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Original article

# Pre-symptomatic prediction of morbitidies in preterm infants with patent ductus arteriosus by targeted neonatal echocardiography and brain-type natriuretic peptide

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## Abstract

**Objectives:** Our objective was to compare patent ductus arteriosus (PDA) diameter, PDA score and brain-type natriuretic peptide (BNP) measurements at 48-72 hours of life, for prediction of neonatal morbidities. We hypothesized that use of a PDA score with BNP, may improve pre-symptomatic prediction of PDAs associated with adverse outcomes.

**Method:** Infants < 31 weeks GA were prospectively studied by targeted neonatal echocardiogram (TNE) at 48-72 hours age, composite PDA score and serum BNP assay; the clinical team remained blinded. PDA was independently diagnosed by echocardiography at time of clinical suspicion (6 ± 2 days), and treated at discretion of the clinical team. Primary outcome was survival with one or more of adverse outcomes (intraventricular hemorrhage [IVH], bronchopulmonary dysplasia [BPD], retinopathy of prematurity [ROP], necrotizing enterocolitis [NEC]).

**Results:** A PDA was present in 56 of 70 infants studied at 48-72 hours; 30 were eventually diagnosed with PDA but never required treatment, 19 required medical treatment, 7 surgical ligation. After adjustment for gestation, PDA diameter did not predict any adverse outcome, PDA score was associated with increased risk of any adverse outcome and high BNP was associated with IVH, BPD, or survival with any adverse outcome.

**Conclusions:** Comprehensive PDA evaluation at 48-72 hours of age may predict the subsequent occurrence of adverse outcomes and may be useful to define the PDA treatment threshold.

**Keywords**

Preterm infants, patent ductus arteriosus, targeted neonatal echocardiography, brain-type natriuretic peptide.

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## Introduction

Patent ductus arteriosus (PDA) is the most common cardiovascular problem in preterm neonates, with an incidence as high as 33% in infants < 31 weeks gestation, and is associated with adverse outcomes [1-4]. Determination of whom to treat and when to treat in order to minimize PDA-related morbidity remains challenging for neonatologists [5].

Prior studies have focused on ductal diameter as the echocardiographic marker of choice. However, treatment decision-making based on a single parameter can be flawed due to operator-dependent error [2]. Furthermore, acute physiologic changes and neonatal morbidity are more likely to be related to shunt volume across the PDA, rather than merely its patency. Whilst the volume of the shunt may not be calculated directly using echocardiography, surrogate markers of pulmonary over-circulation and systemic hypo-perfusion provide an indirect appraisal of the magnitude and consequences of the shunt [6]. A more comprehensive and standardized echocardiographic assessment of the PDA shunt, including ductal diameter, and also Doppler patterns of ductal and aortic flow, may refine the early diagnosis of PDA, allowing for accurate estimation of its hemodynamic significance [7, 8]. The likelihood of operator-dependent error from individual measurements could thus be minimized. In the first few days of life however, shunt volume is often low due to elevated pulmonary vascular resistance. This adds to the challenges of selecting those patients with PDA who may benefit from early targeted intervention.

Ascertainment of the hemodynamic significance of a PDA may benefit from the inclusion of biochemical markers, together with echocardiographic evaluation. One candidate is brain-type natriuretic peptide (BNP), secreted by ventricular myocytes in response to volume overload of the ventricles [9]. BNP measurements are reported useful for the diagnosis of PDA in preterm infants [10].

A clinically significant PDA has been linked to common neonatal morbidities such as intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC), but there is still scant evidence that pre-symptomatic diagnosis and treatment improves these outcomes [11]. We performed a hypothesis-generating pilot study to compare the utility of PDA diameter, a PDA scoring system, and serum BNP concentrations, in predicting short-term neonatal outcomes: IVH, retinopathy of prematurity (ROP) of any stage, BPD, NEC Bell stage 2 or greater, cumulative days on oxygen during admission in NICU, receipt of medical treatment with either indomethacin or ibuprofen, or surgical ligation of PDA, The primary outcome was survival with any one or more of the following neonatal outcomes: IVH, ROP of any stage, BPD, NEC Bell stage 2 or greater.

