

# Comparing Death or Neurodevelopmental Outcomes of Haemodynamically Significant Patent Ductus Arteriosus in Very Low Birth Weight Preterm Infants

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## Research article

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# Abstract

## Background

Optimal management of haemodynamically significant patent ductus arteriosus (HsPDA) remains controversial for premature infants. Treatment options include conservative treatment with fluid restriction and diuretics, medical treatment with cyclo-oxygenase (COX) inhibitors or surgical ligation. Our primary objective is to compare the death and/or adverse neurodevelopmental outcomes among very low birth weight (VLBW) infants with HsPDA who were managed with conservative, medical and/or surgical treatment. The secondary objectives are to examine antenatal factors predisposing to surgical treatment and the neonatal short-term morbidities between three groups.

## Methods

This was a retrospective, gestational age-stratified study of VLBW infants born in National University Hospital (NUH) in Singapore and admitted to the intensive care unit from 2007–2016.. Perinatal variables, short-term neonatal outcomes and neurodevelopmental outcomes were studied. Statistical analysis were performed with chi square and t-test..

## Results

124 infants were included. 17 VLBW infants managed conservatively [C] were identified and compared with 83 VLBW infants managed medically [M] and 24 VLBW infants managed surgically [S]. The main group analysis compared outcomes between infants managed [C] and those who received either medical or surgical treatment [M+S]. The subgroup analysis compared outcomes between infants managed [C] vs [M] and [C] vs [S]. The main group analysis found group M+S infants had a higher incidence of chronic lung disease (CLD) ( $p=0.005$ ) than group C. The odds ratio (OR) of group M+S developing CLD was significant (OR 6.83). They were significantly shorter ( $p=0.017$ ) and had a smaller head circumference ( $p=0.039$ ) at discharge. Group S infants were older at discharge, due to a longer NICU stay, and were lighter, shorter and had a smaller head circumference ( $p<0.05$ ). No significant differences in death, composite outcome of death and global development delay and neurological outcomes such as hearing loss, cerebral palsy (CP) and speech delay were found.

**Conclusions:** Comparing the management, infants requiring surgical treatment for hsPDA were more likely to have short-term complications such as CLD, longer hospitalization, and poorer growth. Despite a more turbulent postnatal course, death and/or adverse neurodevelopmental outcomes were not worse in these infants. Further randomized control studies will be useful to verify these findings.

## What Is Known

PDA treatment range from conservative to medical and surgical

Optimal management is controversial

## What is New

CLD incidence in those managed medical and surgical is more common than those managed conservatively

Length of stay and growth failure more common in those managed surgically

Death and adverse neurodevelopment outcomes in VLBWs comparable at 18 months

## Introduction/background

In term infants, the patent ductus arteriosus (PDA) normally constricts after birth and closes within 24–48 hours of life [1]. In preterm infants, the closure is often delayed due to a lower intrinsic tone of the ductus and increased ductus sensitivity to the vasodilating effects of prostaglandin E2 and nitric oxide (NO) [1]. There is an inverse relationship between the rate of ductal closure and the birth weight (BW) and gestational age (GA) [2–5].

In infants with PDA, blood flows from the left to right circulation from the aorta into the pulmonary arteries, increasing the blood flow in the pulmonary circulation. This “ductal steal” phenomenon may result in pulmonary over-circulation and diversion of blood from the systemic circulation [6]. Depending on the magnitude of the shunt, infants may be asymptomatic or symptomatic. As there is no universally accepted definition for hemodynamically significant patent ductus arteriosus (HsPDA), HsPDA is defined based on the patient’s clinical status, clinical signs, 2D echocardiography findings and other objective assessments [7].

Prolonged exposure to PDA is also associated with neonatal mortality and multiple neonatal morbidities such as chronic lung disease (CLD), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) and adverse long-term neurodevelopmental outcomes [8]. The management of HsPDA ranges from conservative management with fluid restriction and diuretics, medical treatment with cyclo-oxygenase inhibitors (COX) such as ibuprofen and indomethacin to surgical ligation.

To date, the optimal management of HsPDA remains controversial and is largely guided by professional opinions [9, 10]. The medical treatment adopted in our institution is intravenous ibuprofen or indomethacin, which may be given up to two courses. Surgical ligation is considered when the PDA failed to close after conservative or medical treatment and the child remains mechanically ventilated.

