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Intraventricular hemorrhage among very low birth weight infants in a South African cohort: a retrospective study of trends & short-term outcomes

Gloria Akuamoah-Boateng[1], Troy D. Moon[2], Gustavo Amorim[3], Rossella Bandini[4] and Daynia Ballot[4*]

Abstract

Background Intraventricular hemorrhage (IVH) is one of the critical complications of prematurity with severe forms, associated with irreversible brain damage. We hypothesized that infants born in South Africa may have different modifiable risk factors and outcomes for severe IVH compared to that reported in studies in neonatal populations in higher resource settings. Our study aimed to define the prevalence of IVH with further characterization of risk factors based on IVH severity, with the goal of providing guidance on modification of protocols for the management and prevention of severe IVH.

Methods This was a retrospective cohort study of very low birth weight infants admitted to the NICU of Charlotte Maxeke Academic Hospital in Johannesburg (CMJAH) from January 1, 2016, to December 31, 2020. Our study included all infants, weighing less than 1500 g, admitted to the hospital regardless of place of birth who had had at least one cranial ultrasound in the first week of life. Infants with other intracranial malformations than IVH, birth weights greater than 1500 g, and significant amount of missing data were excluded from the study. Maternal and neonatal information were extracted from an existing neonatal database and analyzed using R statistical software. Multivariable logistic regressions were used to investigate risk factors associated with increased odds of having IVH and its impact on mortality.

Results A total of 2,217 very low birthweight (VLBW) infants admitted to the NICU at CMJAH during the study period met eligibility criteria. Median gestational age (GA) and birth weight (BW) were 28 weeks and 900 g, respectively. IVH prevalence was 22.6% with high grade IVH (grade 3 or 4) accounting for 6.8% of the cases. Infants with high grade IVH had 4-fold increase odds of dying (OR = 4.843, 95% CI = 2.984; 7.86, $p < 0.001$). Acidosis was associated with increased odds of high grade IVH (OR = 2.27; 95%CI: 1.42; 3.64). Similarly, infants with early onset sepsis had higher odds of high grade IVH (OR = 2.22; 95%CI: 1.04; 4.75).

Conclusions Acidosis and sepsis had a significant association with the occurrence of severe IVH. Antenatal steroids showed an association with occurrence and severity suggesting it may play an important role, but did not reach

*Correspondence:
Daynia Ballot
Daynia.Ballot@wits.ac.za

Full list of author information is available at the end of the article

significance so must be further evaluated. Having severe IVH substantially increased the odds of death. Based on these findings, future directions could include collaborative QI projects with obstetricians to improve uptake of antenatal steroids and promotion of neonatology led QI projects to reduce risk factors associated with severe IVH.

Keywords Intraventricular hemorrhage, Very low birth weight, Prematurity, South Africa

Background

Intraventricular hemorrhage (IVH) is a major cause of morbidity and mortality in preterm infants. It has been estimated that about one-third of preterm infants are affected by IVH with the highest incidence in infants born less than 26 weeks' gestation, with risk being inversely proportional to gestational age. The prevalence of IVH in studies in sub-Saharan Africa has ranged from 16.2 to 34.2% [1]. The global incidence of severe IVH has been reported as ranging from 5 to 52% [2].

Premature infants have an inherent risk of IVH due to poor cerebral autoregulation and fragile germinal matrix vasculature. This risk is compounded by a complex interplay of prenatal and postnatal factors [3]. Multiple prenatal and postnatal factors have been implicated including: mode of delivery, lack of antenatal steroids and magnesium sulphate, chorioamnionitis, hypoglycemia, hypothermia, electrolyte abnormalities, acidosis and hemodynamic instability [3–8]. Most germinal matrix-intraventricular hemorrhages (GM-IVH) occur within the first week of life and clinical presentation ranges from asymptomatic to saltatory presentation with insidious onset of symptoms or catastrophic bleed with acute deterioration [9]. Radiologic classification is based on the extent of bleed into the ventricles, the presence of ventricular dilatation and parenchymal hemorrhage [5, 6]. Two widely used classifications are the Papile or Volpe classifications and most outcomes have been predicted based on these classifications [5, 6].

