Lung Ultrasound Score has Better Diagnostic Ability Than NT-PROBNP to Predict Moderate–Severe Bronchopulmonary Dysplasia

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Research Article

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Abstract

Purpose: N-terminal end of B-type natriuretic peptide (NT-proBNP) and lung ultrasound (LUS) score have been proven to be adequate early biomarkers of bronchopulmonary dysplasia (BPD) in preterm infants. Our aim was to study if the predictive capacity of each one is increased by analyzing them together.

Methods: We included infants born before 32 weeks, with NT-proBNP and LUS score on the first day of life (DOL), 3rd, 7th and 14th DOL, and compare the diagnostic ability for moderate-severe BPD (msBPD) of each biomarker and in combination. We also compared them with a multivariate model of msBPD using only clinical variables.

Results: The sample size was 133 patients, and twenty seven (20%) developed msBPD. LUS score on 7th DOL had better performance, compared to NT-proBNP at the same moment: area under the receiver operating characteristic curve (AUC) 0.83 (0.75-0.89) versus 0.66 (0.56-0.75), p=0.003, without differences in the rest of times studied. This values did not increase using the combination of both. A multivariate regression model that included birth weight and invasive mechanical ventilation (IMV) at 7th DOL predicted msBPD with the same AUC-ROC than NT-proBNP, LUS score or both. Neither the addition of any of these biomarkers, nor together, increase the diagnostic accuracy of the clinical model.

Conclusion: LUS score is better predictor of msBPD on 7th DOL than NT-proBNP in preterm infants born before 32 weeks, although they have similar diagnostic accuracy on 14th DOL. Neither of them, nor together, have better AUC for msBPD than a clinical model with birthweight and the need of IMV at 7th DOL.

What Is Known

NT-proBNP and LUS score are early predictors of moderate-severe bronchopulmonary dysplasia (msBPD).

WHAT IS NEW:

- The combination of both NT-proBNP and LUS score does not increase the predictive ability of each separately.

- LUS score shows better AUC-ROC than NT-proBNP for msBPD at 7th DOL.

- A multivariate model with clinical variables predicted msBPD with similar diagnostic accuracy than LUS score, NT-proBNP or both, at 7th DOL.

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of preterm infants secondary to premature birth that arrests foetal lung development in both the parenchymal and vascular components of the lung. Influenced by the pro-inflammatory environment, the lung suffers alveolar simplification, interstitial

fibroproliferation and disruption in vascular growth that finally leads to an established BPD[1]. As the lung is included in the cardiorespiratory system, high vascular resistance also affects the developing myocardium; this lung–heart interaction would explain the usefulness of exploring heart function to test lung development.

Pressure and volume overload in the myocardium stimulate the ventricular secretion of B-type natriuretic peptide (BNP). NT-proBNP is the N-terminal end of this prohormone that is easy to detect in a blood sample. NT-proBNP has a good correlation with echocardiographic diastolic parameters and thus could be useful as an early marker of diastolic ventricular dysfunction in very-low-birth-weight infants (VLBWIs) [2]. In the lung of a patient with BPD, the vascular resistances increase, so the right ventricle is subjected to pressure overload: this explains why NT-proBNP is elevated in VLBWIs with BPD[3] and its relation to the degree of severity. Recent studies have explored the role of NT-proBNP as an early biomarker of BPD: increased plasma NT-proBNP levels seem to be related to further development of BPD[4–6]. Furthermore, plasma NT-proBNP levels during the first two weeks of life can be useful to detecting VLBWIs with a higher risk of BPD[7–9]. This relationship is independent of the coexistence of patent ductus arteriosus (PDA), but it is detected mainly in patients with haemodynamically significant PDA (hsPDA)[8, 10].

Nevertheless, lung ultrasound (LUS) is a non-invasive technique applicable to newborns for the diagnosis of acute respiratory complications, such as pneumothorax or pleural effusion[11], encompassed in the concept of point-of-care ultrasound. Furthermore, the LUS score has been explored in the neonatal population to guide the differential diagnosis of respiratory distress syndrome[12] and to guide surfactant treatment in the respiratory distress syndrome of preterm infants[13]. In recent years, many studies have explored the usefulness of LUS to predict BPD[14–19]. Serial LUS has shown that the LUS score improves from the first week of life in VLBWIs without BPD and remains high in those who later develop BPD[20].

