"ESTIMATION OF SERUM N-TERMINAL BRAIN NATRIURETIC PEPTIDE LEVELS IN PRETERM NEWBORN WITH PATENT DUCTUS ARTERIOSUS (PDA) – A ONE YEAR HOSPITAL BASED PROSPECTIVE OBSERVATIONAL STUDY"

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Sub: Institutional Ethical Clearance for the study.

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ABBREVIATIONS

ASD	Atrial septal defect
asPDA	Asymptomatic PDA
BNP	B-type natriuretic peptide
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
COX-I	Cyclooxygenase-inhibitor
CPAP	Continuous positive airway pressure
DA	Ductus arteriosu
ELBW	Extremely low birth weight
GDF-15	Growth differentiation factor 15
hsPDA	Hemodynamically significant patent ductus arteriosus
IVH	Intra-ventricular haemorrhage
kDa	Kilo Dalton
MCP-1	Monocyte chemotactic protein 1
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal peptide of Brain natriuretic peptide
PAP	Pulmonary artery pressures
PDA	Patent ductus arteriosus
PGDH	Prostaglandin D_2 synthase
RCTs	Randomized controlled trials
RDS	Respiratory distress syndrome

RV	Right ventricle
SD	Standard deviation
sPDA	Symptomatic PDA
uIPs	Urinary Isoprostanes
VATS	Video-assisted thoracoscopic surgery
VLBW	Very low birth weight
VSD	Ventricular septal defect

ABSTRACT

Background: Patent ductus arteriosus (PDA) is frequent in neonates with a gestational age of less than 28 weeks. While clinical and echocardiographic signs determine the hemodynamic significant PDA. N-terminal peptide of Brain natriuretic peptide (NT- Pro BNP) has been suggested as a screening tool for PDA in preterm infants.

Objectives: This study aims to estimate serum NT-proBNP levels in preterm newborns with PDA and assess its relationship with Hemodynamically significant PDA (Hs-PDA).

Methodology: A hospital based observational study was conducted on 49 preterm infants (<37 weeks gestation) admitted to the NICU at KLEH Dr. Prabhakar Kore Hospital, Belgaum, from December 2023 to December 2024. Clinical parameters, 2D echocardiography, and serum NT-proBNP levels were recorded. NT-proBNP levels were measured using chemiluminescence on 2ml blood samples collected in plain vacutainers after obtaining consent from parents. The samples are processed in biochemistry lab. Data were entered into Excel for statistical analysis using R version 4.2.3, with $p < 0.05$ considered significant.

Result: Among the participants, 25 (51%) were male and 24 (49%) were female. The mean age of the infants was 8.49 ± 6.01 days. The mean gestational age was 32.52 ± 3.08 weeks. The infants were categorized as 4 (8.16%) extreme preterm, 10 (20.41%) very preterm, 19 (38.78%) late preterm, and 16 (32.65%) early preterm. The mean birth weight of the neonates was 1368 ± 545 g. The distribution of birth weight categories included 18 (36.73%) very low birth weight, 17 (34.69%) extremely low birth weight, and 14 (32.65%) low birth weight. Clinical characteristics showed that

24 (48.98%) infants had a murmur, and 23 (46.94%) required oxygen. Apnea and birth asphyxia were less common, affecting 2 (4.08%) and 3 (6.12%) infants, respectively. The mean PDA size was 2.69 mm, with a range from 0.70 mm to 6.50 mm. PDA sizes were classified into small, moderate, and large categories, with 12 (24.49%) small, 12 (24.49%) moderate, and 25 (51.02%) large PDAs. Closure interventions were noted, with 21 (42.86%) undergoing pharmacological closure and 5 (10.20%) requiring surgical closure. Survival rate was high, with 42 (85.71%) infants surviving. Non-survivors (14.29%) presented complications like sepsis, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress, and pulmonary hemorrhage. ANOVA revealed a significant difference in gestational age among PDA size groups ($p=0.013$), with larger PDA sizes associated with smaller gestational ages. Pearson correlation showed a weak negative association between PDA size and gestational age ($r=-0.15$, $p=0.311$). PDA size by birth weight categories indicated significant differences ($p=0.025$), with lower mean PDA sizes in the low birth weight group. No significant differences were observed in mean PDA size between extremely low and very low birth weight groups. The mean NT-proBNP level was 17398 ± 16966pg/mL, with values ranging from 853 pg/mL to 70000 pg/mL. A significant correlation ($r=0.52$, $p=0.0002$) was found between PDA size and NT-proBNP levels, suggesting that larger PDA sizes are associated with higher NT-proBNP levels. Patients with hsPDA had significantly larger PDA sizes ($p=0.0001$) and higher NT-proBNP levels (median 26605 pg/mL) compared to those without hsPDA (median 5976 pg/mL, $p=0.036$). Surviving infants had significantly lower NT-proBNP levels (median 10281 pg/mL) than non-survivors (median 34593 pg/mL, $p=0.034$).

Conclusion: The study indicates a significant association between PDA size and NT-proBNP levels in preterm infants, with larger PDAs correlating with higher NT-proBNP levels. NT-proBNP can be a useful marker for diagnosing and managing PDA in preterm newborns. Further research is needed to validate these findings and refine the clinical utility of NT-proBNP in this setting.

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1. INTRODUCTION

Patent Ductus Arteriosus (PDA) is a heart defect that can occur in newborns shortly after birth. The ductus arteriosus, is a fetal vasculature that connects the pulmonary artery and the aorta, allows blood to bypass the lungs before birth. In most cases, the PDA closes on its own shortly after birth as the baby starts breathing independently[1]. However, if the PDA remains open (patent), it can lead to excessive blood flow to the lungs, causing strain on the heart and potential complications like fluid build up in the lungs[1]. PDA is more common in premature infants and can be associated with other heart defects[2].

The incidence of PDA in premature neonates varies based on gestational age and respiratory status, with failure of PDA closure potentially resulting in a left-to-right shunt across the duct[2]. While indomethacin and ibuprofen are common medical treatments for PDA, a conservative approach involving restricted fluid intake and continuous positive airway pressure (CPAP) can also be effective[3]. The three main treatment options for PDA are medication, catheter-based procedures, and surgery[4]. Treatment is necessary if the PDA is large enough to cause lung overload or increase the risk of heart infections like endocarditis[5]. Treatment decisions depend on whether the PDA is clinically significant, with options ranging from conservative management to medication or surgical ligation, especially in cases where the PDA causes respiratory deterioration or other complications[6,7]. Closing the PDA can prevent complications and promote better heart function[8].

Symptoms of PDA can include cyanosis (skin turning blue), fast or hard breathing, trouble feeding, infections, poor weight gain, and fatigue. Diagnosis of PDA in preterm neonates often requires Doppler flow echocardiography to confirm

the presence and significance of the condition. Early detection, accurate diagnosis, and appropriate management of PDA in newborns, particularly preterm infants, are crucial to prevent potential long-term health issues associated with this heart defect[2].

Several biomarkers have been identified as potential indicators for PDA in infants, particularly preterm newborns. Inflammation plays a significant role in the pathogenesis of PDA in preterm infants. Biomarkers associated with the perinatal inflammatory process, such as growth differentiation factor 15 (GDF-15), monocyte chemotactic protein 1 (MCP-1), platelet aggregation, and prostaglandin D_2 synthase (PGDH), have been linked to persistent PDA. These biomarkers are related to tissue hypoxia, inflammation, acute injury, oxidative stress, and thrombus formation, highlighting their potential as diagnostic tools for PDA in premature infants[9].

Isoprostanes (uIPs) have emerged as reliable biomarkers for predicting the development of hemodynamically significant PDA (hsPDA) in preterm infants. Early measurement of uIPs, either alone or in combination with other markers, has shown promise in identifying infants at risk of developing hsPDA. These biomarkers offer a non-invasive and painless method for assessing PDA progression and guiding management decisions in clinical practice[10].

Biochemical markers associated with the persistence of PDA in extremely preterm infants include growth differentiation factor 15, monocyte chemotactic protein 1, platelet-derived growth factor, and erythropoietin. High levels of inflammatory markers and erythropoietin have been linked to persistent PDA and failure to respond to pharmacological treatment. These markers provide valuable insights into the risk factors and outcomes associated with PDA in preterm infants[11].

Biomarkers related to cardiac function, such as brain-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), have been explored for their potential in diagnosing and monitoring PDA in preterm infants. While these biomarkers show overlap in concentrations across different PDA severities, they remain valuable tools for assessing cardiac status and guiding treatment decisions in infants with PDA[12,13]. The serum NT-proBNP levels in preterm newborns with PDA have been extensively studied. Research indicates that the expression levels of NT-proBNP are higher in PDA patients compared to non-PDA patients. Specifically, in the PDA group, NT-proBNP levels are higher in symptomatic PDA (sPDA) patients than in asymptomatic PDA (asPDA) patients. The level of serum NT-proBNP on the 3rd day after birth is positively correlated with the diameter of the ductus arteriosus, showing clinical value for early diagnosis of PDA[14,15]. Additionally, studies have shown that NT-proBNP concentrations can be predictive of PDA persistency beyond 10 days despite pharmacological treatment, with concentrations above a certain threshold being significant predictors[15]. Furthermore, B-type natriuretic peptide (BNP) and NT-proBNP have been used as screening tools for PDA in preterm infants, with elevated plasma BNP levels associated with the presence of PDA[16]. These findings highlight the importance of serum NT-proBNP levels as a valuable marker for diagnosing and predicting outcomes related to PDA in preterm newborns. NT-proBNP is a biomarker produced primarily by the ventricular myocardium in response to increased wall stress and volume overload[17]. In the context of cardiac health, elevated NT-proBNP levels in newborns may indicate cardiac stress, ventricular dysfunction, or structural heart abnormalities[18].

Some studies suggest that serum NT-proBNP levels may be useful in assessing the need for pharmacological or surgical intervention in preterm infants

with PDA, particularly when combined with other clinical and echocardiographic parameters[19]. Elevated NT-proBNP levels in the context of a hemodynamically significant PDA may prompt clinicians to consider medical or surgical closure to prevent complications such as pulmonary hypertension, necrotizing enterocolitis, or bronchopulmonary dysplasia[20]. Further research is needed to elucidate the precise role of NT-proBNP in the diagnosis, management, and prognostication of PDA in newborn babies, with the ultimate goal of optimizing outcomes and reducing morbidity associated with this common congenital heart defect. Therefore current study titled "Estimation of serum N-terminal peptide of Brain natriuretic peptide levels in preterm newborn with Patent Ductus Arteriosus (PDA)- a one year prospective observational study" was carried out in in KLE's Dr Prabhakar Kore Hospital, Belgaum to estimate the NT-proBNP in preterm babies with PDA and to correlate it with the size of the PDA.

1. AIMS AND OBJECTIVES

Primary objective:

To estimate the serum NT-proBNP in preterm newborns with PDA

Secondary objective:

To correlate the level of serum NT-proBNP with size of PDA (hs-PDA) in preterm newborns

2. REVIEW OF LITERATURE

2.1. Patent ductus arteriosus

Preterm infants with respiratory distress syndrome (RDS) frequently develop patent ductus arteriosus (PDA), and 60–70% of these infants undergo medication and/or surgical treatment for PDA. The ductus arteriosus (DA), is a hole in a developing baby's circulatory system, often closes soon after delivery[7]. Throughout intra-womb life, the DA is a physiological structure that allows blood to detour the lungs by flowing from the pulmonary artery to the descending aorta. PDA occurs when this vessel fails to close as it normally should after birth. PDA is one of the most common heart conditions in preterm newborns. It is characterized by the failure of the DA to close within the first 72 hours of life. This condition permits oxygen-poor blood from the pulmonary artery to mix with oxygen-rich blood from the aorta, resulting in excessive blood flow to the lungs, which strains the heart and increases blood pressure in the pulmonary arteries.[1]

The DA, which joins the pulmonary artery to the aorta, develops throughout the embryonic stage of life. Babies do not need lungs to provide oxygen when they are in the womb because they are getting it from placenta while they are still in the womb[21]. It is not essential for the heart to pump blood to the lungs in order for a baby to breathe because the baby's lungs cannot create oxygen. All babies have the DA, a blood vessel, while they are still developing in embryonic stage. The newborn's lungs must start supplying the rest of the body with oxygen after the umbilical cord is cut and the baby is delivered.[22] The DA generally closes, the lungs expand, and the blood vessels vasodilate within the first few hours of a newborn's life to allow for a higher flow of blood through them[23]. After a particular amount of time, the DA may

occasionally fail to seal by itself. A PDA — sometimes spelled "open"—describes this situation. Full-term newborns are not exempt from the danger of contracting this sickness, despite the fact that preterm children are more likely to suffer from it[24].

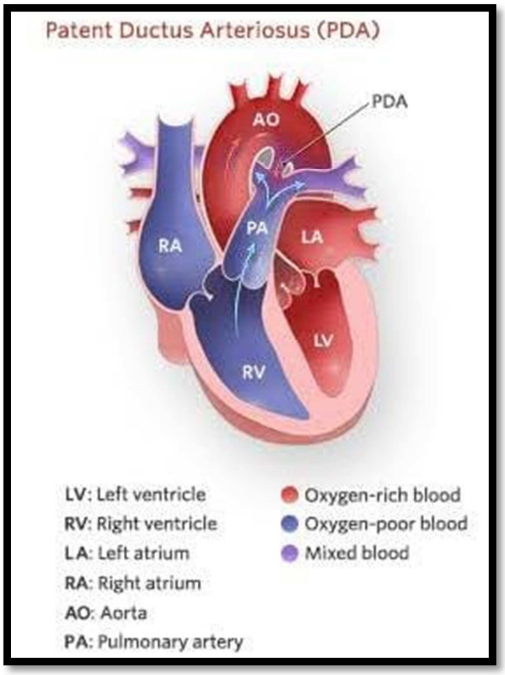

Figure 1: Diagram of a cross-section through a heart with PDA[25]

Ibuprofen and indomethacin are the two drugs that are typically prescribed to patients in the beginning stages of treatment for PDA which are effective in closing the ductus with 70-80% closure rate. Studies has found that Ibuprofen has better safety profile when compared to indomethacin and may be preferred over later[26]. Loading dosage for Ibuprofen is 10mg/kg/dose and subsequent dose of 5mg/kg/dose 24 hourly X 2 doses is recommended. Due to safety concerns about NSAIDs in neonates, paracetamol has lately been utilized to decrease prostaglandin synthesis via peroxidase. A meta-analysis study found that paracetamol could cause an early PDA closure with no obvious negative effects[27]. Dosage of 15mg/kg every 6 hours for 3 day was recommended for paracetamol. Paracetamol is available as both an injectable and an oral formulation.

The clinical, radiological, and echocardiographic examination that is currently utilized to identify a PDA that is substantial from a hemodynamic standpoint has considerable limitations. Echocardiography has always been seen as the gold standard that most reliably produces accurate results. Because the size does not correspond to the extent of shunting, there is no general agreement on how to define hemodynamically significant PDA using echocardiographic criteria[28]. This is one of the reasons why there is no agreement.There are indirect signs of left ventricular volume overload and pulmonary blood flow that can be found in biomarkers such as NT-proBNP. In response to an increase in the stress placed on the ventricles, cardiac myocytes produce NT-proBNP, which is a biomarker that can be easily measured[29]. It is easy to identify, and the chemi-luminescent immunoassay system in the biochemistry lab at the KLE hospital is used to determine its concentration (Figure 2). The degree of mechanical strain and volume stress, both of which affect the prognosis of the disease, is connected with their concentrations. In addition, it has been revealed that their concentrations are significantly higher in conditions such as congenital anomalies, syndromic syndromes, renal failure, and neonatal sepsis. Hence, NT-proBNP can be utilized as a diagnostic tool for a variety of diseases and conditions. Monitoring the levels of NT-proBNP in preterm newborn diagnosed with PDA would make earlier intervention possible and provide insight into the progression of the condition after medication has been administered[30].

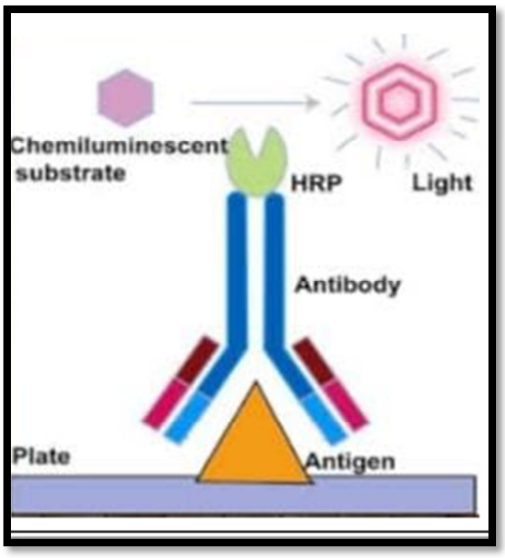

Figure 2: Chemiluminescent immunoassay system[25]

The presence of a PDA in this population of infants has been linked in a number of studies to an increased risk of mortality as well as severe neonatal morbidity, such as congestive cardiac failure, intra-ventricular haemorrhage (IVH), pulmonary bleed, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC)[13]. On the other hand, the prevalence of these disorders is not affected by the therapeutic methods currently in use for PDA[31]. Therefore, there are still many contentious and unresolved issues regarding the need for treatment and management strategies for hemodynamically significant patent ductus arteriosus (hsPDA)[32]. These issues can be broken down into two categories: management strategies and treatment strategies. Even though echocardiography is currently considered as definitve for the diagnosis and evaluation of hsPDA, the data obtained from echocardiogram have insufficient predictive value for the closure of DA on its own[33]. Hence, there is a growing interest in identifying biochemical markers that are linked with PDA and diseases that are associated with PDA and that may be used to not only confirm hsPDA but also prove that treatment is beneficial[34,35]. B-type natriuretic peptide, also known as BNP, is a hormone that is secreted by the cardiomyocytes of the ventricles

of the heart in response to the volume expansion and pressure overload. Inside the cardiomyocytes, the pro-BNP is cleaved to produce the biologically active form known as BNP as well as the inert N-terminal pro-brain natriuretic peptide fragment known as NT-proBNP [17].

Plasma NT-proBNP has the physiological effects of diuresis, natriuretic excretion, vasodilation, and decreased peripheral vascular resistance. It can reflect left ventricular burden and pulmonary blood volume. It is particularly significant in the prediction of hs-PDA and can effectively control the cell alterations in peripheral blood. Many researchers have found varied results when comparing PDA with NT-proBNP, and these disparities can be attributed to different detection techniques and observational populations[36].

2.2. History

PDA is a common condition in newborns with a gestational age under 28 weeks. Its hemodynamic significance is determined by clinical and echocardiographic criteria, though these do not necessarily indicate the need for intervention in the newborn period. BNP has been suggested as a screening tool for PDA in preterm infants. In a prospective blinded study, plasma BNP was measured by chemiluminescence immunoassay in 67 preterm infants (median gestational age 26 weeks) on the second day of life to determine if BNP levels could indicate the need for PDA intervention based on specific clinical and echocardiographic findings[16].

Despite numerous randomized clinical trials over the past three decades, there is no consensus on the best therapeutic strategy for ductal closure in premature newborns. Studies indicate that surgical ligation can be as effective as medical treatment with cyclooxygenase (COX) inhibitors like indomethacin and ibuprofen[37].