## Methods

This was a prospective cohort study of premature neonates (< 31 weeks gestation) admitted to the Neonatal Intensive Care Units (NICU) of Health Sciences Center and St. Boniface General Hospitals in Winnipeg, Manitoba, Canada between August 2010 to November 2011. With institutional Research Ethics Board approval, infants were recruited, independent of clinical suspicion for PDA, following informed parental consent. Infants with right-to-left PDA shunt or congenital heart disease (other than patent foramen ovale) were excluded. Prophylactic indomethacin was not used, and treatment given only for symptomatic PDA. In all study infants, transthoracic targeted neonatal echocardiography (TNE) was performed after 48 and before 72 hours of age; serum BNP was measured concurrently with each TNE. The clinical team, blinded to TNE findings, independently determined whether the PDA was symptomatic; their decision to treat was based on clinical features and echocardiography confirmation of an unrestrictive left-to-right shunt by

the Pediatric Cardiologist. While there were no pre-specified guidelines, clinical features considered by the clinical team included (not limited to) signs of pulmonary over-circulation (pulmonary hemorrhage), extubation failure or need for re-intubation due to increased respiratory work, persistent apnea requiring stimulation, pH < 7.25 and/or $pCO_2$ > 60 mm Hg), and signs of systemic hypo-perfusion (hypotension requiring inotropic support). The medical treatment strategy was intravenous indomethacin or ibuprofen for maximum of 2 consecutive or separated courses. Surgical ligation of the PDA was considered if medical treatment failed or was contraindicated.

*Measurement of serum BNP*

Blood was drawn from an indwelling catheter or heel poke at the time of routine blood draw for clinically necessary laboratory tests, avoiding study-specific blood collection. BNP was determined in 0.3 ml whole blood by Triage® BNP bedside immunoassay (Biosite Diagnostics Inc., San Diego, CA, USA), measuring BNP in filtered serum using a murine polyclonal fluorescence-tagged anti-BNP antibody with detection range 5-5,000 pg/ml [10].

*Targeted neonatal echocardiography*

Targeted neonatal echocardiographic studies were performed using Vivid-7® (GE Healthcare, Waukesha, WI, USA) or HP SONOS® 5500 (Phillips, Andover, MA, USA) echocardiographic systems with 7-10 MHz transducers. TNE studies were performed by a single operator (YE) as per published guidelines [12]. Imaging data were stored digitally; off-line echocardiography analysis was performed 1-3 months after the study, to avoid recall bias of neonatal outcomes.

Clinical team members were blinded to TNE studies. TNE assessment was performed at 48-72 hours of age, irrespective of clinical symptoms. If a PDA was suspected by the clinical team, echocardiography for assessment and management of the PDA was independently performed by the Pediatric Cardiology consultation service. No enrolled infant received medical treatment of the ductus before TNE.

The following parameters were measured.

**PDA features**

*Ductal diameter:* using 2-D mode at high parasternal (ductal) view, the narrowest transductal diameter was obtained, expressed as the mean of 3 measurements [13]. Color Doppler was used to identify flow across the PDA. The scale of the color was adjusted upwards to remove aliasing [14].

*Peak PDA flow velocity:* the direction and peak velocity of transductal flow was assessed by pulse- and continuous-wave Doppler [8, 15].

**Parameters reflecting left heart volume overload and pulmonary over-circulation**

*Ratio of left atrial diameter to aortic root diameter (LA/Ao):* measured from the short axis parasternal view at the level of the aortic valve, using m-mode [15].

*Ratio of mitral inflow E wave peak velocity to A wave peak velocity:* interrogation of trans-mitral valve flow was performed using pulse-wave Doppler at the tips of the mitral valve leaflets from an apical 4-chamber view [7, 15].

*Left ventricular output (LVO):* the velocity time integral (VTI) of aortic flow was obtained at the level of the hinge point of the aortic valve using pulse-wave Doppler from an apical five chamber view. Trans-aortic root diameter was measured at the hinge points of the valve from parasternal long axis view using m-mode. LVO was then calculated as (Ao CSA x VTI x heart rate) / weight, where Ao CSA = cross sectional area of aortic valve and expressed as ml/kg/min [7, 16].

*Left ventricular end diastolic dimension (LVEDD):* measured at the tips of the mitral valve leaflet using m-mode from a parasternal long axis view of left ventricle; expressed in mm [12].

**Parameter of systemic hypoperfusion**

*Diastolic aortic flow (DAO):* the arch was visualized by maintaining the ductal view described above, moving the probe slightly right of the sternum, with pulse-wave Doppler placed 1 cm below the opening of the ductus if present. Peak systolic and end-diastolic velocities were measured using pulse-wave Doppler. Absent or retrograde (negative) diastolic flow was considered an indicator of significant PDA shunt, suggestive of diastolic "steal" from the systemic circulation [17].

**Patent foramen ovale (PFO)**

PFO was evaluated from subxyphoid long axis view; size measured using Color Doppler methods. The direction and pattern of the shunt were estimated

using pulse and color Doppler. The presence of a PFO with un-restrictive left-to-right shunt was recorded, as flow via the PFO might volume-unload the left atrium and thus influence the measured BNP [18].