Together, lung and heart studies can provide global information on lung development and improve the capacity to predict which VLBWIs are developing BPD. However, this is a novel approach, as previous research has been performed only from the point of view of the heart or lung. Our hypothesis is that the combined use of the LUS score and NT-proBNP could improve the ability to predict moderate–severe BDP (msBPD) in the first weeks of life.

Material And Methods

This is a case–control observational study performed in two neonatal intensive care units (NICUs). We included preterm infants born before 32 weeks of gestation from January 2017 to January 2021 with NT-proBNP and LUS scores on the first day of life (DOL) and on the 3rd, 7th and 14th DOL. Infants with major malformations, chromosomopathies, palliative care since birth, transfer or death before 36 weeks postmenstrual age (PMA) were excluded from the analysis.

The main objective was to test the diagnostic accuracy of both the LUS score and NT-proBNP levels for msBPD in preterm infants born before 32 weeks of gestation at the 7th and 14th DOL.

We defined msBPD as any respiratory support at 36 weeks of PMA (we performed a room-air challenge in those with oxygen < 30%, and only those who failed the reduction were diagnosed with moderate BPD).

NT-proBNP measurements

The remaining 0.5 mL of each sample obtained for a routine venous blood test was collected in ethylenediaminetetraacetic acid (EDTA), transported at room temperature, and processed immediately for analysis. NT-proBNP levels were calculated using the electroluminescence immunoassay kit (ECLIA) with the Elecsys proBNP II test (Roche Diagnostics). The measuring range of the test was 5–35000 pg/ml, but with dilutions, we could determine values up to 70000 pg/ml.

Lung ultrasound

The study's protocol was described in a previous publication[20]. We calculated the LUS score using the previously reported definition[13]. We used different ultrasound machines, but all of them had high-frequency linear probes (10–15 mHz). The single focus was set at the level of the pleural line (0.5 cm), and no harmonics were used. We used a prewarmed gel, and another person helped the operator to contain the patient during the exam. All LUS exams were performed with the infant in the supine position for at least one hour before, as this is the time needed for the lung's water content to distribute in the dependent areas [21].

In each centre, all LUS procedures were performed by one or two neonatologists with extensive experience in LUS. Every LUS exam was obtained after at least 1 hour in the supine position. Each centre calculated the LUS scores of each patient independently, and interobserver agreement was calculated using twenty anonymous LUS images.

Statistics

Demographic data and outcomes are summarized using descriptive statistics. Diagnostic accuracy based on receiver operating characteristic curve (AUC) analysis was calculated for NT-proBNP, LUS score and both at different time points. As multiple comparisons were performed, we used Bonferroni's correction.

Multivariate logistic regression was used to test whether the variables obtained on the 3rd, 7th or 14th DOL provided added diagnostic value compared to msBPD prediction based on clinical variables. Due to the distribution of NT-proBNP values in our sample and according to previous studies[8, 10], we applied a log transformation. Only clinical covariates that are readily available at the time of prediction were considered: birth weight, gestational age (GA), chorioamnionitis, the need for invasive mechanical ventilation (IMV) at the 3rd or 7th DOL, clinical risk index for babies-II (CRIB-II) [25] and score for neonatal acute physiology (SNAPPE-II) [26] at birth. Chorioamnionitis was defined clinically[22] or histologically [23]. Patent ductus arteriosus (PDA) was defined as clinically significant when it had hemodynamic and respiratory repercussions and was treated by the attending neonatologists. We diagnosed respiratory distress syndrome (RDS) when the patient developed signs of respiratory distress since birth, LUS

showed a thick pleural line and diffuse interstitial infiltration [12], and the patient received surfactant treatment.

The discriminative capacity of the selected models was assessed by the AUC and adjusted R^2. The goodness of fit was estimated by means of the Hosmer–Lemeshow test. The AUCs of the different models at each time point were compared using the DeLong test.