PDA was the first congenital heart defect successfully repaired surgically. In 1938, Dr. Robert E. Gross performed the landmark surgery, pioneering the surgical repair of several previously untreatable lesions. This historic achievement was preceded by centuries of work from various surgeons, physicians, and anatomists, including Galen of Pergamon in 129 AD, who first described aspects of fetal circulation, including the PDA and foramen ovale, although he did not understand their significance[38]. In the early 20th century, John Cummings Munro suggested surgical closure of the ductus based on postmortem findings, presenting his method in 1907. Evarts Ambrose Graham also considered surgical treatment for PDA in the 1920s, believing it to be both desirable and feasible[39]. In the 1970s, Michael A. Heymann and colleagues used non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and indomethacin to close PDA in premature infants, demonstrating their efficacy. In 1991, François Laborde performed the first PDA closure using video-assisted thoracoscopic surgery (VATS), a highly favored method among low-birth-weight infants due to its minimal morbidity and zero mortality in a series of 332 patients[40]. The first successful transcatheter PDA coil embolization was performed in 1992 by Cambier and associates, adapting a technique used for embolizing vascular anomalies. This method became popular for its safety, efficacy, and applicability across all age groups[41]. Current therapeutic options for PDA include pharmacologic closure, percutaneous closure in the catheterization lab, VATS hemoclip occlusion, and conventional thoracotomy with ligation. Pharmacologic closure remains the initial therapeutic approach in most clinics, but percutaneous closure is also effective for both children and adults [39,41].

2.3. Patent ductus arteriosus condition and mechanism

The DA connects the aorta and the pulmonary artery, which are two significant arteries that transport blood out from the heart. Blood is transported from the heart by the aorta and the pulmonary artery. In fetal life oxygenation is done by the placenta. The DA carries oxygenated blood from the lungs and delivers it for systemic circulation. Once a newborn starts breathing and using their lungs, the ductus normally closes on its own[22].

In patent ductus arteriosus, oxygenated and deoxygenated blood mix together. Because of this, an abnormally large volume of blood flows into the lungs, which exerts strain on the heart and causes pulmonary hypertension. In extremely premature newborns, PDA is one of the major contributors to morbidity. Since elevated plasma level of BNP is a characteristic that frequently occurs in adult patients with heart illness.

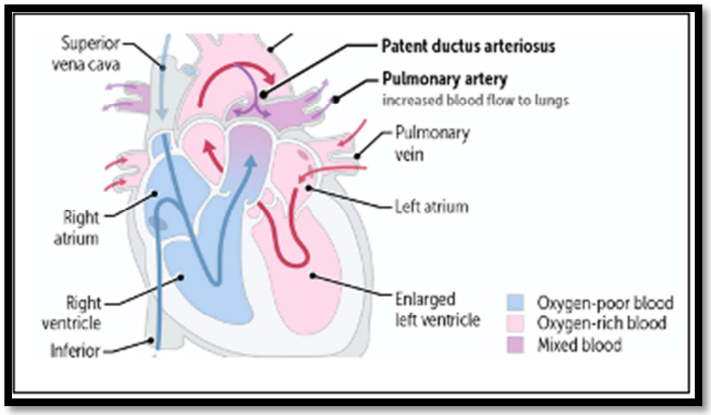

Figure 3: Illustration of PDA[42]

DA develops from the sixth embryonic arch along with other large vessels but the anatomical structure of the ductus is quite different from the aorta or pulmonary arteries[43] (Figure 3). An internal lamina can be found within a muscle layer that surrounds it. This muscular layer is supplied by vasa vasorum and smooth muscle

cells (SMC) absorb oxygen through diffusion from the lumen. Both of these processes take place inside the lumen. Low oxygen tension, high levels of prostaglandins, nitric oxide, and carbon monoxide, as well as high levels of adenosine, intracellular cyclic adenosine monophosphate and cyclic guanosine monophosphate, and an atrial natriuretic peptide, all of which exert their effects through activation of potassium channels on the SMC membrane, all contribute to the ductus remaining open throughout the fetal life[44].

The literature defines PDA in neonates based on its size, which is categorized into small, moderate, and large. The exact dimensions used to classify PDAs vary slightly across studies, but generally, they are defined as follows:

i. Small PDA - Typically considered to be less than 1.5 mm in diameter[2,45]

ii. Moderate PDA - Ranges between 1.5 mm and 3 mm in diameter[2,45]

iii. Large PDA- Exceeds 3 mm in diameter[2,45]

These categories are used to assess the hemodynamic significance of the PDA and guide treatment decisions.

PDA may cause the right ventricle (RV) to function differently and become hyperdynamic, with the latter affecting a premature infant's long-term prognosis. Once tachycardia, a cardiac murmur, and a high pulse pressure raise the clinical suspicion of hsPDA. Echocardiography assists evaluate heart anatomy, ventricular function, the ratio of estimated pulmonary to systemic blood flow, and pulmonary artery pressures (PAP) in addition to confirming ductal patency[46]. However, due to the complicated anatomy of the RV and the physiological hemodynamic changes that occur during the first week of life, conventional echocardiography has limits. In

reaction to cardiac failure, the heart, brain, and other organs produce hormones called brain natriuretic peptides. BNP lowers systemic vascular resistance and arterial pressure by causing vasodilatation and diuresis[36]. NT-proBNP has been reported to be a helpful biomarker for the severity of hsPDA in preterm newborns[47,48].

B-type natriuretic peptide, also known as BNP or B-type natriuretic peptide, is another form of natriuretic peptide that belongs to the same family as cardiac natriuretic peptide (ANP). The majority of BNP is released by ventricular myocytes, which are activated in response to the ventricular load. BNP is broadly dispersed throughout the body, including the brain, spinal cord, heart, and lungs, with the heart having the highest BNP level[49].

Hs-PDA is associated with considerable mortality and morbidity[7,13]. Left-to-right shunting across the patent ductus arteriosus results in pulmonary over circulation, which leads to respiratory decompensation, which in turn increases the risk of BPD[6], IVH[3], NEC, and death[50]. Nonetheless, the majority of research uses a mix of clinical symptoms and echocardiographic criteria to describe this illness[51].

Table 1: Clinical and echocardiographic criteria for hsPDA diagnosis

ECHOCARDIOGRAPHIC CRITERIA	CLINICAL CRITERIA
LA/Ao ratio >1.4	Inc respiratory effort,Fio2 >30 %
PDA diameter >50 % wider than PA	Dec systolic or MBP,Inc Pulse presure
Large volume Lt to Rt shunt	Pulm.congestion,cardiomegaly,hepatomegaly, hyperdymaic precordium,bounding pulses.

Although there has not been an international consensus achieved on the classification of hsPDA, it is important to note that. It has been demonstrated that the sensitivity of a variety of clinical symptoms is low[19]. Clinical symptoms are the best way to determine whether or not a patient has hsPDA, although echocardiography is still the gold standard.

It is common for premature infants to have a PDA, and the likelihood of having one is inversely related to the amount of time spent in gestation. Aorto-pulmonary shunting caused by the patent ductus arteriosus results in an excessive amount of blood overflowing into the pulmonary system, which prolongs the patient's dependence on a ventilator. This also contributes to bronchopulmonary dysplasia, difficulty feeding, necrotizing enterocolitis, intracranial hemorrhage, and death[52–54]. When determining whether a preterm newborn needs medicinal treatment or surgical ligation during the first few days of life, echocardiography and physical examination are insufficient for determining whether the patient has hsPDA. Randomized clinical trials have shown that the value of prophylactic intervention (within the first 24 hours after birth) is debatable; nonetheless, early therapy with indomethacin is thought to minimize the risk of morbidity. BNP is produced by cardiac myocytes as a 108-amino acid prohormone (proBNP). This 108-amino acid prohormone is then cleaved to produce the 32-residue BNP and the 76-residue N-terminal fragment of proBNP (NT-proBNP). Natriuresis, diuresis, vasodilatation, and antagonism of the renin–angiotensin–aldosterone system are the mechanisms that BNP uses to modulate extracellular fluid volume as well as blood pressure. Both BNP and NT-proBNP have been applied to the problem of determining whether or not humans have cardiac dysfunction[16,55].

B-type natriuretic peptide, also known as BNP, is a hormone that is secreted by the cardiomyocytes of the ventricles of the heart in response to the volume expansion and pressure overload. Inside the cardiomyocytes, the pro-BNP is broken into the biologically active form known as BNP and the inactive NT-proBNP fragment. Both of these forms are then released into the bloodstream. Holmstrom *et al*., (2007)[56] conducted research that demonstrated a strong correlation between the

levels of plasma BNP and NT-proBNP and echocardiographic indicators of hsPDA. As a result, a number of studies have been carried out to examine the utility of these markers in diagnosing PDA that needs treatment and monitoring the efficiency of the treatment. Bagnoli *et al*[57]., in 2010 found that the sensitivity of the corresponding values ranged anywhere from 65% to 90%, while the specificity revealed values anywhere from 55% to 85%. According to the findings of a number of studies, particular levels of BNP measured in the first few days after delivery can accurately predict whether or not the patent ductus arteriosus will close. Nevertheless, the statistics that are accessible are scant and inconsistent with one another[15]. Figure 5 depicts the synthesis of and release of BNP

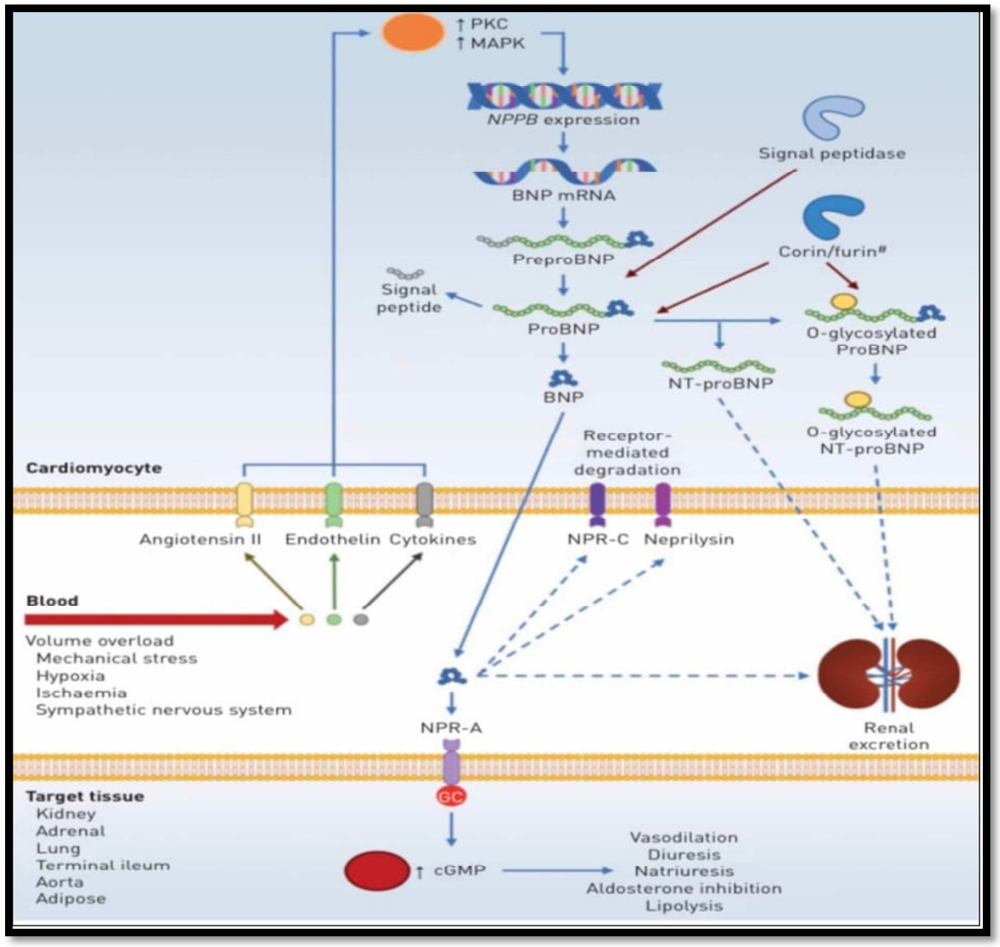

Figure 4: Synthesis and release of BNP and NT-proBNP[58]

The amount of BNP in the plasma of healthy pre-term newborns begins to rise almost as soon as they are born. The concentration is at a pretty high level during the first week, but it subsequently begins to dramatically decline. After then, the level of BNP steadily goes down even further and eventually reaches a level that is stable 1 month after the baby is born. This causes an increase in the volume and pressure load of the ventricle, which in turn stimulates the synthesis of BNP in the left and right atrium and ventricle, which then secretes it into the circulation after birth. The change in perinatal circulation is also caused by the redistribution of blood from the placenta to the lungs. Yet, the amount of BNP in fetal plasma is higher than that of the placenta, which indicates that the placenta has an influence on BNP clearance. This may also explain why there is an increase in the level of BNP in newborn plasma. The reduction in plasma BNP can be accounted for by the fact that the pulmonary circulation pressure steadily rose with age and by the fact that diuresis occurs concurrently with the maturity of the kidneys[59].

Many different groups have, up until this point, published the reference range of plasma BNP at various stages after birth. Neves *et al*[60]., in 2016 provided a summary of the pertinent data; nonetheless, there are some discrepancies to be found as a result of differences in gestational age. According to Cantinotti *et al*[61]., the levels of plasma BNP were at their maximum in the first two days after birth and then gradually fell in the days and weeks that followed. In addition, there was no correlation found between the sex of the mother and the method of delivery and the BNP levels.

2.4. Prevalence

PDA, is a common problem that affects preterm neonates. It affects roughly 33% of very preterm infants and 65% of extremely preterm infants[62]. According to the findings of a number of studies, the presence of PDA in this population of infants is linked to an increased risk of mortality as well as severe neonatal morbidity, which can include renal failure, IVH, pulmonary hemorrhage, BPD, NEC, and heart failure[63,64]. Nevertheless, the currently available treatments for patent ductus arteriosus do not significantly lower the incidence of these disorders[65]. Regarding the necessity of therapy and management techniques for hsPDA, there are thus still a great deal of contentious debates and questions that have not been satisfactorily answered[66]. Although echocardiography is now considered the gold standard for the diagnosis and assessment of hsPDA, research suggests that the data obtained from echocardiography have insufficient predictive value for spontaneous DA closure[34]. Hence, there is a growing interest in identifying biochemical markers that are linked with PDA and diseases that are associated with PDA and that may be used to not only confirm hsPDA but also prove that treatment is beneficial[34,35].

In term neonates, the documented incidence of PDA is only one in every two thousand births; it is responsible for 5-10% of all congenital cardiac disease[67]. The prevalence of PDA is significantly higher in preterm neonates, with figures ranging from 20% to 60% (depending on the demographic and diagnostic criteria) of affected babies. This is due to the fact that the prevalence of PDA is significantly higher in preterm neonates[2]. The higher incidence of PDA found in premature infants can be attributed to their immaturity, which prevents them from developing the typical closure mechanisms. It has been discovered that a PDA in preterm neonates has a high link with both the gestational age and the weight of the infant. To be more

specific, a PDA is present in 80% of neonates that weigh less than 1,200 g at birth, but it is present in just 40% of children that weigh less than 2,000 g at birth[68,69]. In addition to this, symptomatic PDA can be detected in 48 percent of newborns who were born weighing less than one kilogram. This is an abnormality that occurs when the DA does not close properly after it is formed[70]. A description of this negative association between birth weight and the occurrence of PDA is provided in findings from the Newborn Research Network of the National Institute of Child Health and Human Development (NICHD)[71,72].

Researchers are trying to determine the factors that affect whether the DA remains open after the first 24 to 48 hours of a newborn's life. It is undeniable that premature delivery increases the incidence of ductal atresia, however this is due to physiological factors associated with it rather than an abnormality that is innate to the ductus itself[73]. The majority of occurrences in term infants seem to be sporadic, although there is mounting evidence that inherited factors contribute to the development of patent ductus in some patients. The majority of patent ductus cases affect premature babies. However, it appears that other variables, such as prenatal infection, contribute to some cases of the illness.

A study by Potsiurko found that DA closure occurred within the first 10 days of birth in 70% of treated children and 44% of expectantly managed newborns ($p > 0.05$). Newborns with PDA at 10 days had significantly higher early concentrations of NT-proBNP. By the eighth day, NT-proBNP levels had decreased in both groups but remained higher in those with PDA. On the second day of life, NT-proBNP levels could predict DA closure within 10 days in treated infants (AUC 0.81, $p < 0.05$), but not in expectantly managed infants[15].

A study in Belgium, published in the Journal of Pediatric Cardiology, examined the potential of NT-proBNP to predict spontaneous closure of PDA in preterm neonates born before 32 weeks or weighing less than 1500 g. This prospective, blinded study compared NT-proBNP levels with simultaneous echocardiography to validate the biomarker's relevance. The predictive potential of NT-proBNP for identifying PDA requiring treatment was also assessed using a protocol based on clinical signs and echocardiographic assessment[74].

In Kolkata, India, a study published in the International Journal of Research and Review investigated the use of serum NT-proBNP levels as a diagnostic tool for high-risk PDA (hs-PDA). The study included 40 PDA patients, 24 of whom met echocardiographic criteria for hs-PDA, while the remaining 16 had negligible PDA. The study found that infants with hs-PDA had significantly higher NT-proBNP levels, exceeding the 95th percentile. Therefore, NT-proBNP measurement, combined with clinical suspicion, can supplement echocardiography in diagnosing hs-PDA[19].

2.5. Diagnosis

The fetal circulation is not complete without the presence of the DA, which is the connection between the pulmonary artery and the aorta. The DA may close on its own depending on the gestational age and the total birth weight of the baby. Forty percent of newborns with birth weights of less than 2000 grams were reported as failing to close[2]. In infants, particularly those born prematurely, persistent DA is one of the most common forms of congenital cardiac disease that can be found. In preterm infants, echocardiography is the diagnostic test of choice for determining whether or not the patient has a hs-PDA. There have been a few studies that have shown that the utilization of a straightforward blood test to identify NT-proBNP may be helpful in

determining the diagnosis of hs-PDA as well as the appropriate treatment for the condition.

It is common for newborns with a gestational age of fewer than 28 weeks to be born with a PDA. The clinical and echocardiographic signals describe the hemodynamic significance of PDA, but they do not tell whether or not PDA intervention is necessary in the first few days of a newborn's life. It has been suggested that BNP, could be used as a screening tool for preterm newborns with patent ductus arteriosus. Plasma BNP was assessed by chemiluminescence immunoassay in 67 preterm infants 28 weeks (median 26) on their second day of life as part of a prospective blinded trial. The purpose of this study was to evaluate whether or not BNP can accurately predict the need for PDA intervention. The patent ductus arteriosus intervention was carried out on the basis of certain echocardiographic and clinical results. Twenty-four patients in the PDA intervention group were given treatment, while 43 individuals in the PDA control group did not get any treatment for their condition. The BNP concentrations in the intervention group were significantly higher (median 1069 pg/mL versus 247 pg/mL, p 0.001) than those in the control group. BNP had a positive correlation with both the size of the ductal openings (R = 0.46, p 0.001) and the atrial/aortic root ratio (R = 0.54, p 0.001). In conclusion, plasma BNP was shown to be a good predictor for ductus intervention (area under the curve: 0.86), with the best cut off at 550 pg/mL on the second day of life in ventilated infants less than 28 weeks gestation (sensitivity: 83%; specificity: 86%). This was found to be the case after the researchers found that the plasma BNP had an area under the curve of 0.86[16].

The heart is the source of a chemical known as a natriuretic peptide. The brain natriuretic peptide, also known as BNP, and the NT-proBNP are the two primary

varieties of these molecules. In a healthy person, trace amounts of BNP and NT-proBNP can be seen floating around in the bloodstream. If the levels are high, it's possible that heart isn't pumping enough blood to meet the demands of the body. Heart failure, also referred to as congestive heart failure, is the medical term used to describe a situation in which this occurs. The amounts of BNP or NT-proBNP that are found in your blood are what are measured by natriuretic peptide assays. NT-proBNP test or a brain natriuretic peptide are helpful in making a diagnosis of heart failure; however, they use very distinct sorts of measurements. Other names for this peptide include NT-proB-type natriuretic peptide test, B-type natriuretic peptide, and brain natriuretic peptide. For the diagnosis of hsPDA in preterm newborns, the reference standard is echocardiography. In the diagnosis and management of hsPDA, a straightforward blood assay for brain natriuretic peptide (BNP) or amino-terminal pro-B-type natriuretic peptide (NT-proBNP) may be helpful; however, a summary of the diagnostic accuracy has not been reviewed in recent years[75].

