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Role of Sequential Functional Echocardiography in Predicting Clinically Apparent Patent Ductus Arteriosus in Preterm Very Low Birth Weight Newborns-An Observational Study

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Running Title-Role of Sequential Functional Echocardiography in Predicting Clinically Apparent Patent Ductus Arteriosus in Preterm Very Low Birth Weight Newborns

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ABSTRACT

Background-The management of patent ductus arteriosus in preterm neonates continues to be a topic of discussion and controversy. Prolonged ductal patency in preterm neonates has been associated with significant short and long term morbidities and with increased mortality however, policy of routine treatment of all during neonatal period has failed to show significant improvement in long term outcome. Echocardiography has emerged as a promising modality to screen the newborns at risk of adverse effects of ductal shunting. This helps in identifying PDAs that require treatment to ultimately prevent unnecessary therapy or delay of necessary therapy. There are multitude of studies that have evaluated large number of echocardiographic markers for their predictive utility but only few have included all ductal markers together in a single study. The reported sensitivity (26-100%) and specificity (6-100%) of echocardiographic markers vary over a wide range. Thus, this study was planned with an aim to assess the predictive utility of all available ductal markers and their added advantage of having all over few ones in clinically apparent PDA in preterm VLBW newborns. **Methods**-It was an observational prospective study conducted in tertiary care NICU at Lady Hardinge Medical College, Delhi. Fifty preterm very low birth weight (VLBW) newborns underwent four sequential Echo scans within first 72 hrs; first scan within 12 hours then at 24 hrs ,48 hrs and 72 hrs of age and were monitored clinically for the signs of PDA up to two weeks of life or discharge whichever comes later. **Results-**The Ductal diameter, pulsatile ductal flow pattern, Left pulmonary artery (LPA) velocity, Left atrial to aortic width (La/Ao) ratio, Left atrial volume index (LAVI), Left ventricle to aortic width (Lv/Ao) ratio, E/A ratio and Left ventricular output/superior vena caval (LVO/SVC) flow ratio predicted clinically apparent PDA during first 72 hours of life.

Conclusion-This study provides insights into the predictive utility of other ductal echo markers along with the routinely measured conventional ones during first 72 hours of life in preterm VLBW newborns.

Key words: Preterm newborns, Echocardiography, PDA .

What is known:

• Ductal diameter, pulsatile ductal flow pattern, LPA velocity and La/Ao ratio predict development of clinically apparent PDA with wide range of sensitivity and specificity.

What this study adds:

• LAVI, Lv/Ao ratio, E/A ratio and LVO/SVC flow ratio also predict symptomatic PDA along with the conventional markers.

BACKGROUND

Prolonged ductal patency in preterm newborns is associated with significant short and long term morbidities with increased mortality[1,2,3,4]. The management of ductus continues to be a topic of interest of many studies. In term infants, the ductus arteriosus constricts soon after birth while in preterm infants, the proportion of patients with a patent ductus and time to closure progressively increases with decreasing gestational age[5]. Approximately 10% infants of 30 to 37 weeks gestation, 80% of 25 to 28 weeks gestation and 90% of those born at 24 weeks gestation would have patent duct by day four of life and 2%, 65%, 87% of these in each gestation strata continue to have PDA till day seven of life[6]. Emerging evidences favour the spontaneous closure of ductus in majority of premature newborns by 44-weeks post-menstrual age (PMA) when left untreated with closure rate as high as 73% in infants >28 weeks gestation and 94% in newborns with birth weight >1000g.[7,8] Echocardiography has emerged as a promising tool to identify patients who may benefit from early therapeutic intervention after scanning their ductal markers profile during first few days of life[5]. Though prolonged patent ductus is associated with poor neurodevelopmental outcome in childhood; policy of universal ductal treatment has failed to demonstrate improvement in long-term outcomes[9]. This has raised the interest of clinicians in studying the predictive utility of echocardiographic markers to identify the high risk infants with increased probabilities of persistent PDA and PDA associated harms[10,11,12]. The goal is to eventually deliver prompt PDA treatment to high risk infants who are most likely to benefit, thereby reducing the side-effects and costs associated with unneces-

sary and potentially harmful PDA over treatment [11,12]. Till date, multitude of studies have evaluated the predictive utility of large number of echocardiographic markers, however there are handful of studies that have included all ductal markers in a single study. The reported sensitivity (26-100%) and specificity (6-100%) of echocardiographic markers vary over a wide range.[13] A comprehensive PDA risk stratification tool based on all echocardiographic markers is thus needed to improve their predictive utility in clinically apparent PDA. Therefore this study included almost all ductal markers with an aim to assess the added advantage of having all over few ones in predicting clinically apparent PDA in preterm VLBW newborns.