Despite improving survival of preterm infants, mortality from IVH remains high, ranging from 30 – 60% [7]. About 50% of survivors with IVH develop cerebral palsy, cognitive deficits, behavioral disorders, posthemorrhagic ventricular dilatation (PHVD), or a combination of these outcomes with some degree of neurodevelopment abnormalities reported in even less severe forms of IVH [8].

IVH has severe and irreversible sequalae and management is supportive; hence prevention is crucial. Factors protective against IVH include administration of antenatal steroids; prompt transfer of pregnant women in preterm labor to a tertiary facility; and optimization of delivery room practices such as maintaining normothermia, ensuring adequate ventilation, and avoiding hypotension [10].

Unfortunately, these protective factors and practices may not always be readily available in resource limited settings which may increase the incidence of IVH in such settings. This study aimed to characterize risk factors associated with severe IVH in very low-birthweight (VLBW) infants in Johannesburg, South Africa. We strive to further guide modification of existing neonatal protocols for management and prevention of severe IVH.

Hypothesis

We hypothesized that infants born in South Africa may have different modifiable risk factors and outcomes for severe IVH compared to those reported in studies in neonatal populations in higher resource settings.

Methods

Study design

This was a single center retrospective cohort study of VLBW infants, weighing less than 1500 g admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa from January 1, 2016, to December 31, 2020.

Setting and patient characteristics

CMJAH is a referral hospital and admits inborn and out born infants from surrounding hospitals and clinics. The study population included all infants, weighing less than 1500 g, admitted to the hospital regardless of place of birth. All infants included in the study had had at least one cranial ultrasound in the first week of life. Infants with other intracranial malformations than IVH, birth weights greater than 1500 g, and significant amount of missing information were excluded from the analysis.

Data collection

Information for this study included maternal and neonatal demographic and clinical characteristics which were extracted from a pre-existing CMJAH Neonatal database housed on a local Research Electronic Data Capture (REDCap) server hosted by University of Witwatersrand [11, 12]. Per the unit's protocol, all VLBW infants were required to have had at least one cranial ultrasound before 28 days of life, ideally within the first 7 days of life. Transcranial ultrasounds were performed and interpreted by attending neonatologists and neonatology fellows at CMJAH. Most out born patients had their transcranial ultrasounds done in our facility per our unit protocol.

Maternal data extracted from the database for analysis included maternal age, gravidity, and parity, mode of delivery, antenatal attendance, antenatal steroid and

magnesium sulphate exposure, co-morbidities such maternal hypertension, diabetes, and maternal infections i.e., chorioamnionitis, maternal HIV, and tuberculosis.

Infant characteristics extracted from the database for analysis included: baseline characteristics such as birthweight; gestational age; sex; intrapartum events: such as APGAR scores and need for delivery room resuscitation; and post-natal events including respiratory support, metabolic abnormalities, early onset sepsis and transcranial ultrasound findings, length of stay, and outcome at discharge.

The definitions of terms used are outlined below in Table 1.

Statistical analysis

Maternal information as well as neonatal demographic and clinical characteristics were extracted from the existing neonatal database and were de-identified. Continuous variables were summarized using means and median (interquartile ranges) and were compared using the Mann-Whitney U test. Categorical variables were compared via Chi-square tests. Infants were subcategorized by gestational age and birthweight for analysis. Prevalence was computed as the proportion of infants diagnosed with IVH at baseline. A multivariable logistic regression analysis, now restricted to patients with IVH only, was used to explore risk factors associated with high grade IVH, adjusting for birthweight, gestational age in weeks, sex, maternal hypertension, maternal HIV status, mode of delivery, place of birth, antenatal steroids use, delivery room resuscitation, ventilation, acidosis, early onset sepsis, hypoglycemia, and blood transfusion. Variables included in the final model were selected from the pre-existing literature and clinical knowledge. Information was missing for the mode of delivery (5.2%), place of birth (0.6%), maternal hypertension (14.8%), antenatal steroid use (19.8%), resuscitation status (14.4%), acidosis (0.4%), early onset sepsis (4.0%), hypoglycemia (0.4%), and need for transfusion (1.8%).