In reaction to a volume overload, cardiac myocytes will release NT-proBNP into the bloodstream. The brain natriuretic peptide, also known as BNP, is produced from the 134-amino-acid precursor known as pre-proBNP. This precursor is then cleaved into the 108-amino-acid prohormone known as proBNP and the 26-amino-acid signal peptide[76,77]. Following this, proBNP is discharged into the circulation, where it is subsequently cleaved by the proteases furin and corin into the physiologically active hormone BNP (77– 108 amino acids) and the inert metabolite NT-proBNP (1– 76 amino acids)[78]. It is a low molecular weight peptide (8.5 kDa) and is eliminated from plasma via passive excretion by organs with a high blood flow, such as the liver and kidneys. Because NT-proBNP is not biologically active, it does not have any active clearance mechanisms[79]. In a ratio of 1:1, BNP and NT-proBNP

are the proteins that are sent into the circulation from the cardiac ventricle. Because BNP is processed in the systemic circulation via natriuretic peptide receptor-C, plasma concentrations of proBNP are significantly higher than those of BNP. This is due to the fact that proBNP is filtered by the kidneys, whereas BNP is not. Under conditions of normal glomerular filtration rate, the half-life of pro-BNP is 120 minutes, whereas the half-life of BNP is only 22 minutes[80,81]. In addition, the chemical structure of pro-BNP is more stable in vitro than that of BNP.

Several studies have explored the potential of NT-proBNP as a marker for high-risk preterm birth in infants. And found that NT-proBNP levels declined in the first week of life, except in premature newborns with PDA. They concluded that NT-proBNP levels on the third day could indicate the need for treatment in these infants. Nuntnarumit *et al.* also identified NT-proBNP on the second day as a sensitive marker for predicting hs-PDA. These studies suggest that decreasing NT-proBNP levels indicate ductal closure[82,83].

Kulkarni's systematic review found that the diagnostic accuracy of NT-proBNP for predicting hs-PDA varied with assay characteristics, threshold levels, and patient characteristics such as gestational and chronological age. He concluded that NT-proBNP validation is necessary before using it to guide treatment decisions for hs-PDA[84]. This study aimed to evaluate the correlation between NT-proBNP levels and hs-PDA prevalence in an Indonesian patient population, potentially highlighting NT-proBNP's value as a diagnostic marker.

Early detection and treatment of hypersplenic pulmonary hypertension in preterm newborns can improve outcomes, such as reducing in-hospital mortality and pulmonary bleeding risk[85,86]. However, the benefit of treating hs-PDA remains uncertain, leading to varied practices among neonatologists[65]. The use of medical and

surgical treatments for hs-PDA has decreased over the past decade[1,12], supported by research showing a high rate of spontaneous PDA closure in very low birth weight (VLBW) infants [87].

Echocardiography, despite its high cost and resource requirements, is the standard for been used for early hs-PDA detection in preterm infants[19]. Clinical symptoms and physical examination results, traditionally used to assess PDA, are unreliable, necessitating echocardiography for documentation[88]. Hemodynamic significance of PDA in preterm neonates is defined by clinical signs, cardiac physical signs, or echocardiographic parameters such as LA/Ao ratio >1.5 and ductal diameter >1.5 mm.

In a prospective blinded study, plasma BNP was measured in 67 preterm infants (<28 weeks) on the second day of life. BNP levels were higher in the intervention group (median 1069 pg/mL) compared to controls (median 247 pg/mL). BNP levels decreased following pharmacological treatment or surgical ligation, indicating cardiac recompensation. Preterm infants needing ductus intervention had significantly larger ductal diameters and higher LA/Ao ratios than controls. BNP levels correlated with LA/Ao ratios and ductal diameters, suggesting BNP's potential for predicting PDA intervention needs[16].

An observational study reported serial NT-proBNP levels and echocardiographic parameters at 28, 32, and 36 weeks gestational age, correlating NT-proBNP cut-off levels with bronchopulmonary dysplasia development[89]. Another study aimed to determine if NT-proBNP could identify hsPDA and its correlation with echocardiographic assessment. In this study, 35 preterm children were evaluated on days 2, 4, and 7 of life, with NT-proBNP levels significantly higher in the hsPDA group on day 2. NT-proBNP levels decreased following treatment in responsive

infants. The NT-proBNP cut-off level of 10,180 pg/mL on day 2 had 100% sensitivity and 91% specificity for predicting hsPDA, indicating NT-proBNP's potential as a sensitive diagnostic tool for hsPDA in premature newborns[83].

2.6. Treatment

The incidence of high-risk preterm delivery at term relies on the features of the study population and is inversely proportional to postmenstrual age as well as birth weight. The chronological age at the time of diagnosis and the echocardiographic diagnostic criteria that are applied are two additional factors that may have an impact on the prevalence of hsPDA. According to the findings of the Neonatal Research Network of the NICHD, PDA is diagnosed in 46% of very low birth weight babies and preterm infants born at less than 28 weeks of gestation[90]. In very low birth weight infants who were diagnosed with PDA, 71% were treated with indomethacin, 13% were treated with ibuprofen, and 27% were treated with surgical closure. PDA was seen in roughly 33% of VLBW newborns in the Vermont Oxford Network[91], and approximately 55% of extremely low birth weight (ELBW) infants (birth weight 1000 grams) in other cohorts[92]. In a national cohort of preterm infants born in France between 24 and 28 weeks of gestation, 32.9% required treatment with Ibuprofen or surgery for PDA[86]. According to several recent research, the spontaneous closure of PDA occurs in the VLBW population on a very regular basis[87]

Neonatal death can be caused by a wide variety of conditions, some of which are present at birth while others develop later in life. These conditions include heart disease, lung disease, sepsis, and many others. B-type natriuretic peptide, also known as BNP, is a peptide hormone that is released by the cells of the ventricle in response to an increase in the wall tension of the ventricle. The actions of brain natriuretic peptide that help regulate blood pressure include vasodilation , diuresis , and sodium

release. BNP is a sensitive measure that reflects ventricular function and has the potential to assist in the diagnosis and monitoring of a variety of conditions that affect neonates. Since the plasma Brain natriuretic peptide concentration of healthy newborns varies with age, reaches a peak in the first week after birth, and then gradually decreases to a stable level, there is currently no consensus on a reference Brain natriuretic peptide level for neonates. This is due to the fact that the concentration of Brain natriuretic peptide in the plasma of healthy newborns varies with age. In disease states, the correlation between the plasma concentration of brain natriuretic peptide and the results of echocardiography is good. This is of great significance in the screening, monitoring, and prognosis evaluation of neonatal cardiovascular diseases, which include congenital heart disease, patent ductus arteriosus, and a variety of other conditions. In addition to this, it makes it easier to evaluate how effective treatment and perioperative management have been. In addition, the monitoring of plasma BNP concentration offers direction for the diagnosis, evaluation, and treatment selection of particular infant respiratory disorders as well as neonatal sepsis[59].

Both the brain natriuretic peptide and the NT-proBNP cardiac biomarker assays are examples of various indicator tests that can be utilized in preterm infants to identify hsPDA. Brain natriuretic peptide is produced in the body as a prohormone called proBNP. This prohormone is then cleaved into two fragments: the active fragment BNP (a fragment consisting of 32 amino acids at the C-terminus) and the inactive fragment NT-proBNP (a fragment consisting of 72 amino acids at the N-terminus). Both of these fragments can be measured in the plasma of the body. In reaction to pressure overload, volume expansion, and increased myocardial wall stress, brain natriuretic peptide and NT-proBNP are generated by cardiac ventricular

myocytes and then released into the circulation. This process takes place within minutes. The kidneys are responsible for clearing both plasma Brain natriuretic peptide and NT-proBNP, the latter has a longer half-life (mean 120 minutes vs mean 20 minutes)[93,94], and it is more stable than BNP in vitro. BNP is eliminated by the kidneys. There is a wide range of variation in serum levels depending on factors such as chronological age, gestational age, test kit, PDA, and renal function. Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are both well-established indicators of heart failure in both adults and children[95,96].

BNP and NT-proBNP normative values in neonates have been reported by numerous research[84]. BNP and NT-proBNP readings reach their peak during the first three days of life and then gradually fall after that. Preterm newborns have levels that are higher than full-term neonates by the first month of life. With postmenstrual age, the presence or absence of PDA, and renal function, plasma levels of Brain natriuretic peptide and NT-proBNP change.

The echocardiographic criteria for hsPDA or a combination of these criteria plus clinical indicators of hsPDA serve as the reference standard for the diagnosis of hsPDA. Before beginning PDA closure therapy, an echocardiogram is necessary to rule out any further cardiac lesions, especially ductal-dependent lesions (such as severe coarctation, pulmonary atresia). For cases of suspected hsPDA, BNP and NT-proBNP tests may be helpful in order to reduce the need for echocardiograms, particularly in settings with limited resources. This situation calls for an echocardiography to be performed if the Brain Natriuretic Peptide or NT-proBNP Assay surpasses threshold cutoffs, therefore a relatively high sensitivity would be preferred. Repeated measurements of NT-proBNP, or brain natriuretic peptide, as directed by the clinical situation may also aid in the identification and monitoring of

hsPDA. BNP has the advantage of serial testing for trends before or after the start of medical therapy, which can be used to guide care without the necessity for serial echocardiograms. It can be used as an add-on test to an echocardiogram. This review will concentrate on using the index test as a triaging tool to help determine whether getting a second echocardiography as part of additional examination is necessary[19].

The echocardiographic criteria for hsPDA serve as the reference standard for the diagnosis of hsPDA. However, a combination of these criteria and clinical indicators of hsPDA can also be used to diagnose hsPDA. The clinical signs of hsPDA can also be used independently as a diagnostic tool. It is essential to undergo an echocardiogram before to beginning PDA closure therapy in order to eliminate the likelihood of any future cardiac lesions, particularly ductal-dependent lesions[19]. This will allow the patient to move through with the PDA closure therapy with peace of mind (such as severe coarctation, pulmonary atresia). Testing for BNP and NT-proBNP may be helpful in minimizing the need for echocardiograms in circumstances in which hsPDA is suspected. This is especially valuable in circumstances in which there are little accessible resources. It is recommended to have a relatively high degree of sensitivity since in this scenario it will be necessary to perform an echocardiography in the event that the Brain Natriuretic Peptide or NT-proBNP Test surpasses the threshold cutoffs[19,49]. BNP also has the ability to test for trends before or after the beginning of medical therapy. In the context of a diagnostic procedure, it is feasible to carry it out in addition to an echocardiogram. This talk will emphasis on using the index test as a form of triage to assist in determining whether or not having a second echocardiography as part of additional inquiry is required. This will be accomplished by referring to the results of the index test[97].

Echocardiogram is the reference standard for the diagnosis of hsPDA, but it is expensive, requires interpretation by a cardiologist, and may not be available in resource-limited settings. A simple blood assay of BNP or NT-proBNP that can diagnose hsPDA reliably may be useful to clinicians, especially in low-resource settings. A decrease in the need for echocardiograms will decrease utilization of resources including personnel and equipment. This can have a significant impact on healthcare costs in that the cost of an echocardiogram is more than 10-fold greater than the cost of Brain natriuretic peptide or NT-proBNP assays. Brain natriuretic peptide and NT-proBNP assays have been used in preterm neonates both for diagnosis and for initiation of medical or surgical treatment for hsPDA. A prior assessment of the diagnostic accuracy of BNP and NT-proBNP for hsPDA indicated significant variations in diagnostic accuracy based on test kit and patient characteristics[84]. N-terminal pro-B-type natriuretic peptide had higher sensitivity but BNP had higher specificity in the diagnosis of a hemodynamically significant patent ductus arteriosus. Advances in assay technology may introduce newer optimal methods for measurement of BNP and NT-proBNP that may change the diagnostic accuracy of these tests[98].

The serum NT-proBNP concentration could reliably predict the development of bronchopulmonary dysplasia or death in very preterm infants with PDA > 1.5 mm at the age of 24–48 h, regardless of the persistence of PDA, with the highest diagnostic value occurring at 8–9 days. This was true regardless of how long the PDA remained. The measurements 17,745 pg/ml taken between the ages of 24 and 48 hours showed a sensitivity of 55% and a specificity of 81% for predicting bronchopulmonary dysplasia or death. The concentrations 3537 pg/ml taken between the ages of 8 and 9 days of life had a sensitivity of 60% and a specificity of 89%. At

2–3 days of life, the serum NT-proBNP values were higher in extremely preterm newborns with hsPDA, and at 8–9 days of life, they were higher in babies with persistent PDA. This was the case regardless of whether or not the infants died later or had bronchopulmonary dysplasia. hsPDA was much more commonly identified in infants who subsequently developed bronchopulmonary dysplasia or died; however, pharmacological therapy of hsPDA did not reliably lower the incidence of bronchopulmonary dysplasia or mortality. hsPDA was significantly more commonly diagnosed in newborns who later developed bronchopulmonary dysplasia or died[15].

In numerous research, including those conducted by Choi *et al*[99]., Sanjeev *et al*[100]., and Czernik *et al*[16]., it was demonstrated that premature newborns with hsPDA have a higher level of serum BNP. In the more recent research, the optimal cutoff value was determined to be 550pg/mL, which had a sensitivity of 83% and a specificity of 86%, respectively. The findings of Sarjeev *et al*[100]. and Bagnoli *et al*[57] are consistent with the observation that the serum BNP level dropped when the hsPDA was shut down. It has been demonstrated that the level of plsma BNP is an accurate predictor for ductal intervention. Intervention is necessary for newborns who have been diagnosed with PDA by echocardiography and whose serum BNP levels are < 450 pg/mL. A successful treatment is indicated when the patient's serum level of BNP returns to normal after having been elevated[101].

2.7 Prevention

One of the most hotly debated issues in the field of neonatal intensive care is how preterm newborns should have their PDA managed. PDAs have been linked, but there is no evidence to suggest that they are the direct cause of a number of adverse outcomes, such as a lengthening of the time that a patient requires assisted ventilation, pulmonary haemorrhage, CLD, NEC, IVH, and death[102,103].

The therapeutic choice to administer preventive PDA treatment utilizing cyclooxygenase-inhibitor (COX-I) medicines has been predominantly motivated by the perceived benefits vs the potential hazards as evaluated by the treating physician. These benefits and risks have been weighed against one another. Randomized controlled trials, also known as RCTs, have not demonstrated a clear benefit of symptomatic patent ductus arteriosus treatment. This is in part due to major methodological challenges, such as high rates of open-label backup treatment in both the experimental and control arms, as well as a lack of high quality data on clinically important outcomes such as NEC, CLD, IVH, and mortality. The question of whether or not a patent ductus arteriosus should be treated, and if so, in whom, when, and with what pharmacotherapeutic agent, as well as the question of when to contemplate the procedural closure of a PDA, continue to be contentious topics of debate[103].

At least eighty randomized controlled trials (RCTs) have been carried out to compare various COX-I medicines, dosages, and methods of administration in order to treat symptomatic PDA. Ibuprofen at the standard dose, which is 10 milligrams per kilogram followed by two doses of 5 milligrams per kilogram at 24-hour intervals, is the most prevalent regimen, and it has a much better safety profile than indomethacin, which was the previous gold standard. Acetaminophen has also surfaced as a prospective therapy option for PDA closure because to the fact that its enteral formulation is just as effective as standard-dose ibuprofen or indomethacin, but it has a substantially better gastrointestinal and renal safety profile[104]. Recent randomized controlled trials, on the other hand, have shown that the PDA closure rate with IV acetaminophen is much lower than that seen with either indomethacin or ibuprofen[105,106].

One recent network meta-analysis of sixty-eight randomized controlled trials (4802 infants) showed that higher doses of ibuprofen (15 mg/kg to 20 mg/kg followed by two doses of 7.5 mg/kg to 10 mg/kg at 24 h-intervals), especially when given enterally, may achieve better PDA closure without increasing the risk for adverse outcomes (such as NEC) in comparison with standard-dose ibuprofen, Acetaminophen, or indomethacin[107]. These findings are comparable with those found in more recent studies which suggested that greater doses of ibuprofen may be required beyond the first three to five days after delivery in order to obtain therapeutic blood levels[108–110].

Intravenous paracetamol at a dose of 15 mg/kg every 6 hours (4 times a day) for 3 days is an effective treatment for closing a hemodynamically significant patent ductus arteriosus (hsPDA) in preterm infants[111–115]. After the 3-day course, echocardiography is performed to evaluate if the ductus arteriosus has closed.Several studies have demonstrated that this intravenous paracetamol regimen results in successful closure of hsPDA in 77-95% of preterm infants[115]. It is particularly effective when started within the first week of life, likely due to higher prostaglandin levels early in postnatal life[112–115]. Intravenous paracetamol has been shown to have similar efficacy to ibuprofen and indomethacin for PDA closure, but with fewer adverse effects[112,114]. It does not cause the reductions in platelet count, urine output, and increases in creatinine and bilirubin that are seen with NSAIDs[112]. Plasma paracetamol concentrations with this dosing regimen remain within the safe range for analgesia in preterm infants[111]. If the ductus does not close after the initial 3-day course, the paracetamol treatment can be extended up to 6 days total before repeating the echocardiogram[115]. Surgical ligation may be needed for infants who do not respond to medical treatment[112]. Intravenous is an effective and well-tolerated

treatment for closing hsPDA in preterm infants and it represents a useful alternative to NSAIDs when those are contraindicated.

2.7. Outcomes

Research has extensively examined NT-proBNP as a marker for high-risk preterm birth in infants. NT-proBNP, a natriuretic peptide released by cardiac ventricles under stress, has shown potential in diagnosing and predicting outcomes in preterm infants with PDA and other cardiovascular complications.

Early research by Ramakrishnan *et al.* found that NT-proBNP levels typically decline in the first week of life, except in preterm newborns with PDA. They concluded that NT-proBNP levels on the third day after birth could indicate the need for treatment in these infants. Nuntnarumit et al. also found that NT-proBNP measured on the second day is a sensitive marker for predicting hsPDA in preterm newborns. These findings suggest that decreasing NT-proBNP levels indicate ductal closure[82,116]. Kulkarni's systematic review highlighted the variability in diagnostic accuracy of NT-proBNP due to differences in assay characteristics, threshold levels, and patient characteristics such as gestational and chronological age. He stressed the need for NT-proBNP validation before using it to guide treatment decisions for hs-PDA[84]. This study aimed to evaluate the correlation between NT-proBNP levels and hs-PDA prevalence in an Indonesian patient population, potentially highlighting NT-proBNP's diagnostic value.

Echocardiography remains the gold standard for diagnosing PDA, despite its high cost and resource requirements. Doppler flow tests during echocardiography can determine ductal flow direction, cardiac anatomy, ventricular function, and pulmonary artery pressures, providing comprehensive diagnostic information[47]. However, clinical

symptoms and physical examination results have proven unreliable for assessing PDA, necessitating echocardiography for confirmation[88(p20)].

In healthy full-term newborns, BNP levels increase post-delivery due to the transition from fetal to adult circulation, followed by a gradual decline[117] BNP is secreted in response to cardiac stress and may contribute to maintaining ductal patency after birth[7]. Preterm infants, especially those under 28 weeks gestation, often experience delayed or absent ductal closure, with up to 60% requiring intervention for PDA[118].

El-Khuffash *et al.* demonstrated that NT-proBNP levels could predict short-term outcomes in preterm infants with PDA. Higher NT-proBNP levels at 48 hours were associated with poor outcomes, such as severe IVH or death. A level of 5500 pmol/L had 80% sensitivity and specificity for predicting severe outcomes related to PDA. NT-proBNP may thus serve as a standalone marker for poor neonatal prognosis, regardless of PDA presence[63].

