University of the Witwatersrand

PREVALENCE AND RISK FACTORS FOR INTRAVENTRICULAR HAEMORRHAGE AND PERIVENTRICULAR LEUKOMALACIA IN VERY LOW BIRTH WEIGHT INFANTS AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

This research report was submitted to the University of the Witwatersrand, Johannesburg in fulfilment of the requirements for the degree of MMed Paediatrics

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Declaration

I [Tshepang Mokoto] student number [0603424G] declare that this Research Report is my own work being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature of Student:  **Date**: 11/03/2020

Name of Supervisor 1: Dr Joy Fredericks **Date**: 11/03/2021

Signature of Supervisor 1: 

Name of Supervisor 2: Dr Tim De Maayer **Date:** 11/03/ 2022

Signature of Supervisor 2: 

Dedication

In the memory of my aunt

Flora Mamogodi Lekutle

1944-2017

Abbreviations:

AAN: American Association of Neurology
ART: Antiretroviral Therapy
BBA: Born Before Arrival
BMV: Bag Mask Ventilation
CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
CPR: Cardiopulmonary Resuscitation
CUS: Cranial Ultrasound
ELBW: Extremely Low Birth Weight
HFOV: High Frequency Oscillation Ventilation
HIV: Human Immunodeficiency Virus
HREC: Human Research Ethics Committee
ICU: Intensive Care Unit
IPPV: Invasive Positive Pressure Ventilation
IVH: Intraventricular Haemorrhage
LISA: Less Invasive Surfactant Administration
MRI: Magnetic Resonance Imaging
NCPAP: Nasal Continuous Positive Airway Pressure
NHRD: National Health Research Database
NVD: Normal Vaginal Delivery
PDA: Patent Ductus Arteriosus
PVL: Periventricular Leukomalacia
REDCap: Research Electronic Data Capture
RMMCH: Rahima Moosa Mother and Child Hospital
VLBW: Very Low Birth Weight

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Abstract

Background: Intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) are major causes of mortality and morbidity in very low birth weight (VLBW) infants. The prevalence and risk factors for IVH and PVL vary between institutions.

Objectives: To determine the prevalence of IVH and PVL in premature infants with a birth weight of <1 500 g at RMMCH. To compare the risk factors and characteristics for IVH and PVL.

Method: This was a retrospective cross-sectional study of infants <1 500 g admitted between the 1st November 2018 and 31st October 2019 at RMMCH. Characteristics of infants with cranial ultrasound or MRI abnormalities were compared to infants with normal cranial imaging.

Results: A total of 432 VLBW infants were screened for inclusion into the study, 30% (128/432) were excluded due to absence of cranial imaging, transfer to other hospitals or early death. The final sample size was 304 infants. IVH was present in 40% (n=122; 95% CI 34.6-45.7). Independent risk factors for IVH were patent ductus arteriosus (p=0.03), metabolic acidosis on the first arterial blood gas (p<0.001) and lack of antenatal booking (p=0.004). Severe IVH was present in 12% (n=37; 95% CI, 8.5-16) of infants. The rate of PVL was 0.3% (n=1; 95% CI 0-0.98).

Conclusion: The prevalence of any IVH in VLBW infants at RMMCH is comparable to that of developing countries. Risk factors were like those described in other centers. Availability of MRI would assist in delineating the extent of PVL in VLBW infants at our centre.

1. Introduction

Premature infants born before 34 completed weeks have an immature central nervous system that is highly vulnerable to injury. Before 32 weeks of gestation the germinal matrix and periventricular white matter are vulnerable regions of the brain with complications including intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) [1]. The aim of this study is to determine the prevalence and associated risk factors for IVH and PVL in premature infants with a birth weight of <1 500 grams at Rahima Moosa Mother and Child Hospital (RMMCH). This topic has never been studied at RMMCH, a teaching hospital of the University of the Witwatersrand.

The prevalence of IVH in very low birth weight (VLBW) infants in first world countries is reported to be about 20% [2]. In a study conducted in Zambia the prevalence was higher at 34.2% [3]. A similar study conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) reported the prevalence of IVH to be 26.7%, which is comparable with first world prevalence [4]. The prevalence of PVL is between 19.8% and 34.1% with cystic periventricular leukomalacia accounting for 2.5 to 23% [5].

