

# Surgical ligation of patent ductus arteriosus in very low birth weight infants: A 9-year single center experience

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## Research article

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# Abstract

## Background

We analyzed the feasibility and outcomes of early surgical ligation in very low birth weight infants (VLBWIs) with hemodynamically significant patent ductus arteriosus (HSPDA) and investigated predictors for surgical treatment after unsuccessful medical management.

## Methods

Medical records from the neonatal intensive care unit of Hanyang University Seoul Hospital from January 2010 to December 2018 were retrospectively reviewed. 233 VLBWIs with HSPDA were enrolled in our study. Of these infants, 134 underwent surgical ligation and were subdivided into the early ligation group (n = 49; within 10 days of age) and the late ligation group (n = 85; after 10 days of age).

## Results

The mean gestational age and birth weight were significantly lower in the patent ductus arteriosus (PDA) ligation group than in the Non-ligation group ( $p < 0.001$ ). PDA ductal diameter  $> 2.0$  mm ( $p < 0.001$ ), low Apgar score at 5 minutes ( $p = 0.033$ ), and chorioamnionitis ( $p = 0.037$ ) were the predictors for receiving surgical treatment for PDA. Early ligation was significantly associated with a low incidence of culture-proven sepsis ( $p = 0.004$ ), mechanical ventilator time  $> 4$  weeks ( $p = 0.007$ ), necrotizing enterocolitis stage (NEC)  $\geq$  III ( $p = 0.022$ ), and intraventricular hemorrhage (IVH) grade  $\geq$  III ( $p = 0.035$ ).

## Conclusions

Early surgical ligation minimizes adverse effects of HSPDA in predicted infants who subsequently require surgical treatment for PDA. We suggest that predicted VLBWIs with HSPDA that is unresponsive to medical treatment should avoid delayed ductal closure to reduce severe NEC, severe IVH, culture-proven sepsis, and facilitate earlier endotracheal extubation.

## Background

Patent ductus arteriosus (PDA) is one of the most common congenital anomalies in premature infants [1–3] and is associated with increased morbidity and mortality due to acute hemodynamic and respiratory compromise [4–5]. Although hemodynamically significant patent ductus arteriosus (HSPDA) in preterm infants has been proven to increase morbidities such as necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), heart failure and renal hypoperfusion [5–8], no randomized clinical trial has shown the benefit or efficacy of surgical ligation compared with no PDA ligation in very low birth weight infants (VLBWIs) with HSPDA that is refractory to medical treatment [9].

If pharmacologic treatment is contraindicated or fails, surgical ligation can be considered. Surgical ligation can be performed at the bedside in the neonatal intensive care unit (NICU) without a high risk of surgical morbidity or mortality [5]. Although PDA surgical ligation after unsuccessful medical treatment is a definitive treatment, studies on the proper timing of surgery for HSPDA are few [4, 6], and the proper timing of surgical ligation remains controversial.

In this study, we analyzed the feasibility of early surgical ligation (within 10 days of age) in VLBWIs with HSPDA and investigated parameters that would be helpful for deciding on early surgery.

## Methods

### Study populations

Hanyang University Seoul Hospital is a tertiary referral center for patients with a multidisciplinary PDA team in Seoul, South Korea. We retrospectively reviewed all the medical records of the NICU at our center from January 2010 to December 2018 to identify VLBWIs (< 1,500 g). Our institutional review board approved this study, and the need for patient consent was waived (IRB number; HYUH 2019-07-004-003).

### Medical Treatment

The direction of treatment for PDA was determined by the neonatologist. Most HSPDA patients were initially treated with 2 or 3 cycles of nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin or ibuprofen. The protocol for indomethacin and ibuprofen treatment is described in Table 1. Contraindications to NSAID treatment at our center were gastrointestinal bleeding, IVH grade > I, poor urine output (< 0.6 mL/kg/hr), high serum creatinine (> 1.8 mg/dL), high blood urea (> 30 mg/dL), positive disseminated intravascular coagulation (DIC) profiles, or thrombocytopenia (< 60,000 /mm<sup>3</sup>), as in our previous publication [4].

Table 1  
Protocol for NSAID treatment.

Age at 1st dose	1st	2nd	3rd
Indomethacin (mg/kg) <sup>a)</sup>			
< 48 hours	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
> 7 days	0.2	0.25	0.25
Ibuprofen (mg/kg) <sup>b)</sup>			
	10	5	5
NSAID, nonsteroidal anti-inflammatory drug.			
a) At 12- to 24-hour intervals. b) At 24-hour intervals.			

## Surgical Treatment

The decision to refer an HSPDA infant to the department of Thoracic and Cardiovascular Surgery for surgical ligation after failure or due to contraindications of medical therapy was performed by a neonatologist specialized in echocardiography. All operations were performed at the NICU bedside with the infant under general anesthesia. A left transaxillary mini-thoracotomy via the 3rd or 4th intercostal space was used as the PDA approach. The ductus arteriosus was ligated using a single medium or medium-large sized titanium Horizon clip (Teleflex Medical, Research Triangle Park, NC, USA). Immediately after the operation, the attending neonatologist checked with echocardiography to determine whether the PDA ligation was successful.

## Endpoints, Definitions And Follow-up

The PDA ligation group comprised patients who underwent surgical ligation, and the Non-ligation group comprised patients who did not undergo surgical treatment. As mentioned above, the early ligation (EL) group comprised patients who underwent PDA ligation within 10 days of age, and the late ligation (LL) group comprised patients who underwent surgery after 10 days of age.

The primary outcome of this study was a comparison of mortality between the PDA ligation and Non-ligation groups and the EL and LL groups. Secondary outcomes were factors associated with PDA surgical ligation and postoperative clinical outcomes such as NEC, BPD, IVH (grade  $\geq$  III), sepsis, retinopathy of prematurity (ROP), and periventricular leukomalacia (PVL).

