6, 7]. Three gestational age (GA) groups were defined by setting GA cutoffs at 24 and 27. To control for gestational age group, analyses were carried out (and compared) for each group separately, as well as across the three groups jointly. Associations between the binary IVH group (used as the response) and the variables of interest (covariates) were investigated using univariate logistic regressions; for a numerical covariate X, this effectively models the probability of the severe IVH as a continuous function of X. Additionally, we investigated the differences between variables of interest (X, now used as the response) across the IVH groups using parametric (t-tests) and nonparametric (Kruskal-Wallis and Wilcoxon) tests whenever X was quantitative [8, 9]. For categorical variables X, we evaluated the associations with the IVH grade using tests for contingency tables (Fisher's exact test and chi-square test). Boxplots were used throughout for visualization.

3. RESULTS

3.1 Patient demographics and study profile.

The study population included 69 outborn neonates born at ≤ 30 weeks' gestation who were transported to the UF Health Neonatal Intensive Care Unit between January 2016 and December 2021 and diagnosed with GMH-IVH by head ultrasound (HUS) within the first 7 days of life. The mean gestational age was 26.4 ± 2.6 weeks, and the mean birth weight was 1028 ± 368 grams. Neonatal characteristics were stratified by GMH-IVH severity, categorized as low-grade (Grades 1 and 2) or high-grade (Grades 3 and 4), as determined by HUS (Table 1). Overall, 36% of neonates were diagnosed with high-grade GMH-IVH, while 63.2% had low-grade GMH-IVH (Fig. 1).

Table 1
Characteristics of the Sample and Demographic Data

Gestational Age, median, weeks	**Low Grade GMH-IVH n = 42**	**High Grade GMH-IVH n = 27**	**p-Value**
	28 (22,30)	**24 (22,30)**	**0.0023**
Birth Weight, Median, gr	1137 (555,1750)	715 (450,1690)	0.002
Mode of Delivery, n (%)			
NVD	18 (42)	12(44)	0.65
CS	24 (58)	15 (56)	0.6
Emergent Delivery, n (%)	16(38)	9(33.3)	0.79
CPR at Delivery, n (%)	6 (13)	4 (14)	0.88
Pressor Requirement, n (%)	10(23)	8(29)	0.4
Advance Airway at Delivery, n (%)	32(76)	22(81)	0.14
Prenatal Betamethasone, n (%)	25(59)	9(33.3)	0.05
Age of Diagnosis (Days)	7 (0.5,73)	4 (0.5,18)	0.21
Shunt Placement	0(0)	3(9)	0.05

Birth weight was significantly lower in the high-grade GMH-IVH group (p = 0.002). The mode of delivery was similar between groups: 18 neonates (42%) in the low-grade GMH-IVH group and 12 neonates (44%) in the high-grade group were delivered via normal vaginal delivery (p = 0.65). In the low-grade GMH-IVH group, 25 neonates (59%) received at least one dose of prenatal betamethasone, compared to 9 neonates (33.3%) in the high-grade group. No significant differences were observed between groups with respect to mode of delivery, pressor requirements, or need for cardiopulmonary resuscitation (CPR) at birth. Additional clinical characteristics are presented in Table 1.

3.2 Comparison of transport characteristics in neonates with high-grade GMH-IVH vs neonates with low-grade GMH-IVH.

Data on transport distance (return leg, in miles), transport duration (return leg, in minutes), and primary mode of transport (ambulance, helicopter, or fixed-wing aircraft) were collected for both groups. A significant association was found between transport duration and the occurrence of high-grade GMH-IVH in preterm neonates born at ≤ 30 weeks' gestation with the median transport time for neonates with low-grade GMH-IVH being 26.5 minutes (IQR 16.5,45.5), compared to 42 minutes (IQR 17,62) in those with high-grade GMH-IVH (p = 0.04) (Fig. 1A).