*PDA score*

A PDA scoring system was developed based on previously described criteria determining hemodynamic significance of a shunt [6, 15, 19]. Each parameter was scored between 0 and 3 according to median and interquartile (IQ) range of each echocardiography parameter, with maximal score 21 (**Tab. 1**).

*Outcomes*

We reported neonatal morbidities before discharge from NICU: (i) IVH as determined by pediatric radiologist-performed head US at one week after birth [20, 21]; (ii) ROP of any stage [22]; (iii) BPD defined as need for oxygen at 36 weeks post-menstrual age; (iv) NEC Bell stage 2 or greater [23]; (v) cumulative days on oxygen during admission in NICU [24]; (vi) medical treatment of PDA with either indomethacin or ibuprofen; (vii) need for surgical PDA ligation [19]. The primary outcome was survival with any one or more of the following neonatal outcomes: any IVH, ROP of any stage, BPD, NEC Bell stage 2 or greater, as studies have demonstrated an association between PDA, PDA ligation and mortality [25].

*Statistical analysis*

We calculated the median and interquartile ranges for BNP, PDA score and PDA diameter to construct severity classifications. Comparisons between severity classifications as determined above were analyzed by ANOVA to describe differences between subgroups. Odds ratios for survival with adverse outcomes were calculated for BNP, PDA score and PDA diameter before and after adjustment for gestational age (GA) using logistic regression. Receiver operator characteristic (ROC) curves were constructed for BNP, PDA score, and PDA diameter in predicting survival with any adverse outcome. Pearson correlation was used to correlate PDA score with BNP levels. SPSS® v. 21 (SPSS Inc, Chicago, IL, USA) was used to perform the statistical analysis. Data are presented as mean ± SD, or median with interquartile range as appropriate; $p < 0.05$ was considered significant.

## Results

Seventy-one (71) of 132 eligible infants were enrolled in the study. The main reason for non-enrollment was lack of parental consent prior to 72 hours of age. One infant was withdrawn from the study after enrollment due to parental request. Thirty seven infants of the enrolled group were males (53%). Mean ± SD of birth weight and GA of the enrolled group were 28 ± 1.6 weeks and 1,101 ± 280 grams respectively, lower limit for GA was 24 weeks and for birth weight was 520 grams. A PDA was present in 56 of 70 (80%) infants at 48-72 hours of life, 31 of them were on CPAP support during the time of TNE, 18 were on conventional mechanical ventilation, and 7 were on high frequency jet ventilation support. Fourteen infants had PDA closed at 48-72 hours of life (20%), 12 of them were on CPAP support and 2 were on conventional ventilation. Clinical presentation of the PDA was at 6 ± 2 days. Nineteen infants (34% of infants with PDA at 48-72 hours) received either one or two courses of indomethacin or ibuprofen for

**Table 1.** PDA score based on interquartile ranges.

| Scoring | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| **PDA size (mm)** | < 1.0 | 1-1.39 | 1.4-1.8 | > 1.8 |
| **PDA V max (m/sec)** | > 2.8 | 2.4-2.8 | 1.7-2.3 | < 1.7 |
| **LA:Ao ratio** | < 1.0 | 1-1.2 | 1.3-1.5 | > 1.5 |
| **Mitral E:A ratio** | < 1.0 | - | 1.0 | > 1.0 |
| **LVO (ml/kg/min)** | < 235 | 235-287 | 288-321 | > 321 |
| **Descending Ao diastolic flow** | Present | - | Absent | Reversed |
| **LVEDD (mm)** | < 1.34 | 1.34-1.43 | 1.44-1.56 | > 1.56 |

PDA: patent ductus arteriosus; LA:Ao: left atrial to aortic ratio; LVO: left ventricular output; BNP: brain-type natiuretic protein; E:A ratio: the ratio of mitral inflow E wave peak velocity to A wave peak velocity; Ao: aortic; LVEDD: left ventricular end-diastolic diameter.

a PDA. Seven (27%) of neonates with clinical PDA underwent surgical ligation after failure to close with medical treatment; these neonates all received 2 courses of treatment.

Infants with higher PDA scores, greater PDA diameters, and higher BNP concentrations were of lesser birth weight and lower gestation (**Tables 2**, **3** and **4**). Infants who underwent PDA ligation had higher BNP concentrations (639 ± 286 pg/ml vs. 70 ± 115 pg/ml; p = 0.002) and large PDA diameters (2.1 ± 0.6 vs. 1.1 ± 0.7 mm). Three of 7 neonates who underwent ligation had high PDA scores while 4 had moderate scores.