Echocardiography was performed within 3 days of birth, and subsequent echocardiographic parameters were obtained on day 6 ( $\pm$  1 day), day 9 ( $\pm$  1 day), and day 14 ( $\pm$  2 days) to identify symptomatic PDA in

preterm infants. Symptomatic PDA indicated HSPDA, which was defined as a ductal diameter  $\geq 1.5$  mm, or a ratio of 1.5 or more of the size of the left atrium to the diameter of the aortic root on at least one echocardiography (HD11 Diagnostic Ultrasound Imaging System and Transducers; Philips Ultrasound, Bothell, WA, USA). This definition was based on the description of the previous publication [9]. Associated symptoms with HSPDA classified at our center have been described previously [4].

IVH was classified by Volpe's grading system [10]. Culture-proven sepsis was defined as the presence of positive findings in one or more blood cultures and clinical symptoms of infection. NEC was defined using Bell's modified staging criteria [11]. BPD was defined by Jobe and Bancalari's criteria [12]. The stages of ROP were classified using the international classification of retinopathy of prematurity [13].

## Statistical Analyses

Data were expressed as either the mean  $\pm$  standard deviation or frequency and proportion. Comparisons between groups were performed with chi-square tests and Fisher's exact tests for categorical variables. Two sample Student's t-tests were used for continuous variables when a normal distribution was found. The Mann-Whitney U test was used for variables with skewed distributions. All tests were two-tailed. Logistic regression analysis was used to determine risk factors between the PDA ligation and Non-ligation groups, and clinical morbidities between the EL and LL groups. Receiver operating characteristic (ROC) curves were constructed for the assessment of significant factors associated with PDA surgical ligation. All p values of less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS, version 22.0 (SPSS, Chicago, IL, USA).

## Results

A total of 383 VLBWIs were diagnosed in the NICU from January 2010 to December 2018. Infants with other congenital anomalies (n = 9), incomplete data including echocardiography findings (n = 4), and a diameter less than 1.5 mm (n = 57) were excluded, along with 29 patients who died within 10 days of birth. After the exclusion of 51 infants who were diagnosed with HSPDA but did not undergo any treatment such as surgical or medical therapy, 233 VLBWIs with HSPDA were ultimately enrolled in our study. Of these infants, 134 (57.5%) underwent surgical ligation and were subdivided into the EL group (n = 49, 36.6%) and the LL group (n = 85, 63.4%). The conditions of 99 infants improved with medical treatment alone (Fig. 1).

The baseline characteristics of the patients in the PDA ligation and Non-ligation groups are summarized in Table 2. Regarding maternal characteristics, histologic chorioamnionitis was significantly higher in the PDA ligation group than in the Non-ligation group (p = 0.027), while pregnancy-induced hypertension (PIH) was significantly lower in the PDA ligation group than in the Non-ligation group (p = 0.031). Regarding infant characteristics, gestational age (GA), birth weight, length, head circumference, and Apgar scores at 1 minute and 5 minutes were significantly lower in the PDA ligation group than in the Non-ligation group. In contrast, time on a mechanical ventilator or on oxygen therapy, total parenteral

nutrition and hospitalization, and age at PDA closure were significantly higher in the PDA ligation group than in the Non-ligation group. Additionally, PDA size ( $2.13 \pm 0.84$  mm vs  $1.68 \pm 0.92$  mm,  $p < 0.001$ ) and the proportion of infants with PDA ductal diameters larger than 2.0 mm (52.2 vs 22.2%,  $p < 0.001$ ) were significantly different between the PDA ligation and Non-ligation groups.

Table 2  
 Characteristics of preterm infants of the PDA ligation and Non-ligation groups.

Variables	PDA ligation (n = 134)	Non-ligation (n = 99)	P value
Maternal characteristics			
Maternal age, years	32.58 ± 4.30	33.29 ± 4.10	0.205
Mother's education level			0.946
High, n (%)	9 (6.7)	6 (6.1)	
Intermediate, n (%)	88 (65.7)	67 (67.7)	
Low, n (%)	37 (27.6)	26 (26.3)	
GDM	10 (7.5)	10 (10.1)	0.488
PIH	9 (6.7)	16 (16.2)	0.031
PPROM	56 (41.8)	42 (42.4)	> 0.999
Histologic chorioamnionitis	104 (77.6)	63 (63.6)	0.027
Infant characteristics			
Gestational age, weeks	26.27 ± 2.28	27.37 ± 1.90	< 0.001
Birth weight, grams	882.05 ± 226.61	1053.23 ± 244.76	< 0.001
Length	33.69 ± 4.59	35.96 ± 3.36	< 0.001
Head circumference	24.60 ± 3.10	25.58 ± 2.37	0.010
Cesarean section	98 (73.1)	81 (81.8)	0.157
Male sex	69 (51.5)	41 (41.8)	0.183
Apgar score at 1 minute	2.10 ± 1.30	2.73 ± 1.33	< 0.001
Apgar score at 5 minutes	4.58 ± 1.67	5.40 ± 1.55	< 0.001
Antenatal corticosteroids	92 (68.7)	73 (73.7)	0.467
Postnatal corticosteroids	57 (42.5)	31 (31.3)	0.101
Age at PDA closure, days	15.57 ± 8.94	8.10 ± 2.71	< 0.001

PDA, patent ductus arteriosus; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.

Data are the mean ± SD or number (%).