We used multiple imputation via Markov chains, with 20 imputations, to impute all missing values [15]. Final results, e.g., odds ratios (ORs) and 95% confidence intervals (CI), were obtained via Rubin's rule in order to properly account for multiple imputation [16]. A p-value < 0.05 was interpreted as statistically significant. All statistical analyses were performed using R-programming language software version 4.3.1 [17].

Table 1 Table of definitions

Term	Definition
Out born patients	Patients born at home or referral hospitals
Hypothermia	Temperature less than 36.5 degrees Celsius measured within 1 h of admission
Hypoglycemia	Serum glucose less than 2.6mmol/L
Early onset sepsis	Bacterial sepsis on or before day three of life
Patent ductus arteriosus (PDA)	Hemodynamically significant PDAs requiring pharmacologic intervention or PDA ligation.
Metabolic acidosis*	Base deficit less than minus 16
IVH Grade (Papile Classification)	
Grade 1	Hemorrhage limited to the germinal matrix
Grade 2	Hemorrhage within the ventricular system without ventricular distension
Grade 3	Hemorrhage in the ventricles with associated dilatation
Grade 4	IVH with parenchymal extension

* Reference [13] and [14] For analysis, the grades were subcategorized into low-grade referring to Grades 1 and 2 and high-grade referring to grades 3 and 4 IVH. Neonates with records of cranial ultrasound performed but no recorded findings were assumed to have normal ultrasounds

Results

Prevalence of IVH

A total of 2,217 VLBW infants were admitted into the NICU at CMJAH during the study period and met eligibility criteria. IVH was defined as a positive result on ultrasound. If ultrasound was performed but no abnormal ultrasound finding was recorded, we counted that child as negative for IVH As such the prevalence of IVH in our population was 22.6% (502/2,217).

Median gravidity and parity were two and one, respectively. The median gestational age was 28 weeks, with a significantly higher proportion of high grade IVH among children in the < 28-week gestational age category (p-$value < 0.001$). Median birth weight was lower for those infants classified as high grade IVH (990 g) vs. those with lower grade IVH (1,035 g) (p-$value < 0.001$). No differences in IVH grade were seen by gender or place of birth. Overall, the median length of NICU stay was 26 days and 44% of all children with IVH died. A statistically significant lower length of NICU stay was seen for newborns with high grade IVH (13 days) compared to low grade IVH (39 days), presumably due to the higher proportion of deaths seen in the high grade IVH (70%) compared to those with low grade IVH (33%) ($p < 0.001$) (Table 2).

Mortality

We further assessed risk factors for high mortality and found a fourfold increase of mortality with increased IVH severity. Inborn patient status, birthweight and acidosis were significantly associated with high mortality (Table 3).

Risk factors and their association to IVH severity

Overall, for newborns with IVH, antenatal care attendance by their mothers was 74.3%, with no statistically significant difference in severity of IVH based on attendance. Comparing maternal risk factors with their association to the severity of the newborn's IVH status, a

Table 2 Demographic characteristics of VLBW infants with IVH at Charlotte Maxeke Johannesburg Academic Hospital