Risk factors for IVH can be divided into maternal and neonatal factors. Factors related to the expectant mother include infection and lack of antenatal steroids administration. Risk factors in the premature infant include respiratory distress syndrome (RDS), hemodynamic instability, patent ductus arteriosus (PDA), platelet dysfunction, coagulopathies, and inter- hospital transportation [6]. There have been postulations about the relationship between factor 5 Leiden and IVH. Normal vaginal delivery has been associated with increased incidence of IVH, due to the increase in cerebral venous pressure as the foetal head compresses onto the pelvis [6].

Risk factors for PVL include hypoxic ischaemic injury, maternal chorioamnionitis and preterm rupture of membranes [6].

There are two grading systems for IVH: the Papile and Volpe systems. The Papile grading system is more widely used in literature. Papile describes four grades of IVH based on radiological appearance. Grade I IVH involves bleeding in the subependymal germinal matrix, in grade II IVH the bleeding is intraventricular without ventricular dilatation, grade III IVH is an intraventricular bleed with ventriculomegaly and in grade IV IVH the bleed extends into the adjacent parenchyma [6]. Periventricular leukomalacia is also classified into four grades based on cranial ultrasound (CUS) features. Grade I PVL is transient echodensities that persist for longer than 7 days, in grade

II PVL the echodensities evolve into small frontoparietal cysts,in grade III PVL the cysts become more extensive involving the periventricular region and in grade IV PVL the cysts involve the deep white matter [7].

Intraventricular haemorrhage commonly presents in a silent manner that may go undiagnosed unless actively screened for with neuro-imaging [6]. MRI is the gold standard for neuroimaging, however, CUS is more accessible [8]. The sensitivity of CUS to detect IVH is reported to be 60% and the specificity is 100% [9]. In 2002 the American Academy of Neurology (AAN) published a paper recommending routine CUS screening in all infants born before 30 weeks stipulating that timing for these cranial sonars should be between 7-14 days of life and repeated at 36 to 40 weeks post-menstrual age [10]. Almost all IVHs occur in the first 72 hours but after detection of the initial bleed there may be progression in 20-40% of the infants 3-5 days after the initial diagnosis [8]. One study reported the prevalence of IVH to be 38% after 24 hours of life, while another study reported the prevalence of IVH to be 82.4% within 72 hours of life [3, 11].

2. Method

2.1. Data collection

This was a retrospective cross-sectional descriptive study conducted at RMMCH in the neonatal unit. A total of 432 infants with a birth weight of <1 500 g were born between the 1st of November 2018 and 31st of October 2019 according the ward admission register. This included all infants admitted to the general neonatal ward, neonatal high-care area and neonatal intensive care unit (NICU).

Data was retrieved from the neonatal research electronic data capture (REDCap) system using these names and missing entries were captured by retrieving hospital admission notes.

At RMMCH CUS are performed by the neonatal specialists in the unit routinely at or after day 7 of life and repeated at 36 weeks corrected age or at discharge. Some are done before day 7 of life if the treating clinician suspects an IVH that may affect the patient's management. The CUS with the most severe grade of IVH was captured. Only the presence of cystic PVL and not echodensities was captured.

Relevant maternal and neonatal factors were retrieved from the REDCap system. Maternal factors included booking status, human immunodeficiency virus (HIV) status, antiretroviral therapy (ART) and duration of ART, administration of antenatal steroids and obstetric diagnosis of chorioamnionitis.

Complications such as respiratory distress syndrome (RDS), PDA, anaemia, thrombocytopaenia, pneumothorax and sepsis were also captured. Sepsis was defined as a positive blood culture excluding contaminants and included both early and late onset sepsis. Mild IVH was defined as IVH grade I and II. Severe IVH was defined as IVH grade III and IV.

2.2. Data analysis

Statistical analysis was done using Stata version 11 (Statacorp, USA). Associations with CUS abnormalities was tested using Chi square tests (with Fisher exact statistics where appropriate) for categorical variables, and Student t –tests or Mann-Whitney U tests for continuous variables, depending on data distribution. Statistical significance was set at a p-value < 0.05. A multivariate regression analysis was then performed on all significant risk factors with a p-value <0.05 to identify independent risk factors.