Variables	PDA ligation (n = 134)	Non-ligation (n = 99)	P value
Body weight at surgical ligation	911.87 ± 270.16	-	-
IVH	50 (37.3)	43 (43.4)	0.417
IVH grade II	8 (6)	3 (3)	0.241
IVH grade ≥ III	21 (15.7)	17 (17.2)	0.858
PVL	10 (7.5)	9 (9.1)	0.809
Culture-proven sepsis	83 (61.9)	55 (55.6)	0.347
NEC	12 (9.0)	10 (10.1)	0.823
NEC stage ≥ III	41 (30.8)	22 (22.2)	0.180
BPD	74 (55.6)	44 (44.9)	0.112
ROP	80 (60.2)	54 (55.1)	0.501
Days on mechanical ventilator	30.62 ± 18.63	16.20 ± 14.55	< 0.001
Days of oxygen therapy	68.70 ± 52.01	49.41 ± 28.20	0.001
TPN days	44.44 ± 25.64	36.59 ± 21.21	0.014
Hospital days	96.00 ± 40.44	79.89 ± 28.56	0.001
PDA size	2.13 ± 0.84	1.68 ± 0.92	0.001
PDA ductal diameter > 2.0 mm	70 (52.2)	22 (22.2)	< 0.001
Deaths	1 (0.7)	2 (2)	0.576
PDA, patent ductus arteriosus; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PPRM, preterm premature rupture of membranes; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; TPN, total parenteral nutrition.			
Data are the mean ± SD or number (%).			

The baseline characteristics of the patients in the EL and LL groups are summarized in Table 3. Age at PDA closure ( $8.18 \pm 2.14$  vs  $19.44 \pm 8.82$  days,  $p < 0.001$ ) and body weight at surgical ligation ( $847.96 \pm 201.73$  vs  $948.71 \pm 297.58$  grams,  $p = 0.037$ ) were significantly different between the EL and LL groups. The baseline maternal characteristics and preoperative status did not differ significantly between the EL and LL groups. Regarding infant characteristics, cesarean section was significantly higher in the EL group than in the LL group ( $p = 0.044$ ). In contrast, culture-proven sepsis ( $p = 0.026$ ), NEC stage  $\geq$  III ( $p = 0.030$ ), and time on a mechanical ventilator ( $p = 0.048$ ) was significantly lower in the EL group than in the LL group.

Table 3  
 Characteristics of preterm infants of the early ligation and late ligation groups.

Variables	Early ligation (n = 49)	Late ligation (n = 85)	P value
Maternal characteristics			
Maternal age, years	33.22 ± 5.16	32.21 ± 3.71	0.205
Mother's education level			0.835
High, n (%)	3 (6.1)	6 (7.1)	
Intermediate, n (%)	31 (63.3)	57 (67.1)	
Low, n (%)	15 (30.6)	22 (25.9)	
GDM	2 (4.1)	8 (9.4)	0.325
PIH	5 (10.2)	4 (4.7)	0.287
PPROM	15 (30.6)	41 (48.2)	0.068
Histologic chorioamnionitis	42 (85.7)	62 (72.9)	0.131
Infant characteristics			
Gestational age, weeks	26.67 ± 2.52	26.04 ± 2.11	0.123
Birth weight, grams	878.78 ± 216.77	883.94 ± 233.34	0.899
Length	33.10 ± 3.05	34.03 ± 5.27	0.259
Head circumference	24.48 ± 2.30	24.68 ± 3.49	0.719
Cesarean section	41 (83.7)	57 (67.1)	0.044
Male sex	24 (49)	41 (48.2)	> 0.999
Apgar score at 1 minute	2.08 ± 1.27	2.11 ± 1.33	0.918
Apgar score at 5 minutes	4.76 ± 1.58	4.48 ± 1.72	0.367
Antenatal corticosteroids	34 (69.4)	58 (68.2)	> 0.999
Postnatal corticosteroids	17 (34.7)	40 (47.1)	0.205
Age at PDA closure, days	8.18 ± 2.14	19.44 ± 8.82	< 0.001

GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PPRM, preterm premature rupture of membranes; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; GI, gastrointestinal; TPN, total parenteral nutrition; PDA, patent ductus arteriosus.

Data are the mean ± SD or number (%).

<b>Variables</b>	<b>Early ligation (n = 49)</b>	<b>Late ligation (n = 85)</b>	<b>P value</b>
Body weight at surgical ligation	847.96 ± 201.73	948.71 ± 297.58	0.037
IVH	18 (36.7)	32 (37.6)	> 0.999
IVH grade II	4 (8.2)	4 (4.7)	0.240
IVH grade ≥ III	4 (8.2)	17 (20.2)	0.086
PVL	3 (6.1)	7 (8.2)	0.746
Culture-proven sepsis	24 (49)	59 (69.4)	0.026
NEC	18 (36.7)	24 (28.2)	0.337
NEC stage ≥ III	2 (4.1)	15 (17.6)	0.030
BPD	25 (52.1)	49 (57.6)	0.588
ROP	32 (66.7)	48 (56.5)	0.273
Pneumothorax before ligation	2 (4.1)	2 (2.4)	0.623
Pulmonary hemorrhage before ligation	3 (6.1)	8 (9.4)	0.746
GI hemorrhage before ligation	1 (2.0)	7 (8.2)	0.257
Hypotension before ligation	11 (22.4)	21 (24.7)	0.836
Hypotension after ligation	2 (4.1)	3 (3.5)	> 0.999
Days on mechanical ventilator	26.38 ± 15.31	33.02 ± 19.95	0.048
Days of oxygen therapy	59.88 ± 33.88	74.51 ± 56.89	0.107
TPN days	40.73 ± 21.45	47.41 ± 28.36	0.156
Hospital days	94.53 ± 38.86	95.88 ± 41.52	0.853
PDA size	2.06 ± 0.67	2.16 ± 0.92	0.481
PDA ductal diameter > 2.0 mm	25 (51.0)	45 (52.9)	0.859
Deaths	0 (0)	1 (1.2)	> 0.999
GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PPRM, preterm premature rupture of membranes; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; GI, gastrointestinal; TPN, total parenteral nutrition; PDA, patent ductus arteriosus.			
Data are the mean ± SD or number (%).			

