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ORIGINAL ARTICLE

NTproBNP is a useful early biomarker of bronchopulmonary dysplasia in very low birth weight infants

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Abstract

Bronchopulmonary dysplasia (BPD) is a severe complication of prematurity that impacts survival and neurodevelopment. Currently, no early marker exists which could help clinicians identify which preterm infants will develop BPD. Given the evidence that NTproBNP is elevated in children with BPD, we hypothesized that it could be used as an early marker of BPD development. We conducted a prospective cohort study including very low birth weight infants (VLBWI) admitted to our NICU between January 2015 and January 2017 in which we determined serial NTproBNP levels on days 1 and 3 and then weekly, until 49 days of life. A total of 101 patients were recruited (mean birth weight 1152 g (SD 247.5), mean gestational age 28.9 weeks (SD 1.9)). NTproBNP levels differed among infants who did and did not develop BPD from 14 to 35 days of life with the greatest difference on day 14 of life (non-BPD group ($n = 86$): 1155 (IQR 852–1908) pg/mL, BPD ($n = 15$): 9707 (IQR 3212–29,560) pg/mL; $p = 0.0003$). The presence of HsPDA did not account for higher levels of NTproBNP at day 14 ($p = 0.165$). We calculated an optimal cutoff point of 2264 pg/mL at 14 days of life (sensitivity 100%, specificity 86% and AUC 0.93).

Conclusions: NTproBNP at 14 days of life could be used as an early marker of later BPD development in VLBWI.

What is Known:
- *Children with BPD have elevated NTproBNP levels, which are related to the severity of BPD and the development of pulmonary hypertension.*

What is New:
- *NTproBNP at 14 days of life is higher in those who later develop BPD, regardless of the presence of hemodynamically significant patent ductus arteriosus.*
- *A calculated cutoff point of 2264 pg/mL of NTproBNP at 14 days has a sensitivity of 100% and specificity of 86% in the prediction of BPD.*

Keywords Bronchopulmonary dysplasia · Pro-brain natriuretic peptide · Preterm infant · Biomarkers

Abbreviations

AUC	Area under the curve
BNP	Brain natriuretic peptide
BPD	Bronchopulmonary dysplasia
CRIB	Clinical risk index for babies
EDTA	Ethylenediaminetetraacetic acid
GA	Gestational age
HsPDA	Hemodynamically significant patent ductus arteriosus
IQR	Interquartile range
NEC	Necrotizing enterocolitis
NPV	Negative predictive value
NTproBNP	N-terminal pro-brain natriuretic peptide
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
PMA	Postmenstrual age
PPV	Positive predictive value
ROC	Receiver operator curve
ROP	Retinopathy of prematurity
SD	Standard deviation
Se	Sensitivity

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Sp	Specificity
VLBWI	Very low birth weight infants

Introduction

Bronchopulmonary dysplasia (BPD) is a pulmonary complication which impacts the short- and long-term outcome of very low birth weight infants (VLBWI). Despite the increasing survival rates achieved in the last decades, up to 25% of very low birth weight infants (VLBWI) develop BPD [1]. VLBWI with BPD have an increased length of stay at hospital and greater morbidity and mortality [2, 3].

B-type natriuretic peptide (BNP) is secreted in the ventricular myocardium stimulated by volume or pressure overload. The inactive N-terminal end of its prohormone, N-terminal pro-B-type natriuretic peptide (NTproBNP), appears to be more stable and have a longer half-life than BNP [4]. In recent years, there has been increased research interest in the association of NTproBNP with neonatal morbidities such as persistent pulmonary hypertension [5], respiratory distress syndrome [6, 7], diaphragmatic hernia [8], and hemodynamically significant ductus arteriosus (HsPDA) [9, 10].