A significant association was observed between transport distance (return leg) and the occurrence of high-grade GMH-IVH, with a median transport distance of 36 miles (IQR 6.7, 48) for neonates with low-grade GMH-IVH compared to 42.5 miles (IQR 7.7,151) for those with high-grade GMH-IVH (p = 0.02) (Fig. 1B).

Transport mode was analyzed across four categories: ambulance, helicopter, fixed-wing aircraft, and mixed air–ground transport. Of the 41 neonates transported by ambulance, 25 had low-grade GMH-IVH and 16 had high-grade GMH-IVH. Among the 25 neonates transported by helicopter, 17 had low-grade and 8 had high-grade GMH-IVH. The single neonate transported by fixed-wing aircraft was diagnosed with high-grade GMH-IVH. Two neonates required mixed-mode transport (air and ground), both of whom developed high-grade GMH-IVH. Despite these observed distributions, there was no statistically significant association between mode of transport and the incidence of high-grade GMH-IVH (Table 2).

Table 2
Association between transport (Time, Distance and Type) with grade of GMH-IVH

Time of transport, Median (min)	**Low Grade GMH-IVH* (n = 42)**	**High Grade GMH-IVH* (n = 27)**	**p-Value**
	26.5 (10,151)	**42(6.4,400)**	**0.03**
Distance of transport (Miles)	36.2 (6.4,128)	42.05(13,153)	0.013
Type of Tranport, n (%)			0.88
Helicopter	17 (40.4)	8 (29.6)	
Fixed-Wing Aircraft	0	1 (3.7)	
Ambulance	25 (59.5)	16 (59)	
Mixed (Air+Ground)	0	2 (7.4)	

3.3 Comparison of transport characteristics in neonates with high-grade GMH-IVH versus neonates with low-grade GMH-IVH stratified into groups based on gestational age.

Three gestational age (GA) groups were defined using cutoffs at 24 and 27 weeks (First group: 22–24 weeks GA, n = 24; Second group: 25–27 weeks GA, n = 14; Third group: 28–30 weeks GA, n = 31). Analysis by GA group demonstrated a significant association between transport duration and high-grade GMH-IVH in neonates born at 28–30 weeks GA (p = 0.01), whereas no significant associations were observed in the 22–24 weeks GA group (p = 0.22) or the 25–27 weeks GA group (p = 0.25) (Fig. 2A).

Similarly, transport distance was significantly associated with high-grade GMH-IVH in the 28–30 weeks GA group (p = 0.01) but not in the 22–24 weeks (p = 0.30) or 25–27 weeks (p = 0.50) groups (Fig. 2B).

Transport mode was not significantly associated with high-grade GMH-IVH in any GA group (22–24 weeks, p = 0.28; 25–27 weeks, p = 0.68; 28–30 weeks, p = 0.27).

3.4 Comparison of gestational age and birthweight in neonates with high-grade GMH-IVH versus neonates with low-grade GMH-IVH

Gestational age and birth weight were analyzed in relation to GMH-IVH severity. The median gestational age was 28.5 weeks (IQR 25,30) in neonates with low-grade GMH-IVH and 24 weeks (IQR 23,28) in those with high-grade GMH-IVH ($p = 0.0034$) (Fig. 3A). Similarly, the median birth weight was 1137 grams (IQR:790,1507) in the low-grade group and 715 grams (IQR:620,1160) in the high-grade group. Birth weight was also significantly associated with the incidence of high-grade GMH-IVH ($p = 0.0039$) (Fig. 3B).

3.5 Comparison of delivery characteristics and pressors requirements in neonates with high-grade GMH-IVH vs Neonates with low-grade GMH-IVH

Additional perinatal factors were assessed for their association with GMH-IVH severity, including cardiopulmonary resuscitation (CPR) at delivery, emergent delivery, need for advanced airway management at birth, and requirement for inotropic support. The mode of delivery was similar between groups. Emergent delivery occurred in 16 neonates (38%) with low-grade GMH-IVH and in 9 neonates (33%) with high-grade GMH-IVH, with no significant association observed ($p = 0.79$; Table 1). Although a higher proportion of neonates with high-grade GMH-IVH required CPR at delivery (14%) and advanced airway management (81%) compared to those with low-grade GMH-IVH (13% and 76%, respectively; Fig. 4), these differences were not statistically significant ($p = 0.88$ and $p = 0.14$, respectively).