No patients died during their operations. Two infants required reoperation due to residual flow of PDA, as diagnosed by immediate postoperative transthoracic echocardiography. Three patients died during the postoperative hospital day. In the LL group, one infant died 100 days after PDA ligation due to NEC. In the Non-ligation group, two infants died 12 and 17 days after birth, and the cause of death was sepsis. There were no statistically significant differences in mortality rate between the PDA ligation and Non-ligation groups ( $p = 0.576$ ), or between the EL and LL groups ( $p > 0.999$ ).

The logistic regression analysis for factors associated with PDA surgical ligation is presented in Fig. 2. PDA ductal diameter  $> 2.0$  mm ( $p < 0.001$ ), low GA ( $p = 0.004$ ), low Apgar score at 5 minutes ( $p = 0.033$ ), and histologic chorioamnionitis ( $p = 0.037$ ) remained significant after the analysis was controlled for GA, histologic chorioamnionitis, PIH, Apgar score at 5 minutes, and PDA ductal diameter  $> 2.0$  mm.

The ROC curve for the ability to predict PDA surgical ligation showed that PDA ductal diameter  $> 2.0$  mm predicted surgical treatment with an area under the curve (95% confidence interval (CI)) of 0.650 (0.579–0.721). Histologic chorioamnionitis showed an area under the curve (95% CI) of 0.570 (0.495–0.645), making it statistically significant in relation to the factors associated with PDA surgical ligation (Fig. 3).

The clinical factors that were shown to affect the postoperative clinical outcomes of the patients (EL versus LL) in the multivariate model are shown in Fig. 4. Clinical outcomes with associations with  $p < 0.1$  in the univariate analyses were analyzed by multivariate logistic regression with adjustments for cesarean delivery, weight on PDA ligation and PDA diameter  $> 2.0$  mm. After adjustments were made for confounders, EL was found to be significantly associated with a low incidence of IVH grade  $\geq$  III ( $p = 0.035$ ), culture-proven sepsis ( $p = 0.004$ ), NEC stage  $\geq$  III ( $p = 0.022$ ) and time on a mechanical ventilator  $> 4$  weeks ( $p = 0.007$ ).

## Discussion

In this retrospective cohort study of VLBWIs with HSPDA that is unresponsive to pharmacological treatment, there was no statistically significant difference in mortality rate between the PDA ligation and Non-ligation groups. PDA ductal diameter  $> 2.0$  mm, low GA, low Apgar score at 5 minutes, and histologic chorioamnionitis were related to the need for surgical ligation of HSPDA. Additionally, early surgical ligation was not significantly associated with increased mortality among VLBWIs with HSPDA. The LL group was significantly related to an increased risk of NEC (stage  $\geq$  III), IVH (grade  $\geq$  III), culture-proven sepsis and time on a mechanical ventilator  $> 4$  weeks.

The role of HSPDA surgical ligation in VLBWIs is still controversial. Although surgical treatment can close HSPDA immediately, multiple postoperative comorbidities such as left recurrent laryngeal nerve injury, bleeding, chylothorax, development of coarctation and acute hemodynamic compromise, can be associated with in-hospital mortality [5]. In addition, previous observational studies have demonstrated that surgical treatment is associated with an increased risk of chronic lung disease (CLD), ROP, and neurodevelopmental impairment (NDI) [5, 14–19]. In contrast, a recent observational study demonstrated that there was no significant difference in NDI between the PDA ligation and Non-ligation groups [9].

Furthermore, another previous publication suggested that the preferred option for PDA after unsuccessful medical management should be surgical ligation to avoid prolonged low levels of cerebral saturation [20].

PDA surgical ligation is a viable option that is safe and effective [21], and it can be performed at the bedside in the NICU without transfer to the operating room [5, 22]. In our cohort, no infants died during their operations, and there was no statistically significant difference in mortality rate between the PDA ligation and Non-ligation groups, and between the EL and LL groups. Although this was a small retrospective study with only three infants who died and although its statistical power may be limited, this result was shown to be noninferior to those of previous publications [6, 9].

In this study, histologic chorioamnionitis, which is diagnosed by histologic biopsy of the maternal placenta, showed a significant association with factors related to PDA surgical ligation. The role of infection in maintaining the patency of PDA can be considered [23]. Infection may induce the production of cyclooxygenase (COX) -2 and inducible nitric oxide synthetase (iNOS), and together, they increase the production of vasodilatory prostaglandins such as COX-1 and NOS [24]. The infant born from a mother with chorioamnionitis can have PDA with a persistent opening due to increased levels of vasodilatory prostaglandins and nitric oxide. In addition, clinical factors such as the PDA ductal size and signs reflected in the Apgar score should be emphasized when considering surgical intervention to improve clinical outcomes.

In VLBWIs with HSPDA, it is important to determine the optimal timing of surgical ligation [21, 25]. Our results showed that the EL group was associated with lower odds of severe NEC and IVH than the LL group. This may be explained by the diastolic steal of systematic circulation through HSPDA, which can induce intestinal ischemia resulting in NEC, renal hypoperfusion, and a reduction in the blood flow rate in the middle cerebral artery [26] and increase the risk of IVH [27]. In our previous publication, early surgical ligation had the benefit of reducing the incidence of NEC and improving feeding intolerance [4]. The difference between this previous study and the current observational study is embodied, and there is a significant difference in severe NEC (stage  $\geq$  III) between the EL and LL groups.