*Outcome by PDA score*

We classified PDA scores into trivial, low, moderate, and high based on the IQ ranges. The PDA score at 48-72 hours significantly correlated with BNP concentration at 48-72 hours, r = 0.69 (p < 0.001). PDA scores were strongly associated with more days of supplemental oxygen, BPD, and medical treatment of symptomatic PDA (p < 0.001) (**Tab. 2**). PDA scores were also less strongly associated with IVH overall, NEC, surgical ligation, and survival with any adverse outcome (p < 0.05). PDA score when adjusted for GA was associated with increased odds for survival with any adverse outcome (OR = 1.2; CI 1.01 to 1.24, p = 0.03) but was not associated with increased odds of IVH (p = 0.28) or BPD (p = 0.13) (**Tab. 5**).

*Outcome by BNP*

We subdivided the BNP concentrations into 4 groups based on the IQ ranges of the measurements at 48-72 hours (**Tab. 3**). Increased BNP concentrations at 48-72 hours were associated with larger PDA diameter, higher PDA score, more days on oxygen and medical treatment for symptomatic PDA (p < 0.001). Fifty percent of infants with moderate (34-120 pg/ml) and all infants with high (> 120 pg/ml) BNP concentrations at 48-72 hours eventually were treated for PDA. Higher BNP concentrations were associated with pulmonary hemorrhage, IVH grade I or II, IVH overall (p < 0.05), and need for surgical ligation (p = 0.05). Twenty percent of infants with moderate and twenty one percent of infants with high BNP concentrations underwent surgical ligation. When adjusted for GA BNP was still associated with increased odds for any IVH (p = 0.01), BPD (p = 0.03), or survival with any adverse outcome (p = 0.01) (**Tab. 5**).

*Outcome by PDA diameter*

We classified PDA diameters into closed or trivial, small, medium, and large based on IQ

**Table 2.** PDA score and outcomes.

| | Trivial PDA score (< 5) n = 30 | Low score (5-11) n = 19 | Moderate score (12-16) n = 9 | High score (> 16) n = 12 | p-value (ANOVA) |
|---|---|---|---|---|---|
| **Gestation (weeks)** | 29 (28, 30) | 28 (27, 29) | 27 (26, 28)[a] | 27 (25, 28)[a] | **< 0.001** |
| **Birth weight (grams)** | 1,236 ± 250 | 1,162 ± 236[b] | 991 ± 275[a] | 850 ± 175[a] | **< 0.001** |
| **PDA diameter (mm)** | 1.0 ± 0.2 | 1.3 ± 0.3[b] | 2.0 ± 0.5[a] | 2.1 ± 0.4[a] | **< 0.001** |
| **BNP (pg/ml)** | 15 (6, 24) | 33 (23, 72)[a,b] | 97 (34, 141)[a,b] | 405 (141, 682)[a] | **< 0.001** |
| **Pulmonary hemorrhage** | 0 | 1 (5%) | 0 | 2 (13%) | 0.09 |
| **IVH I-II** | 3 (10%) | 5 (26%) | 3 (33%) | 4 (33%) | 0.2 |
| **IVH III-IV** | 1 (3%) | 1 (5%) | 1 (11%) | 3 (25%) | 0.13 |
| **IVH ALL** | 4 (13%) | 6 (32%) | 4 (44%) | 7 (58%) | **0.02** |
| **ROP** | 3 (10%) | 3 (16%) | 2 (22%) | 4 (33%) | 0.3 |
| **NEC** | 3 (10%) | 0 | 0 | 4 (33%) | **0.02** |
| **BPD** | 4 (13%) | 3 (16%) | 3 (33%) | 9 (67%) | **< 0.001** |
| **Days on oxygen** | 18 (4, 32) | 26 (10, 45)[b] | 55 (45, 62)[a] | 82 (57, 95)[a] | **< 0.001** |
| **Medical treatment** | 0 | 0 | 9 (100%) | 10 (83%) | **< 0.001** |
| **Surgical treatment** | 0 | 0 | 4 (21%) | 3 (25%) | **0.02** |
| **Any adverse outcome** | 8 (27%) | 6 (32%) | 3 (33%) | 10 (83%) | **< 0.05** |

Data is presented as mean ± standard deviation or median (interquartile range); p is in bold where significant.
[a] p < 0.05 vs. trivial PDA score; [b] p < 0.05 vs. high PDA score.
PDA: patent ductus arteriosus; BNP: brain-type natriuretic peptide; IVH: intraventricular hemorrhage; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia.