The decision to treat HsPDA with medical treatment or surgery has its risks. Treatment with COX inhibitors is associated with renal impairment, intestinal perforation and altered cerebrovascular regulation [11]. Surgical ligation is associated with haemodynamic and respiratory instability [12] and vocal cord palsy in up to 9% of infants with low recovery rates [13].

The primary objective of this study is to compare the death and/or adverse neurodevelopmental outcomes in early childhood among very low birth weight (VLBW) infants with HsPDA who were managed with conservative [C], medical [M] and/or surgical [S] treatment. The secondary objectives are to examine antenatal factors predisposing to surgical treatment and the neonatal short-term morbidities between three groups.

## Materials And Methods

This is a retrospective, gestational age-stratified study of VLBW infants ( $BW \leq 1500$  g) born in National University Hospital (NUH), Singapore from 2007–2016 and admitted to the neonatal intensive care unit (NICU).

Ethics approval was given by the National Health Group Domain Specific Ethics Review Board (NHG DSRB ref 2020/00001).

The inclusion criteria were: (1) GA between 24 + 0 weeks–28 + 6 weeks, (2) VLBW, and (3) diagnosed with a HsPDA. Infants with duct dependent cardiac lesions, those died before the initiation of PDA closure and those lost to follow up were excluded. We limited the study to infants < 29 weeks as more mature infants tend to have spontaneous closure of PDA [3, 6, 14].

We defined HsPDA based on combination of echocardiographic and clinical parameters. Echocardiography criteria were: PDA diameter  $\geq$  1.5 mm, Left Atrium: Aortic Root (LA:Ao) ratio  $\geq$  1.5:1, absent or reversed diastolic flow in the post-ductal descending aorta or organ arteries [4, 6, 15]. Clinical features suggestive of HsPDA include hyperdynamic precordium, bounding pulses, widened pulse pressure and cardiac failure [6, 15, 16]. The assessment is aided by radiological findings of stigmata of pulmonary edema and increasing respiratory support requirements [10].

Treatment arm constituted infants who received medical [M] or surgical [S] treatment or both. The primary composite outcome was 1) death and 2) adverse clinical neurodevelopment outcomes up to 5 years. Neurodevelopmental outcomes studied include hearing loss requiring implants/hearing aids, cerebral palsy (CP) and isolated speech delay. CP was defined if the child had either diplegia, hemiplegia or quadriplegia between 18–24 months of age. The secondary outcomes were predisposing factors specific to treatment complications and short-term neonatal morbidities. General demographics, antenatal and neonatal data were collected from electronic medical records and include gender, mode of delivery, GA, birth and discharge anthropometric measures. We used the Fenton's growth chart [17] to derive the Z-score from the GA and respective parameters (birth weight, length or head circumference). Perinatal and immediate neonatal factors, complications associated with treatment and short-term neonatal morbidities were collected. A low 5-minute APGAR score was defined as < 7. High Clinical Risk Index for Babies (CRIB II) score was defined as > 12 [18]. Severe Respiratory Distress Syndrome (RDS) was defined as grade 2–4 [19]. Severe IVH was defined as Grade 3 or 4 IVH [20]. Definite NEC was defined as at least stage 2 [21] or if complications developed. Severe ROP was defined as threshold ROP stage 3 or 4 requiring laser treatment [22]. CLD was defined as infants requiring supplemental O<sub>2</sub> or mechanical support with continuous positive airway pressure (CPAP)/ventilator after 36 weeks of post-menstrual age [23]. Treatment specific medical complications like raised serum creatinine and spontaneous intestinal perforation were collected. Surgical complications like vocal cord paralysis post PDA ligation and aspiration pneumonia were also determined.

Data was analysed using SPSS version 25 (IBM Corp, Armonk, NY, USA). Continuous normally distributed data was presented as mean with standard deviations unless stated otherwise and was analysed using Student *t*-test with conservative arm as the comparator. Categorical data was presented as frequency and analysed using Chi Square test with either 2 × 2 or 3 × 2 tables. Odds ratio (OR) was determined by comparing the conservative and treatment arm. A confidence interval of 95% is provided and a P-value of < 0.05 is considered significant.