2.3. Ethics

Consent was obtained from the hospital CEO, the National Health Research Database (GP_ 202002_024) and the Human Research Ethics Committee of the University of the Witwatersrand (M200149). Anonymised identifiers were used to maintain confidentiality.

3. Results

3.1. General characteristics

A total of 128/432 (30%) infants were excluded from the study because they did not meet the inclusion criteria outlined in Table 1 below. Of those that were excluded 83/432 (19%) had missing files, and 1/432 (0.2%) had a major congenital anomaly. A further 44/432(10%) infants did not have CUS screening due to early transfer to other facilities or early death (Fig. 1).

Table 1: Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
• Birth weight < 1 500 g • CUS or MRI done	• Major congenital abnormalities • Other CUS or MRI abnormalities (congenital hydrocephalus, lissencephaly, corpus agenesis, etc.) • Missing files

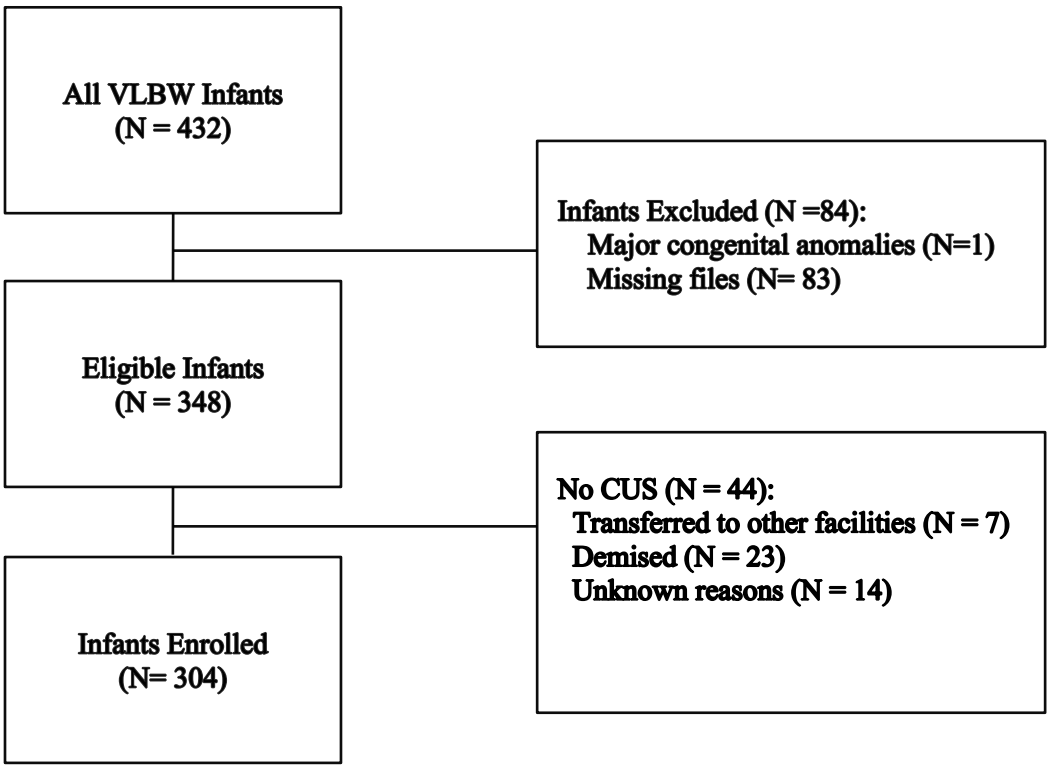

Figure 1: Sampling and enrolment process

The sample size was 304 VLBW infants born between 1 November 2018 and 31 October 2019. The general characteristics of the population are shown in Table 2 below.

A total of 49/300 (16%) mothers were not booked for antenatal care. A third (30%) of the mothers were HIV positive. The majority (91%) of infants were inborn. More infants were born via caesarean section (51%). There were more female than male infants (54% vs 46%).

Intraventricular haemorrhage was present in 40% (n=122; 95% confidence interval (CI), 34.6-45.7) of VLBW infants. Most of the IVHs were grade II (14 %), followed by grade I IVH (13 %). Severe IVH was found in 12% (n= 37; 95% CI 8.5-16) while mild IVH was found in 28% (n= 85; 95% CI, 23-33) of infants. The rate of cystic PVL detected on CUS was 0.3% (n=1; 95% CI, 0-0.98). None of the participants had an MRI brain scan.