NTproBNP levels are increased both at 28 days of life and at 36 weeks postmenstrual age (PMA) related to the degree of BPD [11, 12], and it has been suggested as a marker for BPD associated PH [13, 14]. While a few studies have linked NTproBNP levels in the first 72 h of life with the development of BPD [15, 16], the role that NTproBNP levels play in the first days of life as a predictor of BPD is unclear, given the physiological changes in the transition from fetal to neonatal circulation [17, 18]. This study aims to evaluate NTproBNP levels as an early marker of BPD and to identify the earliest time point when NTproBNP could be used as a predictive marker of BPD in VLBWI.

Materials and methods

This prospective observational study included VLBWI admitted between January 2015 and January 2017 to the Neonatal Intensive Care Unit of the University Hospital Puerta del Mar (Cadiz, Spain). The institutional research ethics committee approved the study, and written informed consent was obtained from the parents or guardians. Patients with birth weights less than or equal to 1500 g (g) and gestational age of less than or equal to 32 weeks were included. Exclusion criteria were congenital heart disease (except patent foramen ovale or atrial septal defect, ventricular septal defect < 2 mm, or patent ductus arteriosus (PDA)), genetic syndrome or major congenital malformations, death in the first week, and lack of informed consent of parents/guardians.

The following variables were collected: gestational age, birth weight, sex, premature rupture of membranes, chorioamnionitis, five-minute Apgar score, clinical risk index for babies (CRIB) [19], prenatal steroids, sepsis, intraventricular hemorrhage and/or parenchymal infarction, white matter injury, HsPDA, retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC). The need for and duration of mechanical ventilation were also recorded. BPD was defined as the need for oxygen or respiratory support at 36 weeks' postmenstrual age (PMA); BPD was classified as moderate if the infant required $\leq$ 30% supplemental oxygen and severe if the infant required >30% supplemental oxygen and/or positive pressure support [20]. We did not use any physiological challenge such as the Walsh test [21]. On each echocardiogram HsPDA was determined by a ductal diameter greater than 1.5 mm on two-dimensional imaging, parasternal sagittal view.

Serial venous blood NTproBNP levels were performed on days 1, 3, 7, 14, 28, 35, 42, and 49 after birth. Each 0.5 mL blood sample was collected in ethylenediaminetetraacetic acid (EDTA), transported at room temperature, and processed immediately for analysis. NTproBNP levels were calculated through the electroluminescence immunoassay kit (ECLIA) with the Elecsys proBNP II test (Roche Diagnostics). The measuring range is 5–35,000 pg/mL (defined by the limit of detection and the maximum of the master curve); the limit of quantification is 50 pg/mL.

Serial echocardiograms were performed on the same days as NTproBNP level determinations. The exams were acquired and analyzed by two neonatologists (PMA, PZR) with specific training in neonatal echocardiography and more than 5 years of experience, using a Philips iE33, with an 8–3-Hz transducer and following the recommendations of the American Society of Echocardiography [22].

Statistical analysis

The quantitative variables are described as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Qualitative variables are expressed in frequency and percentage. The bivariate analysis was performed with parametric or nonparametric techniques after checking the normality of the distribution of the variables to be compared (Shapiro-Wilk test). Logistic regression, adjusting for the presence of HsPDA, was used to analyze the predictive value of NTproBNP in the development of BPD. The following diagnostic accuracy indices were calculated: sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and the area under the curve (AUC). The optimal cutoff point of NTproBNP is calculated using the Liu method which maximizes the product of the sensitivity and specificity [23]. Statistical analysis was performed using Stata 15.0 software (StataCorp, College Station, TX). A p value of < 0.05 was considered statistically significant.

Results

During the recruitment period, 120 VLBWI were admitted to the Neonatal Intensive Care Unit, and of those, 101 subjects were included in the study (Fig. 1). Nine VLBWI were not included because of death in the first week of life. Among participants, mean birth weight was 1152 ± 247.45 g and mean gestational age was 28.85 ± 1.85 weeks. Fifteen patients met the diagnostic criteria for BPD, five moderate and ten severe. Four of the participants died during admission, one of them with severe BPD caused by a fungal endocarditis. The patients who developed BPD had lower gestational age and birth weights and were more likely to have had severe ROP and HsPDA than non-BPD patients. They also had a higher CRIB score and were ventilated for longer duration (Table 1).