Similarly, no significant association was observed between inotrope requirement during hospitalization and GMH-IVH severity ($p = 0.40$). Inotropic support was required in 10 neonates (23%) with low-grade GMH-IVH and 8 neonates (29%) with high-grade GMH-IVH. Stratified analysis by GA group also revealed no significant associations (22–24 weeks GA, $p = 0.40$; 25–27 weeks GA, $p = 0.10$; 28–30 weeks GA, $p = 0.54$).

4. DISCUSSION

Multiple studies have demonstrated that outborn neonates requiring transport have a higher incidence of GMH-IVH. In our study, we specifically evaluated transport-related factors that may contribute to the risk of GMH-IVH in preterm infants transferred to UF Health for specialized care. Identifying these factors is a critical step toward developing neuroprotective strategies aimed at mitigating transport-associated brain injury in neonates born at Level I and II facilities. We found a significant association between both transport distance and duration and the occurrence of high-grade GMH-IVH. However, no significant association was observed between the mode of transport (helicopter, fixed-wing aircraft, or ground ambulance) and the incidence of high-grade GMH-IVH. A study conducted at St. Louis Children's Hospital between 2009 and 2015 evaluated very low birth weight (VLBW) infants (gestational age < 32 weeks and/or birth weight < 1500 g) transported within 24 hours of birth found no association between GMH-IVH and the type of transport vehicle or the distance traveled [10]. Similarly, in our study, we found no significant association between the mode of transport (helicopter, fixed-wing, or ambulance) and the

occurrence of high-grade GMH-IVH. However, unlike the St. Louis study, we did observe a significant association between the distance traveled and the occurrence of high-grade GMH-IVH. Specifically, longer transport distances (return leg) were associated with a higher incidence of severe hemorrhage. It is important to mention the population included in St Louis Hospital study included neonates whose gestational age was less than 32 weeks and/or birth weight < 1500 g [10], while our study included neonates born at ≤ 30 weeks' gestation.

Antenatal steroid administration is a well-established neuroprotective intervention. A study from the United Kingdom demonstrated that, even after adjustment for antenatal steroid use in a multivariable regression model, transported infants born at less than 28 weeks' gestation remained at increased risk for severe IVH [11]. In our cohort, 59% of neonates with low-grade GMH-IVH received antenatal steroids, compared to 33.3% of those with high-grade GMH-IVH. Although this difference was not statistically significant, the observed trend suggests a potential protective effect of antenatal steroids. A larger sample size may be necessary to determine whether this association reaches statistical significance.

While several studies have reported higher rates of GMH-IVH in transported (outborn) infants compared to inborn infants [10, 11, 12, 14, 16, 17], few have explored the underlying factors contributing to this increased risk. In our study, we examined specific transport-related variables; transport distance, duration, and mode of transport, as potential contributors to the higher incidence of high-grade GMH-IVH in outborn neonates. We also evaluated non-transport-related clinical factors, including gestational age and birth weight. Our analysis demonstrated a significant association between lower gestational age, lower birth weight, and the development of high-grade GMH-IVH.

When the data were analyzed by gestational age group, some subgroup differences reached statistical significance (e.g., duration and distance of transport with high-grade GMH-IVH in the 28–30 weeks GA group), whereas others did not (e.g., mode of transport in the 22–24 weeks and 25–27 weeks GA groups). It is important to note that the smallest GA groups (22–24 weeks and 25–27 weeks) had the lowest sample sizes, whereas the group with significant findings (28–30 weeks) had the largest sample size. Similar to the analysis of antenatal steroid use, a larger sample size may be required to determine whether these associations achieve statistical significance in the lower GA subgroups. It is important to note the observed association between both transport duration and transport distance and the occurrence of high-grade GMH-IVH, particularly among neonates born at 28–30 weeks' gestational age. These findings support the hypothesis that the transport environment itself may contribute to an increased risk of GMH-IVH. This observation is consistent with findings reported by Shirpley et al. from the University of Nottingham, United Kingdom, in which preterm infants born at < 32 weeks' gestation who were transported within the first 72 hours of life demonstrated a higher risk of early severe intraventricular hemorrhage compared with inborn neonates, even in the presence of antenatal corticosteroid exposure [11].