METHODS

AIMS- The primary objective was to assess the predictive utility of all available echocardiographic markers in clinically apparent PDA in preterm VLBW newborns and secondary objective was to study the course of ductus arteriosus in newborns with clinically apparent and not clinically apparent PDA.

Clinically apparent PDA was defined as presence of any one of following signs[14]: 1) Hyperactive precordium (visible precordial pulsation in >2 rib spaces) 2) Systolic murmur (usually ejection systolic murmur of grade ≥III at 1st /2nd Left ICS. 3) Bounding peripheral pulses (easily palpable dorsalis pedis).[14,15]

Following echocardiographic parameters related to ductal size, shunt magnitude and it's hemodynamic consequences on pulmonary and systemic circulations and on cardiac functions were measured.[16] 1-Ductal diameter 2-Peak systolic velocity across PDA 3-Transductal Velocity Ratio (Ratio of peak systolic velocity at pulmonary end and peak systolic velocity at aortic end) 4-Direction of ductal shunting 5-Shunt flow pattern: There are five Doppler shunt patterns; Pulmonary hypertension pattern , Growing pattern , Pulsatile pattern, Closing pattern and Closed pattern. 6-LPA diastolic velocity 7-La/Ao ratio 8-Left Atrial Volume Index (LAVI) 9-Left ventricular dimensions (left ventricular end-diastolic dimension (LVEDD), left ventricle end systolic dimension (LVESD) 10-

Lv/Ao ratio 11-Fractional Shortening (FS) 12-Ejection fraction (EF) 13-E wave/A wave ratio 14-Global left ventricular function /Left ventricular Myocardial perfomance index (LV MPI /TEI INDEX) 15-LVO/SVC flow ratio 16-Diastolic flow in post-ductal aorta 17-Diastolic flow in superior mesenteric artery (SMA) and anterior cerebral artery (ACA).

STUDY DESIGN, INCLUSION AND EXCLUSION CRITERIA- This prospective observational study was conducted in neonatal unit of Lady Hardinge Medical College, a tertiary level hospital in New Delhi, India from January 2015 to May 2016.

All preterm VLBW newborns admitted to NICU were assessed for eligibility and newborns with 5 minute Apgar score ≤ 6, with complex congenital heart disease, with recognisable chromosomal/ congenital malformations, who died before having last confirmatory scan at 2 weeks of life or at discharge whichever was later and whose parents not consented were excluded from the study. The study protocol was approved by the institution's ethics committee.

METHODOLOGY- All enrolled newborns underwent their first echocardiographic scan within 12 hours of birth and subsequent scans later at 24 hrs ,48 hrs and 72 hrs of age. These scans were performed with a Toshiba 580A ultrasound system using phased array probe 7 MHz for real-time scanning and pulsed/continuous wave/colour Doppler echocardiography and curved probe 6 MHz for doppler scans of anterior cerebral and superior mesenteric arteries (ACA&SMA). Standard acoustic windows and scanning planes (apical four-chamber view, left parasternal long axis and short axis view, ductal view, suprasternal view and subcostal views) were used to get a complete 2D picture of cardiac anatomy with M-mode measurements of chambers and Doppler evaluation of intra cardiac blood flow. These scans were done by single examiner trained in comprehensive ECHO. All recordings were measured in triplicate and averaged to remove intra observer variation. Images were ob-

tained with the narrowest sector angle to maximize frame rate (goal frame rate >100 frames/s) for optimal image quality. Images were interpreted by a single paediatric cardiologist who was masked to patient and clinical data. The data was collected, coded and stored until final analysis.

These babies were monitored clinically for signs of PDA up to two weeks of age or discharge whichever was later. It has been seen in previous studies that approximately 50% of VLBW infants and nearly two-thirds of infants with birth weight > 1000 g undergo spontaneous ductal closure by end of first week; therefore two weeks was chosen as a optimal cut off point for clinical monitoring[8]. Those who became clinically apparent during this period underwent confirmatory echo scan on that very day while rest who remained free of signs, underwent their last scan at either 14th day of life or at discharge whichever was later to ascertain the closure or persistence of asymptomatic duct. Neonates with clinically apparent PDA received medical (oral ibuprofen or oral/intravenous paracetamol) and surgical interventions for ductal closure as per unit protocol if they were symptomatic along with presence of Hemodynamic significant (Hs) PDA.[15]

Symptomatic and Hs PDA was diagnosed if: La/Ao ratio was ≥ 1.5 and ductus size measured >1.5 mm and presence of any one of the following symptoms[15] :

1-Features of congestive heart failure 2-Requiring prolonged respiratory support (invasive or non-invasive) unlikely to be due to other reasons 3-Unexplained oxygen requirement (FiO2 ≥ 30%) or rising O2 requirement on respiratory support 4-Recurrent apnea requiring respiratory support (CPAP/Nasal IMV/invasive ventilation) attributed to PDA .