**Table 3.** BNP and outcomes.

| | Trivial BNP (0-15 pg/ml) n = 13 | Low BNP (16-33 pg/ml) n = 23 | Moderate BNP (34-120 pg/ml) n = 20 | High BNP (> 120 pg/ml) n = 14 | p-value (ANOVA) |
|---|---|---|---|---|---|
| **Gestation (weeks)** | 29 (28, 30)[b] | 29 (28, 30)[b] | 28 (26, 30)[a] | 27 (26, 28)[a] | **0.01** |
| **Birth weight (grams)** | 1,182 ± 282 | 1,248 ± 264 | 1,043 ± 240[a] | 942 ± 142[a] | **0.002** |
| **PDA diameter** | 1.1 (0.85, 1.35) | 1.0 (0.9, 1.3) | 1.4 (1.3, 2.0)[a] | 1.8 (1.7, 2.3)[a] | **< 0.001** |
| **PDA score** | 3.4 ± 1.6 | 4.9 ± 3.3[a,b] | 9.4 ± 5.1[a,b] | 15.6 ± 4.0[a] | **< 0.001** |
| **Pulmonary hemorrhage** | 0 | 0 | 0 | 2 (14%) | **0.04** |
| **IVH I-II** | 0 | 3 (13%) | 4 (20%) | 6 (43%) | **0.04** |
| **IVH III-IV** | 1 (8%) | 0 | 1 (5%) | 3 (21%) | 0.1 |
| **IVH ALL** | 1 (8%) | 3 (13%) | 5 (25%) | 9 (64%) | **0.003** |
| **ROP** | 0 | 2 (9%) | 4 (20%) | 5 (36%) | 0.06 |
| **NEC** | 1 (8%) | 1 (4%) | 1 (5%) | 2 (14%) | 0.68 |
| **BPD** | 1 (8%) | 2 (9%) | 7 (35%) | 5 (36%) | 0.13 |
| **Days on oxygen** | 18 ± 19 | 21 ± 19[b] | 46 ± 30[a,b] | 76 ± 24[a] | **< 0.001** |
| **Medical treatment** | 0 | 2 (9%) | 6 (30%) | 11 (79%) | **< 0.001** |
| **Surgical treatment** | 0 | 0 | 4 (20%) | 3 (21%) | 0.05 |
| **Any adverse outcome** | 3 (23%) | 3 (13%) | 6 (30%) | 5 (36%) | 0.4 |

Data is presented as mean ± standard deviation or median (interquartile range); p is in bold where significant.
[a]$p < 0.05$ vs. trivial BNP concentration; [b]$p < 0.05$ vs. high BNP concentration.
PDA: patent ductus arteriosus; BNP: brain-type natiuretic protein; IVH: intraventricular hemorrhage; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia.

**Table 4.** PDA diameter and outcomes.

| | Trivial (< 1.0 mm) or closed PDA n = 29 | Small PDA (1.0-1.39 mm) n = 15 | Medium PDA (1.4-1.8 mm) n = 12 | Large PDA (> 1.8 mm) n = 14 | p-value (ANOVA) |
|---|---|---|---|---|---|
| **Gestation (weeks)** | 29 (28, 30) | 28 (27, 29)[a] | 26 (25, 29)[a] | 27.5 (26, 28) [a] | **< 0.001** |
| **Birth weight (grams)** | 1,263 ± 246 | 1,112 ± 243 | 969 ± 158[a] | 930 ± 226[a] | **< 0.001** |
| **BNP** | 16 (7.5, 24.5) | 28 (17.5, 68.2)[b] | 121 (39, 347)[a] | 213 (98, 661)[a] | **< 0.001** |
| **PDA score** | 3.7 ± 2.0 | 6.3 ± 2.2[a,b] | 12.3 ± 3.8[a,b] | 16.4 ± 3.5[a] | **< 0.001** |
| **Pulmonary hemorrhage** | 0 | 0 | 2 (17%) | 1 (7%) | 0.08 |
| **IVH I-II** | 3 (10%) | 3 (20%) | 5 (42%) | 6 (43%) | 0.06 |
| **IVH III-IV** | 1 (3%) | 1 (7%) | 1 (8%) | 4 (29%) | 0.1 |
| **IVH ALL** | 4 (14%) | 4 (26%) | 6 (50%) | 10 (71%) | **0.002** |
| **ROP** | 3 (10%) | 2 (13%) | 3 (25%) | 4 (29%) | 0.45 |
| **NEC** | 2 (7%) | 1 (7%) | 1 (8%) | 2 (14%) | 0.84 |
| **BPD** | 3 (10%) | 3 (20%) | 5 (42%) | 9 (64%) | **0.003** |
| **Days on oxygen** | 14 (2, 24) | 31 (16, 45)[b] | 51 (45, 82)[a] | 71 (52, 84)[a] | **< 0.001** |
| **Medical treatment** | 0 | 2 (13%) | 10 (83%) | 7 (50%) | **< 0.001** |
| **Surgical treatment** | 0 | 0 | 0 | 7 (50%) | **< 0.001** |
| **Any adverse outcome** | 5 (17%) | 6 (40%) | 6 (50%) | 10 (71%) | **< 0.05** |