There is no consensus on the ideal timing for surgical intervention for PDA in preterm infants, nor is there conclusive evidence that elective surgical closure results in successful outcomes. Ibrahim[119] (2015) compared early and late PDA ligation in 120 preterm infants, finding that early ligation was associated with better short-term cardiorespiratory and nutritional outcomes, although the differences were not statistically significant. Early ligation was linked to shorter hospital stays and lower mortality.

Cassady *et al*[120] suggested that early PDA ligation in extremely low birth weight infants reduces feeding intolerance and NEC, likely due to improved intestinal blood flow. Jaillard *et al*[121]. (2006) found that early surgical closure was

associated with quicker attainment of full oral feeding and improved body growth compared to late closure. These findings indicate that early intervention may improve nutritional and ventilatory status in preterm infants with symptomatic PDA.

Several studies have highlighted NT-proBNP's potential as a predictive marker for PDA and related outcomes. It was found significantly higher NT-proBNP levels in preterm infants with PDA compared to those without. NT-proBNP had 90% sensitivity and 84% specificity for diagnosing severe PDA. Additionally, NT-proBNP levels above 10,000 pg/mL at 48 hours of age had high predictive values for ruling out spontaneous ductal closure[74].

Ding *et al*[122]. (2014) reported that NT-proBNP levels decreased significantly in preterm infants treated for PDA with oral ibuprofen, suggesting its potential for monitoring treatment efficacy. Hammerman *et al*[123], found that a significant reduction in NT-proBNP levels post-treatment indicated successful ductal closure, although NT-proBNP alone may not be a definitive diagnostic tool for PDA.

There is a paucity of normative values of NT-proBNP in neonates (Table 2). The reference ranges that are cited in the research literature shift depending on when the test was performed, which kits were applied, and whose populations were analyzed[124]. The majority of reference ranges that are cited are for term, healthy infants; as a result, they do not represent the group treated in critical care. Since it is believed that NT-proBNP does not pass through the placenta, any variance in newborns must be accounted in terms of their fundamental characteristics[125].

Table 2: Reference ranges for NT-proBNP

Study	N	Age range/source	Kit	NT-proBNP levels
Mir *et al.*[126]	153	Day 1	Biomedica	Mean: 641 pmol/L
		Venous/cord		Range: 254–1272
Mir *et al.*[126]	153	Day 3	Biomedica	Mean: 246
		Venous/cord		Range: 110–430 pmol/L
Nir et al.[124]	43	0–2 days	Elecsys	Median: 376 pmol/L
			1010/2010	Range: 30–1560 pmol/L
Bar-Oz *et al.*[125]	122	Day 1	Elecsys	Mean: 68 pmol/L
		Cord blood	1010/2010	SD: 41 pmol/L
	33	Day 1	Elecsys	Mean: 359 pmol/L
		Plasma	1010/2010	SD: 210 pmol/L
Schwachtgen *et al.*[127]	62	Day 1	ECLIA	Mean: 97 pmol/L
		Cord blood	Roche	Range: 33–306 pmol/L
Hammerer-Lercher *et al.*[128]	42	Day 1	Elecsys	Mean: 65 pmol/L
		Cord blood	1010	IQR: 49–98 pmol/L
Bakker *et al.*[129]	67	32–42wk	Elecsys	Mean: 79.5 pmol/L
		Cord blood	2010	SD: 42.9 pmol/L
Rauh and Koch[130]	13	<1 month	Elecsys	Range: 132–913 pmol/L
		Plasma		
Soldin *et al.*[131]	40 ♂	<31Days	Dade RxL	97.5th percentile: 3352 pmol/L
		Plasma	Dimension	
	53 ♀	<31days	Dade RxL	97.5th percentile: 4940 pmol/L
		Plasma	Dimension	

The association between NT-proBNP and PDA levels was replicated in three other studies. The cut-off levels for the detection of a PDA vary by 2- to 3-fold amongst the studies. This might be because different researches define a hsPDA differently and because diverse populations were evaluated. The three other trials lacked any echocardiographic evaluations of pulmonary circulation and systemic hypoperfusion[83,116]. They only used the LA: Ao ratio and ductal diameter. These indicators alone do not provide a reliable evaluation of the level of ductal steal and pulmonary overcirculations. Hence, using a lower criterion could lead to an overdiagnosis of a major patent ductus arteriosus [63]. Ao had a greater connection with LA (r = 0.77, P =.001), according to Nuntnarumit et al[83]. Also, it was shown that gestation and birth weight had no impact on NT-proBNP levels. Interestingly, Farombi-Oghuvbu *et al*[132]. discovered a marginally negative connection (r 2 = 0.16, P =.02) between gestational age and NT-proBNP levels on day 1. NT-proBNP reported to rise significantly in the presence of a PDA (Table 3).

Table 3: The use of NT-proBNP in PDA diagnosis

Study	Gestation mean (wks)	Birth weight mean (Kg)	Day of life	*N* no PDA	NT-proBNP (pmol/L)	*N* PDA	NT-proBNP (pmol/L)	Cut off NTpBNP (pmol/L)	ROC (95% CI)	Sensitivity	Specificity
El-Khuffash *et al.*[63]	28	1.06	2	35	740	45	6046	4000	0.88 (0.79–0.96)	70%	89%
Nuntnarumit *et al.*[83]	30	1.30	2	23	463	12	1934	1203	0.96 (0.91–1.02)	100%	91%
Farombi *et al*[132].	30	1.22	3	31	372	18	3891	1347	0.98 (0.93–1.03)	100%	95%
Ramakrishnan *et al.*[116]	29	1.22	2	36	1206	20	6952	2850	0.90 (0.81–0.99)	90%	89

*ROC: Receiver Operating Characteristics Curve; *N* no PDA: number without PDA; *N* PDA: Number with PDA. All studies used the Roche Elecsys system.

In the adult population, NTpBNP has a significant diagnostic function. NTpBNP is a marker of heart illness in children and can be used to track treatment effectiveness. These NTpBNP have enormous neonatological potential. It is used to screen for patent ductus arteriosus's, monitor therapy effectiveness, and possibly even provide prognostic data. Further research is required to examine the potential functions of NT-Pro BNP in the control of sepsis and monitoring of heart function. These two potential confounding variables could reduce the validity of the diagnosis of patent ductus arteriosus and the treatment response[63].

Neonatal sepsis continues to be a significant source of morbidity and mortality despite improvements in its identification and treatment. The goal of the study by Deger and Ceylan[133] in 2022 was to find out how well N-terminal pro-B-type natriuretic peptide (NT-ProBNP) levels can be used to diagnose and predict newborn sepsis. The study comprised 50 neonates who were identified as having clinical sepsis in the neonatal critical care unit. 50 newborns in the control group were in good health. A statistically significant difference between the groups was found in terms of NT-proBNP, C-reactive protein, leukocyte count, platelet count, and I/M ratio (p 0.05) as a consequence of the study. The case group's NT-ProBNP level was 19624.1–15027.6 pg/ml while the control group's was 3203.8–4506.8 pg/ml. In the case group, there was a direct association between NT-ProBNP and newborn sepsis. It was discovered that NT-ProBNP levels were significant in discriminating newborn sepsis. In the case group, 33 patients were released after making a full recovery, 17 patients passed away, and the mean NT-Probrain natriuretic peptide levels were, respectively, 12732.21±2954.3 pg/ml and 35000pg/mL. In statistically significant greater amounts, dead patients had higher NT-Probrain natriuretic peptide levels.

2.8. To correlate the levels of serum NT-proBNP with hsPDA in preterm newborns

A PDA in preterm newborns can lead to significant complications, including IVH, pulmonary hemorrhage, NEC, CLD/bronchopulmonary dysplasia, and an increased risk of death. hsPDA is particularly concerning due to the associated hemodynamic instability it causes. Identifying hsPDA accurately and early is crucial for appropriate management to prevent these severe outcomes.

Biochemical markers, in conjunction with clinical and echocardiographic assessments, are invaluable in determining the hemodynamic significance of PDA. Among these markers, BNP and its inactive counterpart, NT-proBNP, have garnered attention. BNP is secreted by ventricular myocytes in response to volume overload, promoting diuresis, natriuresis, and vasodilation, which help in managing intravascular volume and ventricular preload. Elevated BNP levels correlate with the shunt volume in PDA, suggesting their utility in assessing hsPDA.

Echocardiography remains the gold standard for diagnosing PDA. It assesses the shunt's size and hemodynamic impact, providing critical insights into pulmonary over-circulation and systemic hypoperfusion . Studies have demonstrated that NT-proBNP levels are significantly higher in preterm infants with hsPDA and show a rapid decline following successful PDA closure. El-Khuffash *et al*[63]. (2007) found that NT-proBNP levels peaked on Day 2 in preterm infants with hsPDA and dropped swiftly post-treatment. Similarly, Farombi-Oghuvbu *et al*[132]. observed elevated NT-proBNP levels on Day 3 in neonates with hsPDA compared to Days 1 and 10, reinforcing the optimal timing for NT-proBNP measurement as Days 2-3 for predicting hsPDA.

The correlation between NT-proBNP levels and echocardiographic parameters further supports its diagnostic value. Occhipinti *et al*[134]. (2014) reported that NT-proBNP concentrations were associated with ductal size and left atrial dilatation in preterm infants . Additionally, Khosroshahi *et al*[101]. established a significant relationship between NT-proBNP levels and the degree of shunt in infants with ventricular septal defect (VSD), atrial septal defect (ASD), or PDA, highlighting the peptide's sensitivity and specificity for detecting significant shunts.

Hamed *et al* [135]. (2022) investigated the diagnostic accuracy of BNP for hsPDA in preterm infants, revealing that higher BNP levels were significantly associated with hsPDA as confirmed by echocardiography. A BNP cut-off value of 108.0 pg/mL demonstrated moderate sensitivity but high specificity in diagnosing hsPDA . This finding suggests that NT-proBNP could serve as a reliable screening tool for hsPDA, aiding in early identification and treatment.

Potsiurko[15] (2021) examined serum NT-proBNP levels in preterm infants with PDA, finding that elevated NT-proBNP levels on Days 2-3 and 8-9 reliably predicted BPD or death in infants with PDA larger than 1.5 mm. This suggests that NT-proBNP could be a valuable prognostic marker for adverse outcomes in this vulnerable population.

Nuntnarumit[83] (2008) conducted an observational study on NT-proBNP levels in preterm infants, correlating them with echocardiographic assessments of ductal shunting. NT-proBNP levels on Day 2 were significantly higher in infants with hsPDA compared to those without. The study also demonstrated a strong correlation between NT-proBNP levels and the left atrium to aortic root ratio. A cut-off level of 10,180 pg/mL on Day 2 provided high sensitivity and specificity for predicting hsPDA, indicating NT-proBNP's potential as a diagnostic marker.

Elevated NT-proBNP levels correlate well with the presence of significant ductal shunting and adverse outcomes, making it a useful marker in the clinical management of PDA in preterm newborns. These findings suggest that routine NT-proBNP screening, combined with echocardiographic assessment, could improve the early identification and treatment of hsPDA, potentially mitigating the severe complications associated with this condition.

2.9. Clinical Applications and Future Research

Research indicates that NT-proBNP can be a valuable marker for diagnosing and predicting outcomes in preterm infants with PDA. Its levels correlate with echocardiographic findings and can provide insights into the clinical status of preterm newborns. A study in Yiwu, China, demonstrated the clinical benefits of combining NT-proBNP measurements with echocardiography for diagnosing PDA (Panacea Journal of Medicine).Further research are necessary to standardize NT-proBNP assays and validate its use across different patient populations and clinical settings. Larger studies are required to fully understand the relationship between NT-proBNP levels and PDA treatment outcomes, particularly in diverse and high-risk populations. Understanding these dynamics will enhance the clinical management of preterm infants and improve their long-term health prospects.

4. MATERIALS AND METHODOLOGY

4.1. Source of data:

All preterm babies undergoing echocardiography admitted in NICU of KLEH Dr. Prabhakar Kore Hospital, Belgaum, Karnataka December 2022 to December 2023

4.2. Methods of Collection of Data:

A. STUDY DESIGN:

Observational study

B. PLACE OF STUDY:

Paediatric Department, KLEH Dr. Prabhakar Kore Hospital, Belgaum, Karnataka

C. STUDY PERIOD:

One year (December 2022 to December 2023)

D. SAMPLE SIZE:

The sample size for the current study was calculated using following equation [136]

$$\boldsymbol{n = \frac{Z^2 P(1-P)}{d^2}}$$

Where n= sample size

Z= Z statistic for a level of confidence level at = 1.960

P= Prevalence (80%)

d = precession (10%)

The prevalence of preterm babies in India was found to be 12% as per the study by Jana et al.,[137]. Therefore with p = 12% at 95% confidence with 80% power, the calculated sample size was 49. Hence total 54 patients (10% attrition rate 4 more added to 49) were included in the current study according to inclusion criteria.

E. INCLUSION CRITERIA

All preterm infants born before 37 weeks of gestation admitted to NICU undergoing echocardiography evaluation and obtained informed consent from mothers were considered in the current study.

F. EXCLUSION CRITERIA

The study excluded preterm babies with other congenital heart disease, neonatal sepsis, bronchopulmonary dysplasia, congenital anomalies/malfunctions and bleeding tendency. Preterm babies whose mothers refused to provide consent also were excluded from the study.

G. METHODOLOGY

The current observational study was carried out in KLEH Dr. Prabhakar Kore Charitable Hospital, Belgaum, Karnataka from December 2022 to December 2023. After obtaining approval and clearance from the institutional ethics committee (Annexure -I), the patients fulfilling the inclusion criteria were enrolled for the study. Informed consent (Annexure - II) were obtained from parents of the infants after explaining to them the plan and intention of the study in the language they understood.

Total 49 patients were included in the current study. Information regarding patients like age, sex, birth weight and other clinical parameters were recorded. 2D

echco and serum NT- ProBNP of infants were estimated in the hospital laboratory and recorded. Samples in 2ml plain vacutainer were collected and levels of NT-ProBNP were estimated by using chemiluminescence. Every piece of information was meticulously entered into an excel spread sheet and used for statistical analysis.

4.3. STATISTICAL ANALYSIS:

Continuous variables were represented as mean ± SD (standard deviation) whereas categorical variable are presented as frequency and percentages (n(%)). Continuous variables were compared using independent T-test or ANOVA/ or a Kruskal-Wallis test, and categorical variables were compared using a $\chi 2$ test or fisher's exact test to test for differences across groups. P value < 0.05 was considered statistically significant. R version 4.2.2 statistical software was used for the statistical analyses. Microsoft word and Excel was used to generate graphs, tables etc wherever required.

5. RESULT

To estimate the serum NT-proBNP in preterm newborns with PDA and to the level of serum NT-proBNP with size of PDA in preterm newborns, a hospital based observational study was conducted on preterm neonates with PDA who undergoing echocardiography admitted in NICU of KLEH Dr. Prabhakar Kore Hospital, Belgaum, Karnataka from December 2023 to December 2024. 49 preterm babies who matched the inclusion and exclusion criteria and whose parents provided informed consent to participate in the study were included in the study.

In the current study out of 49 preterm infants there were 25(51%) male and 24(49%) female as shown in the pie chart (Figure 4).

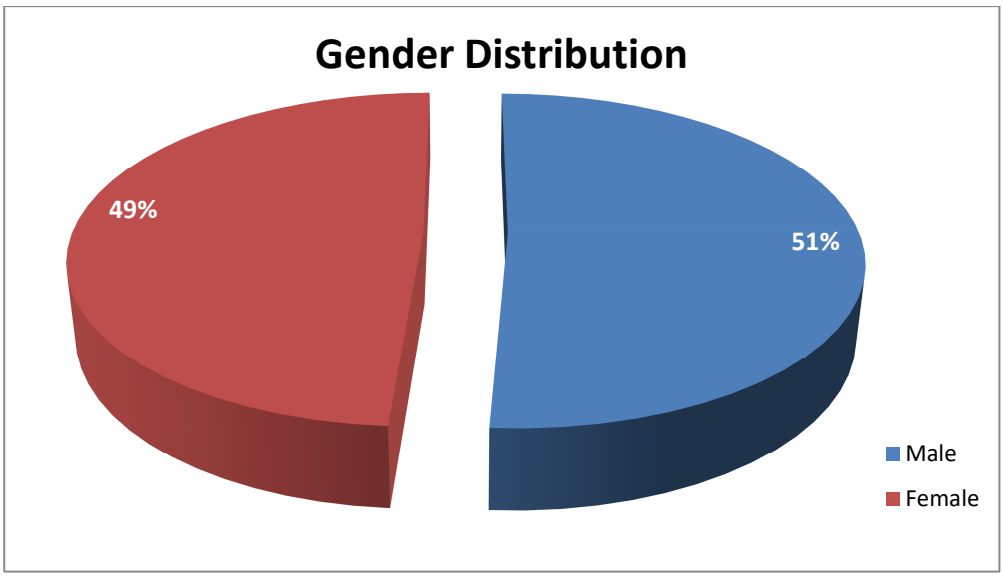

Figure 5: Pie chart for the distribution of patients based on gender (n=49)

Mean (±SD) age of preterm babies in the study was calculated to be 8.49 ± 6.01days with 2 days and 28 days as minimum and maximum age respectively. Figure 5 depicts the age distribution of study population with help of box plot.

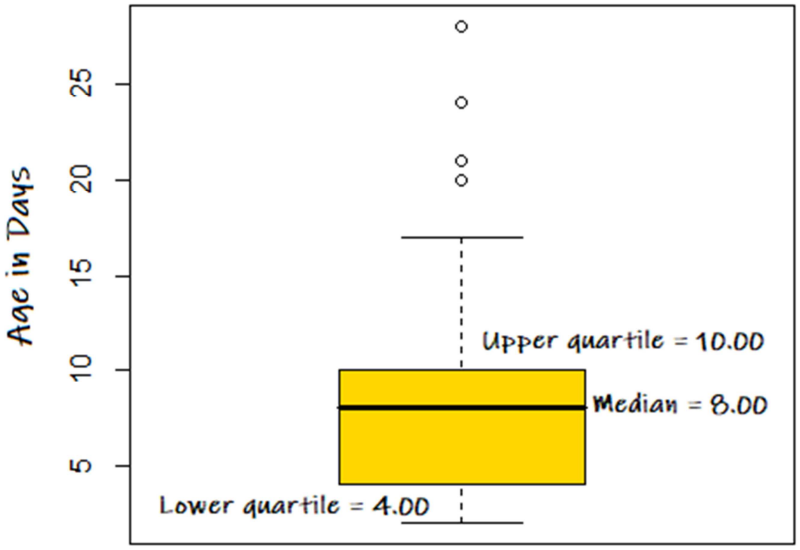

Figure 6: Box plot showing age distribution of study population (n=49)

The mean (±SD) gestational age in the current study was 32.52±3.08 weeks with minimum and maximum age of 25.75 weeks And 38 weeks respectively. Distribution of gestational age is pictorially represented in Figure 6 using box plot.

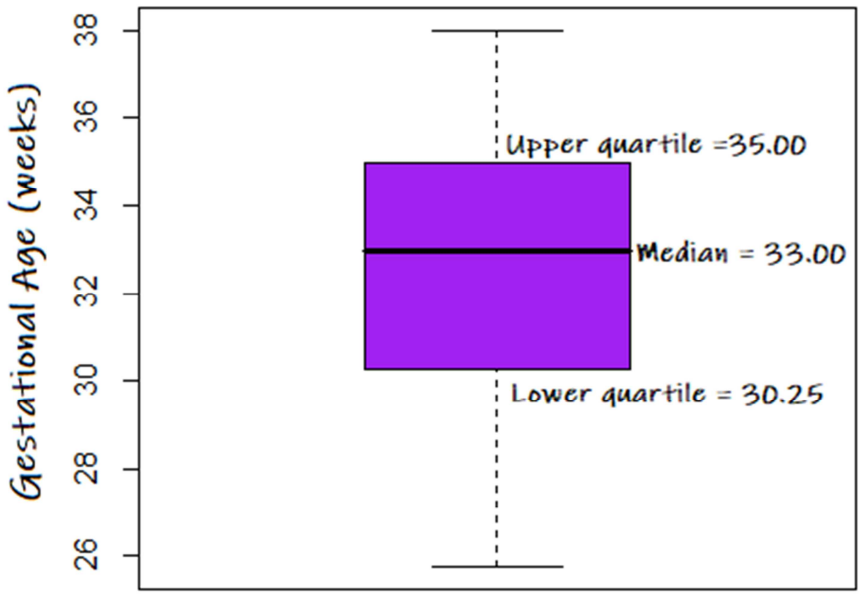

Figure 7: Box plot showing the distribution of gestational age of the study population (n=49)

Based on the gestational age of neonates, they were categorised as extreme (<28 weeks), very (28-31weeks), late (34-36) and, early (37-38 weeks) preterm. Table 4 shows the distribution of patients based on the preterm categories. It was found that 4(8.16%), 10(20.41%), 19 (38.78%) and 16(32.65%) accordingly belonged to extreme, very, late and, early preterm groups. Distribution of neonates based on the preterm categories is graphically shown in Figure 7.