Demographics	Overall	High Grade	Low Grade	No IVH	*P*-value
	N **= 2217**	***N*** **= 150**	***N*** **= 352**	***N*** **= 1715**	
Age(mother)	29.0 [24.0;34.0]	28.0 [24.0;32.0]	29.0 [24.0;33.0]	29.0 [24.0;34.0]	0.377
Race (%):					0.897
Asian	2 (0.09)	0 (0.0)	0 (0.0)	2 (0.1)	
Black	2121 (96.9)	143 (97.3)	345 (98.0)	1633 (96.7)	
Colored	24 (1.1)	1 (0.7)	3 (0.9)	20 (1.2)	
Indian	14 (0.6)	1 (0.6)	0 (0.0)	13 (0.8)	
Other	6 (0.2)	0 (0.0)	1 (0.3)	5 (0.3)	
White	21 (0.9)	2 (1.4)	3 (0.8)	16 (0.9)	
Gravidity(median [IQR])	2.0 [2.0;3.0]	2.0 [2.0;3.0]	2.0 [2.0;3.0]	2.0 [2.0;3.0]	0.715
Parity (median [IQR])	1.0 [0.0;2.0]	1.0 [0.0;2.0]	1.0 [0.0;2.0]	1.0 [0.0;2.0]	0.937
Gestational age(weeks)(median [IQR])	29.0 [27.0;30.0]	28.0 [26.0;29.0]	28.0 [27.0;30.0]	29.0 [27.0;31.0]	< 0.001
Gestational age weeks (%)					.
<= 28	1045 (47.1)	107 (71.3%)	194 (55.1%)	744 (43.4%)	
28–32	954 (43.0)	40 (26.7%)	134 (38.1%)	780 (45.5%)	
Missing'	38 (1.7)	1 (0.67%)	5 (1.4%)	32 (1.9%)	
Birth weight in grams (median [IQR])	1100 [900;1300]	990 [880;1118]	1035 [890;1220]	1140 [900;1330]	< 0.001
Birth weight in grams (%)					.
<= 750	238 (10.7)	9 (6.0)	23 (6.5)	206 (12.0)	
750–1000	613 (27.6)	75 (50.0)	142 (40.3)	396 (23.1)	
> 1000	1360 (61.3)	66 (44.0)	187 (53.1)	1107 (64.5)	
'Missing'	6 (0.3)	0 (0.0)	0 (0.0)	6 (0.3)	
Sex (%)					0.497
female	1147 (51.7)	74 (49.3)	184 (52.3)	889 (51.8)	
male	1059 (47.8)	75 (50.0)	167 (47.4)	817 (47.6)	
intersex	4 (0.2)	1 (0.7)	1 (0.3)	2 (0.1)	
'Missing'	7 (0.3)	0 (0.0)	0 (0.0)	7 (0.4)	
Place of birth (%)					.
Inborn	1737 (78.3)	108 (72.0)	261 (74.1)	1368 (79.8)	
Out born	463 (20.9)	40 (26.7)	91 (25.9)	332 (19.4)	
'Missing'	17 (0.7)	2 (1.3)	0 (0.0)	15 (0.8)	
Length of stay (median [IQR])	26.0 [8.0;45.0]	13.0 [5.0;46.0]	39.0 [19.5;58.5]	25.0 [7.00;42.0]	< 0.001
Outcome (%)					.
Died	731 (33.0)	105 (70.0)	116 (33.0)	510 (29.7)	
Discharged	1307 (59.0)	40 (26.7)	215 (61.1)	1052 (61.3)	
Transferred(%)	173 (7.8)	5 (3.3)	21 (5.9)	147 (8.6)	
'Missing'	6 (0.3)	0 (0.0)	0 (0.0)	6 (0.4)	
Age at death (median [IQR])	5.0 [2.0;15.0]	8.0 [4.0;16.0]	16.0 [8.0;29.5]	3.0 [1.0;10.0]	< 0.001

statistically significant higher proportion of newborns that were classified as having low grade IVH, had mothers with hypertension during pregnancy ($p = 0.034$). Otherwise, there were no statistically significant differences in IVH severity based on maternal diabetes, HIV infection, or TB infection during pregnancy. Among mothers who received antenatal steroids, a higher proportion of their newborns were classified as having low grade IVH compared to high grade ($p = 0.034$). Finally, we found statistically significant differences in IVH severity based on the mode of delivery. The proportion of infants with high grade IVH was significantly higher in those delivered vaginally. (Table 4).

Among children with IVH, 69.3% required delivery room resuscitation. Infants with high grade IVH had a statistically significant higher occurrence of early onset sepsis and acidosis. (Table 5).