A study from Slovenia identified differences in physiological stress markers, specifically heart rate and leukocyte count, when comparing transport modalities. Infants transported by ground during the day

exhibited significantly higher heart rates and leukocyte counts compared to those transported at night or by helicopter during the day, suggesting increased physiological stress associated with daytime ground transport. However, the study did not investigate the underlying causes of these hemodynamic fluctuations [12]. In a separate study by Gajendragadkar et al. and another study by Blaxter et al the effects of vibration during ground ambulance transport were evaluated [13, 15]. Although the use of gel mattresses, alone or in combination with foam mattresses, reduced vibration amplitude, no mattress configuration completely attenuated the vibrations experienced during transport [13]. These findings highlight substantial differences in the physical environment across transport modalities, particularly ground transport, which may contribute to stress and hemodynamic instability in neonates. The pathophysiology of GMH-IVH in transported infants is likely multifactorial, with the transport environment playing a significant role. A critical gap remains in understanding the incidence and mechanisms of transport-associated injury across different transport methods. Further investigation is needed to elucidate these mechanisms and to develop targeted strategies aimed at reducing the risk of adverse outcomes in outborn neonates.

A key strength of this study is the focused analysis of transport-related risk factors contributing to the development of GMH-IVH in preterm infants. Specifically, we evaluated transport distance, duration, and mode of transport, while also adjusting for relevant clinical variables including gestational age, birth weight, antenatal steroid exposure, mode of delivery, CPR at birth, intubation at delivery, use of invasive mechanical ventilation, and inotropic support. However, the study is limited by its sample size, with only 69 transported infants included. This may have limited our ability to detect statistically significant associations, such as the observed trend between antenatal steroid administration and reduced risk of high-grade GMH-IVH. Larger studies are needed to further explore these associations. Another limitation is the timing of cranial imaging; head ultrasounds with finding of GMH-IVH were performed in average at 8 days of life of the neonates included in the study; after arrival at our institution, making it difficult to determine whether IVH occurred before, during, or after transport. This highlights the potential value of incorporating head ultrasound (HUS) capabilities within neonatal transport teams to help determine the timing of hemorrhage and facilitate earlier neuroprotective interventions.

5. CONCLUSION

In conclusion, these findings suggest that transport-related stressors may contribute to the risk of severe hemorrhage in this vulnerable population. This study evaluated the association between transport characteristics and the occurrence of GMH-IVH in preterm infants. Among neonates born at ≤ 30 weeks' gestation, we found a significant association between GMH-IVH severity and both transport distance and duration population. To mitigate this risk, future research should focus on optimizing the neonatal transport process and identifying modifiable risk factors.

Furthermore, the observed association between lower gestational age and increased GMH-IVH severity highlights the need for early neuroprotective strategies. Implementing GMH-IVH prevention bundles at

smaller referring facilities may provide a critical opportunity to reduce the incidence of high-grade hemorrhages prior to transport, thereby improving outcomes for outborn preterm neonates.

Declarations

Statement of financial support: The authors declare no competing financial interests.

Disclosure statement: The author declares that (s)he has no relevant or material financial interests that relate to the research described in this paper.

Category of study: Original Research

Consent Statement: Study was approved by the University of Florida Institutional Review Board with a waiver of informed consent. The study was performed in accordance with the Declaration of Helsinki.