Additionally, sepsis with increased serum levels of inflammatory mediators or prostaglandins can be associated with smooth muscle relaxation of the ductus arteriosus [28]. Thus, as previously mentioned, the role of infection in maintaining the patency of PDA can be considered [23]. EL may reduce the duration of infection exposure and can be expected to minimize the risk of sepsis.

Prolonged patency of PDA increases pulmonary circulation that can be injurious to the capillary endothelium and stimulate an inflammatory cascade that results in pulmonary edema, CLD development, and increased ventilator support [29]. EL may diminish the period of exposure to HSPDA [30], and can decrease pulmonary edema [29] and facilitate earlier endotracheal extubation [9].

This study has several limitations. First, this was a small retrospective study with only 233 patients, and a randomized and prospective trial could not be performed. Thus, the statistical power of population may be limited. Second, all operations were performed by one cardiac surgeon with a high level of experience

in pediatric heart surgery. One goal of future research is to perform a large prospective multicenter study with long-term and close follow-up of VLBWIs with HSPDA that is refractory to pharmacological treatment.

## Conclusions

Early surgical ligation minimizes adverse effects of HSPDA in predicted infants who subsequently require surgical treatment for PDA. We suggest that predicted VLBWIs with HSPDA that is unresponsive to medical treatment should avoid delayed ductal closure to reduce severe NEC, severe IVH, culture-proven sepsis, and facilitate earlier endotracheal extubation. Avoidance of delayed surgical ligation after failure of pharmacologic closure may have beneficial outcomes in terms of postnatal morbidity among preterm infants with risk factors in relation to HSPDA surgical ligation.

## Abbreviations

VLBWI: very low birth weight infant; HSPDA: hemodynamically significant patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NICU: neonatal intensive care unit; NSAID: nonsteroidal anti-inflammatory drug; DIC: disseminated intravascular coagulation; EL: early ligation; LL: late ligation; ROP: retinopathy of prematurity; PVL: periventricular leukomalacia; ROC: receiver operating characteristic; PIH: pregnancy-induced hypertension; GA: gestational age; CI: confidence interval; CLD: chronic lung disease; NDI: neurodevelopmental impairment; COX: cyclooxygenase; iNOS: inducible nitric oxide synthetase

## Declarations

### Ethics approval and consent to participate

Our institutional review board approved this study, and the need for patient consent was waived (IRB number; HYUH 2019-07-004-003).

### Consent for publication

Our institutional review board approved this study, and the need for patient consent was waived (IRB number; HYUH 2019-07-004-003). This manuscript has been reviewed and approved by all the co-authors, and has not been submitted to any other journals for consideration for publication.

### Availability of data and material

Please contact the corresponding author for data requests.

### Competing interests

The authors declare that they have no competing interests.

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## Author's contributions

Lee JH: conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing (original draft, review & editing);

Lee HJ: conceptualization, methodology, supervision, validation, writing (original draft, review & editing)

Park H: formal analysis, supervision, writing (review & editing)

Ahn J: investigation, supervision, validation, writing (review & editing)

Kim HS: project administration, resources, supervision, visualization, writing (review & editing)

Jang HJ: investigation, project administration, supervision, writing (review & editing)

Ro SK: project administration, resources, supervision, visualization, writing (review & editing)

Kim H: conceptualization, data curation, formal analysis, investigation, writing (review & editing)

All authors read and approved the final manuscript.

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## Authors' information

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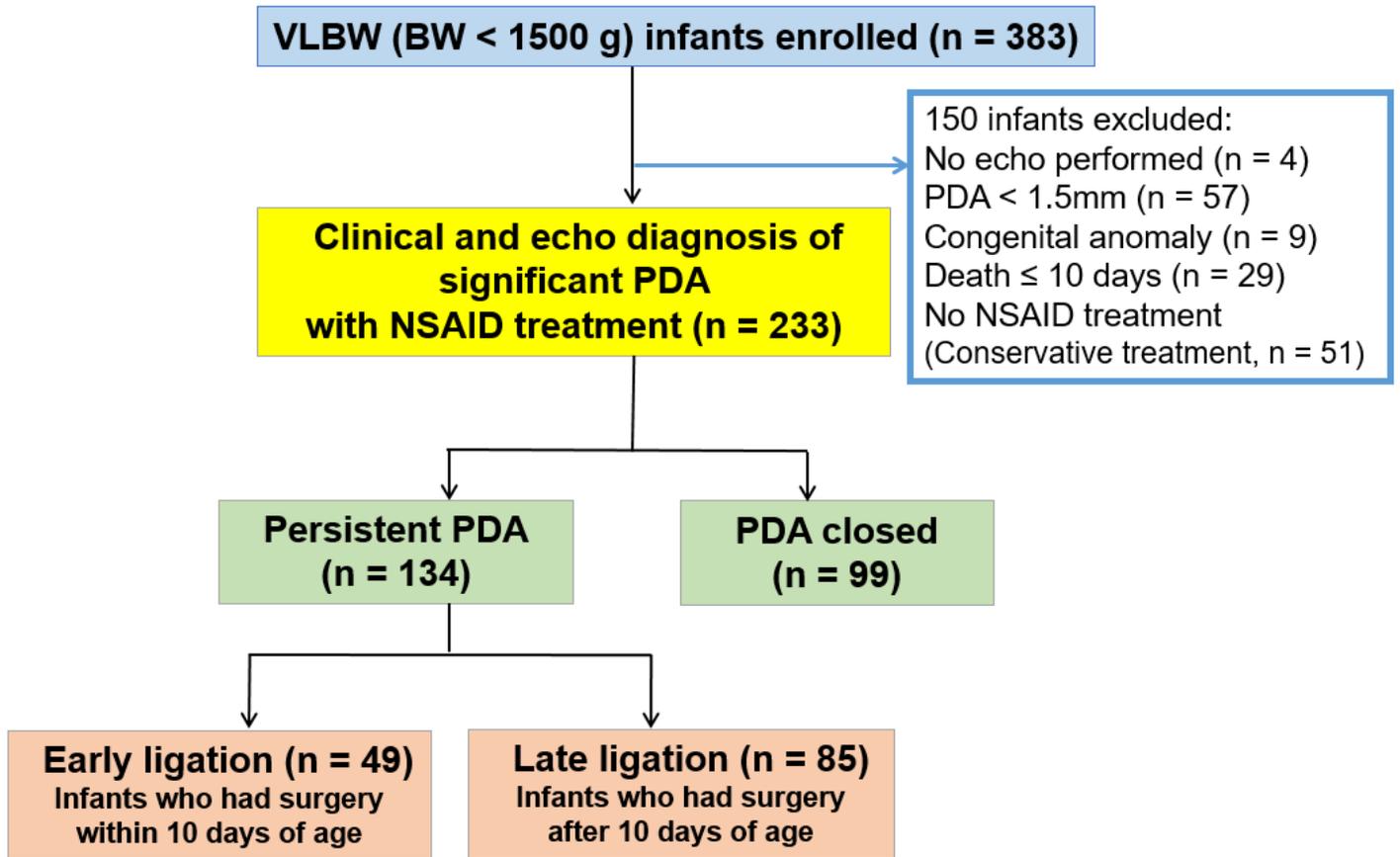
## References