## Results

A total of 474 VLBW infants were admitted in NUH from 2007–2016; of which 124 infants met study criteria (Fig. 1). 438 out of 474 infants (92.4%) survived to discharge. The yearly incidence of HsPDA ranged from

31.3–67.3%. 124 infants were included in the study. The mean GA was  $26.2 \pm 1.3$  weeks and the mean BW was  $890 \pm 191$  g. 77.4% of infants were singleton pregnancies, 21.8% of infants were twins and 0.8% of infants were triplets. The studied infants were not different from those who defaulted ( $n = 15$ ; 3.2%) or were lost ( $n = 4$ ; 0.8%) to follow up.

17 (13.7%) infants were managed conservatively, 83 (66.9%) infants were managed medically and 24 (19.4%) infants were managed with surgical ligation after failure of medical management. Of those managed conservatively, HsPDA were closed in all cases spontaneously before discharge. Of those managed medically alone, all had closure prior to discharge and did not require surgery. All infants with HsPDA that failed to close after medical treatment were managed with surgical ligation.

We conducted a main group analysis and a subgroup analysis. The main group analysis compared the outcomes between infants managed conservatively [C] and infants who received either medical or surgical treatment ([C] vs [M + S]). The subgroup analysis compared the outcomes between infants managed by each treatment arm ([C] vs [M] and [C] vs [S]).

## **Main Group Analysis: Analysis of infants managed with conservative [C] vs treatment [M + S]**

### **Perinatal characteristics and short-term morbidities**

Table 1 presents the perinatal characteristics and short-term morbidities between infants managed conservatively [C] and those who received either medical or surgical treatment [M + S]. Analysis of the antenatal and perinatal characteristics revealed that group M + S infants were of higher acuity at birth as measured by CRIB II ( $p = 0.046$ ) and had more severe RDS ( $p = 0.04$ ). The incidence of CLD in the group M + S infants was statistically significant ( $p = 0.005$ ). The OR of group M + S infants developing CLD was also significant (OR 6.83 (95% CI 1.49–31.3)) compared to group C infants. At discharge, group M + S infants were significantly shorter ( $p = 0.017$ ) and had a smaller head circumference ( $p = 0.039$ ) than group C infants. The weight at discharge z-score was statistically insignificant ( $p = 0.18$ ).

Table 1  
Perinatal characteristics and short-term morbidities of infants classified by treatment

	Conservative n = 17	Main group analysis		Subgroup analysis			
		Medical and/or surgical n = 107	P value	Medical n = 83	P value <sup>b</sup>	Surgical n = 24	P value <sup>a</sup>
	n (%) / mean ± SD	n (%) / mean ± SD		n (%) / mean ± SD		n (%) / mean ± SD	
Perinatal Characteristics							
Gender							
Male	8 (47.1)	61 (57.0)	0.44	49 (59.0)	0.55	12 (50.0)	0.55
Mode of Delivery							
LSCS	8 (47.1)	51 (47.7)	0.96	43 (51.8)	0.28	8 (33.3)	0.28
GA (weeks)	26.5 ± 1.2	26.2 ± 1.3	0.28	26.4 ± 1.3	0.63	25.5 ± 1.0	<b>0.004<sup>a</sup></b>
BW (g)	914.4 ± 160.5	885.6 ± 195.3	0.57	915.7 ± 200.0	0.98	781.8 ± 136.5	<b>0.007<sup>a</sup></b>
Z-score BW	0.05 ± 0.7	-0.01 ± 0.8	0.77	0.03 ± 0.8	0.93	-0.1 ± 0.8	0.40
Z-score birth length	0.04 ± 1.0	-0.3 ± 1.1	0.19	-0.3 ± 1.0	0.22	-0.4 ± 1.1	0.21
Z-score birth head circumference	0.4 ± 0.8	0.08 ± 1.0	0.24	0.1 ± 1.0	0.35	-0.1 ± 0.8	0.07
APGAR (5 min) < 7	2 (13.3)	12 (11.7)	0.85	9 (11.4)	0.97	3 (12.5)	0.97
CRIB II > 12	1 (6.3)	32 (29.9)	<b>0.046</b>	21 (25.3)	<b>0.019<sup>b</sup></b>	11 (45.8)	<b>0.019<sup>a</sup></b>
Perinatal Outcomes							
Severe RDS Grade 2–4	8 (47.1)	77 (72.0)	<b>0.04</b>	61 (73.5)	0.10	16 (66.7)	0.10
Surfactant Therapy > 2 doses	2 (11.8)	14 (13.1)	0.88	9 (10.8)	0.43	5 (20.8)	0.43
Sepsis	7 (41.2)	31 (29.0)	0.31	22 (26.5)	0.35	9 (37.5)	0.35
Severe IVH Grade 2–4	2 (11.8)	23 (21.5)	0.35	14 (16.9)	0.06	9 (37.5)	0.06
PVL	0 (0.0)	4 (3.7)	0.42	4 (3.7)	0.36	0 (0.0)	0.36
NEC or NEC with complication/surgery	0 (0.0)	8 (7.5)	0.24	6 (7.2)	0.50	2 (8.3)	0.50