A multivariable logistic regression analysis was used to investigate risk factors associated with higher odds of having a high grade IVH. For the multivariable analysis we removed two infants of intersex gender, so the final sample was reduced to 500 infants (Table 6). Infants with acidosis had a more than two-fold higher odds of having a high grade IVH compared to low grade IVH (OR = 2.274; 95%CI: 1.422; 3.636). Similarly, infants with early onset sepsis had a more than two-fold higher odds of having high grade IVH (OR = 2.266; 95%CI: 1.055;

Table 3 Multivariable regression analysis for risk factors associated mortality

Variables	OR	CI	*p*-value
Severe IVH	4.780	2.886; 7.916	< 0.001
Birth Weight > 1000 g	0.108	0.039; 0.294	< 0.001
Birth Weight < 1000 g	0.344	0.136; 0.870	0.025
Male Sex	1.252	0.796; 1.968	0.334
Vaginal delivery	0.996	0.583; 1.703	0.989
Inborn	0.520	0.288; 0.938	0.035
Antenatal Steroids	1.855	1.115; 3.087	0.053
Maternal Hypertension	0.766	0.418; 1.403	0.438
Maternal HIV status	1.101	0.677; 1.791	0.705
Delivery room resuscitation	0.630	0.357; 1.112	0.184
Acidosis	6.047	3.354; 10.903	< 0.001
Early onset sepsis	2.318	0.923; 5.821	0.08
Hypoglycemia	1.792	0.969; 3.315	0.065

4.868). Although maternal receipt of antenatal steroids was associated with a reduction in the odds of having high grade IVH in univariable analysis, it did not achieve statistical significance at the 5% level after adjusting for other covariates (OR = 0.704; 95% CI: 0.445; 1.112).

Similarly, infants with hypoglycemia at baseline had a 39% reduction in the odds of having high grade IVH compared to infants with normal levels of glucose at baseline (OR = 0.61; 95%CI:0.33; 1.12). This reduction, however, was not statistically significant.

Discussion

Our study sought to determine the prevalence of IVH, and associated risk factors based on IVH severity among VLBW infants. The overall prevalence of IVH in our study population was 22.6%. This is lower than what our same institution reported in 2017 (prevalence of 26.7%) possibly due to improvements in the care of VLBW in South Africa versus decreased survival in extremely low birth weight infants [18]. When compared to other studies from sub-Saharan Africa, our IVH prevalence is similar to what has been reported elsewhere (16.2–34.2%) [1, 19–21]. When we look specifically at the prevalence of high-grade IVH, comparisons become more difficult as this is center dependent. Rates for severe IVH have been reported in some studies range from four to fourteen% [22–25]. In comparison with these studies our rate of high-grade IVH of 29.8% is substantially high.

The overall mortality among infants with IVH in our study cohort was high (44%), particularly among those with high grade IVH (70%). We found a statistically significant association with mortality in our patients who had extremely low birthweight and inborn patient status. Furthermore, patients with instability due to acidosis and/or hypoglycemia were significantly associated with higher odds of mortality. The increased mortality in high grade IVH was consistent with that reported in previous studies [26–28]. Death from IVH can be related to hemodynamic instability associated with the acute bleeding episode or a decision to withdraw from care due to disease severity [26]. We did not elucidate the cause of death in infants who had IVH.

Table 4 Association of Antepartum and Intrapartum Risk factors with IVH by Severity Grading