A total of 223 blood samples were analyzed, 174 (78%) with a paired echocardiogram. NTproBNP values differed among BPD and non-BPD groups from day 14 to day 35 of life (Table 2) with this difference disappearing at day 42 (Fig. 2). The greatest difference was detected at day 14, with NTproBNP levels in the non-BPD group of 1155 (852–1908) pg/mL and in the BPD group of 9707 (3212–29,560) pg/mL ($p = 0.0003$). This NTproBNP level, at day 14 of life, is associated with later development of BPD ($p = 0.0001$). At 14 days of life, five VLBWI had a persistent HsPDA; only one belonged to the non-BPD group. The presence of HsPDA at any time point did not modify the relationship between the NTproBNP level at day 14 and the development of BPD ($p = 0.165$) nor the presence of HsPDA detected on the paired echo at 14 days of life ($p = 0.125$).

When testing the diagnostic accuracy of NTproBNP levels at day 14 for the development of BPD, we obtained a Se of 50%, Sp of 97%, PPV 75%, NPV of 92%, and an estimated AUC of 0.964 (95% CI 0.91–1). The optimal cutoff value of NTproBNP levels at 14 days of life was 2264 pg/mL, with a Se of 100%, Sp of 86%, and AUC 0.93 (Fig. 3).

Discussion

In this prospective study, we found that VLBWI who later develop BPD have elevated NTproBNP levels from day 14