	Conservative n = 17	Main group analysis		Subgroup analysis			
		Medical and/or surgical n = 107		Medical n = 83		Surgical n = 24	
Threshold ROP Stage 3-4	3 (17.6)	21 (21.6)	0.71	12 (16.4)	0.08	9 (37.5)	0.08
CLD <sup>c</sup>	2 (11.8)	51 (47.7)	<b>0.005</b>	33 (39.8)	<b>0.000<sup>b</sup></b>	18 (75.0)	<b>0.000<sup>a</sup></b>
Discharge Parameters of Survivors							
Length of Stay of survivors (days)	87.1 ± 29.3	99.2 ± 37.9	0.21	90.3 ± 33.1	0.71	126.7 ± 39.2	<b>0.001<sup>a</sup></b>
Discharge GA (weeks)	38.9 ± 3.7	40.4 ± 4.8	0.22	39.3 ± 4.0	0.67	43.6 ± 5.6	<b>0.004<sup>a</sup></b>
Weight at Discharge z-score	-2.4 ± 1.0	-2.8 ± 1.2	0.18	-2.6 ± 1.2	0.48	-3.4 ± 1.0	<b>0.003<sup>a</sup></b>
Length at Discharge z-score	-2.7 ± 1.1	-3.8 ± 1.4	<b>0.017</b>	-3.6 ± 1.5	0.07	-4.3 ± 1.1	<b>0.001<sup>a</sup></b>
Head circumference at Discharge z-score	-1.4 ± 0.8	-2.1 ± 1.0	<b>0.039</b>	-2.0 ± 1.0	0.08	-2.4 ± 1.2	<b>0.026<sup>a</sup></b>
<sup>a</sup> P value for comparison between surgical and conservative treatment							
<sup>b</sup> P value for comparison between medical and conservative treatment							
<sup>c</sup> We assumed the worst case scenario that infants who died prior to 36 weeks developed CLD							

## Death and neurodevelopment outcomes

Table 2 presents death and neurodevelopmental outcomes. The primary composite outcome of death and/or qualitative neurodevelopmental delay was not significantly higher in group M + S infants as compared to group C infants (OR 3.35 (95% CI 0.72–15.5, p = 0.105)).

Table 2  
Primary outcomes death and neurodevelopmental morbidities

	Conservative n = 17	Main group analysis		Subgroup analysis			
		Medical and/or surgical n = 107	P value	Medical n = 83	P value <sup>b</sup>	Surgical n = 24	P value <sup>a</sup>
	n (%) / mean ± SD	n (%) / mean ± SD		n (%) / mean ± SD		n (%) / mean ± SD	
Death	0 (0.0)	13 (12.1)	0.13	12 (14.5)	0.11	1 (4.2)	0.11
Global developmental delay (GDD)	2 (11.8)	20 (21.3)	0.37	14 (19.7)	0.53	6 (26.1)	0.53
Death or GDD	2 (11.8)	33 (30.8)	0.11	26 (31.3)	0.26	7 (29.2)	0.26
CP	1 (5.9)	9 (9.6)	0.63	6 (8.5)	0.71	3 (13.0)	0.71
Abnormal hearing test at Discharge	1 (5.9)	7 (7.4)	0.83	4 (5.6)	0.52	3 (12.5)	0.52
Hearing loss requiring hearing aids or implants	1 (5.9)	6 (6.4)	0.94	4 (5.6)	0.87	2 (8.7)	0.87
Isolated speech delay	3 (17.6)	16 (17.0)	0.95	11 (15.5)	0.79	5 (21.7)	0.79
<sup>a</sup> P value for comparison between surgical and conservative treatment							
<sup>b</sup> P value for comparison between medical and conservative treatment							

## Treatment specific complications

In the analysis of treatment specific complications (Table 3), the only statistically significant finding was the highest measured creatinine level. Highest creatinine was recorded during 2–4 weeks of life in group C infants, and up to 72 h from the last dose of COX inhibitors in group M + S infants. Of note, one infant in group C had an out-of-trend creatinine level of 256 µmol/L due to underlying kidney disease. This infant was excluded. The highest measured creatinine was significantly higher in group M + S (p = 0.000) than in group C.