According to our hypothesis that combining both variables together will improve diagnostic accuracy compared to each alone, the study sample size was calculated based on comparative AUC analysis between the NT-proBNP and LUS score on the 7th DOL (which we considered to be the optimal time point for msBPD prediction). Considering an AUC of 0.8 (from studies using the LUS score) and an expected AUC of 0.91 for the combination of NT-proBNP and LUS score, as well as an estimated overall prevalence of msBPD in our cohort of 25%, we would need a sample of 126 patients (α-error and β-error of 5% and 20%, respectively).

Weighted kappa scores and intraclass correlation coefficients (ICC) were calculated to assess interobserver agreement in LUS interpretation between the three investigators who performed LUS.

All tests used were considered statistically significant if p values were less than 0.05. All analyses were performed using STATA v.14.2 (StataCorp. 2015) statistical package.

Ethics

The study protocol was approved by each regional Ethics Committee with the code number LUS-NEO-17-02, and parents provided written informed consent. The study was conducted following the STROBE statement guidelines[27].

Results

We included 133 patients born before 32 weeks: twenty-seven (20%) developed msBPD. The flow chart of patient inclusion is detailed in Fig. 1. Descriptive statistics of the patients included are shown in table 1. Interobserver agreement of LUS scores between the investigators was high: kappa score of 0.79–0.83; consistency ICCs of 0.79 (0.54–0.91) and 0.80 (0.55–0.92); and absolute ICCs of 0.88 (0.70–0.96) and 0.89 (0.71–0.96).

The median and interquartile ranks of the LUS scores and NT-proBNP on the 1st, 3rd, 7th and 14th DOLs are described in Fig. 2. We found statistically significant differences in the LUS scores on the 3rd, 7th and 14th DOLs, as well as in NT-proBNP scores on the 7th and 14th DOLs, between groups.

Univariate prediction of msBPD

The diagnostic accuracy of both the LUS scores and NT-proBNP for msBPD was estimated with the AUC, as presented in table 2. The LUS score at the 7th DOL had better performance than NT-proBNP at the

same moment: 0.83 (0.75–0.89) versus 0.66 (0.56–0.75), p = 0.003. However, we were not able to find significant differences between the AUCs at the other scheduled points (table 2).

Multivariate prediction of msBPD

The best logistic regression model for msBPD prediction using only clinical variables (model 1) included birth weight and IMV on the 7th DOL; in model 2, we added the LUS score on the 7th DOL to model 1; model 3 included model 1 and ln NT-proBNP values on the 7th DOL; and model 4 comprised model 1 plus the LUS scores and ln NT-proBNP on the 7th DOL. The diagnostic accuracy of the four models is presented in table 3, and all of them reached statistical significance and optimal performance to predict msBPD. When AUCs were compared, analysis by means of the DeLong test did not show significant differences among models (table 3).

Discussion

We have shown that LUS has higher diagnostic accuracy for msBPD on the 7th DOL than NT-proBNP in preterm infants. Both variables have increasing diagnostic accuracy from birth until the 14th DOL, when both have similar and adequate AUCs. However, the AUC for the LUS score is at its maximum on the 7th DOL, with similar results on the 14th DOL, and it shows good performance at this early time point. On the other hand, NT-proBNP shows maximum diagnostic accuracy on the 14th DOL, as previously published[28], while the AUC on the 7th DOL is still low, which makes it an unsuitable predictor at this very early stage. However, other studies have shown better results at an earlier time point, namely, birth, for predicting msBPD or death among preterm infants[29].

Contrary to our hypothesis, the combination of the LUS score and NT-proBNP does not increase the diagnostic accuracy of the two individual variables. The LUS score has been negatively correlated with oxygenation indexes in preterm infants with SDR[13] and with evolving BPD[18], and it has a positive correlation with inflammatory markers in preterm infants with SDR[30]. Different multicentre studies have demonstrated that the LUS score is also a good predictor of msBPD in children born before 32 weeks after the first 3–7 DOLs[17, 18, 31]. In addition, NT-proBNP is related to msBPD prediction in the first DOLs[8, 29, 32], even after adjusting for haemodynamically significant PDA[7, 8], and it remains related to pulmonary hypertension in preterm infants with BPD[33, 34].