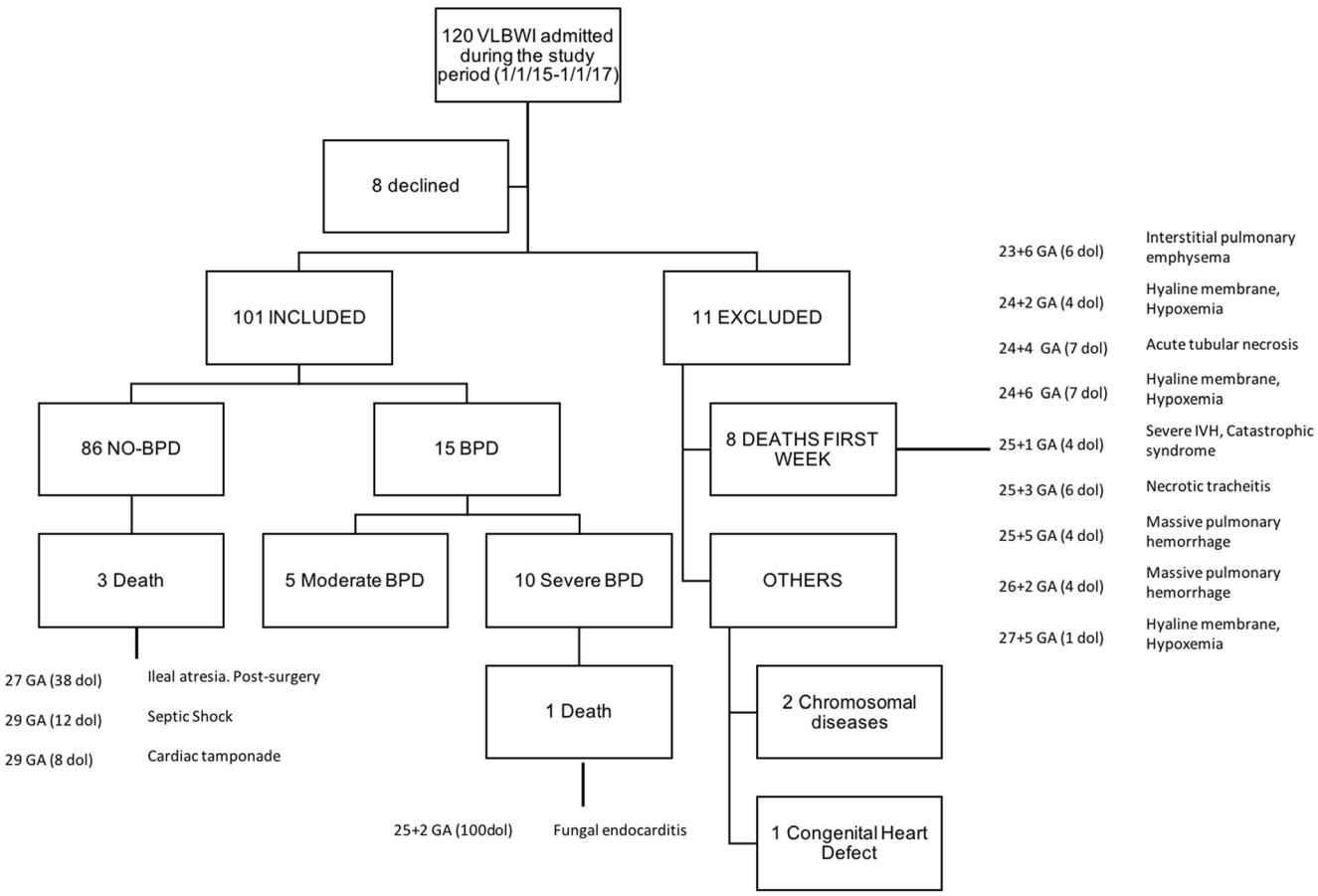

Fig. 1 Flow diagram of the VLBWI population in the recruitment period

Table 1 Perinatal variables in no-BPD and BPD groups

	No-BPD ($n = 86$)	BPD ($n = 15$)	p
Gestational age (weeks)	29.13 ± 1.79	27.27 ± 1.3	0.0002*
Weight (g)	1200 (600–1500)	850 (580–1400)	0.0001*
Sex, male	45 (52.33%)	11 (72.3%)	0.13
Apgar 5	8 (4–10)	7 (4–8)	0.002*
CRIB	1 (0–7)	5 (1–12)	0.0001*
Chorioamnionitis	12 (13.95%)	4 (26.67%)	0.2
Prenatal steroids (≥ 1 dose)	72 (83.72%)	14 (93.33%)	0.33
Cesarean section	72 (83.72%)	12 (80%)	0.72
Early onset sepsis	1 (1.16%)	0	0.67
Late onset sepsis	12 (13.95%)	5 (33.33%)	0.064
Mechanical ventilation	53 (61.63%)	14 (93.33%)	0.016*
Days of mechanical ventilation	3 (0–39)	40 (0–173)	0.0001*
HsPDA	14 (16.28%)	7 (46.67%)	0.014*
Severe IVH	2 (2.33%)	1 (6.67%)	0.39
White matter injury	2 (2.33%)	1 (6.67%)	0.39
Severe ROP	7 (8.14)	5 (33.33)	0.016*
NEC	3 (3.49%)	0	1.00

BPD bronchopulmonary dysplasia, HsDA hemodynamically significant patent ductus arteriosus, severe IVH grade III intraventricular hemorrhage or parenchymal hemorrhagic infarction, severe ROP retinopathy of prematurity ≥ grade 2, NEC necrotizing enterocolitis

*Statistical significance (p) < 0.05

of life. At this age, the optimal empirical cutoff point of NTproBNP for predicting BPD development is 2264 pg/mL.

Previous studies have found elevated NTproBNP in VLBWI with BPD, especially among the most severe cases. Joseph et al. found that NTproBNP levels were higher in BPD patients at 28 days of life in a sample of 34 preterm infants under 34 weeks' GA [11]. Kalra et al. found higher BNP levels at 36 weeks' PMA in VLBWI with BPD, related to the severity of BPD [12].

Elevated levels of NTproBNP have been related to the presence of PDA, especially in those with HsPDA [9, 10]. As PDA is more frequent in those VLBWI who develop BPD, we tested whether the presence of HsPDA acts as a confounder in the relationship between NTproBNP and BPD. Consistent with the findings reported in Montaner et al.'s retrospective study, where a greater risk of BPD or death was found in those with elevated NTproBNP levels at 48–72 h of life, independent of HsPDA [15], we found that the increase in NTproBNP at day 14 is independent of HsPDA.