Data is presented as mean ± standard deviation or median (interquartile range); p is in bold where significant.
[a]$p < 0.05$ vs. trivial/closed PDA; [b]$p < 0.05$ vs. large PDA.
PDA: patent ductus arteriosus; BNP: brain-type natiuretic protein; IVH: intraventricular hemorrhage; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia.

ranges. Enlarged PDA diameter was significantly associated with elevated BNP at 48-72 hours, higher PDA score, days on oxygen, medical treatment of symptomatic PDA, or surgical ligation ($p < 0.001$) (**Tab. 4**). We found a significant association with IVH overall, BPD, and survival with any adverse outcome ($p < 0.05$). When adjusted for GA, PDA diameter showed no significant increase in odds for IVH, BPD, or survival with any adverse outcome (**Tab. 5**).

**Table 5.** Odds ratios for adverse outcomes calculated for PDA score, BNP, and PDA diameter after adjustment for GA using logistic regression.

| | PDA score OR (0.95% CI) | p-value | BNP OR (0.95% CI) | p-value | PDA diameter OR (0.95% CI) | p-value |
|---|---|---|---|---|---|---|
| **IVH ALL** | 1.1 (0.9-1.2) | 0.28 | 1.003 (1.001-1.006) | **0.01** | 2.2 (0.7-6.7) | 0.16 |
| **BPD** | 0.9 (0.8-1.03) | 0.13 | 1.98 (1.09-10.3) | **0.03** | 0.35 (0.07-1.75) | 0.2 |
| **Any adverse outcome** | 1.2 (1.01-1.24) | **0.03** | 1.37 (1.23-1.55) | **0.01** | 1.1 (0.96-9.3) | 0.06 |

P-value is in bold where significant.
PDA: patent ductus arteriosus; BNP: brain-type natiuretic protein; GA: gestational age; IVH: intraventricular hemorrhage; BPD: bronchopulmonary dysplasia.

*ROC curves*

ROC curves were constructed to assess the ability of the PDA scores, BNP levels, and PDA diameters to predict survival with any adverse outcome in the population. BNP concentrations predicted adverse outcomes best with an area under the curve (AUC) of 0.86 (95% CI 0.76-0.96, $p < 0.001$) compared to AUC of 0.69 (95% CI 0.55-0.83 $p < 0.05$) for PDA score and AUC of 0.64 (95% CI 0.49-0.79, $p = 0.08$) for PDA diameter (**Fig. 1**). A cut-off value for BNP of 90 pg/ml had a sensitivity of 71%, a specificity of 95%, a positive predictive value of 90%, and a negative predictive value of 82%. A cut-off PDA score of 10 had a sensitivity of 66%, a specificity of 88%, a positive predictive value of 78%, and a negative predictive value of 80%

*The effect of PFO on other echocardiographic parameters and BNP*

For infants with medium to large PDA diameter (≥ 1.4 mm) and a PFO with non-restrictive left-to-right shunt, there was no significant difference in serum BNP concentration, LA/Ao ratio, LVO, LVEDD, and PDA flow velocity, compared to infants with restrictive or no PFO with same PDA size (data not shown).

## Discussion

We examined the predictive value of PDA diameter, echocardiographic score, and the bio-marker BNP, determined in the pre-symptomatic phase, for adverse outcomes in infants < 31 weeks. Although a clinically significant PDA is understood to be associated with poorer outcomes, no studies have examined whether these associations exist in the pre-symptomatic phase.

Higher PDA scores in preterm infants < 31 weeks gestation associated with IVH, NEC, need for surgical ligation, and presence of any adverse outcome. After adjustment for GA, PDA score only remained associated with increased odds of survival with any adverse outcome. Most clinical trials to date have defined a significant PDA based on diameter only [26]. Our proposed scoring system uses PDA diameter together with parameters reflecting pulmonary over-circulation and systemic hypoperfusion. Our intent was beyond simple evaluation of PDA size, to predict adverse outcomes. Other groups using a similar composite PDA score calculated at the time of treatment for symptomatic PDA, report an association between high score and increased incidence of subsequent chronic lung disease [19].

We found an association between PDA diameter and IVH, BPD, or any adverse outcome. These associations were lost when adjusted for GA. On the contrary, comparable data reported by Sellmer et al. indicate that, in infants < 28 weeks, those with larger PDA diameter on day 3 had higher odds of IVH, BPD, and of the composite outcome of death or severe morbidity, but only after adjusting for GA [26]. Kluckow et al. also recently concluded that targeted treatment of PDA > 1.7 mm during first 12 hours of life resulted in a reduction of early pulmonary hemorrhage and later need for medical treatment, but had no effect on incidence of death or abnormal cranial ultrasound [27]. Although not statistically significant, we found risks of pulmonary haemorrhage, IVH grade III to IV and NEC trended higher in infants with medium and large PDA.