STATISTICAL ANALYSIS -For this study, a convenient sample size of 50 neonates was chosen. Qualitative variables were statistically analysed using chi square test or a Fisher exact test and continuous variables were analysed using Student's t test or Mann-Whitney U test. Univariate analysis and multiple logistic regression analysis were done to assess the association between echocardiographic parameters and clinically apparent PDA. Significance was defined as a p value of less than

0.05. Cut off points, sensitivity and specificity of significant variables were calculated by plotting ROC curves. The statistical software package SPSS-20 was used for data analysis.

RESULTS

The study flow is depicted in Fig. 1. The studied cohort of fifty preterm VLBW newborns had a mean gestational age of 30.2 ± 1.5 weeks (mean±SD) and mean birth weight of 1071±142 gram (mean±SD). Eleven of these 50 newborns had signs of clinically apparent PDA and rest 39 didn't have sign of apparent PDA. The baseline characteristics of newborns are described in Table-1. There were no baseline differences between the two groups, except for the number of ELBW babies which was significantly higher (36%) in clinically apparent PDA group.

The incidence of PDA was 26% in our study which included clinically not apparent newborns as well because some of them had persistent PDA which was picked up at last echo scan. Two newborns of not clinically apparent PDA group, had small PDA <1.5 mm which was detected later in their last discharge scan. Ten babies of clinically apparent PDA group, received medical treatment as per unit protocol for symptomatic and Hs PDA and one of them received 2 courses of medical treatment while none required surgical ligation. The overall spontaneous closure rate was 4% at 48 hrs of life , 40% at 72 hrs and 74% by discharge. Almost one-third of extremely low birth weight (ELBW) babies and nearly two-thirds of babies with birth weight 1000-1500gm exhibited spontaneous closure by discharge. In clinically apparent PDA group, 4 (36.4%) babies presented with isolated murmur, 2 (18%) with both murmur and hyperkinetic precordium, 1 (9%) with murmur and bounding pulses and 4 (36.4%) with all three signs of clinically apparent PDA. The mean age of presentation was fifth day of life. Several echocardiographic markers were found to predict clinically apparent PDA; each with different cutoff value, sensitivity and specificity at different hours of life during first 3 days of life. These significant qualitative and quantitative parameters measured at different hours of life along with their p value are described in table 2 & 3 and the cut off value,

AUC (Area under curve), sensitivity and specificity of these parameters are described in table 4. The four echocardiographic parameters in first scan; **ductal diameter** ≥1.7 mm, **La : Ao ratio** ≥1.40, **Lv: Ao ratio** ≥2.0 and **LVO/SVC ratio** ≥2.5, six parameters in second scan; **shunt flow pattern**, **ductal size** ≥ 1.50 mm, **La:Ao ratio** ≥1.4, **Lv:Ao ratio** ≥2 and **LVO/SVC ratio** ≥2.7, six parameters in third scan; **shunt flow pattern**, **ductal diameter** ≥ 1.5 mm, **diastolic velocity in LPA** ≥32.5 cm/sec, **La/Ao ratio** ≥ 1.4, **Lv/Ao** ≥ 2.0 and **LAVI ≥ 5 ml/m2** and seven parameters in fourth scan; **shunt flow pattern, duct size** ≥1.5 mm, **ductal diameter/weight** ≥1.4 mm/kg, **La:Ao ratio** ≥1.4, **Lv:Ao** ≥2.2, **LAVI** ≥5.5 and **altered blood flow in systemic vessels** predicted clinically apparent PDA. The wider ductal diameter ≥1.7 mm predicted PDA with sensitivity of 91% and specificity of 80% within 12 hrs of life while the lesser ductal diameter ≥ 1.5 mm at 24, 48 and 72 hrs predicted same with sensitivity of 90-95% and specificity of 70%-92.3%. The diastolic LPA velocity ≥30 cm/sec at 24 hrs of life, ≥32.5 cm/sec at 48 hrs and 72 hrs of life predicted PDA with sensitivity and specificity of 90% & 85%, 89% & 85%, and 92% & 87% respectively. The La/Ao ratio ≥ 1.4 predicted clinically apparent PDA with the sensitivity of 46%, 55%, 73% and 91% and specificity of 77% ,77%, 90% and 85% respectively at 12 hrs, 24 hrs, 48 hrs and 72 hrs of age. LAVI at a cut-off value of ≥ 5 ml/m2 at 48 hrs and ≥ 5.5 ml/m2 at 72 hrs predicted clinically apparent PDA with the sensitivity of 81.8% and 73% and specificity of 56.8 and 53% . E/A ratio ≥ 0.95 and ≥1 at 48hrs and 72hrs predicted clinically apparent PDA with the sensitivity of 87% and 88% and specificity of 82% and 81% . In this study Lv/Ao ≥2 at 12 hrs, 24 hrs, 48 HrS of age and ≥ 2.2 at 72 hrs of age predicted clinically apparent PDA with the sensitivity of 82%, 85%, 90% and 89% and specificity of 80%, 80%, 68% and 82% respectively. Another parameter LVO/SVC ratio ≥ 2.5 at 12 hrs, ≥ 2.7 at 24 hrs and ≥ 2.9 at 48 and 72 hrs of age predicted clinically apparent PDA with the sensitivity and specificity of 72% & 77%, 87%&56%, 90%&85%, 90%&87% respectively. Altered (absent/retrograde) post ductal flow within the first 72 hrs was found to predict clinically apparent PDA with sensitivity of 55% and specificity of 100%. Altered blood flow in ACA and SMA was