Endothelial injury, high vascular resistance and right ventricular failure are described in the pathophysiology of BPD[35], and NT-proBNP is secreted by cardiac myocytes in response to volume–pressure overload[36]. A possible explanation for the lack of improvement in the early diagnosis of BPD using both biomarkers is that the increase in vascular and myocardium pressure in these infants generates an effect in the developing lung that acts as another intermediate factor in the cascade towards lung damage in BPD, as well as mechanical ventilation[37], chorioamnionitis[38], late-onset sepsis[39] or malnutrition[40]. According to this hypothesis, NT-proBNP and the LUS score would detect this aberrant lung development, but from different points of view.

In the present study, we were not able to demonstrate that any biomarker alone or together increases the diagnostic accuracy of clinical variables, birth weight and the need for IMV on the 7th DOL. Many different multivariate models have been proposed to predict msBPD at birth, on the 1st DOL or on the 7th DOL[41–44] to adjust for possible treatments and ventilatory strategies for babies with a higher risk of the disease[45]. Nevertheless, none of these models have been universally adopted in NICUs, mainly because they include subjective variables that vary between different centres. The need for IMV in preterm babies can meet the requirements of a subjective variable, as the rate of IMV or NIV is different across NICUs throughout the world. However, we believe that LUS is more objective[46], has high interobserver agreement[47], and can be performed by neonatologists with low expertise in LUS without secondary effects. We propose to study and validate BPD predictive models using the LUS score, as well as clinical variables that are not subject to variability in clinical practice between centres[17].

Although this is a multicentre study, which increases the external application of its results, we believe that the main limitation of this study is its sample size, as we included only twenty-seven patients with msBPD. Other variables that may influence both NT-proBNP and/or the LUS score, such as GA or pro-inflammatory conditions, cannot be addressed in a study with a small sample size. We have tried to use a practical hsPDA definition to reduce the variability detected in previous studies (size of PDA, echocardiographic score); however, the decision to treat hsPDA may be influenced by multiple variables as well as the subjective judgement of the neonatologist, which can reduce the external reproducibility of our results. More investigation in this field is warranted, as we still are not able to detect all babies who will develop msBPD as early as the 7–14th DOL to study which treatment would be more suitable to apply to these infants.

Despite these limitations, we conclude that the LUS score is a better predictor of msBPD on the 7th DOL than NT-proBNP in preterm infants born before 32 weeks, although they have similar diagnostic accuracies on the 14th DOL. Neither of them individually nor together have a better AUC for msBPD than a clinical model with birthweight and the need for IMV on the 7th DOL.

Abbreviations

AUC
area under the receiver operating characteristic curve
BNP
B-type natriuretic peptide
BPD
bronchopulmonary dysplasia
CRIB-II
clinical risk index for babies-II
DOL
day of life
EDTA

ethylenediaminetetraacetic acid
ECLIA
electroluminescence immunoassay kit
GA
gestational age
hsPDA
hemodynamically significant patent ductus arteriosus
ICC
intraclass correlation coefficient
IMV
invasive mechanical ventilation
LUS
lung ultrasound
msBPD
moderate-severe bronchopulmonary dysplasia
NIV
non-invasive ventilation
NT-proBNP
N-terminal end of B-type natriuretic peptide
PDA
patent ductus arteriosus
PMA
postmenstrual age
PT
preterm infants
RDS
respiratory distress syndrome
SNAPPE-II
score for neonatal acute physiology
VLBWI
very low birth weight infants.

Declarations

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CODE AVAILABILITY: Not applicable.

AUTHOR CONTRIBUTIONS: AAO, PMA, PZR and SLL contributed to the study conception and design. Data collection was performed by AAO, PAQ and IOE. Analysis were performed by AAO. The first draft of the manuscript was written by AAO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL: The study protocol was approved by each regional Ethics Committee with the code number LUS-NEO-17-02.

CONSENT TO PARTICIPATE: Parents gave informed consent for participation in this study.