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Author Contributions:

KM and MW conceptualized and designed the study, collected data and carried out initial data analysis, and drafted the manuscript. MW critically reviewed and revised the manuscript. NB conceptualized study, carried out data analysis, critically reviewed and revised the manuscript. HK, JCR, FP, DV, LS, DR conceptualized and designed the study, critically reviewed and revised the manuscript

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Figures

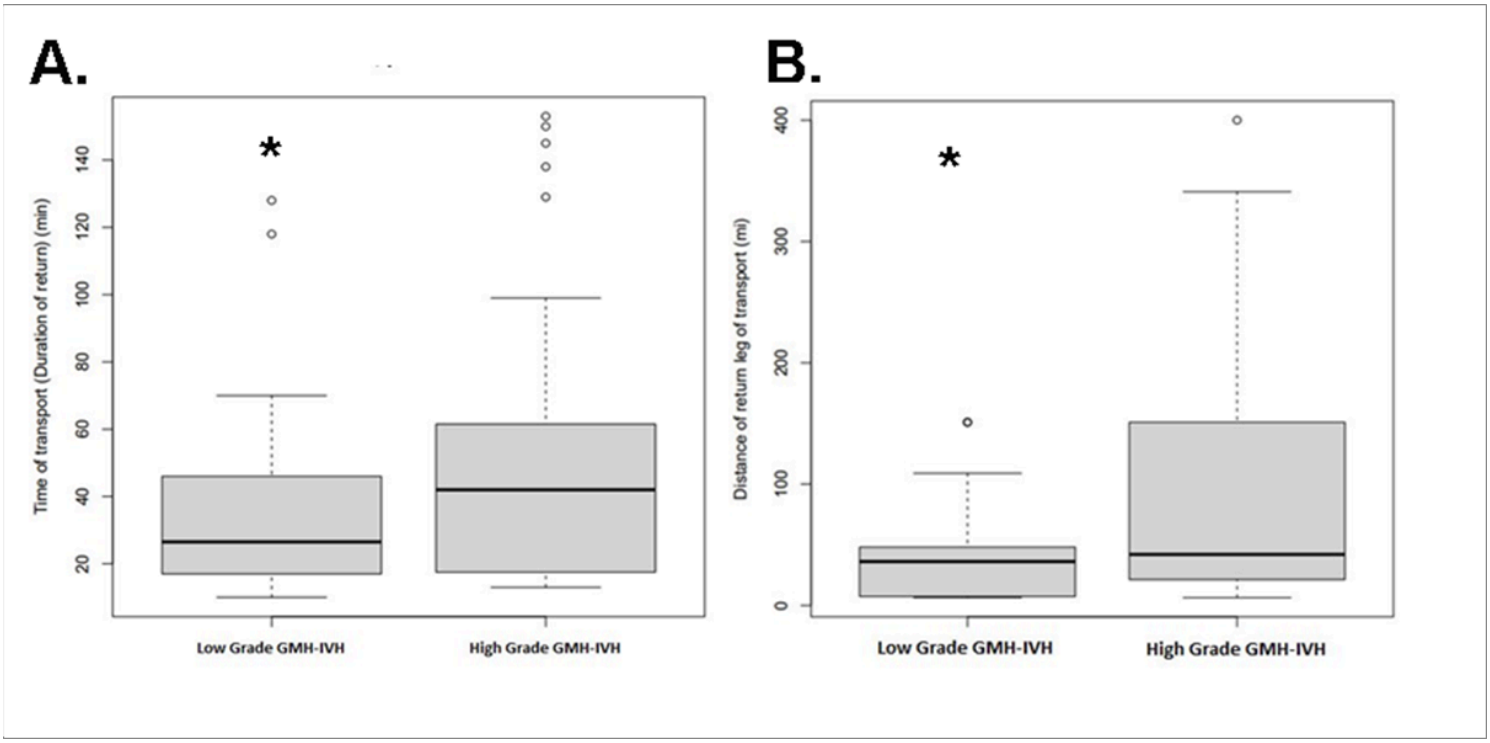


Figure 1

Transport Time and Distance in Outborn Neonates With Low- Versus High-Grade GMH-IVH. (A) Comparison of transport time among outborn neonates with low-grade versus high-grade germinal matrix–intraventricular hemorrhage (GMH-IVH) (p = 0.03).
(B) Comparison of transport distance among outborn neonates with low-grade versus high-grade GMH-IVH (p = 0.01).