also found to be significantly associated with later development of clinically apparent PDA. Factors such as birth weight, surfactant treatment, RDS, male gender, sepsis, anemia and history of maternal chorioamnionitis were not significant according to multiple logistic regression analysis for the development of a clinically apparent PDA.

DISCUSSION

The reported incidence of persistent PDA (PDA beyond day 3 of life) in VLBW infants varies from 18% to 77% in inverse relationship with birth weight and gestational age[17,18]. The incidence of PDA was 26% in our study which was closer to lowest limit of reported incidence. This low incidence can be explained by two possible reasons: first; the studied cohort was relatively mature with average birth weight of 1071gm with only 12% proportion of ELBW babies and second; our policy of giving selective therapeutic interventions to newborns with symptomatic Hs PDA only in accord to recent evidences supporting spontaneous ductal closure in majority of premature patients[19]. In this study 74% of newborns had spontaneous ductal closure by discharge. The closure rate was higher in more mature newborns as nearly two-third of babies with birth weight > 1000 g compared to only one-third of ELBW babies underwent spontaneous ductal closure. Our results were similar to other studies that had found that more than half of the VLBW infants undergo spontaneous ductal closure by 44 weeks post menstrual age if left untreated[7,8]. Nemerofsky et al. reported closure rate of 71% in VLBW newborns with two times higher rate among infants whose birth weight >1000 g than among those infants with birth weight <1000 g (67% versus 31% $p<0.01$)[8]. In an another study by Koch et al., 35% of extremely low birth weight infants were shown to have spontaneous ductal closure within the first 10 days of life[7]. He found the direct relationship between gestational age and spontaneous closure and estimated that for each additional week above 23 weeks, the odds of spontaneous closure increased by a ratio of 1.5[7]. These findings thus suggest that exposure to the risks of therapeutic interventions for ductal closure might not be warranted in all VLBW newborns.

The most common presenting sign of clinically apparent PDA was heart murmur which had been seen in majority of previous studies too[20]. Beyond 12 hrs of life, ductal diameter ≥ 1.5 mm predicted clinically apparent PDA with sensitivity of 90-95% and specificity of 70%-92.3% and within 12 hrs of life, wider ductal diameter ≥1.7 mm was required to had same predictive value. The utility of ductal diameter in predicting ductal patency had already been validated in many of previous studies[21,22,23,24]. In this study, pulsatile shunt flow pattern across the duct was found to predict the ductal patency with sensitivity of 91% and specificity of 100%. Very few studies have assessed the predictive role of shunt flow pattern in PDA and that too with mixed results[22,25,26]. Su et al. and Harling et al. found that the pulsatile ductal flow pattern could predict symptomatic PDA while Visconti et al. did not find significant difference in transductal flow pattern between two groups of newborns with and without PDA[22,25,26]. Normally pulmonary artery has only systolic laminar flow with velocity <1.5 m/s while in presence of PDA, it shows diastolic flow along with turbulence in systolic flow pattern[16]. Thankavel et al. found the role of LPA diastolic velocity < 30 cm/sec measured at 72 hrs of life in predicting closure of ductus in preterm newborn < 30 weeks[27]. We too had similar results but with different cutoff at different hours of life. The diastolic LPA velocity ≥30 cm/sec at 24 hrs of life, ≥32.5 cm/sec at 48 hrs and 72 hrs of life predicted PDA with sensitivity and specificity of 90% & 85%, 89% & 85%, and 92% & 87% respectively. The predictive role of La:Ao ratio for PDA is well established but with wide variation in sensitivity and specificity across the available literature[22,23,28.] Moreover, it is considered to be an inferior marker of PDA severity than LAVI[29,30]. There are three explanations to this; 1-La: Ao ratio measures atrial enlargement along the AP axis only and if LA dilates predominantly in the superior-inferior and medial-lateral directions, it can underestimate atrial enlargement 2-Decompression of left atrium via patent foramen ovale may also underestimate the magnitude of ductal shunt even in the presence of large duct. 3-In many preterm newborns, the size of the aorta is also enlarged and thus even if the left atrium increases, the La/Ao ratio may remain unchanged. Though left atrial volume index (LAVI) remains higher in newborns with