1. Kitterman JA, Edmunds LH Fr, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ductus arteriosus in premature infants: incidence, relation to pulmonary disease and management. *N Engl J Med* 1972;287:473-7.
2. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;343:674-81.
3. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;39:1890-900.

4. Lee JH, Ro SK, Lee HJ, Park HK, Chung WS, Kim YH, et al. Surgical ligation on significant patent ductus arteriosus in very low birth weight infants: Comparison between early and late ligations. *Korean J Thorac Cardiovasc Surg* 2014;47:444-50.
5. Chang YH, Lee JY, Kim JE, Kim JY, Youn Y, Lee EJ, et al. The Aristotle score predicts mortality after surgery of patent ductus arteriosus in preterm infants. *Ann Thorac Surg* 2013;96:879-84.
6. Youn Y, Moon CJ, Lee JY, Lee C, Sung IK. Timing of surgical ligation and morbidities in very low birth weight infants. *Medicine* 2017;96(14):1-4.
7. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. *J Pediatr* 1994;125:270-7.
8. Lee HJ, Sim GH, Jung KE, Lee JA, Choi CW, Kim EK, et al. Delayed closure effect in preterm infants with patent ductus arteriosus. *Korean J Pediatr* 2008;51:1065-70.
9. Weisz DE, Mirea L, Resende MH, Ly L, Church PT, Kelly E, et al. Outcomes of surgical ligation after unsuccessful pharmacotherapy for patent ductus arteriosus in neonates born extremely preterm. *J Pediatr* 2018;185:292-6.
10. Volpe JJ. Intraventricular hemorrhage in the premature infant - current concepts. Part I. *Ann Neurol* 1989;25:3-11.
11. Kamitsuka MD, Horton MK, Williams MA. The incidence of necrotizing enterocolitis after introducing standardized feeding schedules for infants between 1250 and 2500 grams and less than 35 weeks of gestation. *Pediatrics* 2000;105:379-84.
12. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723-9.
13. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005;123:991-9.
14. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007;150:229-34.
15. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. *Pediatrics* 2014;133:e1024-46.
16. Mirea L, Sankaran K, Seshia M, Ohlsson A, Allen AC, Aziz K, et al. Treatment of patent ductus arteriosus and neonatal mortality / morbidities: adjustment for treatment selection bias. *J Pediatr* 2012;161:689-94.
17. Madan JC, Kendrick D, Hagadorn JI, Frantz ID 3rd. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics* 2009;123:674-81.
18. Clyman R, Cassady G, Kirklin JK, Collins M, Philips JB. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. *J Pediatr* 2009;154:873-6.
19. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *J Pediatr* 2007;119:1165-74.