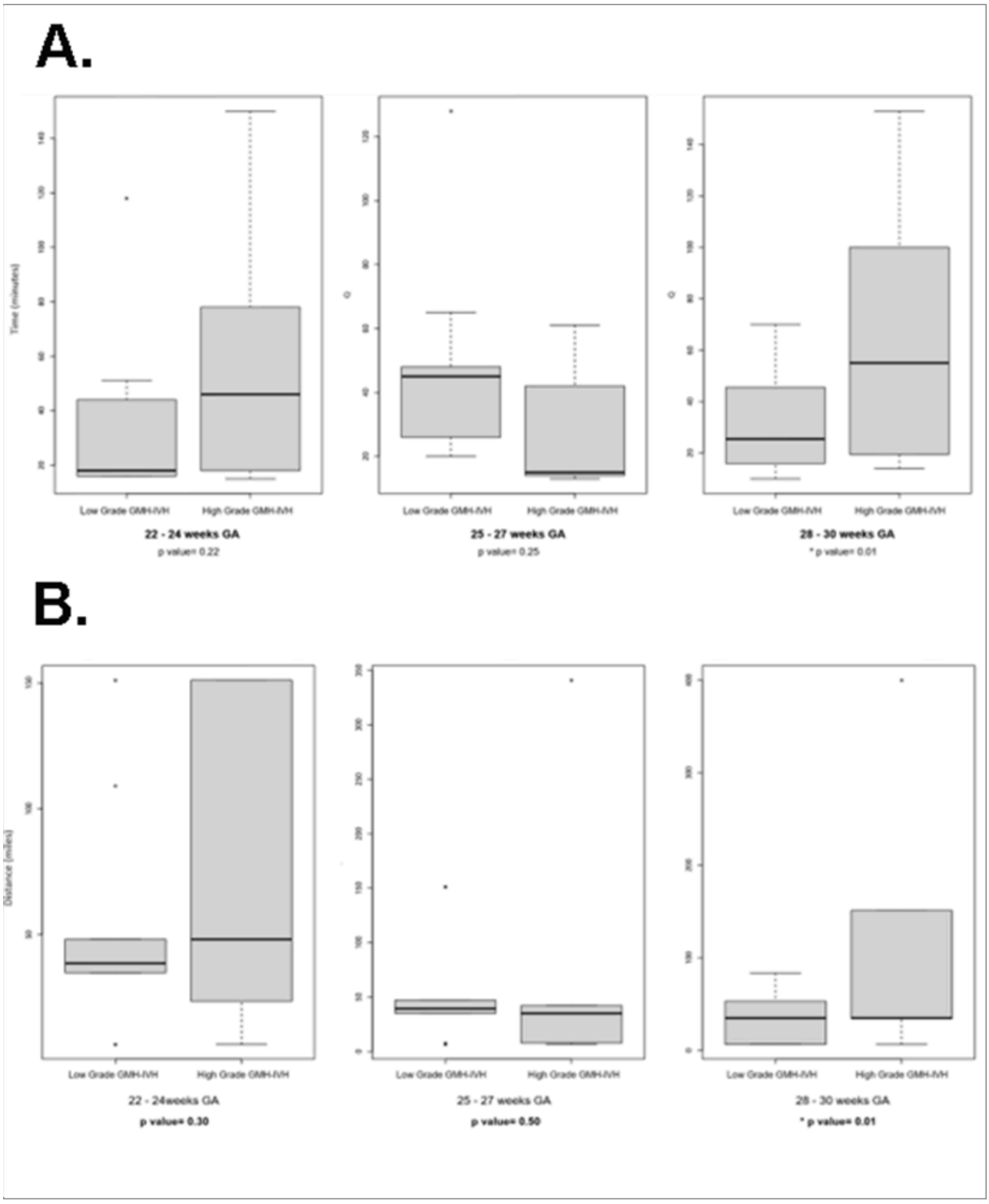


Figure 2

Gestational Age–Stratified Transport Time and Distance in Outborn Neonates With Low- Versus High-Grade GMH-IVH. (A) Comparison of transport time stratified by gestational age in outborn neonates with low-grade versus high-grade GMH-IVH.
(B) Comparison of transport distance stratified by gestational age in outborn neonates with low-grade versus high-grade GMH-IVH.