Hs PDA; predictive utility of this marker for PDA is not studied much till date[30]. In our study, LAVI at a cut-off value of ≥ 5 ml/m2 at 48 hrs and ≥ 5.5 ml/m2 at 72 hrs predicted clinically apparent PDA with sensitivity of 81.8% and 73% and specificity of 56.8 and 53% respectively. We did not find significant differences in LVED dimension, LVES dimension, LVEF and FS between newborns who later developed clinically apparent PDA and those who remained asymptomatic during the course of study. The same results were obtained in other studies too[21,26]. E/A ratio, Lv/Ao and LVO/SVC are the parameters which had been extensively studied in context to diagnosing Hs PDA but their predictive role for determining persistence of ductus were not studied much till date[21,27,31,32]. In our study, all these three parameters were found to predict PDA; each with different cut-off values at different hours of life. Altered blood flow in aorta, anterior cerebral and in superior mesenteric vessels seen within 72 hrs of life was also found to predict the persistence of ductus arteriosus much before its clinical detection. Kluckow et al. showed that the altered post ductal aortic diastolic flow (unclear direction to flow or retrograde flow) at 19 hours of life could predict symptomatic PDA with sensitivity of 68% and specificity of 85% in preterm babies[23]. Our observations confirm it and further add to the limited existing literature on predictive PDA markers.

This is one of the few studies that have been done to date on all predictive markers of PDA being assessed together in a single study. Though this study does not analyse the natural course of ductus in preterm newborns but it reflects the current conservative approach for PDA management. In view of current clinical standards, it would be impossible to devise a study without PDA treatment.

There are some limitations to our study. This was a prospective cohort study with very small sample size of 50 newborns only. The studied cohort was relatively mature in terms of weight and gestational age with less no of ELBW babies who are actually the most susceptible population to suffer PDA related morbidities. The clinical and biochemical markers related to ductal patency were not studied in conjunction with echocardiographic markers for their predictive role.

CONCLUSION

This study provides insights into the predictive utility of other less studied markers eg Lv/Ao ratio, LAVI, E/A ratio and LVO/SVC flow ratio along with conventional ones e.g. ductal diameter, pulsatile ductal flow pattern, LPA velocity and La/Ao ratio in clinically apparent PDA during first 72 hours of life. An another research with larger sample size is warranted in future for formulating a comprehensive predictive tool using all these parameters along with clinical and biochemical factors in extremely preterm neonates to guide the early and selective treatment approach.

Abbreviations: LPA-Left pulmonary artery, La: Ao-Left atrial to aortic width, LAVI-Left atrial volume index, Lv:Ao-Left ventricle to aortic width, LVO/SVC Left ventricular output/superior vena cava, NICU-Neonatal intensive care unit, PDA-Patent ductus arteriosus, VLBW-Very low birth weight.

Declarations:

Ethics approval and consent to participate- The study protocol was approved by the institution's ethics committee. Informed written consent was taken from parents/gaurdian before enrolling the case in to study.

Consent for publication- Not applicable

Availability of data and materials- The datasets used and/or analysed during the current study are available from the corresponding author on request.

Competing interests- The authors declare that they have no conflict of interest.

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Authors' contributions-AS-contributed to conception or design, AB-drafted the manuscript DY-contributed to acquisition, analysis, or interpretation, AK, AS-critically revised the manuscript.