CONSENT TO PUBLICATION: Not applicable.

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Tables

Table 1. Descriptive statistics of the patients included: data are presented as medians (interquartile ranks) or absolute numbers (percentages). BPD: bronchopulmonary dysplasia; DOL: days of life; IMV: invasive mechanical ventilation; NIV: non-invasive ventilation; RDS: respiratory distress syndrome.

	No moderate–severe BPD (n=106)	Moderate–severe BPD (n=27)	p
Gestational age (weeks)	30 (29–31)	27 (25–29)	<0.001
Birth weight (g)	1300 (1100–1445)	905 (620–1000)	<0.001
Male sex	57 (54%)	18 (67%)	0.22
Chorioamnionitis	5 (5%)	6 (22%)	0.03
Antenatal steroids	97 (92%)	23 (85%)	0.53
Vaginal delivery	35 (33%)	11 (41%)	0.45
CRIB	1 (0–2)	5 (1–8)	<0.001
CRIB-II	6 (4–8)	12 (9–14)	<0.001
SNAPPE-II	8 (1–26)	24 (14–41)	0.03
RDS	43 (41%)	19 (70%)	0.003
Intraventricular haemorrhage–periventricular stroke	11 (10%)	1 (4%)	0.012
Late-onset sepsis	21 (20%)	16 (59%)	<0.001
Haemodynamically significant PDA	6 (6%)	9 (33%)	<0.001
Days of IMV	0 (0–3)	6 (0–45)	0.0002
Days of NIV	6 (2–13)	20 (12–37)	<0.001
Days of respiratory support	17 (7–44)	97 (82–140)	<0.001
IMV at 3 DOL	21 (20%)	15 (56%)	<0.001
IMV at 7 DOL	15 (14%)	12 (44%)	<0.001
Postnatal steroids	2 (2%)	10 (4%)	<0.001
Oxygen at discharge	3 (3%)	15 (56%)	<0.001
Length of admission (d)	49 (36–60)	82 (73–104)	<0.001

Table 2. Area under the receiver operating characteristic curve (AUC) and 95% confidence intervals of NT-proBNP and LUS scores at different times, for moderate–severe bronchopulmonary dysplasia prediction; p: p values for DeLong test to compare AUCs.

	LUS score	NT-proBNP	p	LUS score+NT-proBNP
1st day of life	0.41 (0.33–0.50)	0.54 (0.45–0.62)	0.35	0.43 (0.06–0.80)
3rd day of life	0.52 (0.43–0.61)	0.38 (0.16–0.62)	0.16	0.58 (0.11–1)
7th day of life	0.83 (0.75–0.89)	0.66 (0.56–0.75)	0.03	0.84 (0.74–0.94)
14th day of life	0.85 (0.77–0.90)	0.86 (0.69–0.95)	0.56	0.85 (0.75–0.93)

Table 3. Diagnostic accuracy of different models for moderate–severe BPD prediction on the 7th day of life. DeLong test results for AUC comparisons between models: model 1 versus model 2 (p=0.11); model 1 versus model 3 (p=0.25); model 1 versus model 4 (p=0.19); model 2 versus model 3 (p=0.21); model 2 versus model 4 (p=0.83); model 3 versus model 4 (p=0.24); AUC: area under the receiver operating characteristic curve; BPD: bronchopulmonary dysplasia.

	Adjusted R^2	AUC (95% confidence interval)	Hosmer–Lemeshow (p)
Model 1: clinical	0.295	0.86 (0.78–0.94)	0.13
Model 2: clinical + LUS	0.368	0.90 (0.85–0.96)	0.24
Model 3: clinical + NT-proBNP	0.280	0.86 (0.76–0.96)	0.06
Model 4: clinical + LUS + NT-proBNP	0.356	0.90 (0.84–0.96)	0.27

Figures

Figure 1

Flow diagram for patient inclusion. PT: preterm infants.

Figure 2

LUS score (A) and NT-proBNP (B) at birth and on the 3rd, 7th and 14th DOLs: data are presented as medians and interquartile ranks. BPD: bronchopulmonary dysplasia; DOL: day of life; *: p<0.05.