Prenatal & Intrapartum Risk Factors	Overall	High Grade	Low Grade	
	N = 502	*N* = 150	*N* = 352	*p*-value*
Antenatal Care(%)				
Yes	335 (74.3)	93 (68.9)	242 (76.6)	0.111
No	116 (25.7)	42 (31.1)	74 (23.4)	
Hypertension(%)				0.034
Yes	106 (21.1)	23 (15.3)	83 (23.6)	
No	322 (64.1)	107 (71.3)	215 (61.1)	
Missing	74 (14.7)	20 (13.3)	54 (15.3)	
Maternal Diabetes(%)				1.000
Yes	4 (0.8)	1 (0.7)	3 (0.9)	
No	447 (89.0)	138 (92.0)	309 (87.8)	
Missing	51 (10.2)	11 (7.33)	40 (11.4)	
Maternal HIV(%)				1.000
Yes	160 (31.9)	48 (32.0)	112 (31.8)	
No	324 (64.5)	96 (64.0)	228 (64.8)	
Missing	18 (3.59)	6 (4.0)	12 (3.4)	
Maternal Tuberculosis(%)				1.000
Yes	4 (0.8)	1 (0.7)	3 (0.9)	
No	439 (87.5)	135 (90.0)	304 (86.4)	
Missing	59 (11.8)	14 (9.3)	45 (12.8)	
Magnesium sulphate(%)				0.379
Yes	27 (5.4)	6 (4.0)	21 (5.9)	
No	377 (75.1)	122 (81.3)	255 (72.4)	
Missing	98 (19.5)	22 (14.7)	76 (21.6)	
Chorioamnionitis(%)				1.000
Yes	14 (2.8)	4 (2.7)	10 (2.8)	
No	409 (81.5)	126 (84.0)	283 (80.4)	
Missing	79 (15.7)	20 (13.3)	59 (16.8)	
Antenatal Steroids(%)				0.034
Yes	201 (40.0)	52 (34.7)	149 (42.3)	
No	202 (40.2)	73 (48.7)	129 (36.6)	
Missing	99 (19.7)	25 (16.7)	74 (21.0)	
Mode of delivery (%)				0.001
Normal vaginal delivery	237 (47.2)	85 (56.7)	152 (43.2)	
Assisted vaginal delivery	1 (0.2)	0 (0.0)	1 (0.3)	
Vaginal breech	14 (2.8)	9 (6.0)	5 (1.4)	
Caesarean section (elective)	14 (2.8)	4 (2.7)	10 (2.8)	
Caesarean section (emergency)	210 (41.8)	45 (30.0)	165 (46.9)	
Missing	26 (5.2)	7 (4.7)	19 (5.4)	

*p-values calculated using complete data only

Table 5 Post-natal risk factors Associated with IVH by severity grading

Post-natal Risk factors	Overall *N* = 502	High Grade *N* = 150	Low Grade *N* = 352	*p*-value*
DR Resus (%)				
No	82 (16.3)	21 (14.0)	61 (17.3)	0.332
Yes	348 (69.3)	111 (74.0)	237 (67.3)	
Missing	72 (14.3)	18 (12.0)	54 (15.3)	
CPR (%)				0.832
No	368 (73.3)	110 (73.3)	258 (73.3)	
Yes	55 (11.0)	18 (12.0)	37 (10.5)	
Missing	79 (15.7)	22 (14.7)	57 (16.2)	
ET tube (%)				0.061
No	392 (78.1)	114 (76.0)	278 (79.0)	
Yes	31 (6.2)	15 (10.0)	16 (4.6)	
Missing	79 (15.7)	21 (14.0)	58 (16.5)	
PDA (%)				0.543
No	409 (81.5)	122 (81.3)	287 (81.5)	
Yes	87 (17.3)	25 (16.7)	62 (17.6)	
Missing	6 (1.2)	3 (2.0)	3 (0.9)	
Acidosis (%)				< 0.001
Yes	114 (22.7)	52 (34.7)	62 (17.6)	
No	386 (76.9)	97 (64.7)	289 (82.1)	
Missing	2 (0.40)	1 (0.7)	1 (0.3)	
BT (%)				0.458
No	149 (29.7)	39 (26.0)	110 (31.2)	
Yes	344 (68.5)	108 (72.0)	236 (67.0)	
Missing	9 (1.8)	3 (2.0)	6 (1.7)	
EOS (%)				0.015
No	450 (89.6)	131 (87.3)	319 (90.6)	
Yes	32 (6.4)	16 (10.7)	16 (4.6)	
Missing	20 (3.9)	3 (2.0)	17 (4.8)	
LOS (%)				0.092
No	237 (47.2)	81 (54.0)	156 (44.3)	
Yes	262 (52.2)	68 (45.3)	194 (55.1)	
Missing	3 (0.6)	1 (0.7)	2 (0.6)	