Table 2 NTproBNP median values (and IQR) during the first 42 days of life according to BPD category

Days	No-BPD median (IQR)	BPD median (IQR)	p
1	5246 (2095–13,629)	3808 (2728–6793)	0.69
3	4189 (1450–11,251)	9597 (5375–22,155)	0.224
7	1565 (995–2333)	11,239 (11239–11,239)	0.14
14	1155 (852–1908)	9707 (3212–29,560)	0.0003*
21	597 (364–1192)	6358 (1877–10,838)	0.025*
28	618 (446–1522)	3525 (1085–5964)	0.043*
35	864 (441–1270)	3195 (1797–8905)	0.047*
42	1049 (862–1816)	816 (428–1030)	0.267

NTproBNP in pg/mL

BPD bronchopulmonary dysplasia, IQR interquartile range

While some studies suggest that NTproBNP levels at 12 h of life are a good marker of myocardial function in VLBWI, and are not influenced by GA, birth weight, or sex [24], other studies have found that NTproBNP levels in the first 72 h of life among VLBWI are not correlated with right and left cardiac output or shortening fraction [25]. In our study, we did not find significant differences in NTproBNP levels obtained on days 1, 3, and 7 among the BPD and non-BPD groups. The disparity of results regarding NTproBNP levels in the first days of life could be partly explained by the physiological changes in the transition from fetal to neonatal circulation [17, 18].

Few previous studies have investigated the utility of NTproBNP as a predictor of the development of BPD beyond the first 72 h of life. Montgomery et al. observed that higher NTproBNP levels at 36 weeks' PMA predict the existence of PH in patients with BPD [13], and recently, Dasgupta et al. studied the relationship of NTproBNP with BPD and PH at 28 weeks' PMA in children under 30 weeks' GA [26]. They found a good correlation of NTproBNP with the development of BPD with and without PH. Nevertheless, analyzing

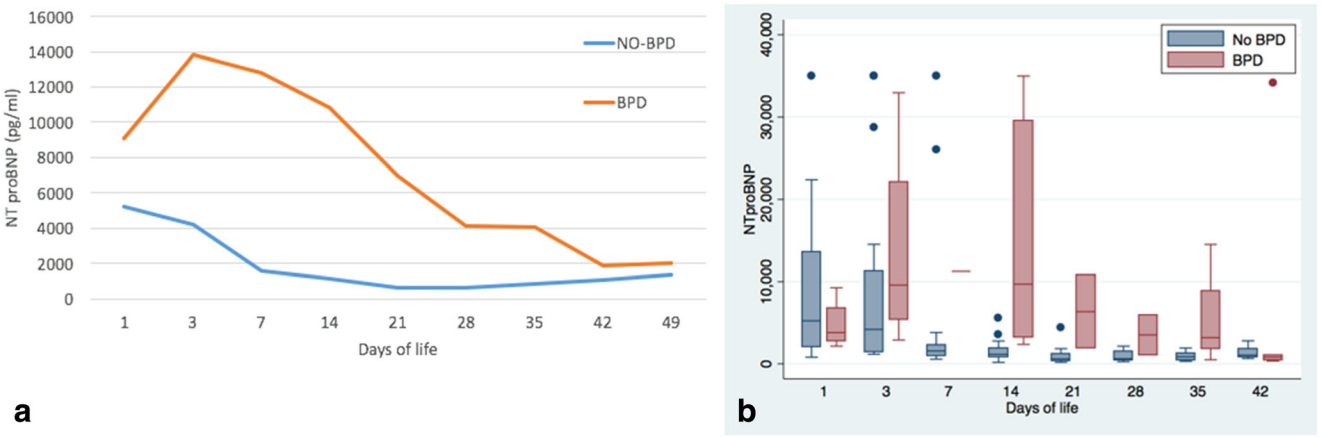

Fig. 2 Temporal evolution of NTproBNP levels in BPD and non-BPD groups. **a** Median values of NTproBNP levels. **b** Box-and-whisker plot of NTproBNP levels

NTproBNP according to PMA instead of chronological age could make the reproducibility of these results more difficult by including VLBWI at different days of life. After increasing in the first 72 h of life, NTproBNP levels decline progressively [17, 27], at a much slower rate among VLBWI who develop BPD. This decline in accordance with chronological age suggests that measurements of NTproBNP levels by days of life may be a better approach than PMA.