PDA diameter is subject to measurement error and inter-observer variability and accurate estimation is challenging [26]. In addition, overestimation of transductal diameter may occur when measurements are exclusively based on color Doppler, due to high Doppler gain [13]. Beyond the immediate transitional phase, once the PDA shunt is established and shunt volume is likely to be greater, we propose that a combination of TNE parameters are likely to avoid individual measurement error and the confounding influence of a progressive atrial septal defect shunt

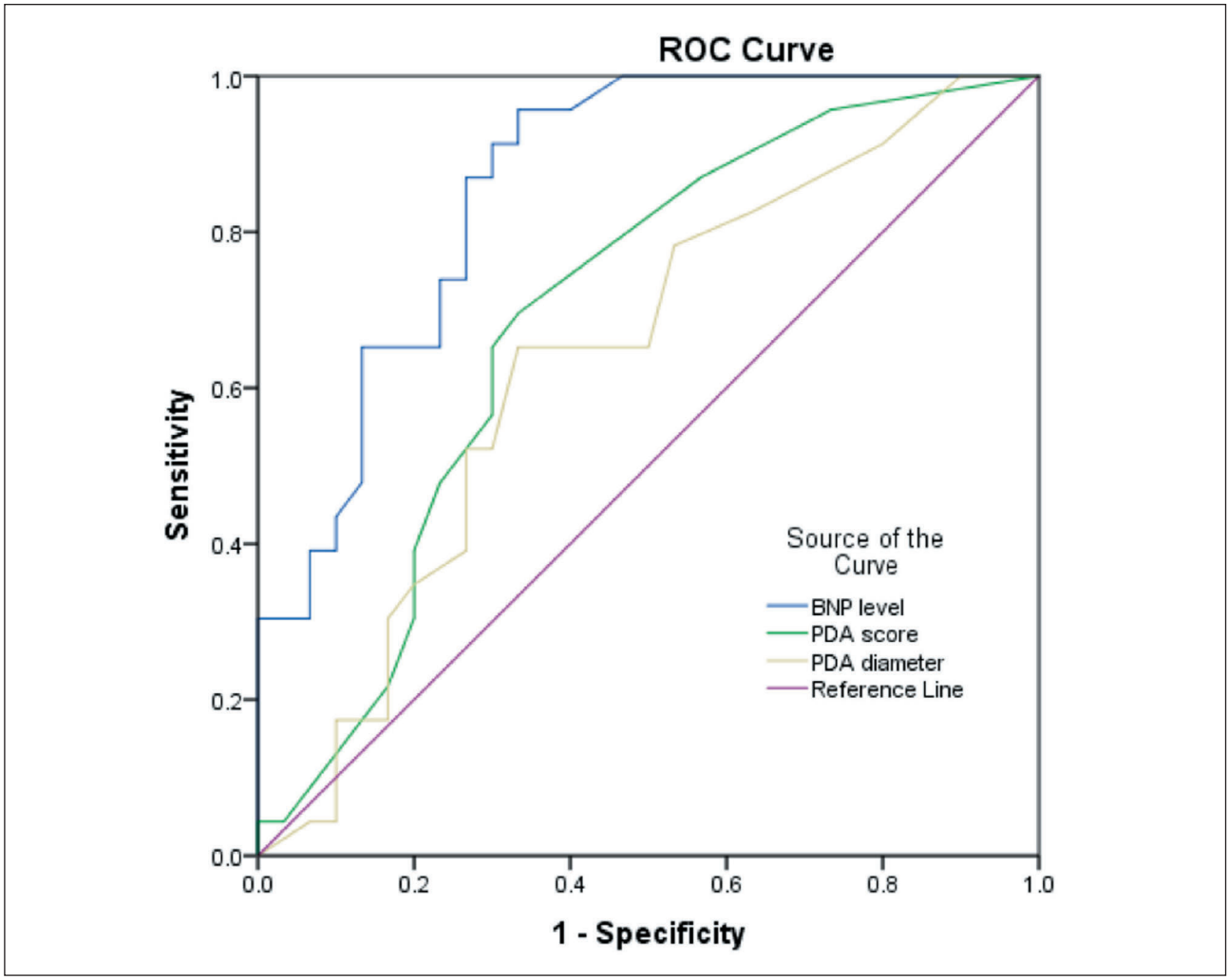


**Figure 1.** ROC curves for BNP, PDA score, and PDA diameter in predicting survival with any adverse outcome.

secondary to atrial volume loading [19]. This hypothesis requires prospective evaluation.