CPR = cardiopulmonary resuscitation; PDA = patent ductus arteriosus; DR Resus = Delivery room resuscitation; EOS = Early onset sepsis, LOS = Late onset sepsis; ET tube = endotracheal intubation; BT = Blood transfusion; p-values calculated using complete data only

*p-values calculated using complete data only

Table 6 Multivariable logistic regression of risk factors for high grade IVH

Variables	OR	95% CI	*p*-value
Birth weight (for every 250 g increase)	1.072	0.774; 1.486	0.677
Sex (Male)	1.063	0.702; 1.608	0.774
Gestational Age in weeks	0.857	0.760; 0.967	0.013
Mode of delivery (Vaginal)	1.545	0.951; 2.510	0.085
Birth location (Inborn)	1.067	0.639; 1.783	0.808
Antenatal steroids (Yes)	0.704	0.445; 1.112	0.165
Maternal Hypertension (Yes)	0.923	0.511; 1.667	0.803
Maternal HIV status (Yes)	0.874	0.559; 1.368	0.565
Delivery room resuscitation (Yes)	1.445	0.840; 2.487	0.259
Acidosis (Yes)	2.274	1.422; 3.636	0.001
Early onset sepsis (Yes)	2.266	1.055; 4.868	0.039
Hypoglycemia (Yes)	0.613	0.333; 1.126	0.118
Blood Transfusion (Yes)	1.307	0.815; 2.096	0.274

Abbreviations: OR odds ratio; CI, confidence interval

We found an inverse relationship between the severity of IVH with birth weight and gestational age, which is consistent with other studies [19, 20, 29–31]. Furthermore, in multivariate regression analysis we found a 14% reduced likelihood of developing high grade IVH with every one-week increase in gestational age. On the contrary, the influence of birthweight on the severity of IVH was not evident on multivariate analysis. There have been past reports to suggest a female advantage with regards to neonatal outcomes. However, this association has not been consistently reported in other studies [32–34]. Our study showed that the odds of a male infant having high grade IVH was higher compared to females, however this was not statistically significant.

Multiple prenatal and postnatal factors have been implicated in the occurrence and severity of IVH [31, 35–37]. Antenatal steroids have been reported to be protective against IVH through modulation of vascular growth factors that results in the stabilization of the germinal matrix [38–40]. In our study, we found that antenatal steroid use was associated with a 30% reduction in the odds of developing high grade IVH. (OR: 0.704, 95% CI = 0.445;1.112, $p = 0.165$). This reduction was however not statistically significant perhaps because of the low rate of antenatal steroids administration in our study (40.0%).

A preterm infant's mode of delivery has been reported to have an impact on IVH rate and severity. Caesarean section deliveries have been associated with decreased IVH rates in some studies [36, 41, 42]. Our study showed increased odds of developing high grade IVH in infants delivered vaginally. This difference was however not statistically significant (OR:1.545 95% CI = 0.951;2.510, $p = 0.083$) The associated higher odds of high grade IVH in infants delivered vaginally could be explained by the fact that perhaps these deliveries were precipitous and there was not ample time to administer antenatal steroids.

Maternal and neonatal infections have been cited in previous studies as risk factors for IVH [4, 43–45]. Early onset sepsis has been reported as a risk factor for the occurrence and deterioration of IVH. The proposed mechanism is sepsis induced inflammatory cytokine release resulting in disruption of the blood brain barrier and cerebral autoregulation with resultant increased propensity of cerebral rupture. This inflammatory response also results in disruption of cerebral autoregulation hence increases vulnerability of the neonate's brain to blood pressure fluctuations [15, 22, 44, 45]. We found that early onset neonatal sepsis was significantly higher in infants

with IVH and there was an associated 2-fold increase in the odds of developing high grade IVH (OR:2.266, 95% CI = 1.055;4.868, $p = 0.039$). On the contrary, maternal HIV status and presence of chorioamnionitis showed no difference between infants with IVH compared to those without IVH. We did not find a significant association on maternal chorioamnionitis either due to under-recognition or reporting and as a limitation of our study, there was missing data on the maternal chorioamnionitis status in 15% of study subjects.