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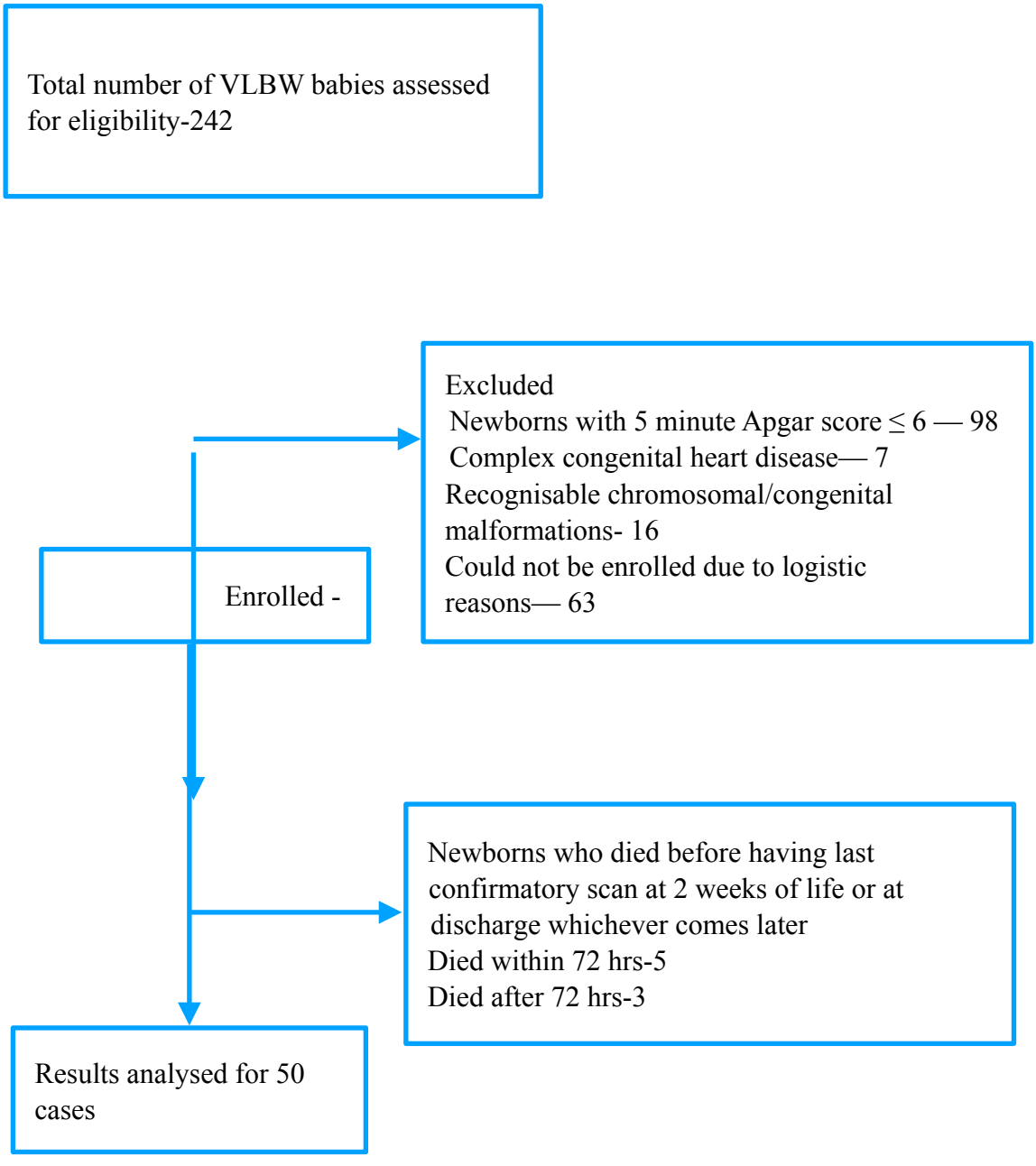

Fig 1: Study Flow

TABLES

Parameters	Newborns with clinically apparent PDA(n=11)	Newborns without clinically apparent PDA (n=39)	p value
Birth weight in gm (mean ±SD)	1002±140	1140±144	0.53
ELBW n (%)	4(36)	2(5)	0.02*
Gestational age in weeks (mean ±SD)	29.9±1.5	30.2±1.6	0.67
Small for gestational age n (%)	1(9)	4 (10)	0.32
No of Females n (%)	4(36)	19(49)	0.35
No of Vaginal delivery n (%)	7(64)	25(64)	0.35
No of ANS uncovered n (%)	8(73)	23(59)	0.44
No of newborns received Surfactant n (%)	8(72)	26(67)	0.50
No of newborns required mechanical ventilation n (%)	3(27)	8(21)	0.46

Table-1 Baseline characteristics of newborns with and without clinically apparent PDA.