Table 3  
Complications of treatment observed in infants classified by treatment

	Conservative n = 17	Main group analysis		Subgroup analysis			
		Medical and/or surgical n = 107	P value	Medical n = 83	P value <sup>b</sup>	Surgical n = 24	P value <sup>a</sup>
	n (%) / mean ± SD	n (%) / mean ± SD	P value	n (%) / mean ± SD	P value <sup>b</sup>	n (%) / mean ± SD	P value <sup>a</sup>
Pulmonary haemorrhage	1 (6.3)	19 (17.8)	0.25	14 (6.9)	0.46	5 (20.8)	0.46
Oliguria (< 1 ml/kg/h)	0 (0.0)	5 (4.7)	0.38	2 (2.4)	0.06	3 (12.5)	0.06
Acute kidney injury	0 (0.0)	4 (3.7)	0.43	2 (2.4)	0.26	2 (8.3)	0.26
No. of courses of medical therapy	0.0 ± 0.0	1.4 ± 0.5	0.45	1.3 ± 0.5	0.59	2.0 ± 0.5	0.06
Highest creatinine	48.3 ± 11.8	81.1 ± 24.1	<b>0.000</b>	79.7 ± 20.9	<b>0.000<sup>b</sup></b>	85.7 ± 32.6	<b>0.004<sup>a</sup></b>
Intestinal perforation	0 (0.0)	5 (4.7)	0.36	4 (4.8)	0.65	1 (4.2)	0.65
Vocal cord paralysis	0 (0.0)	6 (5.6)	0.32	0 (0.0)		6 (25.0)	<b>0.000<sup>a</sup></b>
Aspiration pneumonia	0 (0.0)	1 (0.9)	0.69	0 (0.0)		1 (4.2)	0.12
<sup>a</sup> P value for comparison between surgical and conservative treatment							
<sup>b</sup> P value for comparison between medical and conservative treatment							

**Subgroup Analysis: Analysis of infants managed with Conservative [C] vs Medical [M] and [C] vs Surgical [S]**

## Perinatal characteristics and short-term morbidities

Table 1 presents the perinatal and short-term morbidities between infants managed with conservative [C], medical [M] and surgical [S] treatment. Infants in both group M (#p = 0.019) and S (\*p = 0.019) were of higher acuity at birth, but presence of severe RDS was not statistically significant (#p = 0.10, \*p = 0.10). The incidence of CLD the in both group M (#p = 0.000) and S (\*p = 0.000) was higher than C group. Group S infants were more likely than group C infants to develop CLD. The OR of group S infants developing CLD was 22.50 (95% CI 3.95–128.3, p = 0.000) when compared to group C infants. Similarly, group M infants were also more likely to develop CLD than group C infants (OR 4.95 (95% CI 1.06–23.1, p = 0.027)).

There were notable differences in the birth and discharge anthropometric data between the treatment groups. Group S infants were significantly younger by 1 week (\*p = 0.004) and lighter by 130 g (\*p = 0.007) as compared to group C infants. At discharge, group S infants continued to have poorer growth with lower z-scores in all anthropometric parameters – weight (\*p = 0.003), length (\*p = 0.001), head circumference (\*p = 0.026) as

compared to group C. The infants in group S also had a longer stay in the NICU (\*p = 0.001) and thus discharged at an older GA (\*p = 0.004) as compared to group C infants.

## Death and neurodevelopment outcomes

The primary composite outcome of death and/or qualitative neurodevelopmental delay was not different for the infants in group M or S (Table 2).

## Treatment specific complications

The highest measured creatinine was significantly higher in group M (#p = 0.000) and S (\*p = 0.004) infants than in group C infants. No infant developed vocal cord palsy in group C or M. However, incidence of vocal cord palsy was 25% in group S (\*p = 0.000). The OR of developing vocal cord palsy for group S as compared to group C was 1.94 (95% CI 1.41–2.68, p = 0.026) (Table 3).