Table 2: General trial population.

VARIABLES	RESULTS
Inborn - no/total (%)	272/299 (91)
Transfer-ins - no/total (%)	27 /299 (9)
Booked – no/total (%)	251/300 (84)
Unbooked - no/total (%)	49 /300 (16)
Median parity - (IQR)	2 (0-2)
HIV positive mother - no/total (%)	91/301 (30)
Black - no/total (%)	274/297 (92)
Coloured - no/total (%)	14/297 (5)
White - no/total (%)	5/297 (2)
Indian - no/total (%)	4 /297 (1)
Male - no/total (%)	140/302 (46)
Female - no/total (%)	162/302 (54)
Median gestational age - (IQR)	30 (28-31)
Average birth weight (in grams)	30 (980-1310)
NVD - no/total (%)	144/295 (49)
Caesarean section - no/total (%)	151/295 (51)
Median Apgar at: 1 minute - (IQR)	4 (5-9)
5 minute - (IQR)	3 (7-10)
Multiple pregnancy - no/total (%)	56/292 (19)
IVH I - no/total (%)	41/304 (13)
IVH II - no/total (%)	44/304 (14)
IVH III - no/total (%)	24/304 (8)
IVH IV - no/total (%)	13/304 (4)
Mean length of stay - (in days)	28(17-45)
Discharged - no/total (%)	232/295 (79)
Demised - no/total (%)	56/295 (19)
Transfer to other facilities - no/total (%)	7/295 (2)
Notes: IQR= Interquartile Range	

3.2. Clinical characteristics

The significant risk factors for IVH identified in this study are indicated in Table 3 below. These include lack of antenatal booking ($p<0.001$), Apgar score of less than 6 at 1 minute ($p=0.01$), low birth weight ($p=0.004$) and early gestational age ($p=0.008$). Primiparity ($p=0.742$), place of birth ($p=0.063$) and sepsis ($p=0.790$) were not significant risk factors for IVH. Resuscitation ($p=0.001$) and ventilation ($p<0.001$) were risk factors for IVH and were analysed in an ordinal

form. The rate of pneumothorax was 1/304 (0.3%). Antenatal steroids were administered in 139/304 (46%) of the infants in the study. IVH occurred more in those without maternal antenatal steroids administration (61% vs. 39%, p= 0.034). The prevalence of IVH was inversely proportional to birth weight and gestational age.

There were significantly higher proportions of severe IVH among infants with metabolic acidosis, earlier gestational age, lower birth weight, those who had received mechanical ventilation and lack of antenatal steroids administration.

The overall mortality rate from any cause among those with IVH was 40/115 (35%) and 16/180 (9%) in those without IVH. In mild IVH the mortality rate was 27%, while the mortality rate was significantly higher in infants with severe IVH at 51% ($p<0.001$).

The results of the multivariate regression analysis showed three independent risk factors for IVH: PDA (Odds ratio (OR): 2.9, 95% CI; 1.1-7.4, p=0.03), lack of antenatal booking (OR: 3.2, 95% CI; 1.4-7.2, p=0.004) and metabolic acidosis (OR: 4.6, 95%CI; 2.1-10.3, $p<0.001$) on the first ABG.