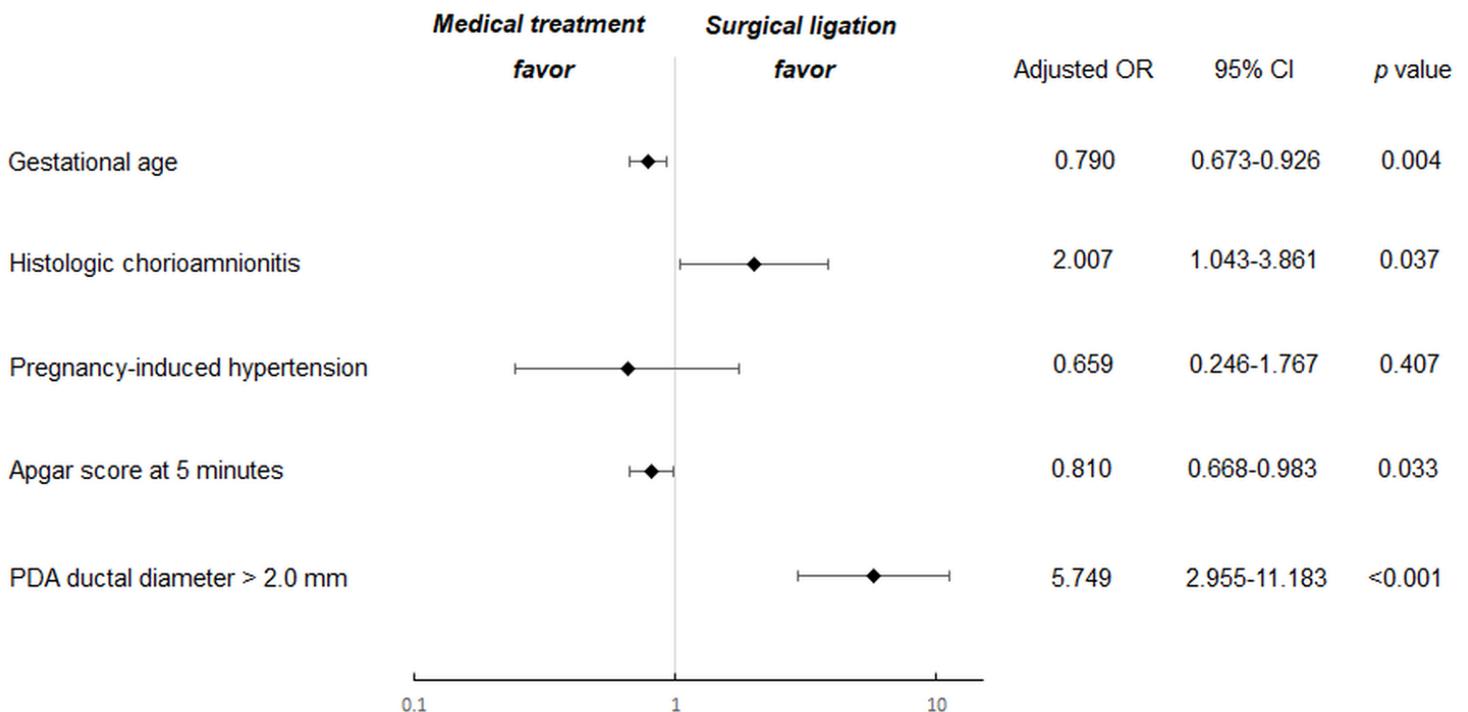
20. Lemmers PM, Benders MJ, D'Ascenzo R, Zethof J, Alderliesten T, Kersbergen KJ, et al. Patent ductus arteriosus and brain volume. *Pediatrics* 2016;137(4):e20153090.
21. Vida VL, Lago P, Salvatori S, Boccuzzo G, Padalino MA, Milanesi O, et al. Is there an optimal timing for surgical ligation of patent ductus arteriosus in preterm infants?. *Ann Thorac Surg* 2009;87:1509-16.
22. Avsar MK, Demir T, Celiksular C, Zeybek C. Bedside PDA ligation in premature infants less than 28 weeks and 1000 grams. *J Cardiothorac Surg* 2016;11:146-50.
23. Park HW, Choi YS, Kim KS, Kim SN. Choriamnionitis and patent ductus arteriosus: a systematic review and meta-analysis. *PLoS One* 2015;10(9):e0138114.
24. Yeung MY. Hypotension, persistent ductus arteriosus and the underlying adrenal insufficiency in low gestation newborns. *World J Pediatr* 2006;1:8-13.
25. Raval MV, Laughon MM, Bose CL, Phillips JD. Patent ductus arteriosus ligation in premature infants: who really benefits, and at what cost? *J Pediatr Surg* 2007;42:69-75.
26. Weir FJ, Ohlsson A, Myhr TL, Fong K, Ryan ML. A patent ductus arteriosus is associated with reduced middle cerebral artery blood flow velocity. *Eur J Pediatr* 1999;158:484-7.
27. Osborn DA, Evans N, Kluckow M. Effect of early targeted indomethacin on the ductus arteriosus and blood flow to the upper body and brain in the preterm infant. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F477-82.
28. Vucovich MM, Cotton RB, Shelton EL, Goettel JA, Ehinger NJ, Poole SD, et al. Aminoglycoside-mediated relaxation of the ductus arteriosus in sepsis-associated PDA. *Am J Physiol Heart Circ Physiol* 2014;307(5):H732-40.
29. Mashally S, Nield LE, McNamara PJ, Martins FF, El-Khuffash A, Jain A, et al. Late oral acetaminophen versus immediate surgical ligation in preterm infants with persistent large patent ductus arteriosus. *J Thorac Cardiovasc Surg* 2018;156:1937-44.
30. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. *Pediatrics* 2009;123:e138-44.