Table 4: Distribution of patients based on preterm categories (n=49)

Preterm category	Number of patients	Percentage of patients
Extreme	4	08.16
Very	10	20.41
Late	19	38.78
Early	16	32.65

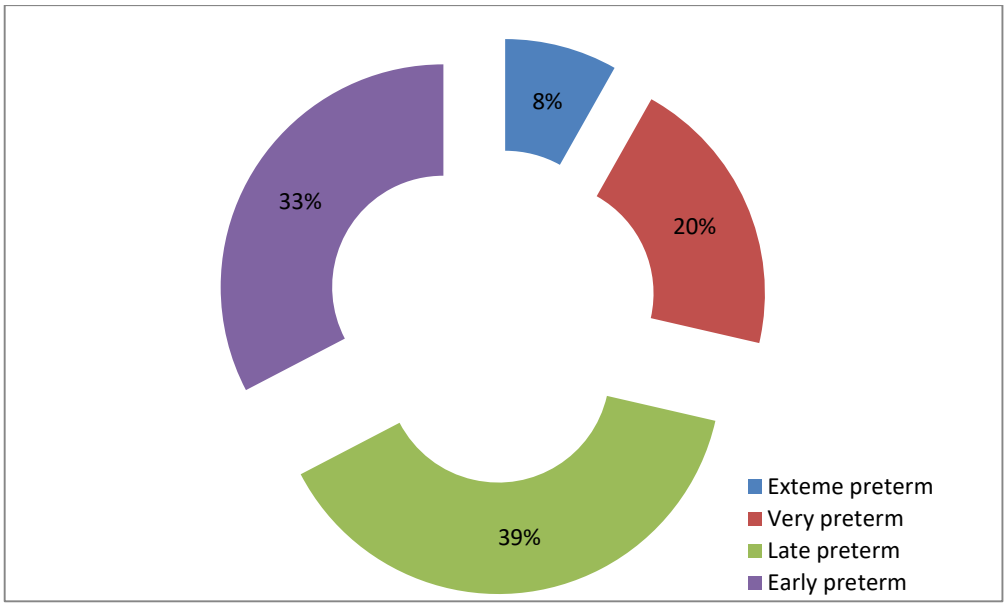

Figure 8: Doughnut graph for the distribution of patients based on preterm categories (n=49)

Mean (±SD) birth weight of the 49 neonates included in the study was 1368± 545.00g. The minimum weight was found to be 614g where as maximum birth weight was 2800g (Figure 8). Birth weight of premature babies were classified as extremely low birth weight (<1000 g), Very low birth weight (≥1000<1500 g), and Low birth weight (≥1500). Table 5 show cases the distribution of 49 patients based on low birth weight classification. It was observed that, 18(36.73%) neonates belonged to very low weight followed by 17 (34.69%) and 14(32.65%) neonates to extremely low birth weight and low birth weight respectively (Figure 8).

Table 5: Distribution of patients based on low birth weight classifications (n=49)

Birth Weight	Number of patients	Percentage of patients (%)
Extremely Low Birth Weight	17	34.69
Very Low Birth Weight	18	36.73
Low Birth Weight	14	32.65

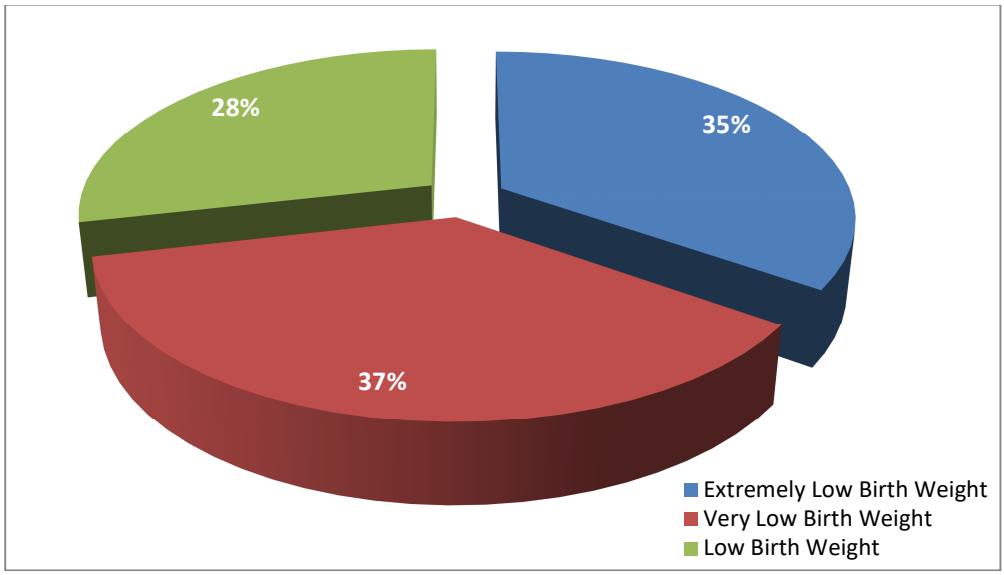

Figure 9: Pie chart showing distribution of patients based on low birth weight classifications (n=49)

Symptoms like murmur, oxygen requirement, apnea, tachycardia, hyperactive precordium, heart failure and birth asphyxia were recorded in the preterm neonates (Table 6). Out of 49 neonates in the study, 24(48.98%), 23(46.94%) babies had murmur and oxygen requirement respectively. Whereas 7(14.29%) and 6(12.25%) patients had respectively heat failure and tachycardia. Only 2(4.08%) and 3(6.12%) babies had Apnea and birth asphyxia respectively (Figure 9). Those who had heart failure, 6 out of 7 babies had tachycardia (85.71%), 3 hyperactive precordium (42.86%), 1 each had hematomegaly, apnea, and birthasphyxia (14.29% each); 4 babies required oxygen (57.14%) and 2 had murmer (28.57%).

Table 6: Distribution of patients based on symptoms

Symptoms		Number of patients	Percentage of Patients (%)
Murmur	Yes	24	48.98
	No	25	51.02
Oxygen requirement	Yes	23	46.94
	No	26	53.06
Apnea	Yes	2	4.08
	No	47	95.92
Birth asphyxia	Yes	3	6.12
	No	46	93.88
Tachycardia	Yes	06	12.25
	No	43	87.75
Hyperactive precordium	Yes	3	6.12
	No	46	93.88
Heart failure	Yes	7	14.29
	No	42	85.71

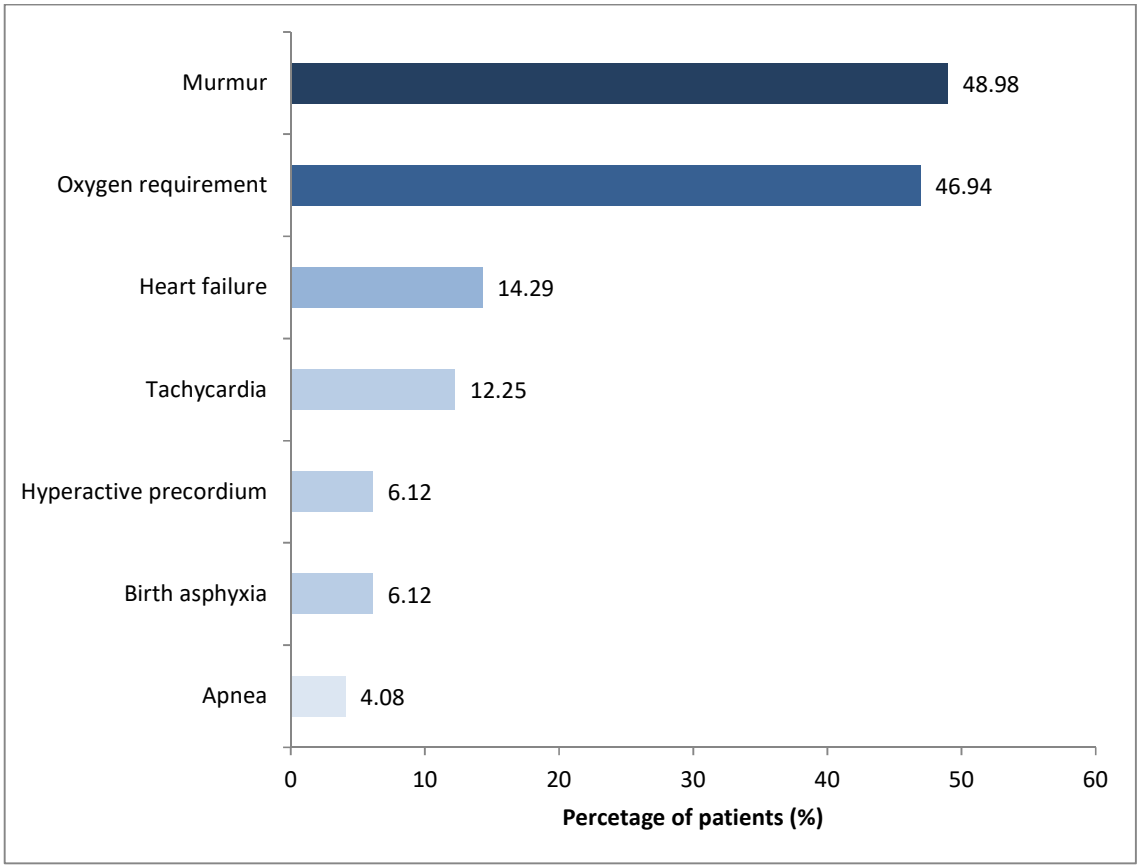

Figure 10: Horizontal bar graph showing distribution of patients based on the symptoms (n=49)

Mean size of PDA of 49 preterm babies was determined to be 2.69mm. The minimum size was found to be 0.70 mm and the maximum size was 6.50mm. Distributions of size of PDA of 49 preterm babies are shown in Figure 10 with median and inter quartile values using box plot. Based on the size of the PDA, PDA was divided as small, moderate and large PDA (Table 7). Maximum of 51.02 % (25 out of 49 neonates) of study population was found to have large PDA, where as 24.49% (12 out of 49) each of study population had moderate and small PDA. Figure 11 depicts the distribution of 49 preterm babies based on their PDA sizes.

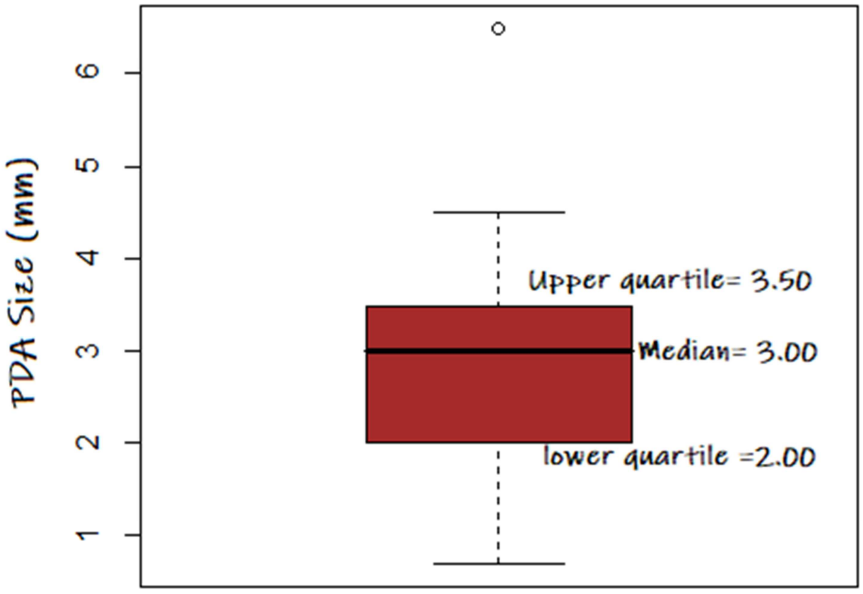

Figure 11: Box plot for distribution of PDA size (n= 49)

Table 7: Distribution of patients based on the PDA size

PDA	Number of patients	Percentage of patients (%)
Small	12	24.49
Moderate	12	24.49
Large	25	51.02

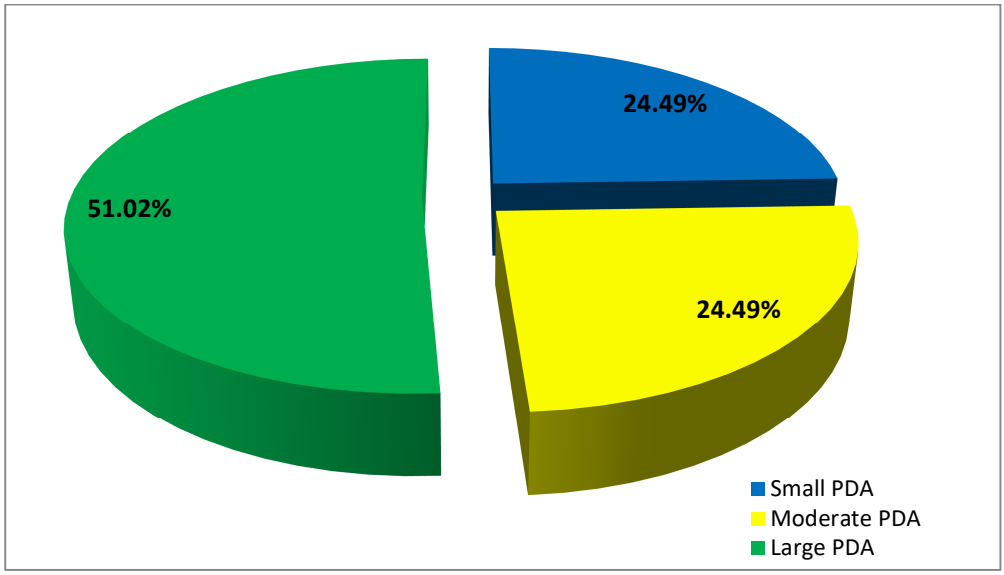

Figure 12: Pie chart showing distribution of patients based on size of PDA (n=49)

Among 49 patients there were 26(53.06%) preterm babies had hemodynamically significant PDA (hsPDA) (Figure 12).

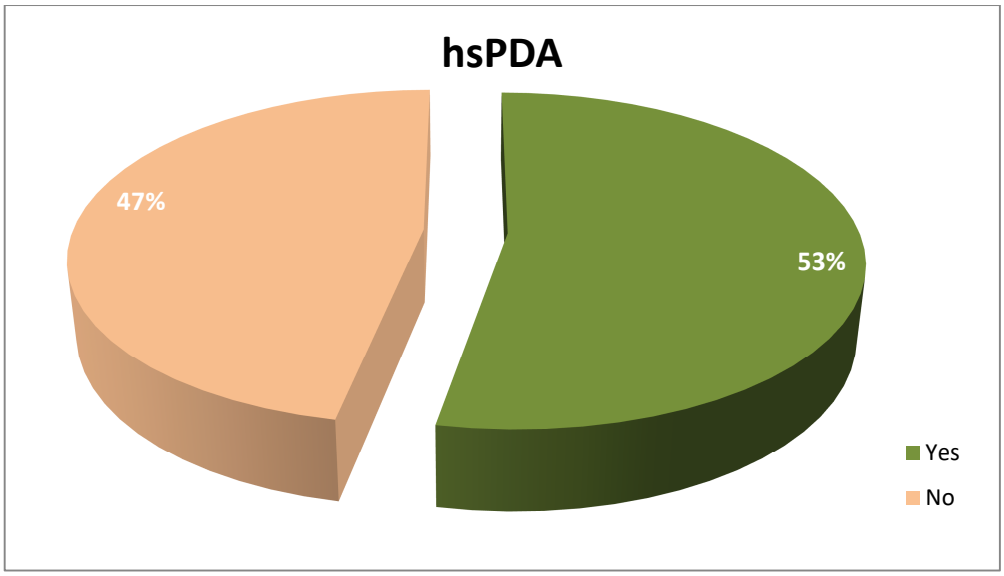

Figure 13: Pie chart depicting the distribution of patients based on hsPDA

Among 49 patients, PDA of some were closed by pharmacological and some by surgical methods (Table 8). Over all 21(42.86%) and 5 (10.20%) preterm babies respectively had pharmacological and surgical closure (Figure 13).

Table 8: Distribution of patients based on type of closure

PDA closure		Number of patients	Percentage of Patients (%)
Pharmacological closure	Yes	21	42.86
	No	28	57.14
Surgical closure	Yes	5	10.20
	No	44	89.80

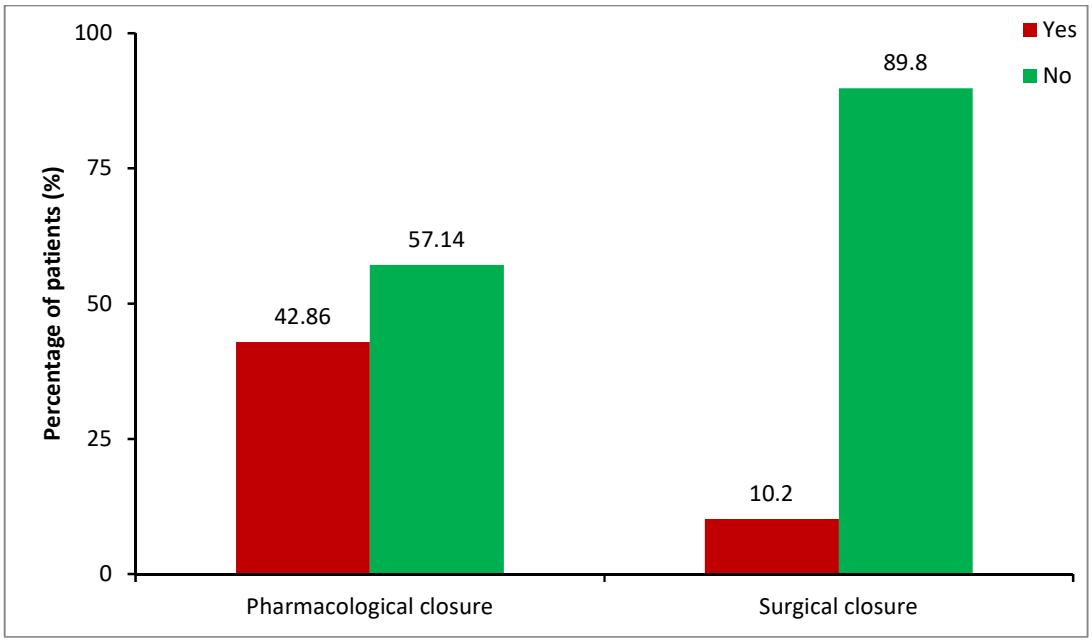

Figure 14: Bar graph depicting the distribution of patients based on the type of closure

In the current study, out of 49 babies with PDA, 42(85.71%) babies survived and only 7 (14.29%) babies did not survive (Figure 14). Survived babies did not show any complications whereas babies died were having conditions like sepsis, persistent pulmonary hypertension of newborn (PPHN), respiratory distress and pulmonary haemorrhage (Table 9). Out of 7 babies, 3(42.86%), 2(28.57%), 1(14.29%) and 1(14.29%) babies had PPHN with sepsis, sepsis alone, respiratory distress and pulmonary haemorrhage respectively (Figure 15).