## Discussion

We examined a cohort of Asian VLBWs with HsPDA. Studies from National Institute of Child Health and Human Development (NICHD) showed that Asian-American are at higher risk of having HsPDA [24]. A comparison between Japan and Canadian neonatal units showed that there is a difference in the composite outcome of morbidity and mortality among VLBW infants, where the Japanese population (46%) had a lower composite outcome than Canadian population (55%) among infants with PDA (OR 0.70 95% CI 0.62–0.80, p < 0.01) [25]. Our study is one of the first to examine the immediate and neonatal outcomes of following various treatment strategies of HsPDA in the Asian population.

We found that surgical treatment of HsPDA in VLBW is associated with several worse short-term outcomes. They had more CLD, a poorer growth at discharge and a longer hospitalization. However, those surgically treated infants were of lower GA and BW, sicker with more severe RDS and a larger proportion of them had higher CRIB II scores. Surgical complications like vocal cord palsy may also contributed to poorer feeding and subsequent growth failure leading to longer hospital stay. Despite this, death and or adverse neurodevelopmental outcomes were not increased in early childhood in surgically treated group. However, a type-II error cannot be excluded as the number of surgically treated infants was small.

In our study, infants requiring surgical treatment were of lower GA and BW which lends further support to earlier studies that found the relationship between the rate of ductal closure, GA and BW [2, 3, 26] to be inversely proportionate. Similarly, in another Asian cohort of VLBW infants, a positive correlation between decreasing GA and lower survival was found and the incidence of major neonatal morbidities such as CLD, sepsis, severe ROP and severe IVH were higher with decreasing gestation, although NEC did not show a similar trend [27].

The effects of medical or surgical treatment of PDA on neurodevelopmental outcomes has become a topic of increasing interest. Yet, there has been no well-established relationship between the two. Two studies determined surgical ligation as a higher risk factor for neurodevelopmental impairment as compared to medical treatment [28, 29]. In contrast, Chorne et al [30] found no relationship between surgical ligation and neurodevelopment outcomes. Whereas, a study reported recently by Janz-Robinson et al. [31] found treatment with medical or surgical treatment to be associated with neurodevelopmental impairment. Our findings are consistent with Chorne et al. [30] and we found no significant differences in neurodevelopmental outcomes in

both the main group analysis and subgroup analysis. The discrepancy in results among different studies highlights the gap in the literature and emphasizes the urgent need for large randomized control trials (RCT) to further evaluate the neurodevelopmental outcomes in the treatment of HsPDA.

We found that the infants in group M + S, group M and group S were sicker compared with infants in group C with a higher incidence of CRIB II score > 12, predicting a greater risk of neonatal mortality among very low BW infants.[18] Base excess, a constituent of the CRIB II score, is an independent predictor of medical PDA closure response [32, 33]. Consequently, it may be challenging to manage the infant with worse base excess conservatively, resulting in the infant receiving either COX inhibitors or surgical ligation. Infants in group M + S, as well as M and S, were more likely to have severe RDS, in which mechanical ventilation is commonly administered [34]. Mechanical ventilation has been identified to be an independent risk factor for failed medical PDA closure [35], and it is possible that severe RDS is in fact part of the causal pathway of HsPDA requiring medical or surgical treatment.

Earlier studies have suggested that prolonged exposure to PDA is associated with multiple neonatal morbidities [30, 36, 37]. We found differing results and determined that the group C infants did not have worse intermediate neonatal outcomes than group M and S infants. Several studies have shown surgical ligation to be associated with CLD [29, 30, 38, 39] which is congruent with our findings. A part of the confounding effect may be these surgical infants had failed medical treatment and had longer ventilation prior to surgical ligation.

The association between medical treatment and CLD is not well defined. Our findings suggest that there is a higher incidence and OR of group M infants developing CLD than group C infants, assuming the worst case scenario, that infants who died prior to 36 weeks had developed CLD. Prolonged exposure to PDA has historically been associated with CLD [36, 40]. Our study supports others [41] who found that the adjusted odds of having CLD for extremely low birth weight (ELBW) infants with persistent HsPDA is > 3 times that of ELBW infants whose PDAs were successfully closed medically. This is in contrast to the recent PDA-Tolerate study [42] where the authors found no difference in CLD or death outcomes but up to 48% of those in the conservative arm required rescue treatment before discharge. Even with medical treatment, up to 32% of the infants in the early treatment had treatment failure and subsequently some had ligation prior to discharge. These infants may hence dilute the effects of treatment in the primary outcomes. This serves as a call for bigger prospective study like the BeneDuctus Trial [43] currently ongoing to validate the true association between HsPDA exposure, management of HsPDA and CLD.