As many of the echocardiography indicators of PDA shunt volume may be insensitive in the transitional period, we studied serum BNP, which plays an important role in regulation of extracellular fluid volume and blood pressure [9], and acts as a component of the adaptive mechanism that helps "unload" the failing myocardium [28]. We found an association between elevated BNP measured at 48-72 hours, and pulmonary hemorrhage, IVH overall, and the need for surgical ligation. When adjusted for GA, the association of high BNP with IVH, BPD, and any adverse outcome remained; AUC of BNP was significantly greater compared to PDA diameter after adjustment to GA suggesting that BNP is an independent marker for survival with any adverse outcome. Flynn et al., using paired echocardiography and BNP measurements at the time of clinical presentation, found a significant correlation between serum BNP concentrations, ductal size and degree of left-to-right shunting; BNP concentrations > 300 pg/ml correlated with clinically significant PDA, whereas BNP concentrations < 105 pg/ml predicted its absence [10]. Measurement of serum BNP cannot differentiate volume overload due to PDA from other causes of either volume or pressure overload; this diminishes its utility when echocardiography is readily accessible. However, in centers without available echocardiography expertise, BNP may be useful as reflector surrogate estimate of volume overload in the setting of a presumed clinically significant PDA [29-31].

BNP secretion may also reflect other physiological changes during postnatal transition. As pulmonary vascular resistance remains high in the first 48 hours of life, the magnitude of shunt volume is generally lower. Consequently echocardiographic and biomarkers of pulmonary over-circulation or systemic hypo-perfusion may

not change substantially, despite ductal patency. Serum BNP concentrations are initially high after birth and normally fall in the first 48 hours [32]. Thus BNP concentrations appear to correlate with echocardiographic criteria only when measured after day 2 of life [10]. We speculate that, due to the confounding effect of transitional cardiovascular physiology, the predictive value of TNE markers of hemodynamic significance, and of BNP, is less when performed before 48 hours age. Failure of the normal postnatal decline in BNP may reflect an augmentation in PDA shunt volume, or ongoing right atrial loading in the setting of pulmonary hypertension. A recent systematic review of PDA diagnosis (inclusive of this study) concluded that BNP should be validated locally for patient location and outcomes, due to wide variability of cut-off limits and predictive values between centres [33].

Different markers (echocardiographic, clinical, BNP) may predict different outcomes. PDA diameter was the best marker for subsequent failure of medical management and subsequent ligation. Elevated BNP was an independent predictor of IVH; regardless of GA or PDA diameter; this association may reflect the physiological role of BNP in a volume-overloaded heart, as an increased circulatory volume is associated with onset of IVH [34]. We speculate that both PDA score and BNP concentrations are superior predictors of adverse outcomes after a period of sustained exposure to a higher volume shunt; however this requires prospective appraisal.

The main limitations of our study are small sample size and lack of standardization of clinical team decision-making about when to intervene by medical treatment or surgical ligation. A larger cohort would allow stratification of the study group according to GA cut-offs. A randomised trial is needed to evaluate the effect of early pre-symptomatic treatment of PDA on neonatal outcomes, as neither prophylaxis before 12 hours of life nor treatment at the time of clinical presentation protect from common adverse outcomes [27].

We suggest a shift from relying only on PDA diameter at 48-72 hours of life (still considered the most reliable single predictor of PDA requiring treatment during the transitional period), to a more comprehensive evaluation of combined biochemical and TNE surrogate markers to delineate the magnitude of shunt volume.

We conclude that a comprehensive evaluation of the status of the ductus arteriosus at 48-72 hours age may predict the subsequent occurrence of adverse outcomes. No single marker predicts all outcomes, and different markers may predict disparate outcomes. BNP and PDA scoring may be useful in addition to PDA size.

## Abbreviations

Ao: aortic
AUC: area under the curve
BNP: brain-type natriuretic peptide
BPD: bronchopulmonary dysplasia
DAO: diastolic aortic flow
E:A ratio: the ratio of mitral inflow E wave peak velocity to A wave peak velocity
GA: gestational age
IVH: intraventricular hemorrhage
LA:Ao: left atrial to aortic ratio
LVEDD: left ventricular end-diastolic diameter
LVO: left ventricular output
NEC: necrotizing enterocolitis
NICU: Neonatal Intensive Care Units
PDA: patent ductus arteriosus
PFO: patent foramen ovale
ROC: receiver operator characteristic
ROP: retinopathy of prematurity
TNE: targeted neonatal echocardiography

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## Declaration of interest

The Authors declare no conflict of interest.

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