Table 3: Clinical characteristics

Risk factor	Mild IVH * (N=85)	Severe IVH * (N=37)	No IVH * (N= 182)	p-value *
Demographics				
Race:				
Black	79/84(94%)	34/37(92%)	161/180(89%)	
Coloured	2/84(2%)	2/37(5%)	10/180(6%)	
Indian	3/84(4%)	0/37(0%)	1/180(0.5%)	
White	0/84(0%)	0/37(0%)	5/180(3%)	
Other	0/84(0%)	1/37(3%)	3/180(2%)	0.154
Gender:				
Male	39/85(46%)	22/37(59%)	79/180(44%)	
Female	46/85(54%)	15/37(41%)	101/180(56%)	0.296
HIV exposed	26/84(31%)	12/37(32%)	53/181(29%)	0.694
Primiparous mother	13/59(22%)	8/26(31%)	40/150(27%)	0.742
Chorioamnionitis	3/85(4%)	0/85(0%)	2/182(1%)	0.353
Place of birth:				
Inborn	71/84(85%)	34/37(92%)	167/179(93%)	
Transfer-in	3/84(4%)	3/37(8%)	6/179(3%)	
BBA	10/84(12%)	0/37(0%)	6/179(3%)	0.063
1 minute Apgar of <6	6/73(14%)	5/35(14%)	14/171(92%)	0.010
Unbooked mother	21/83(26%)	10/37(27%)	18/180(10%)	<0.001
Multiple pregnancy	11/79(14%)	9/36(25%)	36/177(20%)	0.532
Birth weight:				
ELBW	23/85(27%)	19/37(51%)	36/182(20%)	
VLBW	62/85(73%)	18/37(49%)	146/182(80%)	0.004
Gestational age:				
<30 weeks	40/84(48%)	25/37(68%)	69/180(38%)	
>30 weeks	44/84(52%)	12/37(32%)	111/180(62%)	0.008
Complications				
Anaemia	24/85(28%)	9/37(24%)	36/182(20%)	0.138
Thrombocytopenia	22/85(26%)	13/37(35%)	27/182(15%)	0.003
Sepsis	27/49(55%)	14/25(56%)	41/77(53%)	0.790
Hypotension	12/85(14%)	7/37(19%)	5/182(3%)	<0.001
PDA	14/85(16%)	7/37(19%)	12/182(7%)	0.004
Metabolic acidosis	26/85(31%)	18/37(49%)	13/182(7%)	<0.001
RDS	71/85(87%)	36/37(97%)	147/182(81%)	0.004
Interventions				
Resuscitation:				
No resuscitation	48/85(56%)	10/37(27%)	129/182(71%)	
Assisted breath	27/85(32%)	22/37(59%)	40/182(22%)	
CPR	9/85(11%)	3/37(8%)	11/182(6%)	
CPR and adrenaline	1/85(1%)	2/37(5%)	2/182(1%)	0.001
Ventilation:				
No ventilation	33/85(39%)	3/37(8%)	96/182(53%)	
NCPAP	35/85(41%)	16/37(43%)	65/182(36%)	
IPPV	13/85(15%)	12/37(32%)	19/182(10%)	
HFOV	4/85(5%)	6/37(16%)	2/182(1%)	<0.001
Antenatal steroids:				
Yes	35/85(41%)	12/37(32%)	92/182(51%)	
No	50/85(59%)	25/37(68%)	90/182(49%)	0.034
Outcomes				
Demised	21/78(27%)	19/37(51%)	16/180(9%)	<0.001
Discharged home	53/78(68%)	16/37(43%)	163/180(91%)	<0.001
Transfer to other facilities	4/78(5%)	2/37(5%)	1/180(0.6%)	<0.001

Notes: *p value compares mild IVH vs severe IVH vs no IVH

4. Discussion

The purpose of this study was to determine the prevalence and risk factors for IVH and PVL in infants with a birth weight below 1500 g at RMMCH. This topic is widely studied in other institutions across the world; however, it has never been studied at this institution. It is imperative to know the prevalence and risk factors pertinent to this institution in order to direct care and implement appropriate preventative measures.

The prevalence of IVH in VLBW infants at RMMCH was consistent with that of developing countries, but higher in comparison to first world countries and to that of its sister unit, CMJAH [2,3,4]. Mild IVH was the most frequent as it is for other institutions [3,4,12]. The rate of severe IVH was higher than what is reported in developed countries, but less than that reported in developing countries [3,4,12,13,14,15,16].

The rate of PVL in the present study was like what was found in centers with lack of adequate MRI facility [4]. According to literature the rate of PVL varies depending on the type of diagnostic tool used with MRI being the gold standard. In one systematic review the prevalence of PVL was reported to be 14.7% when using CUS and 32.8% when using MRI scan [17]. It is likely that the lack of MRI access led to low detection of PVLs in this study.