Group S infants had a longer duration of stay and hence discharged at an older GA. This is likely attributed to two reasons. Firstly, group S infants were significantly more premature at birth, with a lower GA (difference of 1 week) and BW (lighter by 130 g). This warrants them a longer inpatient stay, where discharge readiness is often assessed by functional maturation, feeding ability and weight gain [44]. Secondly, group S infants' condition may be affected by the complications of surgery. At discharge, the group M + S infants were smaller in size at discharge compared to group C infants; where the z-score of length and head circumference were significantly lower. Subgroup analysis showed that the group S infants were significantly lighter, shorter and smaller head circumference than the group C infants at discharge; whereas, group M and C infants had comparable discharge anthropometric parameters.

## Limitations and strengths

This study has several limitations due to the retrospective nature. Firstly, there are no definite criteria for the diagnosis of HsPDA as bedside measurement of the PDA can be subjective and the decision for treatment is not standardised due to a lack of universal guidelines. Secondly, there were variations of treatment practices over the years with increasing trend towards conservative treatment. It has only been in the recent years that the trend of PDA treatment has shifted towards a less aggressive approach [24]. As such, majority of the infants with HsPDA in our database from 2007–2016 were treated either medically or surgically. In addition, it is known from the natural history of PDA that more premature and lower BW infants are less likely to have spontaneous closure [2, 3] and hence there is a lower threshold to treat these infants. It was challenging to find infants managed conservatively, particularly those who were 24 and 25 weeks GA. Thirdly, as surgical ligation was only considered when the PDA failed to close after medical or conservative treatment, it was often performed in potentially sicker infants which can result in more surgically-related side effects. Because it is a retrospective study, we can only establish correlations but not determine the causation between the treatment type and the outcomes. Lastly, this is a single centre study with small sample size, thus a type II error cannot be excluded. A strength of our study is the protocol-based treatment. This reduces the variability in the treatment regimen and improve the quality of our results. As it is a single centre, we have removed the variability between cardiac echocardiographic assessment of the HsPDA and the surgical competency of the surgeon.

## Conclusions

We showed in our cohort of Asian infants of < 29 weeks, immaturity and lower BW predict the failure of conservative or medical treatment. Those who required treatment and especially surgical treatment have more neonatal complications of CLD, a longer duration of hospitalization and poorer growth. However, they did not have higher incidence of death or adverse neurological developmental outcomes. We await larger randomized control studies to confirm our findings.

## Abbreviations

Birth weight (BW)

Cerebral palsy (CP)

Chronic lung disease (CLD)

Continuous positive airway pressure (CPAP)

Cyclo-oxygenase inhibitors (COX)

Extremely low birth weight (ELBW)

Gestational age (GA)

Hemodynamically significant patent ductus arteriosus (HsPDA),

High Clinical Risk Index for Babies (CRIB II)

Intraventricular haemorrhage (IVH),

Left Atrium: Aortic Root (LA: Ao)

Medical treatment (M)

National Institute of Child Health and Human Development (NICHD)

National University Hospital (NUH)

Necrotising enterocolitis (NEC)

Neonatal intensive care unit (NICU)

Nitric oxide (NO)

Patent ductus arteriosus (PDA)

Odds ratio (OR)

Periventricular leukomalacia (PVL)

Randomized control trials (RCT)

Respiratory Distress Syndrome (RDS)

Retinopathy of prematurity (ROP)

Surgical treatment (S)

Very low birth weight (VLBW)

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### **Conflicts of interest/Competing interests**

The authors have no conflicts of interest to declare that are relevant to the content of this article.

### **Ethics approval**

Ethics approval was given by the National Health Group Domain Specific Ethics Review Board (NHG DSRB ref 2020/00001)

### **Consent to participate**

The study being retrospective review of existing data, waiver of consent to participate was granted

### **Consent for publication**

Not applicable as the manuscript does not involve any identifiable data

### **Availability of data and material**

Data is confidential and can be shared upon request.