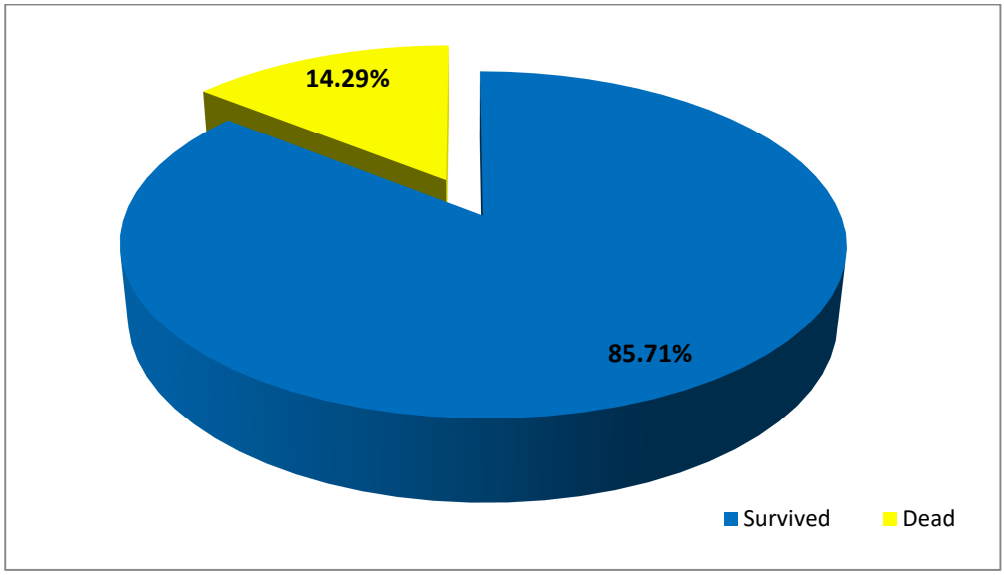

Figure 15: Pie chat showcasing the distribution of preterm babies with PDA based on the survival

Table 9: Distribution of patients based on the cause of death (n=7)

Condition	Number of patients	Percentage of patients (%)
PPHN with sepsis	3	42.86
Sepsis	2	28.57
Pulmonary haemorrhage	1	14.29
Respiratory distress	1	14.29

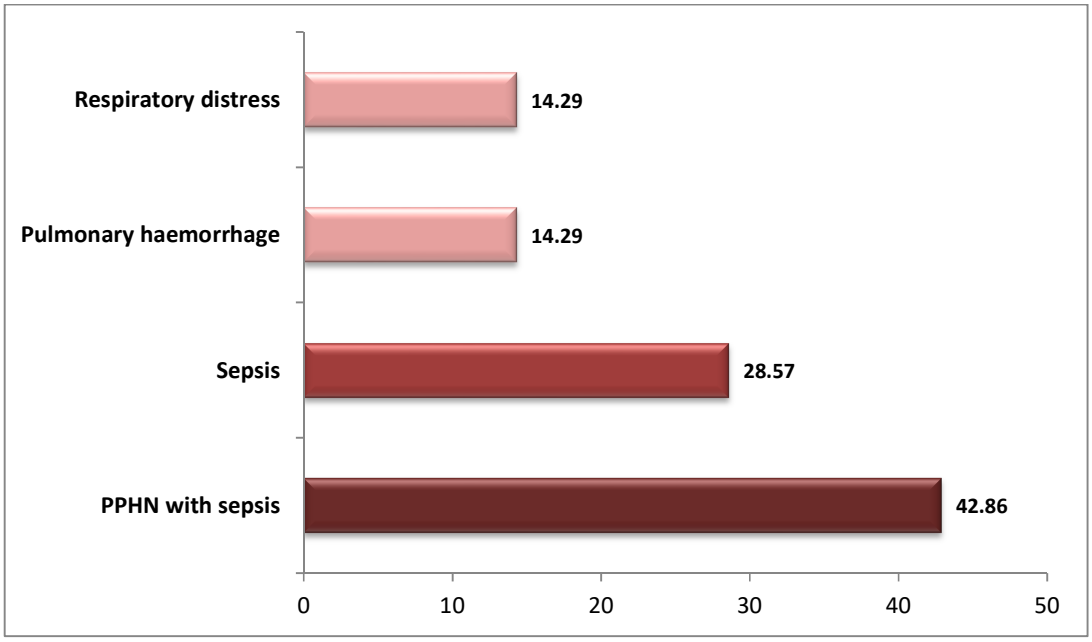

Figure 16: Horizontal bar graph for distribution of patients based on the cause of death (n=7)

NT-proBNP of all the preterm babies was evaluated and the calculated mean (±SD) calculated for 49 babies was 17398±16966pg/mL. Highest NT-proBNP level recorded was 70000pg/mL where as lowest was 853pg/mL. Median value for NT-proBNP was 12241pg/mL. Upper and lower quartile values for NT-proBNP of study population were 32548pg/mL and 2622pg/mL respectively (Figure 16).

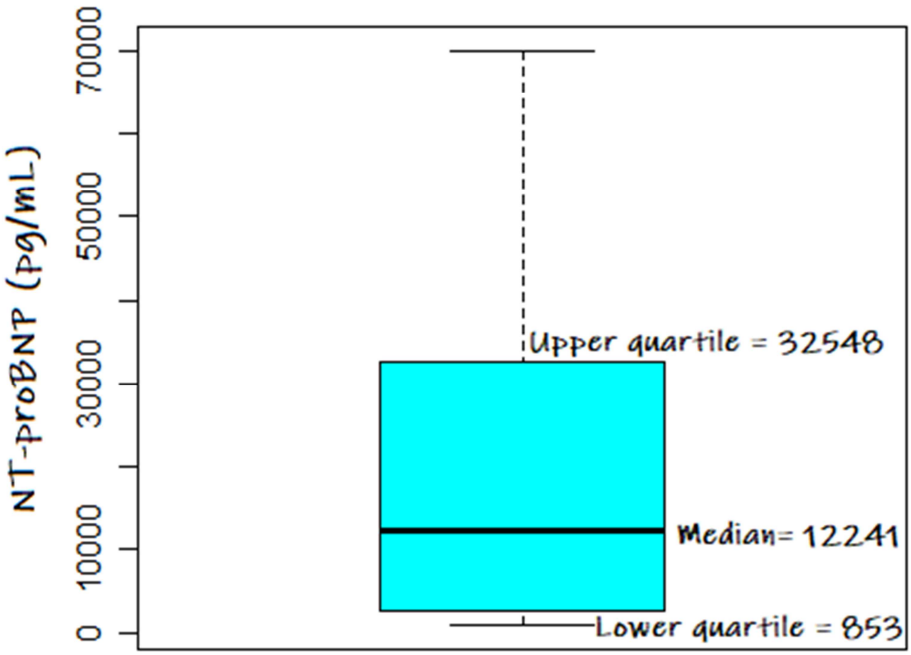

Figure 17: Box plot showing the distribution of NT- proBNP

In the current study, association between the size of the PDA and NT-proBNP, level of serum NT-proBNP with other parameter was studied

Association of PDA size and NT-proBNP in the study population was determined. Initially mean NT-proBNP values for different PDA groups based on size were analysed and the result is shown in Table 10. Mean value of 2727948±16410 pg/mL for NT-proBNP in Large PDA is significantly higher than mean value for NT-proBNP in moderate and small PDA(P value <0.0001). Pictorial representation of distribution of NT-proBNP with respect to PDA size is shown in Figure 17.

Table 10: Association of PDA size and NT-proBNP

PDA size	NT-proBNP (pg/mL) (Mean ± SD)	P value *
Large (n= 25)	27948±16410[†a]	**<0.0001**
Moderate (n= 12)	10954±10328[b]	
Small (n= 12)	1861±578[b]	

*statistically significant if p value < 0.05 for ANOVA;†statistically significant with different superscripts for t-test

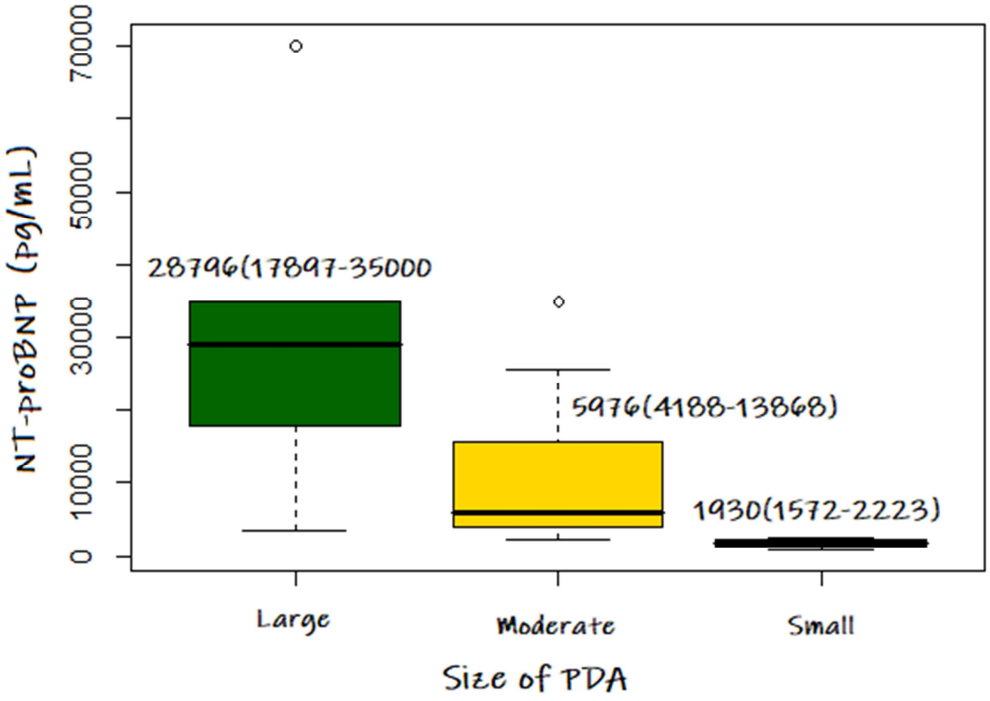

Figure 18: Box plot for distribution of NT-proBNP with respect to large, moderate and small PDA

Pearson correlation between size of PDA and levels of NT-proBNP in the st udy population is shown in Figure 18. With correlation coefficient of 0.52(0.28- 0.70) , NT-proBNP and PDA size are positively associated with moderate correlation. The c orrelation found was statistically significant with P value = 0.0002.

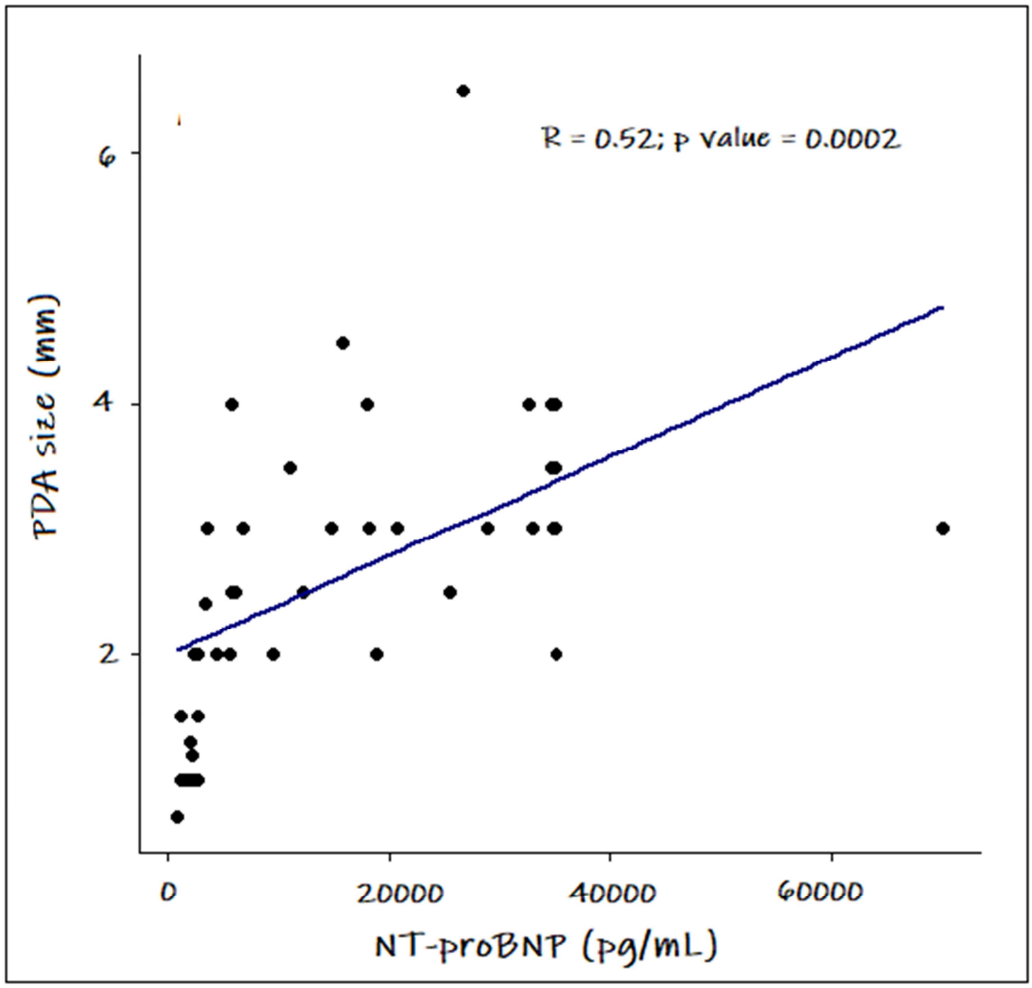

Figure 19: scatter plot showing correlation between PDA size and NT-proBNP levels

Median along with lower and upper quartile values of NT-proBNP values for different preterm groups based on gestational age were analysed and the result is shown in Table 11. Comparison of median between groups using Kruskal -Wallis test indicated no statistically significant variations in NT-proBNP values (p- values =0.050). Pictorial representation of distribution of NT-proBNP with respect to preterm classification is shown in Figure 19.

Table 11: Distribution of NT-proBNP with respect to preterm classifications

Preterm classification	NT-proBNP (pg/mL) Median (lower quartile- upper quartile)	P value *
Extreme preterm (n= 4)	5148(2903-13793)	**0.050**
Very preterm(n= 10)	32697(27153-34898)	
Late preterm (n= 19)	5618(2484-16861)	
Early preterm (n=16)	13491(3143-28584)	

*statistically significant if p value < 0.05 for Kruskal-Wallis test

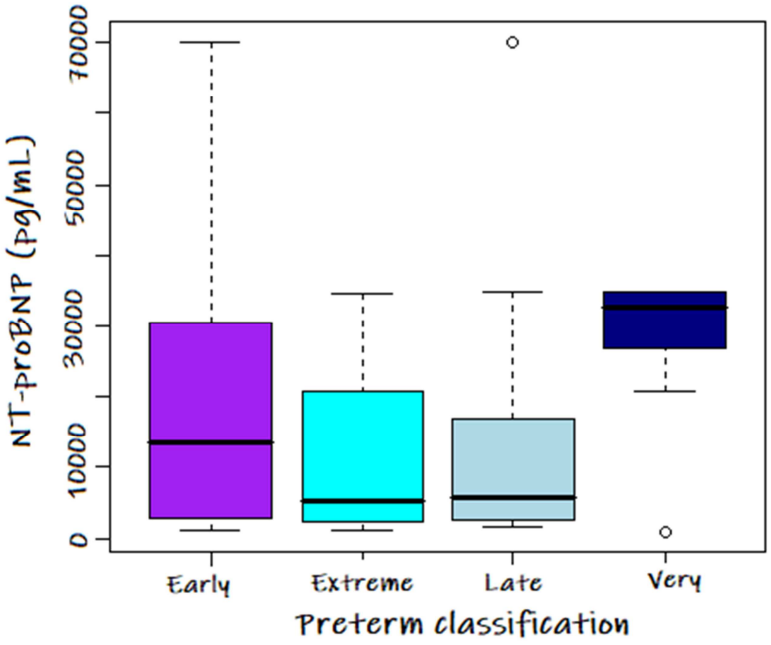

Figure 20: Distribution of NT-proBNP for extreme, very, late and early preterm

Table 12 show cases the comparison of distribution of NT-proBNP values for extremely low, very low and low birth weight neonates. Comparison of median between groups using Kruskal -Wallis test indicated no statistically significant variations in NT-proBNP values (p- values =0.109). Graphical representation of distribution of NT-proBNP with respect to birth weight classification is shown in Figure 20.

Table 12: Distribution of NT-proBNP based on birth weight classifications

Birth weight classification	NT-proBNP (pg/mL) Median (lower quartile- upper quartile)	P value *
Extremely low	20754(3500-34788)	0.109
Very low	18042(5643-32541)	
Low	5110(2060-17379)	

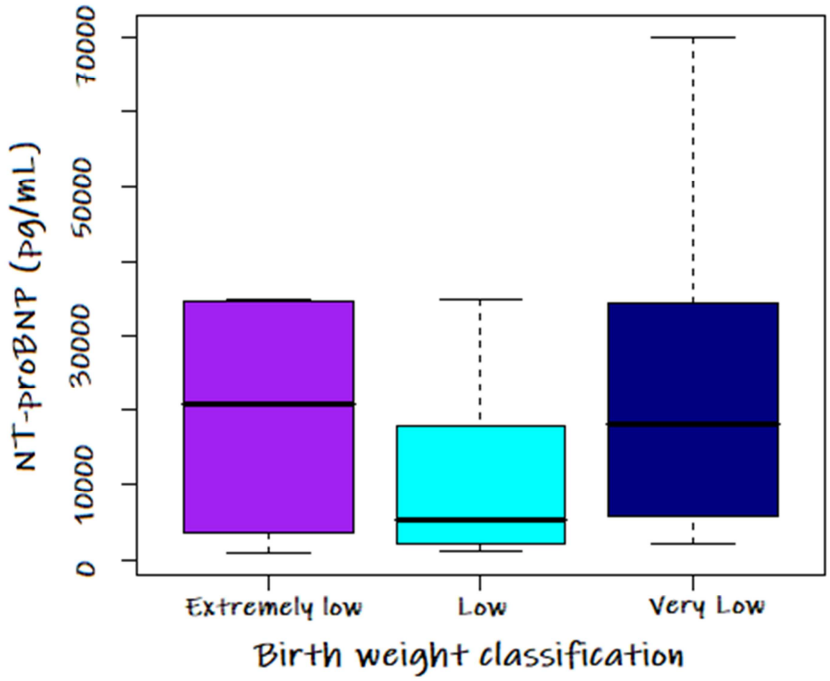

Figure 21: Box plot depicting Distribution of NT-proBNP based on birth weight classifications

Distribution of NT-proBNP for patients with and without hsPDA in terms of median (lower quartile- upper quartile) is compared in Table 13. Wilcoxon test revealed that patients with hsPDA had significantly higher NT-proBNP levels with median value of 26605(13458-34796) pg/mL than that of without hsPDA with median value of 5976(2252-24308) pg/mL). P value for the test was 0.036. Figure 35 shows the distribution of NT-proBNP for patients with and without hsPDA.