In comparison to PVL the rate of severe IVH was higher in this study (12% vs 0.3%), and this could be related to lack of the ideal diagnostic modality for PVL in our facility. Similar results were found in other studies and in our sister unit at CMJAH with the same resources [4,18]. This contrasts with a study in Nigeria which reported the incidence of PVL to be higher than that of severe IVH with CUS as the imaging modality used [19].

The risk factors for any IVH were similar to those mentioned in literature namely, lack of antenatal steroids and antenatal care, early gestational age, lower birth weight,thrombocytopenia, PDA, RDS, hypotension, metabolic acidosis, mechanical ventilation andresuscitation [6]. This study did not find primiparity, sepsis or being out-born as significant risk factors for IVH as was the case in other studies [4,12].

The relationship between low apgar score and metabolic acidosis is well established [20]. In the present study, metabolic acidosis was identified as an independent risk factor for IVH, but not low apgars. Some studies have demonstrated a relationship between low apgars and IVH in premature

infant [12, 21]. Other studies concur with the present study and identify metabolic acidosis as an independent risk factor for IVH [4,15,21,22]. The reason for the distinction is unknown.

Administration of intratracheal surfactant is known to disrupt cerebral blood flow and mean arterial blood pressure in neonates, thus increasing the risk of IVH [23]. New methods of surfactant administration such as the less invasive surfactant administration (LISA) method have been found to reduce the risk of severe IVH [24]. In this study we did not look at surfactant administration and its effect on the incidence of IVH

The risk factors for IVH were like those found at our sister unit at CMJAH. However, in the present study sepsis was not found to be a significant risk factor for IVH as was the case at CMJAH [4].

The finding of metabolic acidosis, mechanical ventilation and lack of antenatal steroids administration being associated with higher risk of severe IVH is in keeping with other studies [4,15,21]. Antenatal steroids were administered in less than 50% of mothers, likely contributing to the higher rate of severe IVH reported in this study. In a large cohort study conducted in California an increase in antenatal steroids was found to significantly reduce the incidence of any IVH and severe IVH [22].

Strategies that have been found to reduce the incidence of IVH include the use of antenatal steroids and magnesium sulphate, treating maternal infection, maintaining normocarbia, normothermia and haemodynamic stability [6]. In the present study the effect of maternal administration of magnesium sulphate on the rate of IVH was not explored.

Mortality rate among infants with severe IVH at RMMCH was comparable to developed countries and better than developing countries [12,25]. However, in comparison to its sister unit CMJAH, the mortality rate among those with severe IVH was proportionally higher at RMMCH (51% vs. 36%) [4], interestingly the mortality rate among infants with mild IVH was higher than those with no IVH (27% vs. 9%). In other studies, there is no significant difference between mortality rate amongst infants with mild IVH and no IVH [12,26]. The infants in our study may have had other comorbidities that contributed to mortality.

From this study three factors contributing to the prevalence of any IVH are PDA, metabolic acidosis on the first ABG, and lack of antenatal booking.

The results of this study can assist in implementing relevant preventative measures for IVH and

aid in prognostication.

4.1. Study limitations

This was a retrospective study that relied on recordkeeping. A total of 84/432 (19%) infants had missing files. Not all infants were accounted for at the end, a total of 9/304 (3%) did not have outcomes recorded. The lack of MRI facility may have resulted in the low prevalence of PVL. The effect of the LISA technique and magnesium sulphate on the prevalence of IVH and PVL should have been explored.

5. Conclusion

The results of this study showed that the prevalence and risk factors for IVH in VLBW infants is comparable with that of developing countries but higher than developed countries. Since severe IVH is associated with high mortality rates, strategies decreasing its prevalence need consideration. This study suggests that improving antenatal care, increasing the uptake of antenatal steroids, improving resuscitation skills to prevent metabolic acidosis and the preferred use of non-invasive ventilation over invasive ventilation, could be appropriate preventative strategies. Early identification and treatment of haemodynamically significant PDAs could also decrease IVH, as PDA was a significant independent risk factor in this study. Multiple studies have identified sepsis and being outborn as risk factors for IVH so measures such as strict infection control and correct referral pathways allowing preterm infants to be born in appropriate health care facilities, should still be given priority. The true prevalence of periventricular leukomalacia was likely under reported in this study because of the lack of MRI facilities and limited late cranial ultrasound screening. This may warrant further studies.

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There was no conflict of interest

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