### **Code availability (software application or custom code)**

Not applicable

### **Authors' contributions**

WJY,J - collected data, did data analysis and wrote the paper first draft

KN - collected data and review the paper

LLY - conceptualised the idea, did data analysis, wrote and review the paper

ZA - wrote and review the paper

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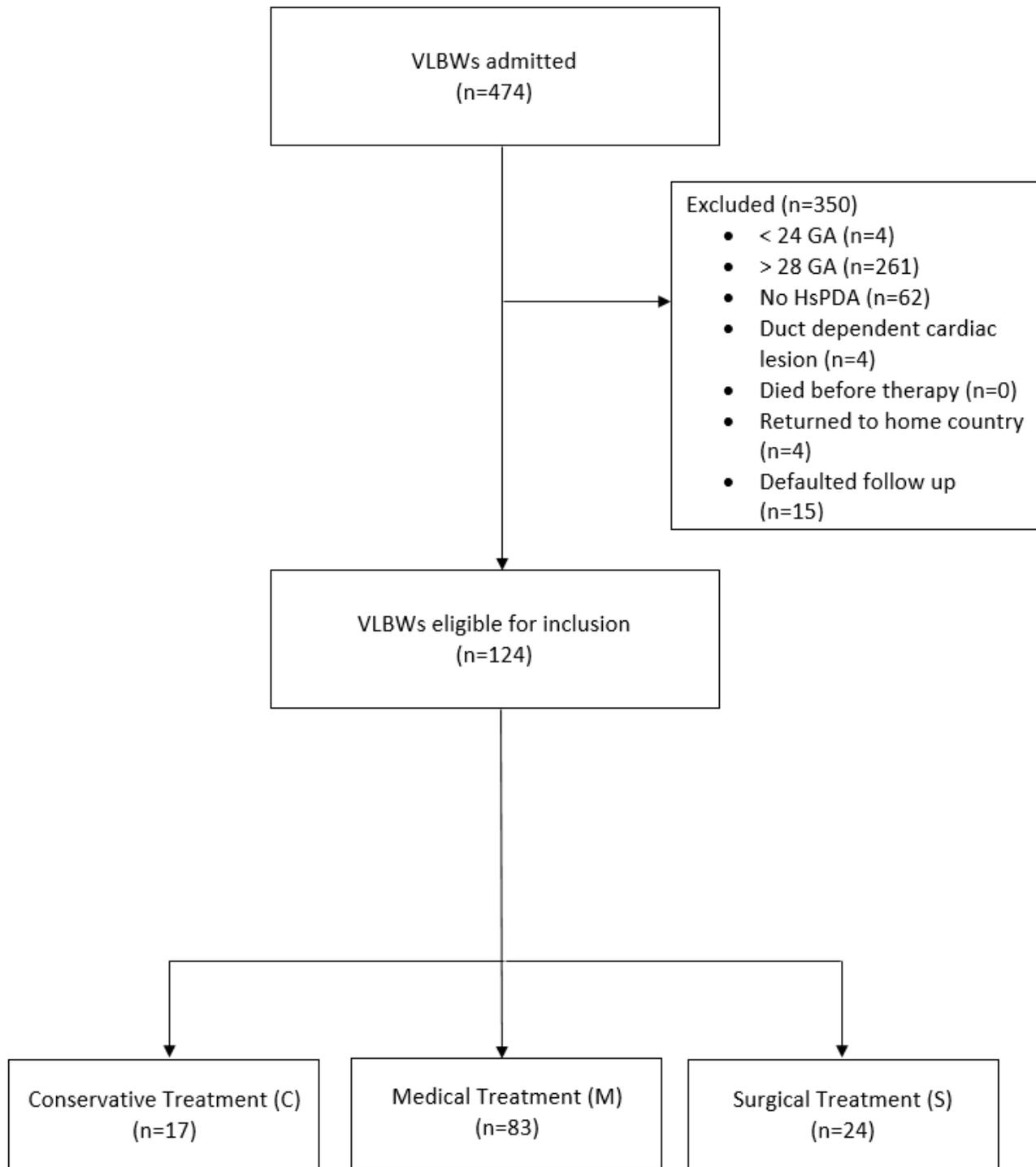
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# Figures



**Figure 1**

A total of 474 VLBW infants were admitted in NUH from 2007–2016; of which 124 infants met study criteria