Postnatal factors implicated in increased IVH rates include extensive delivery room resuscitation, multiple intubation attempts, infant transport, hypothermia, hypotension, electrolyte abnormalities, early onset sepsis, pneumothorax, and symptomatic patent ductus arteriosus. [10, 26, 43, 46–49] In our study, delivery room resuscitation rates were higher in infants with IVH and those with high grade IVH had a 44% increased odds of having received resuscitation although not statistically significant (OR = 1.445, 95% CI = 0.84; 2.487). We found that infants with IVH were more likely to have acidosis documented in their clinical course. The odds of acidosis were 2-fold higher in infants with high grade IVH (OR = 2.274, 95% CI = 1.422; 3.636). Infant transport has been reported to be associated with increased risk of IVH [10, 50]. Our study showed no significant difference in the rate of high grade IVH between out born and inborn patients on initial analysis. Multivariate regression analysis however showed an increased odds of high grade IVH in inborn patients (OR = 1.067, 95% CI = 0.639; 1.783) although not statistically significant. This could be explained by the fact that perhaps infants with severe IVH born in outlying hospitals did not survive to be transported to CMJAH.

Overall, our study identified similar factors cited in prior studies as risks for IVH. We found that acidosis and sepsis had significant influence on IVH occurrence and severity.

Our study is limited by its retrospective nature and the relatively low rate of head ultrasound scans in this cohort. Our reported prevalence might be biased as some extremely low birthweight infants might have died prior to obtaining a head ultrasound. Infants with significant missing data were not included in our analysis. Although all infants had a head ultrasound performed by day of life 7, our data set did not include the exact day of life the first head ultrasound was performed for each neonate, hence we could have missed some cases of IVH, if the ultrasound was performed earlier than the initial bleeding episode. Furthermore, our dataset did not differentiate clearly where an infant's ultrasound was performed hence introducing inter operator variability in ultrasound performance and results for out born patients. Another limitation of our study was that we were not able to assess association of risk factors such as hypotension with need for pressors or hyperglycemia as we did not have all the information needed for analysis in the dataset. Furthermore, our data did not include information on the temporal correlation of risk factors such as acidosis or hypoglycemia to the occurrence of IVH.

Future directions to improve routine head ultrasound scans in the care of VLBW infants could include developing an admission check list that incorporates scheduled point of care head ultrasounds for all VLBW infants admitted to the CMJAH. A multidisciplinary approach with the obstetrics team for management of preterm deliveries might also improve the routine use of antenatal steroids in the care plan for mothers with impending preterm deliveries. Quality improvement projects to improve management of sepsis and acidosis may also improve rates of severe IVH.

Abbreviations

BT	Blood Transfusion
BW	Birth Weight
CEO	Chief Executive Officer
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPR	Cardiopulmonary Resuscitation
DR Resus	Delivery Room Resuscitation
EOS	Early Onset Sepsis
ET tube	Endotracheal Intubation
GA	Gestational Age
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
LOS	Late Onset Sepsis
OR	Odds Ratio
PDA	Patent Ductus Arteriosus
VLBW	Very Low Birth Weight

Supplementary Information

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Supplementary Material 1

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Author contributions

GAB, DB and TM conceptualized the study. RB and GA led data collection and statistical analysis. GAB, TM, and GA drafted manuscripts. DB and RB revised and edited manuscripts. All authors critically reviewed, appraised and approved final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The need for informed consent was waived and approved by the Human Research Ethics Committee of University of Witwatersrand (#M230136 MED23-01-010) and the Vanderbilt University Institutional Review Board (IRB#222290).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pediatrics, Division of Neonatology, Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Nashville, TN 37232, USA
[2]Department of Tropical Medicine and Infectious Diseases, Tulane University School of Public Health and Tropical Medicine, 1440 Canal Street, Suite 2300, New Orleans, Louisiana 70112, USA
[3]Department of Biostatistics, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 1000, Nashville, TN 37203, USA
[4]PRINCE (Project to Improve Neonatal Care), School of Clinical Medicine, University of the Witwatersrand, PO Wits, Johannesburg 2050, South Africa

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