Table 13: Distribution of NT-proBNP for patients with and without hsPDA

hsPDA	NT-proBNP (pg/mL) Median (lower quartile- upper quartile)	P- value*
Yes (n=26)	27700(16343-34947)	**<0.0001**
No (n=23)	2662(2044-5967)	

- Statistically significant if p value < 0.05 for wilcoxon test

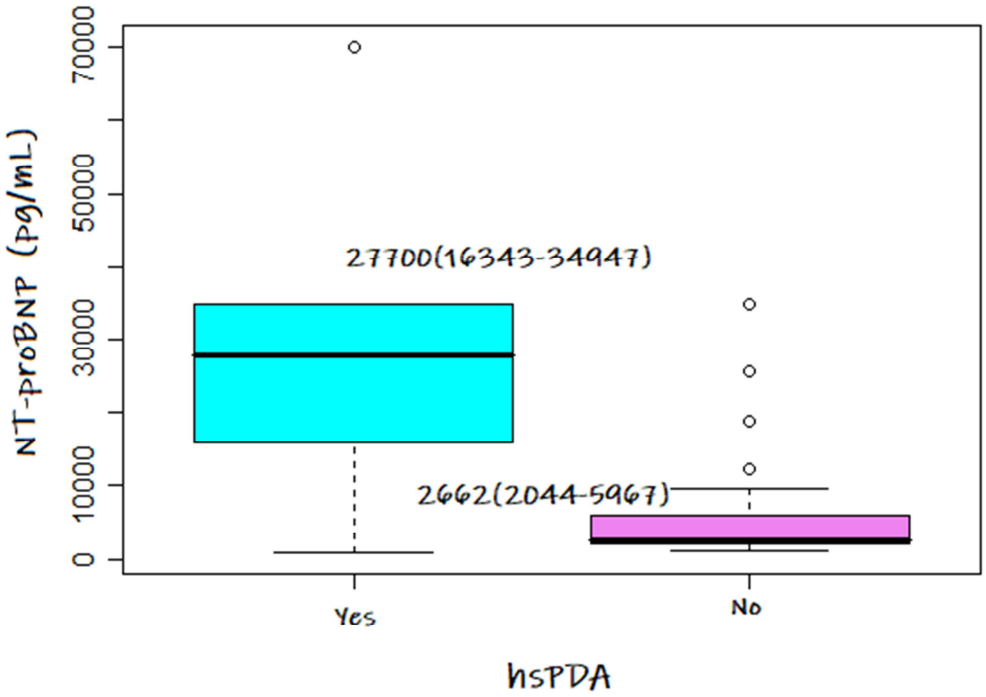

Figure 22: box plot depicting distribution of NT-proBNP for patients with and without hsPDA

Comparison of NT-proBNP with and without heart failure revealed that, babies with heart failure exhibited significantly higher levels of NT-proBNP than the babies without heart failure with statistical significance at 99% confidence interval (Table 4). Median value of NT-proBNP for babies with heart failure was 35000(26605-35000)pg/mL where as for babies without heart failure was 8132(2647-24308)pg/mL (Figure 22)

Table 14: Comparison of NT-proBNP levels between patients with and without heart failure

Heart failure	NT-proBNP (pg/mL) Median (lower quartile- upper quartile)	P- value
Yes	35000(26605-35000)	**0.014**
No	8132(2647-24308)	

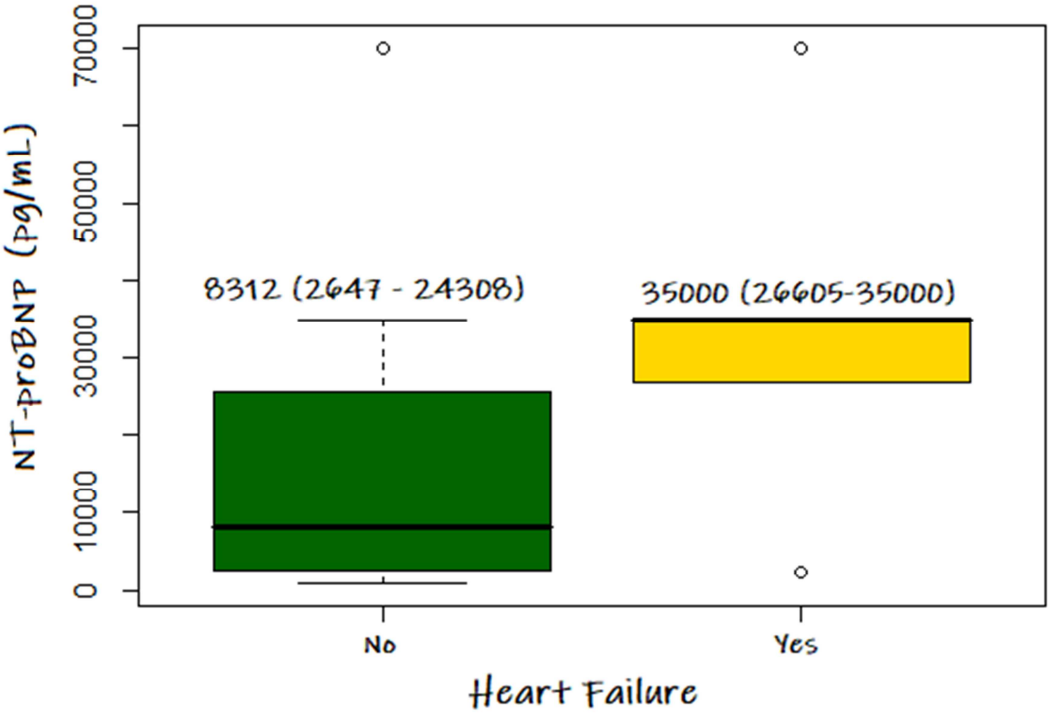

Figure 23: Box plot showing distribution of NT-proBNP for patients with and without hsPDA

Median (lower quartile- upper quartile) of NT-proBNP for survival and non survival patients is using Wilcoxon test and results are tabulated in Table 15. It was found that preterm babies who had survived had significantly lower NT-proBNP levels with median value of 10281(2406-26605)pg/mL than that of babies who did not survive with median value of 34593(12346-52394) with P value was <0.0001. Figure 23 shows the distribution of NT-proBNP based on survival.

Table 15: Distribution of NT-proBNP based on survival

Survival	NT-proBNP (pg/mL) Median (lower quartile- upper quartile)	P- value
Yes	10281(2406-26605)	**0.034**
No	34593(12346-52394)	

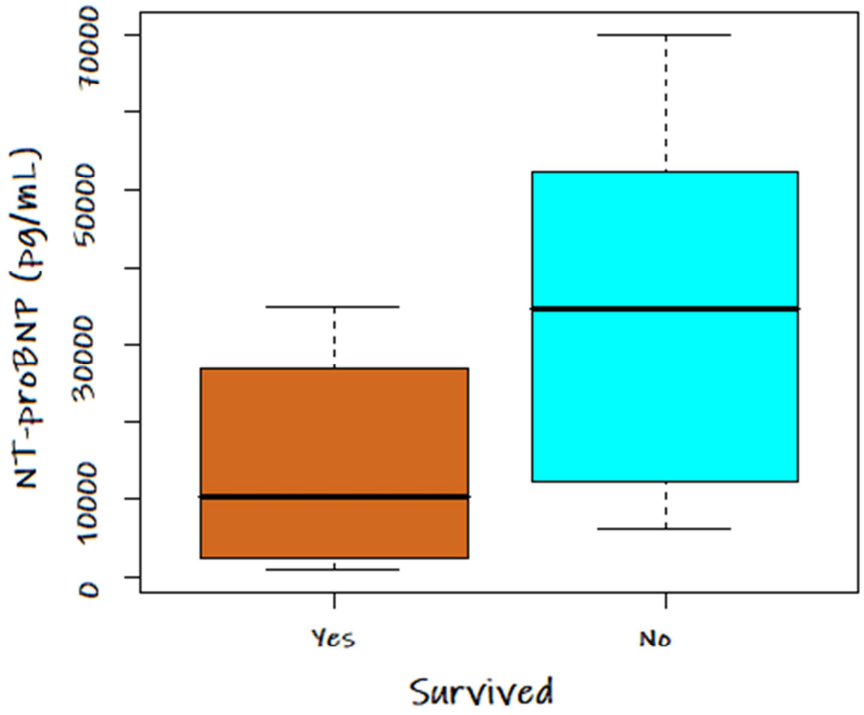

Figure 24: box plot showing distribution of NT-proBNP based on survival

6. DISCUSSION

PDA is a common cardiovascular condition affecting neonates, particularly those born preterm with a gestational age of less than 28 weeks. PDA occurs when the ductus arteriosus, a fetal blood vessel that allows blood to bypass the lungs, fails to close after birth. This condition can lead to significant hemodynamic changes, impacting the neonate's cardiovascular stability and overall health. The clinical management of PDA is challenging, especially in the early days of life. Traditionally, the hemodynamic significance of PDA is assessed using clinical signs and echocardiographic evaluations. However, these methods do not always provide clear indications for when to intervene, leaving clinicians with the dilemma of determining the optimal timing for treatment. B-type natriuretic peptide (BNP), a hormone produced by the heart in response to ventricular volume expansion and pressure overload, has emerged as a potential biomarker for PDA screening in preterm infants.

NT-proBNP is a stable precursor of BNP and can be measured in serum, offering a promising alternative when Doppler echocardiography is not readily available. Therefore the current study titled “Estimation of serum N-terminal peptide of Brain natriuretic peptide levels in preterm newborn with Patent Ductus Arteriosus (PDA) a one year prospective observational study” was carried out at KLEH Dr. Prabhakar Kore Hospital, Belgaum, Karnataka from December 2022 to December 2023 to estimate the serum NT-proBNP in preterm newborns with PDA and to correlate the level of serum NT-proBNP with size of PDA in preterm newborns.

In the current study total 49 preterm babies with PDA were considered based on inclusion and exclusion criteria. Out of the 49 preterm infants included in our study, there were 25 (51%) males and 24 (49%) females, indicating a nearly equal gender

distribution. This balanced distribution suggests that PDA and associated clinical conditions affect both genders equally. Our findings are consistent with previous studies.

For instance, Hamed *et al*[135]. reported a similar gender distribution with 56.5% males and 43.5% females among their study cases. Similarly, a systematic review and meta-analysis involving 146 studies and 357,781 preterm infants found no significant sex differences in the incidence of PDA or the response to pharmacological treatment[138].

The current study evaluated the birth age and gestational age of preterm babies with PDA to better understand the demographic profile and incidence rates in this population. The mean age of the preterm babies was 8.49 ± 6.01 days, with a mean gestational age of 32.52 ± 3.08 weeks. These findings are consistent with the well-documented inverse relationship between gestational age and the incidence of PDA. The preterm infants in the study were categorized based on their gestational age as extreme (<28 weeks), very (28-31 weeks), late (34-36 weeks), and early (37-38 weeks) preterm. The distribution showed that 8.16% were extreme preterm, 20.41% were very preterm, 38.78% were late preterm, and 32.65% were early preterm.

The literature consistently indicates that the incidence of PDA is inversely related to gestational age. According to Parkerson *et al.,* the likelihood of spontaneous permanent closure of the DA is significantly lower in extremely preterm infants (<25 weeks) at 2.1%, compared to 0.53% in infants >29 weeks[139]. This supports the high incidence of PDA observed in extremely preterm infants in our study.

Nemri *et al.* reported that at 30-37 weeks, 10% of neonates have a PDA at 4 days of age, whereas at 25-28 weeks, the incidence rises sharply to 80%[6]. Sung *et al.*

found that the incidence of PDA exceeds 50% in preterm infants ≤28 weeks' gestational age[140]. Our study's findings are in line with these observations, as the extreme and very preterm groups had a notably higher incidence of PDA compared to late and early preterm infants. The incidence rates reported in the literature for various gestational age categories shows that high incidence, ranging from 50% to 80% in Extremely Preterm Infants , incidence ranging from 25% to 50% in Very Preterm Infants, lower incidence, ranging from 10% to 30% in Late Preterm Infants and incidence ranging from 10% to 20% in Early Preterm[5,141]. In our study, the distribution of PDA among these categories corresponds with these findings. The extreme preterm group, though smaller in number, likely had a higher incidence of PDA, while the very preterm and late preterm groups showed a moderate incidence, and the early preterm group had a lower incidence. The incidence of PDA decreases with increasing gestational age.

The birth weight of preterm infants plays a crucial role in the classification and incidence of patent ductus arteriosus (PDA). This study classified the birth weights of preterm babies into three categories: extremely low birth weight (ELBW) (<1000 g), very low birth weight (VLBW) (≥1000 to <1500 g), and low birth weight (LBW) (≥1500 g). The incidence of PDA is notably higher in infants with lower birth weights, with a decreasing trend as birth weight increases. In this study, the mean birth weight of the 49 preterm neonates was 1368 ± 545 grams, with a range from 614 to 2800 grams.

The study by Shi *et al.*[14] supports this observation, indicating a mean birth weight of 1,496 ± 241 grams in preterm infants with PDA. The distribution in our study showed that 36.73% of the neonates were classified as VLBW, 34.69% as ELBW, and 32.65% as LBW. This indicates a significant proportion of the study

population falls into the higher-risk categories for PDA, specifically the ELBW and VLBW groups. The literature consistently supports a higher incidence of PDA in lower birth weight categories. For instance, it has been reported that 55% of infants weighing less than 1000 grams (ELBW) have a symptomatic PDA requiring medical treatment. Similarly, among VLBW infants (501 to 1500 grams), every third infant is expected to have a persistent PDA [2,142]. The incidence of PDA ranges from 15% to 37% in newborns with a birth weight under 1750 grams[143]. In our study, the incidence of PDA aligns with these findings. The trend of increased incidence of PDA with decreased birth weight is alos reported by others researchers. According to Koch et al., the incidence of PDA was approximately 33% and 55% in VLBW and ELBW infants respectively[92]. According to the NICHD Neonatal Research Network, PDA is diagnosed in 46% of VLBW babies and preterm infants born at less than 28 weeks of gestation[90,90].

The symptoms of PDA in preterm infants can vary significantly depending on the size of the PDA. In our study, various symptoms were documented, highlighting the clinical spectrum associated with different PDA sizes and their impact on preterm neonates. In cases of small PDA, infants and children are generally asymptomatic except for the presence of a heart murmur. This was observed in our study, where some neonates with a small PDA did not exhibit significant symptoms beyond the characteristic murmur. Literature supports this finding, indicating that small PDAs may not cause any symptoms other than a heart murmur and that affected infants and children are typically asymptomatic[144,145]. Large PDAs were associated with more severe symptoms in our study, consistent with findings from existing literature. These symptoms included are fast or hard breathing and shortness of breath, particularly during feeding, were common in neonates with large PDA[146].

In our study, 23 infants (46.94%) required oxygen, and 10 of these had large PDAs. Literature supports this, noting that large PDAs can cause significant respiratory distress due to increased pulmonary blood flow. A heart murmur was present in 24 neonates (48.98%), with 14 of these having large PDAs. Additionally, heart failure and tachycardia were more prevalent in infants with large PDAs. Specifically, 7 infants (14.29%) had heart failure, and 6 of these had large PDAs. Tachycardia was observed in 6 infants (12.25%), all of whom had large PDAs. These findings are consistent with the literature, which describes the cardiovascular burden imposed by large PDAs, leading to heart failure and other complications.

Preterm infants with large PDAs may also experience serious complications such as necrotizing enterocolitis, respiratory distress, and apnea. In our study, 2 infants (4.08%) had apnea, and 3 (6.12%) had birth asphyxia, with one case each associated with large PDA. Additionally, symptoms like hyperactive precordium and hepatomegaly were noted in a subset of infants, underscoring the severe systemic effects of large PDAs. The presence of symptoms like tachycardia, heart failure, and hyperactive precordium further highlights the hemodynamic burden imposed by large PDAs.

The mean size of PDA in preterm babies reported is approximately 3.78 mm, with a range of 1.0 mm to 10.0 mm. and the findings of study is in line with the previous reports. Mean size of PDA of 49 preterm babies was determined to be 2.69mm with range of 0.70mm to 6.50mm. PDA is considered small at <1.5 mm, moderate when it ranges between 1.5 and 3 mm, and large if the dimension exceeds 3 mm[45] . In our study, maximum of 51.02 % (25 out of 49 neonates) of study population was found to have large PDA, where as 24.49% each of study population had moderate and small PDA.

The presence of hemodynamically significant patent ductus arteriosus (hsPDA) is a critical factor influencing the clinical outcomes of preterm infants. In our study, 53.06% of the preterm babies (26 out of 49) had hsPDA, with the majority of these cases involving large PDAs. The overall survival rate was 85.71%, with 7 infants (14.29%) not surviving. Among those who did not survive, 6 had large and hsPDA, while 1 had a moderate PDA. The primary causes of death included sepsis, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress, and pulmonary hemorrhage. Our findings are consistent with previous studies that highlight the high incidence of hsPDA in preterm infants.

The Vermont Oxford Network (VON) reported an incidence of approximately 33% in very low birth weight (VLBW) infants, while other studies have indicated an incidence of 55% in extremely low birth weight (ELBW) infants[92]. In our cohort, the incidence of hsPDA was notably higher, reflecting the vulnerability of preterm neonates to significant ductal shunting. Treatment modalities for hsPDA in our study included pharmacological and surgical interventions. Specifically, 42.86% of the preterm infants underwent pharmacological closure with medications, while 10.20% required surgical closure. These treatment patterns are in line with reports from other cohorts.

For instance, VLBW infants with a diagnosis of PDA have been treated with indomethacin (71%), ibuprofen (13%), and surgical closure (27%)[86]. Recent literature also suggests a trend towards spontaneous closure of PDA in the VLBW population[147], emphasizing the variability in clinical management strategies.

The association between hsPDA and adverse clinical outcomes is well-documented. Hemodynamically significant PDA leads to left-to-right shunting, resulting in pulmonary overcirculation and subsequent respiratory decompensation.

This increases the risk of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and ultimately, mortality[54,148,149]. In our study, the complications among the non-survivors included PPHN with sepsis (42.86%), sepsis alone (28.57%), respiratory distress (14.29%), and pulmonary hemorrhage (14.29%). These findings align with the literature that hsPDA is associated with significant morbidity and mortality[7,148].

The mean NT-proBNP level in the current study was 17,398 pg/mL, with a range from 853 pg/mL to 35,000 pg/mL. Notably, NT-proBNP levels in infants with large PDAs were significantly higher than those in infants with moderate or small PDAs (mean value of 27,279 ± 16,410 pg/mL), demonstrating a strong positive correlation between PDA size and NT-proBNP levels (correlation coefficient of 0.52, P = 0.0002). Comparison of NT-proBNP levels across different clinical scenarios revealed significant findings: Infants with hsPDA had higher NT-proBNP levels (median 26,605 pg/mL) compared to those without hsPDA (median 5,976 pg/mL, P = 0.036)

Preterm infants who survived had lower NT-proBNP levels (median 10,281 pg/mL) than those who did not survive (median 34,593 pg/mL, P < 0.0001). Infants with heart failure exhibited significantly higher NT-proBNP levels (median 35,000 pg/mL). These findings align with previous research indicating that elevated NT-proBNP levels are associated with increased mortality and morbidity in preterm infants with hsPDA.

Study by El-Khuffash and Molly[63] reported that infants in the poor outcome group (grade III/IV IVH, death or both) had significantly higher NT-proBNP levels at 48 hours compared to infants without PDA-associated complications (9284 pmol/L vs 5121 pmol/L, p=0.008). In the HsPDA group, 6 infants (27%) died. The HsPDA

group had a significantly higher mortality within 2 weeks compared to the non-HsPDA group (27% vs 4%, p=0.01). The NT-proBNP levels continued to decline over time in both groups, although the mean values remained higher at all times in the HsPDA group[150].

Budde et al., in their study reported of using a cut-off of 5900 pg/mL, NT-proBNP had 96% sensitivity and 90% specificity for accurately diagnosing an HsPDA. Further they asserted from multivariate analysis that NT-proBNP levels were a significant independent predictor of HsPDA. In a subgroup analysis of 12 patients who had NT-proBNP measured both with an HsPDA and later a non-HsPDA, the levels were significantly higher for HsPDA compared to non-HsPDA (24322±3857 pg/mL vs 3381±578 pg/mL, p<0.001)[150].