## Figures



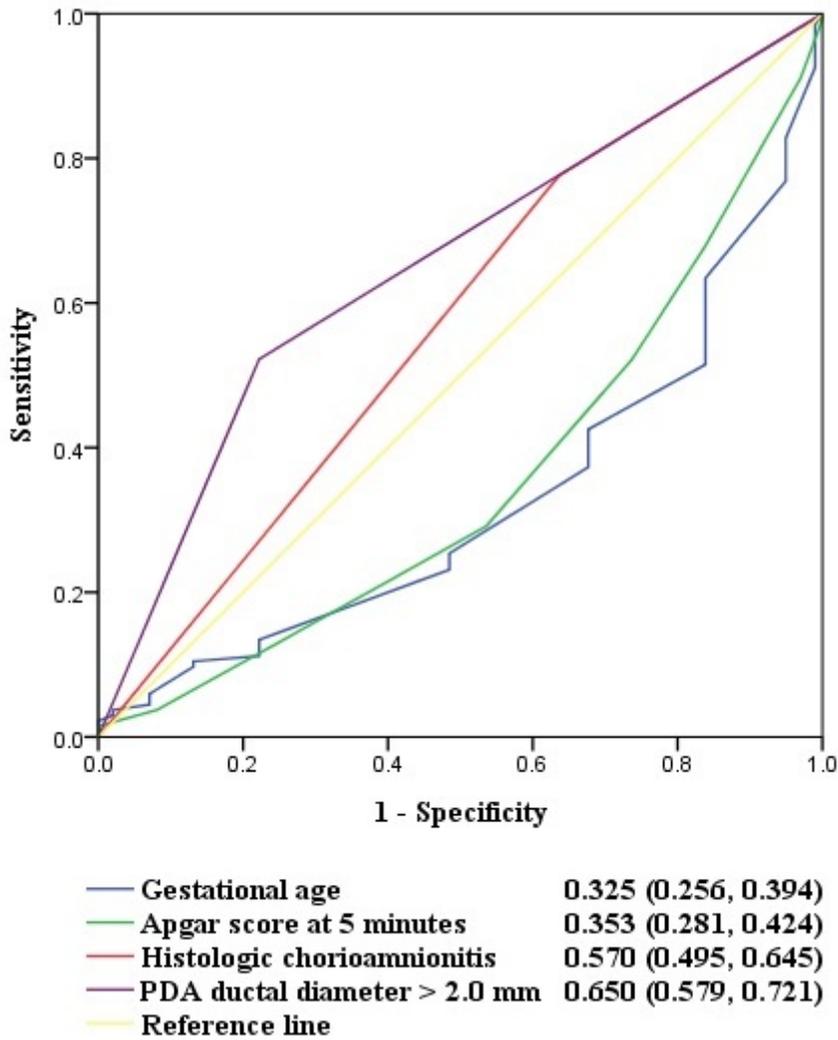
**Figure 1**

Flow diagram of the study patients. VLBW, very low birth weight; BW, birth weight; PDA, patent ductus arteriosus; NSAID, nonsteroidal anti-inflammatory drug.



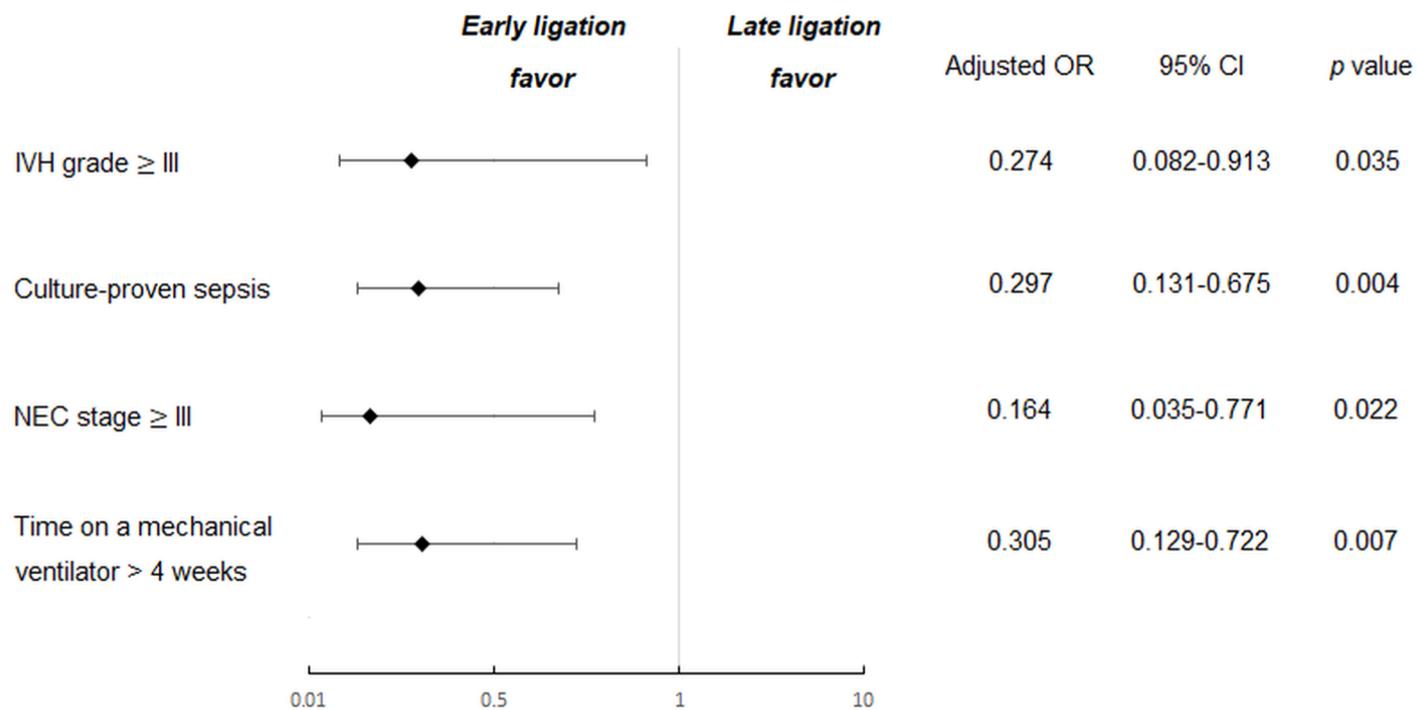
**Figure 2**

Logistic regression analysis for risk factors associated with PDA surgical ligation. OR, odds ratio; CI, confidence interval; PDA, patent ductus arteriosus. \*Odds ratios were adjusted for gestational age, histologic chorioamnionitis, PIH, Apgar score at 5 minutes, and PDA ductal diameter > 2.0 mm.



**Figure 3**

Receiver operating characteristic curve for factors associated with PDA surgical ligation. Figures represent the area under the curve (95% confidence interval). PDA, patent ductus arteriosus.



**Figure 4**

Postoperative clinical outcomes of the patients (early ligation versus late ligation). OR, odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis. Data are the mean  $\pm$  SD or number (%). \*Odds ratios were adjusted for cesarean delivery, weight on PDA ligation, and PDA ductal diameter > 2.0 mm.