The aim of our study was to identify the earliest time point when NTproBNP could be used as a predictive marker of BPD regardless of the later association of PH, and we therefore did not examine the development of PH. A recent study by Harris et al. also studied the relationship between serial NTproBNP levels and the development of BPD in a small study ($n = 51$) infants < 30-week gestational age. They found that NTproBNP on day 10 of life was valuable for the prediction of severe BPD (AUC 0.83). The cutoff point of 189 pmol/L (1598.3 pg/mL) had a Se of 84% and Sp of 75% [9]. Our study suggests that NTproBNP levels a few days later, at 14 days of life, have a higher diagnostic accuracy with an AUC of 0.964. The suggested cutoff value of 2264 pg/mL at that age has a Se of 100% and Sp of 86%. Notably, they also report that chronological but not corrected gestational age determined NTproBNP levels.

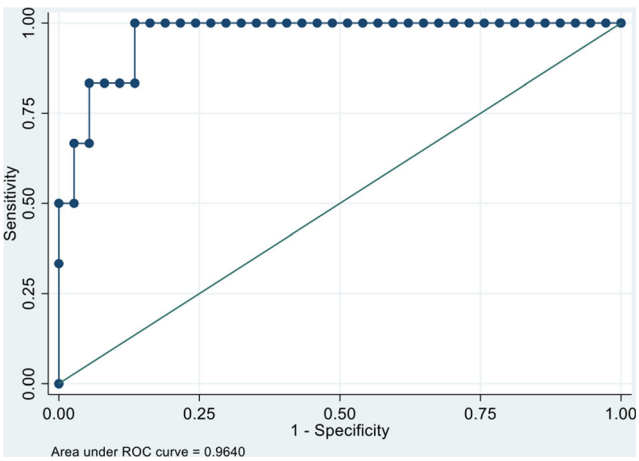

Fig. 3 ROC curve of NTproBNP levels at day 14 of life for prediction of later development of BPD

Although our study has strengths as serial NTproBNP testing paired with heart ultrasound at multiple time intervals with good recruitment, a good size cohort, and good retention, it has several limitations that need to be addressed. While this study has the largest sample size published regarding in this topic, studies with a greater sample size would strengthen our results. In the BPD group, the existence of PH by clinical and/or echocardiographic criteria was not analyzed, nor were the treatments received (diuretics, steroids) that may have modified NTproBNP levels. Other weaknesses include lack of physiological definition of BPD and small numbers with BPD which may relate to low numbers of VLBW under 26 weeks.

Our findings suggest that NTproBNP values could be used as a marker of BPD. As an expanding body of research there might be in the next years answers for some of the findings we were unable to explain, in part due to the limitations of our study. We could hypothesize, for example, that patients with BPD tend to normalize NTproBNP values after several weeks of life and the increased NTproBNP values in the first week of life could mean a delay in the physiological trajectory of NTproBNP values.

Currently, there is no biomarker that can predict BPD risk. We suggest that NTproBNP levels at 14 days of life could be used as a predictive marker of BPD with an optimal cutoff point of 2264 pg/mL. According to our results, NTproBNP can help identify a population that might benefit from a tailored therapeutic approach. Future research with the selection of an intervention group based on this marker could be useful to avoid the risk of exposure to different pharmacological agents among low-risk VLBWI.

Authors' contributions PMA: Concept/design, Data analysis/interpretation, Drafting article, Approval of article, Data collection

PZR: Concept/design, Data analysis/interpretation, Drafting article, Approval of article, Data collection

SLL: Concept/design, Critical revision of article, Approval of article

IBF: Concept/design, Data analysis/interpretation, Critical revision of article, Approval of article, Statistics

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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