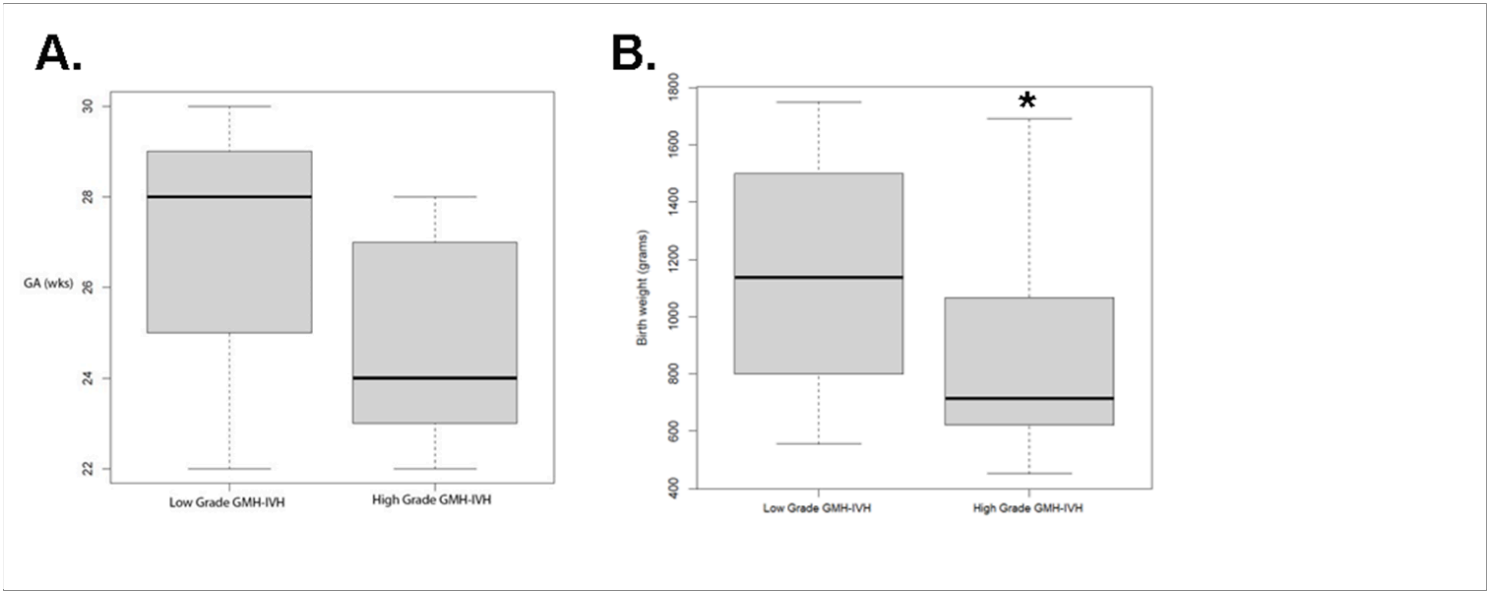


Figure 3

Gestational Age and Birth Weight Differences Between Outborn Neonates With Low- and High-Grade GMH-IVH. (A) Comparison of gestational age in outborn neonates with low-grade versus high-grade GMH-IVH (p = 0.0023). (B) Comparison of birth weight in outborn neonates with low-grade versus high-grade GMH-IVH (p = 0.002).