Rodriguez-Blanco *et al.* found that the optimum threshold for hsPDA in preterm babies was 5099 pg/ml, and the majority of them required pharmacological treatment. NT-proBNP levels were measured with 94% sensitivity and 82% specificity[151].

Permyakova et al. found that median NT-pro-BNP levels were 17,600 pg/mL in neonates with a PDA and 2773 pg/mL in the non-hsPDA group. A NT-pro-BNP cut-off value of more than 8500 pg/mL can indicate hsPDA (84% Sensitivity, 86% Specificity)[152].

Previous literature which indicates that NT-proBNP levels are elevated in the presence of PDA and are positively correlated with the diameter of the ductus arteriosus and the left atrium/aorta (LA/AO) ratio, but not with left ventricular ejection fraction (LVEF). Several factors affect NT-proBNP levels in preterm infants with PDA[14]. Higher NT-proBNP levels were observed in very preterm infants

compared to those born at a gestational age of 32 weeks or more[15]. Infants with a birth weight of less than 1,000 g had higher NT-proBNP levels compared to those weighing 1,000 g or more[14]. The study found a positive correlation between PDA diameter and NT-proBNP levels with correlation coefficient of 0.56 and p value <0.05[14]. Infants with a larger PDA diameter (>1.5 mm) had significantly higher NT-proBNP levels than those with smaller PDAs. A higher LA/AO ratio was associated with elevated NT-proBNP levels, indicating increased left atrial volume and pressure[14].

Thus with our study out come and previous studies reports it is clear that preterm infants with PDA had significantly higher NT-proBNP levels compared to those without PDA. NT-proBNP levels were highly predictive of PDA associated with increased mortality. Persistently elevated NT-proBNP levels over time were also associated with poor outcomes.

7. CONCLUSION

Patent Ductus Arteriosus (PDA) is a prevalent cardiovascular condition in preterm neonates, particularly those born before 28 weeks of gestation. The failure of the ductus arteriosus to close postnatally can result in significant hemodynamic alterations, impacting the infant's cardiovascular stability and overall health. Traditional methods of assessing the hemodynamic significance of PDA through clinical signs and echocardiographic evaluations pose challenges in determining the optimal timing for intervention. However, the hormone B-type natriuretic peptide (BNP) and its stable precursor NT-proBNP, which can be measured in serum, have shown promise as biomarkers for PDA screening.

This study, examined serum NT-proBNP levels in preterm infants with PDA and their correlation with PDA size. The incidence of PDA was higher in infants with lower gestational ages and birth weights, consistent with existing literature. The study also revealed that symptoms and clinical outcomes varied significantly based on the size of the PDA. Larger PDAs were associated with more severe symptoms and complications, such as respiratory distress and heart failure. Hemodynamically significant PDA (hsPDA) was identified in over half of the study population, leading to adverse outcomes and higher mortality rates. Importantly, NT-proBNP levels were found to be significantly higher in infants with larger PDAs and those with hsPDA. Elevated NT-proBNP levels were strongly correlated with PDA size and were predictive of increased morbidity and mortality.

These findings support the use of NT-proBNP as a valuable biomarker in the clinical management of PDA in preterm infants. Overall, this study underscores the importance of timely and accurate diagnosis of PDA in preterm infants and highlights the potential of NT-proBNP as a critical tool in guiding treatment decisions, thereby improving clinical outcomes for this vulnerable population.

8. SUMMARY

A hospital-based observational study was conducted at the NICU of KLEH Dr. Prabhakar Kore Hospital, Belgaum, Karnataka, from December 2022 to December 2023, to estimate serum NT-proBNP levels in preterm newborns with Patent Ductus Arteriosus (PDA) and correlate these levels with the size of PDA. The study included 49 preterm neonates who met the inclusion and exclusion criteria, with informed consent obtained from their parents.

1. Demographics and Clinical Characteristics

i. Out of 49 preterm infants, 25 (51%) were male, and 24 (49%) were female

ii. The mean age of preterm babies was 8.49 ± 6.01 days, ranging from 2 to 28 days

iii. The mean gestational age was 32.52 ± 3.08 weeks, with a range of 25.75 to 38 weeks

iv. Preterm infants were categorized based on gestational age: 8.16% extreme (<28 weeks), 20.41% very (28-31 weeks), 38.78% late (34-36 weeks), and 32.65% early (37-38 weeks) preterm

v. The mean birth weight was 1368 ± 545.00 grams, with a range of 614 to 2800 grams. Neonates were classified as 36.73% very low birth weight, 34.69% extremely low birth weight, and 32.65% low birth weight

vi. Common symptoms included murmur (48.98%) and oxygen requirement (46.94%), while apnea (4.08%) and birth asphyxia (6.12%) were less frequent

2. PDA Size and Management

i. The mean size of PDA was 2.69 mm, ranging from 0.70 to 6.50 mm. The study population was divided into 51.02% with large PDA, and 24.49% each with moderate and small PDA

ii. hsPDA was observed in 53.06% of the preterm infants.

iii. PDA closure was achieved pharmacologically in 42.86% and surgically in 10.20% of the infants.

iv. The survival rate was 85.71%, with 14.29% of the infants not surviving due to conditions such as sepsis, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress, and pulmonary hemorrhage.

3. NT-proBNP Levels

i. The mean NT-proBNP level was 17398pg/mL, with a range of 853 to 35000pg/mL. The median NT-proBNP level was 12241 pg/mL, with upper and lower quartile values of 32548 pg/mL and 2622 pg/mL, respectively

ii. There was a significant association between PDA size and NT-proBNP levels, with mean NT-proBNP values significantly higher in large PDA (27948 pg/mL) compared to moderate and small PDA ($p < 0.0001$).

iii. A moderate positive correlation ($r = 0.52$) between PDA size and NT-proBNP levels was found, which was statistically significant ($p = 0.0002$).

iv. No statistically significant variations in NT-proBNP values were observed across different preterm groups based on gestational age ($p = 0.050$) or birth weight categories ($p = 0.109$).

v. Babies with hsPDA had significantly higher NT-proBNP levels that of non hsPDA (P value <0.0001)

vi. Significantly higher levels of NT-proBNP were observed in babies with heart failure compared to the babies without heart failure (p value 0.013)

vii. It was found that babies survived had significantly lower NT-proBNP levels with median value of 10281 (2406-26605)pg/mL than that of died babies 34593(12346-52394)pg/mL.

These findings suggest that NT-proBNP levels correlate positively with the size of PDA in preterm newborns, providing a potential biomarker for assessing the hemodynamic significance of PDA when echocardiography is not available.

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10. ANNEXURES

ANNEXURE I- CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH

"**Estimation of serum N-terminal peptide of Brain natriuretic peptide levels (NT-pro BNP) in preterm newborns with Patent Ductus Arteriosus (PDA) a one year prospective observational study conducted in Dr.Prabhakar Kore Hospital**"

Investigator: - REG NO: BM0121002

Chief Guide: - Professor,

Pediatric cardiologist, Department of Pediatrics

JNMC Medical College, Belagavi-590010

Co-Guide:- Professor and Head

Department of Neonatology

JNMC Medical College, Belagavi-590010

You have been asked to involve your child in the said study to be conducted at neonatal care unit of department of paediatrics KLE University's Dr Prabhakar Kore Charitable Hospital, Belagavi by REG NO: BM0121002, PG student in department of paediatrics at Jawaharlal Nehru medical college, Belagavi.

Purpose of the study: To estimate the levels of serum NT-pro BNP in preterm newborn undergoing echocardiography helps in determining prognosis and its levels in hs-PDA

Participation of your child will help us to assess the prognosis of the child's heart disease and also helps us to screen a lot of medical conditions also. You are free to discontinue the participation in the study at any time for any reasons and you will not

be paid any reimbursement for participation in the research. Hence involving your child in the study is your Voluntary decision, whether or not to participate will not affect your current or future relationship with KLEs Dr. Prabhakar Kore Hospital & Medical research centre, Belagavi.

Risk and benefits : There are no risks involved.

Use of photography/Identifying details: Any photography or identification details will be disclosed only with your permission.

Privacy and Confidentiality: The only people who will know that you are a research participant are member of the research team. No information about you or provided by you, during research will be disclosed to others without your written consent. When the results of the research are published or discussed in the conferences, no information will be disclosed that would reveal your identity. Any information obtained in connections with this study and that can be identified with you remain confidential and will be disclosed only with your permission.

Financial incentive for participation: You or your child will not be paid any reimbursement for participation in this study

Queries: If you have any queries you may contact

REG NO:BM0121002

Post Graduate Student

Department of Paediatrics

JNMC, Belagavi-590010

If you have any queries regarding or rights or research participation you may contact

PROFESSOR

PEDIATRIC CARDIOLOGIST

Department of Paediatrics,

J.N. Medical College, Belagavi – 590010

If you have any questions about your rights or research participation you may contact

Dr. Harsha Hegde

Chairperson , JNMC,IEC & Scientist D,

ICMR,National Institute of Transfusion Medicine, Belagavi

You will be given a copy of this form for your information and to keep for your records.

STATEMENT OF CONSENT

I hereby voluntarily agree for participation of my child name _____, age _____ in this study. I understand that I have the liberty to withdraw at any time. My signature below indicates that I have read or have been told in the language I understand, about this entire consent form including the risks and benefits and have had all my questions answered. I will be given a copy of this consent form.

Signature of the authorized representative/ parent: _____

Date: _____

Name: _____

Relation to the Subject: _____

Signature of the witness: _____

Date: _____

Name: _____

Signature of investigator:_____

Date: _____

Name: _____

ANNEXURE II- PERFORMA

PATIENT'S PROFORMA

SERIAL NUMBER-

NAME/AGE/SEX-

FATHERS NAME-

MOTHERS

NAME-

ADDRESS-

PHONE NUMBER-

INFORMANT-

DATE OF BIRTH-

GESTATIONAL AGE-

MODE OF DELIVERY-

APGAR SCORE

AT 1MIN-

5MIN-

SYMPTOMS:

FEEDING DIFFICULTY

SWEATING WITH CRYING/EATING FAST BREATHING

EASY TIRING

RAPID HEART RATE

ON CINICAL EXAMINATION

BOUNDING PULSE (easily palpable dorsalis pedis)-

MURMUR (systolic/continous)-

PERSISTENT TACHYCARDIA-

HYPERACTIVE PRECORDIUM (visible pulsation in >2 rib space)-

NEED FOR OXYGEN SUPPORT-

EDEMA-

ON ECHO-CARDIOGRAPHY:

FLOW REVERSAL RATIO

LA/AORTA RATIO

SIZE OF PDA

PULMONARY ARTERY PRESSURE

INTERNAL DIAMETER

LEFT ATRIAL DILATION

DIASTOLIC TURBULENCE

RETROGRADE DIASTOLIC FLOW >30% OF FORWARD FLOW

DATE OF ADMISSION-

DATE OF DIAGNOSIS-

Levels of Nt-Pro BNP (Values)

ANNEXURE III- KEY TO MASTER CHART

Variable	Code	Key
Gender	1	Male
	2	Female
Murmur	1	Yes
	2	No
O2 requirement	1	Yes
	2	No
Apnea	1	Yes
	2	No
Asphyxia	1	Yes
	2	No
Low birth weight class	ELBW	Extreme Low Birth weight
	VLBW	Very Low Birth weight
	LBW	Low Birth weight
Pharmacological closure	1	Yes
	2	No
Surgical Closure	1	Yes
	2	No
Survival	1	Yes
	2	No
Heart failure	1	Yes
	2	No
Tachycardia	1	Yes
	2	No
hyperactive pericardium	1	Yes
	2	No

ANNEXURE IV- MASTER CHART

Age (days)	Gender	Gestational age (weeks)	Preterm	Murmur	O2 requirement	Apnea	Symptoms	Asphyxia	PDA size (mm)	HsPDA	PDA size code	NTPROBNP (pg/mL)	Weight (g)	LBW class	Pharmacological closure	Surgical Closure	Survival	condition	Heart failure	Tachycardia	hyperactive pericardium	other
4	2	29.25	Very preterm	1	2	2	continuous murmur	1	4	1	Large	35000	960	ELBW	1	2	1	None	Yes	tachy cardia	NO	oxygen dependency
10	2	35	Late preterm	1	2	2	Systolic murmur	2	4	1	Large	5718	1140	VLBW	2	2	1	None	No	No	No	No
3	2	36.25	Late preterm	1	1	2	Systolic murmur	1	2.5	2	Moderate	5787	1860	LBW	2	2	1	None	No	No	No	No
10	2	31.75	Early preterm	1	2	2	systolic Murmur	2	3.5	1	Large	35000	1000	VLBW	1	2	1	None	No	No	No	No
12	1	28.75	Very preterm	1	2	2	continuous murmur	2	3	1	Large	32846	800	ELBW	1	2	1	None	No	No	No	No
8	1	35.5	Late preterm	1	2	2	Systolic murmur	2	1	2	Small	2662	1960	LBW	2	2	1	None	No	No	No	No
28	2	37.25	Early preterm	1	2	2	systolic Murmur	2	2.5	2	Moderate	25493	2143	LBW	2	1	1	None	No	No	No	No
8	1	33.25	Very preterm	1	2	2	systolic Murmur, on ventilator	2	6.5	1	Large	26605	1490	VLBW	1	2	1	None	Yes	tachy cardia	hyperactive precordium	bounding pulse

17	2	30.5	Very preterm	2	1	2	Rapid Heart rate,o2 support yes	2	3	1	Large	20754	900	ELBW	1	2	1	None	No	No	No	No
10	2	31.75	Early preterm	2	1	2	Rapid Heart rate,o2 support yes	2	4	1	Large	35000	980	ELBW	1	2	1	None	Yes	tachy cardia	hyp era ctiv e pre cor diu m	No
24	1	36	Late preterm	2	1	2	Systolic murmur, o2 support yes	2	2	2	Mode rate	9470	1750	LBW	2	2	1	None	No	No	No	No
9	1	32.5	Early preterm	2	1	2	Not maitaini ng saturatio n	2	3.5	1	Large	11092	1420	VLBW	1	2	1	None	No	No	No	No
20	1	27.25	extreme preterm	2	1	2	O2 support yes,tach ycardia	2	1.5	2	Small	1111	750	ELBW	2	1	1	None	No	No	No	No
8	1	35.25	Late preterm	2	1	2	Tachyca rdia,o2 support yes	2	4	1	Large	17897	1500	LBW	1	2	1	None	No	No	No	No

21	1	30.25	Very preterm	2	1	2	O2 support yes,tachycardia	2	3	1	Large	35000	734	ELBW	1	2	1	None	Yes	tachy cardia	No	No
15	2	27.25	extreme preterm	2	1	2	O2 support yes,not maintaining saturation	2	3	1	Large	34788	630	ELBW	1	2	2	sepsis	No	No	No	No
9	1	36	Late preterm	2	2	1	Screening echo	2	1	2	Small	2227	2598	LBW	2	2	1	None	Yes	No	Yes	Yes
9	1	35	Late preterm	2	2	1	Screening echo	2	2	2	Moderate	18747	1560	LBW	2	2	1	None	No	No	No	No
9	2	30	Early preterm	2	1	2	Apnea with desaturation	1	1.2	2	Small	2222	699	ELBW	2	2	1	None	No	No	No	No
11	2	34	Early preterm	1	2	2	Screening echo	2	1	2	Small	2084	1134	VLBW	2	2	1	None	No	No	No	No
6	1	35	Late preterm	2	1	2	O2 support	2	2	2	Moderate	35000	2800	LBW	2	2	1	None	No	No	No	No
8	1	32.25	Early preterm	2	1	2	O2 support	2	2.5	2	Moderate	6164	789	ELBW	2	2	2	sepsis	No	No	No	No
3	1	29	Very preterm	2	1	2	Requiring O2 support	2	4	1	Large	32548	2700	LBW	1	2	1	None	No	No	No	No

3	1	38	Late preterm	2	1	2	Requiring O2 support	2	3	1	Large	70000	1180	VLBW	1	2	2	PPHN,sepsis	Yes	tachycardia	hyperactive precordium	hepatomegaly
2	1	35.5	Late preterm	1	2	2	continuous murmur	2	4.5	1	Large	15825	1900	LBW	1	2	1	None	No	No	No	No
7	1	36	Late preterm	1	2	2	Soft systolic mumur	2	2	2	Moderate	5618	1368	VLBW	2	2	1	None	No	No	No	No
2	1	34	Late preterm	1	2	2	Systolic murmur, o2 support	2	1.5	2	Small	2642	1467	VLBW	2	2	1	None	No	No	No	No
8	1	33.25	Early preterm	2	1	2	Requiring O2 support-mechanical ventilation	2	6.5	1	Large	26605	1490	VLBW	2	1	1	None	Yes	tachycardia	No	continuous murmur,
8	2	30	Early preterm	1	2	2	continuous murmur	2	2.5	2	Moderate	12241	972	ELBW	2	2	1	None	No	No	No	No
20	1	29	Very preterm	2	1	2	Requiring O2 support	2	0.7	1	Small	853	956	ELBW	2	2	1	None	No	No	No	No
8	2	34.75	Early preterm	1	2	2	continuous murmur	2	3	1	Large	14741	1976	LBW	1	2	1	None	No	No	No	No

3	2	26	extreme preterm	2	1	2	Ventilation support and Extreme preterm	2	3	1	Large	3500	614	ELBW	1	2	1	None	No	No	No	No
9	2	33	Early preterm	2	1	2	O2 support	2	1	2	Small	1802	1500	LBW	2	2	1	None	No	No	No	No
12	2	34	Late preterm	1	2	2	continuous murmur	2	2	2	Moderate	2327	960	ELBW	2	2	1	None	No	No	No	No
3	2	30.75	Early preterm	1	2	2	continuous murmur	2	3	1	Large	70000	1260	VLBW	2	1	2	PPHN,sepsis	No	No	No	No
2	2	25.75	extreme preterm	1	2	2	continuous murmur	2	3	1	Large	6795	736	ELBW	1	2	2	Pulmonary	No	No	No	No
4	2	35.25	Late preterm	2	1	2	requiring O2 support	2	2	2	Moderate	4434	1567	LBW	2	2	1	None	No	No	No	No
2	2	36.25	Late preterm	2	1	2	requiring O2 support	2	1	2	Small	1855	2000	LBW	2	2	1	None	No	No	No	No
4	1	35.75	Late preterm	1	2	2	Soft systolic mumur	2	1	2	Small	1708	1900	LBW	2	2	1	None	No	No	No	No
12	2	34	Late preterm	2	1	2	requiring O2 support	2	1.3	2	Small	2005	1890	LBW	2	2	1	None	No	No	No	No
6	2	32	Early preterm	2	1	2	Requiring O2 support	2	1	2	Small	1166	1760	LBW	2	2	1	None	No	No	No	No
3	1	34	Late preterm	2	1	2	Requiring O2 support	2	4	1	Large	17897	1240	VLBW	1	2	2	PPHN,sepsis	No	No	No	No

5	1	35	Late preterm	2	1	2	Requiring O2 support	2	2	2	Moderate	2718	1680	LBW	2	2	1	None	No	No	No	No
4	2	30.25	Early preterm	1	2	2	Systolic murmur present	2	2.4	2	Moderate	3450	1240	VLBW	2	2	1	None	No	No	No	No
6	2	30.75	Early preterm	1	2	2	Systolic murmur	2	3	1	Large	18186	1300	VLBW	1	2	1	None	No	No	No	No
8	1	30.25	Very preterm	1	2	2	Systolic murmur	2	3	1	Large	35000	918	ELBW	2	1	1	None	No	No	No	No
3	2	30	Very preterm	1	2	2	Systolic murmur	2	4	1	Large	34593	846	ELBW	1	2	2	Respiratory distress	No	No	No	No
3	1	32	Early preterm	1	2	2	Systolic murmur	2	3.5	1	Large	34520	1180	VLBW	1	2	1	None	No	No	No	No
7	1	29	Very preterm	1	2	2	Systolic murmur	2	3	1	Large	28796	820	ELBW	1	2	1	None	No	No	No	No