Echo scan	Name of parameter	Newborns with clinically apparent PDA n=11 (mean ± SD)	Newborns without clinically apparent PDA n=39 (mean ± SD)	p value
With in 12 hours	Duct size (mm)	1.87 ±.17	1.54±.17	.001*
	Diameter/weight(mm/kg)	1.82 ±.40	1.37±.25	.002*
	La/Ao	1.4±.09	1.3±.09	.03*
	Lv/Ao	2.1±.18	1.9±.19	.001*
	E/A	.81±.05	.78±.05	0.04*
	LVO/SVC	2.8±.08	2.4±.20	.001*
At 24 hrs of life	Ductal size (mm)	1.77±0.33	1.35±0.17	.001*
	Diameter/weight(mm/kg)	1.45±.52	1.20±.24	.03*
	LPA (cm/sec)	31.6±6.7	22.3±3.8	.001*
	La/Ao	1.4±.11	1.3±.11	.01*
	Lv/Ao	1.94±.24	1.74±.13	.001*
	E/A	.91±.07	.80±.06	.001*
	LVO/SVC	2.8±.35	2.5±.23	0.001*
At 48 hrs of life	Ductal size (mm)	1.7±.18	1.2±.38	0.001*
	Diameter/weight(mm/kg)	1.6±.40	1.2±.50	0.016*
	LPA (cm/sec)	46.4±9.3	18.9±3.9	0.001*
	La/Ao	1.4±.09	1.1±.15	0.001*

	LAVI(ml/m2)	5.6±1.7	4.7±.6	0.005*
	Lv/Ao	2.1±.30	1.7±.10	0.001*
	E/A	1.06±.10	0.8±.1	0.001*
	LVO/SVC	3.0±.40	2.5±.21	0.001*
At 72 hrs of life	Ductal size (mm)	1.6±.40	0.73±.70	0.001*
	Diameter/weight(mm/kg)	1.7±.18	0.65±.6	0.001*
	LPA (cm/sec	49.8±4	16±3.2	0.001*
	La/Ao	1.4±.20	1.0±.12	0.001*
	LAVI(ml/m2)	6.9±1.9	4.9±.75	0.01*
	Lv/Ao	2.8±.5	1.7±.5	0.001*
	E/A	.97±.13	.87±.07	0.001*
	LVO/SVC	3.4±.5	2.5±.2	0.001*

Table-2 Quantitative echocardiographic parameters with significant p value on univariate analysis.

	Parameter	**Newborns with clinically apparent PDA n=11**	**Newborns with clinically apparent PDA n=39**	**p value**
At 24 hrs of life				
	Shunt flow pattern n (%)	PH 1(9) Growing 8(73) Pulsatile 2(18)	PH 8(21) Growing 12(31) Closing 19(48%)	0.0001*
At 48 hrs of life				
	Shunt flow pattern n (%)	Growing 2(18) Pulsatile 9(82)	Growing 2(5%) Closing 35(90%) Closed 2(5%)	0.0001*
At 72 hrs of life				
	Shunt flow pattern n (%)	Pulsatile 10 (90.9) Growing 1(9)	Closing 22(56) Closed 17(44)	0.0001*
	Diastolic blood flow in post ductal aorta n (%)	Absent 5 (45.5) Retrograde 4 (36.3)	Normal 39(100)	0.0001*
	Diastolic blood flow in ACA n (%)	Absent 4 (36.3) Retrograde 3 (27.2)	Normal 39(100)	0.0001*
	Diastolic blood flow in SMA n (%)	Absent 4 (36.3) Retrograde 3 (27.2)	Normal 39(100)	0.0001*

Table-3 Qualitative echocardiographic parameters with significant p value on univariate analysis.

	Parameter	Cut off value	AUC	Sensitivity (%)	Specificity (%)
Within 12 hrs					
	Ductal size (mm)	≥1.7	0.921	90.9	79.5
	Ductal size/	≥1.5	0.665	81.8	51.3
	LA:AO	≥1.4	0.692	45.5	76.9
	LV:AO	≥2	0.809	81.8	79.5
	LVO/SVC	≥2.5	0.854	71.7	77.2
At 24 hrs of life					
	Ductal size (mm)	≥1.5	0.923	94	71.8
	Ductal size/	≥1.5	0.709	90.9	56.4
	diastolic velocity	≥30	0.921	90.2	84.6
	LA:AO	≥1.4	0.739	54.5	76.9
	LV:AO	≥2	0.790	85.5	79.5
	LVO/SVC	≥2.7	0.794	86.9	56.4
At 48 hrs of life					
	Ductal size (mm)	≥1.5	0.900	95	92.3
	Ductal size/	≥1.4	0.740	72.7	61.5
	diastolic velocity	≥32.5	0.964	89.3	85.4
	LA:AO	≥1.4	0.925	72.7	89.7
	LV:AO	≥2	0.867	90.4	67.7
	LAVI	≥5.0	0.683	81.8	56.8
	E/A	≥.95	0.864	87.1	82.5
	LVO/SVC	≥2.9	0.854	89.9	84.9
At 72 hrs of life					
	Ductal size (mm)	≥1.5	0.901	95.1	89
	Ductal size/	≥1.4	0.805	90.9	61.5
	diastolic velocity	≥32.5	0.905	92.4	87.3

	LA:AO	≥1.4	0.953	90.9	84.6
	LAVI	≥5.5	0.653	73.4	53.5
	LV:AO	≥2.2	0.930	89.3	82
	E/A	≥1	0.856	88.1	81.4
	LVO/SVC	≥2.9	0.900	89.6	87.2

Table-4 Cut off values of significant echocardiographic parameters and their predictive values.