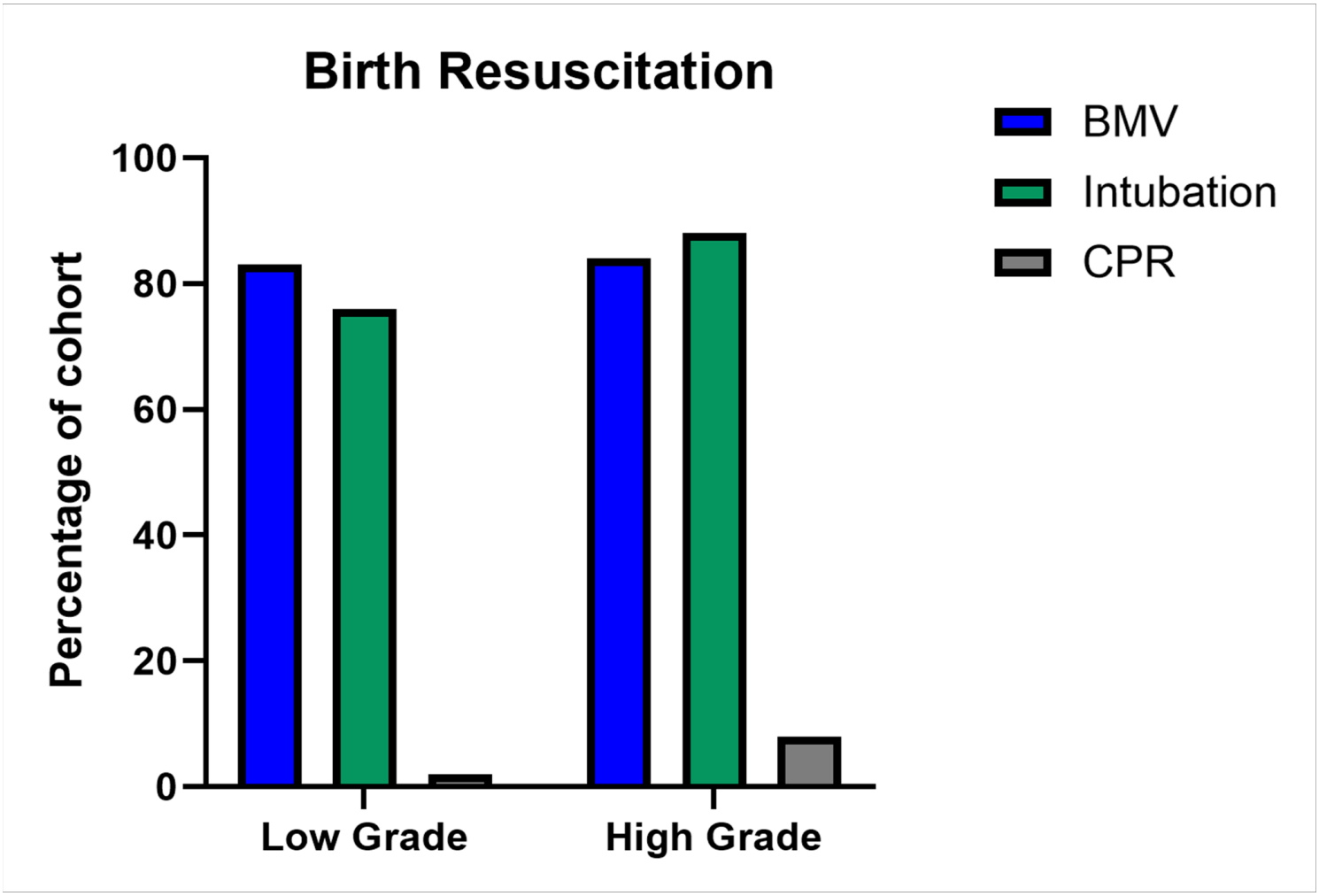


Figure 4

Delivery Room Resuscitation Characteristics in Outborn Neonates With Low- Versus High-Grade GMH-IVH. Comparison of delivery room resuscitation characteristics in outborn neonates with low-grade versus high-grade GMH-IVH.