Figures

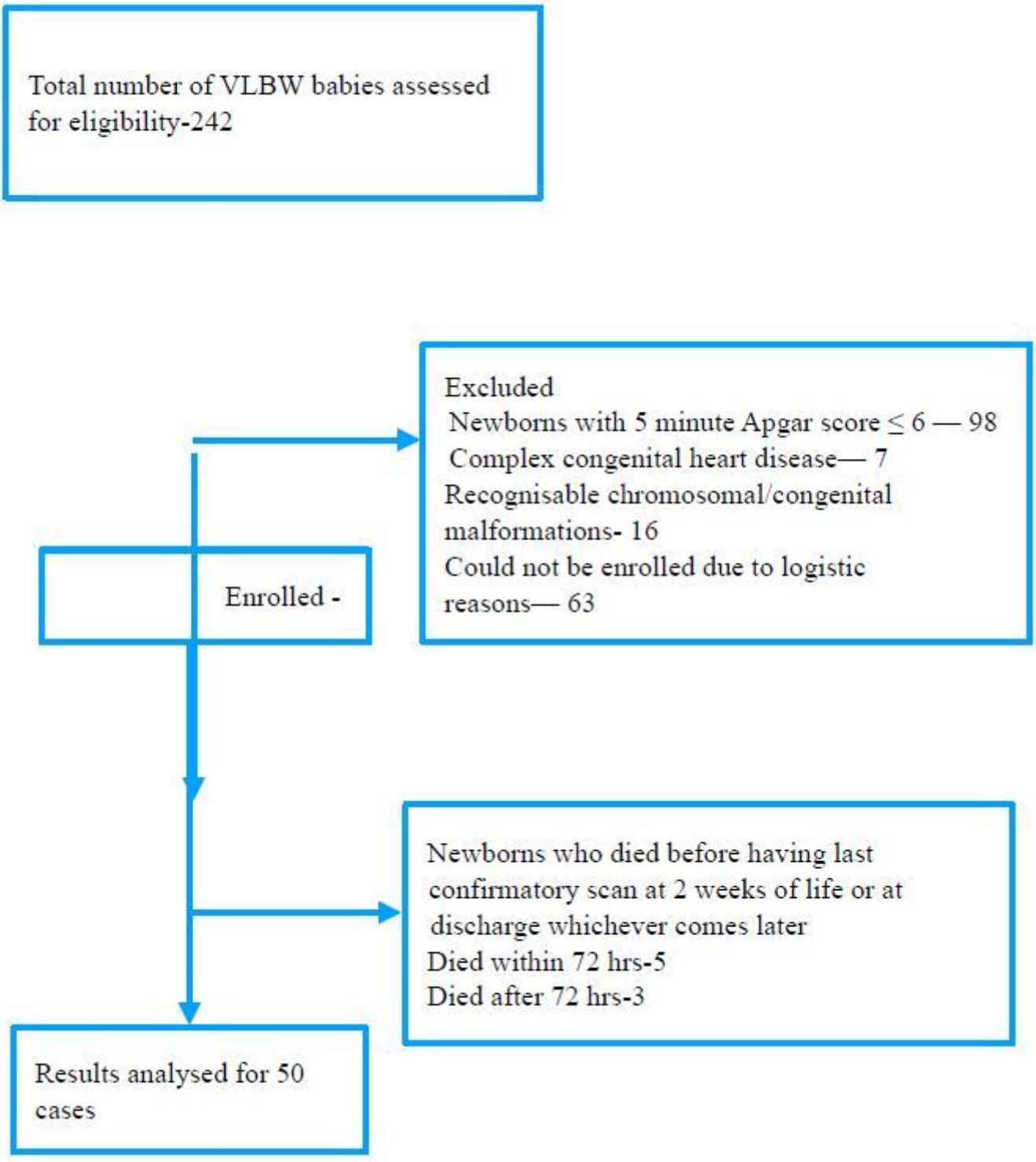

Figure 1

Study Flow