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Prediction of Bronchopulmonary Dysplasia by Diaphragmatic Ultrasound in Preterm Infants: A Prospective Pilot Study

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ABSTRACT

Background: Diaphragmatic ultrasound showed significant differences between patients with established bronchopulmonary dysplasia (BPD) and healthy controls. The aim of this study was to assess whether diaphragmatic ultrasound could predict the development of BPD in preterm infants < 32 weeks of gestational age.

Methods: Diaphragmatic ultrasound was performed on day 3 of life (T_0), and at 7 ± 1 (T_1), 14 ± 1 (T_2), and 21 ± 2 (T_3) days of life. Diaphragmatic excursion (DE), diaphragmatic thickness at end of inspiration (DT_{ins}) and expiration (DT_{exp}), inspiratory and expiratory peak velocities (I-peak and E-peak) and their ratio to body surface area (BSA), and diaphragmatic thickness fraction (DTF) were measured. Logistic regression and ROC curve analyses were performed to evaluate possible role of these variables as predictive factors for BPD and their accuracy for the prediction of BPD.

Results: DE/BSA, DT_{ins}/BSA, DT_{exp}/BSA, and DTF did not differ between patients who developed or did not developed BPD. I-peak/BSA and E-peak/BSA were significantly higher in patients who developed BPD at all timings. I-peak/BSA at T_2 and E-peak/BSA at T_0 and T_1 were independent predictive factors for BPD after adjustment for gestational age and respiratory support. At T_1 I-peak/BSA > 18 cm/s/m^2 and E-peak/BSA > 17.1 cm/s/m^2 accurately predict BPD with sensitivity of 92% and specificity of 92%, and sensitivity of 99% and specificity of 79%, respectively.

Conclusions: I-peak/BSA and E-peak/BSA are independent risk factors for the development of BPD. They can early and accurately predict the risk for BPD in very preterm infants contributing to targeted treatment of patients at higher risk of BPD.

1 | Introduction

Diaphragmatic ultrasound has been recently introduced as a point of care technique in neonatal intensive care unit (NICU) to assess anatomical features and functional properties of the diaphragm, in term and preterm infants [1–17]. Diaphragmatic ultrasound was recently proved to detect ventilator induced diaphragmatic injury in preterm infants < 28 weeks of gestational age, as progressive decreases in diaphragmatic thickness at the end of expiration (DT_{exp}) and diaphragmatic thickness fraction (DTF) were demonstrated during mechanical ventilation [6]. Diaphragmatic ultrasound can help predict extubation failure in preterm infants < 32 weeks of gestational age, with particularly high accuracy of diaphragmatic excursion (DE) [7]. Moreover, diaphragmatic atrophy was significantly associated with extubation failure [7], although a subsequent

study did not confirm this finding [8]. Furthermore, diaphragmatic ultrasound has been used to assess the effect of different modes of noninvasive ventilation on diaphragmatic function [10–12].

Bronchopulmonary dysplasia (BPD) is currently one of the main causes of mortality and morbidity in preterm infants [18, 19]. Preterm infants with BPD assessed by diaphragmatic ultrasound at 36 weeks postconceptional age showed significantly lower DT_{exp} to body surface area (BSA) ratio, and higher DT_{ins} to BSA ratio, DE to BSA ratio and DTF in comparison to healthy controls [15]. These findings indicate an increased diaphragmatic activity aimed to compensate for lung function impairment [15]. Male infants with BPD were found to have lower DT_{ins} and DT_{exp} to BSA ratio in comparison to females with BPD, while no differences were found in healthy controls, suggesting that diaphragmatic impairment may be a sex-related risk factor for the development of BPD [16].

However, previous studies have not evaluated diaphragmatic ultrasound parameters over time in patients at risk of BPD, and their usefulness for the evaluation of the risk for BPD is currently unknown. Particularly, because diaphragmatic motion is increased in patients with established BPD in comparison to controls, likely as compensatory mechanism [15, 16], we hypothesized that DE could predict the risk of BPD. To assess this hypothesis, we carried out an observational prospective study in a cohort of very preterm infants in whom serial diaphragmatic ultrasounds were performed during the first weeks of life.

2 | Methods

2.1 | Study Design and Patients

This single-center, prospective, observational study was carried out after the approval of the Tuscany Pediatric Ethics committee (# 58/2023). This was a pilot study, with recruitment of a relatively limited number of patients during a 1-year period. Infants with gestational age < 32 weeks, respiratory distress syndrome (RDS) requiring respiratory support, and post-natal age ≤ 72 h were enrolled from April 2023 to March 2024 after parental informed consent. RDS was defined as the presence of clinical signs of respiratory distress, oxygen dependence during the first 24 h of life, consistent chest radiograph appearances, and the exclusion of other causes of respiratory failure [20]. Exclusion criteria were the presence of major congenital abnormalities, known or suspected genetic syndromes and inborn errors of metabolism.

2.2 | Diaphragmatic Ultrasound

All infants underwent diaphragmatic ultrasound at 3 (T_0), 7 ± 1 (T_1), 14 ± 1 (T_2), and 21 ± 2 (T_3) days of life. Measurements were performed in supine position, in a relaxed state, with the use of partial swaddling and/or pacifier, as needed, and before feeding or at least 1 h after feeding in case of bolus feeding strategy. Ultrasound evaluations were performed on the right hemidiaphragm through the liver acoustic window [1, 15, 17, 21]. Left hemidiaphragm was not studied because visualization is considered more difficult due to stomach content [15, 17], and to limit the duration of the exam and patients' discomfort. Diaphragmatic ultrasound studies were performed by trained personnel with a minimum experience of 6 months in lung and diaphragmatic ultrasound [15–17].

Measurements were performed as previously described [1, 15, 17, 21]. DT_{ins} and DT_{exp} were measured with a 10–12 MHz high-frequency linear probe positioned perpendicularly to the right hemidiaphragm at the 8th–9th intercostal space, between anterior and middle axillary lines. Following diaphragm identification by B-mode imaging, DT_{ins} and DT_{esp} were assessed by M-mode tracing, as the maximal and minimal distance between the diaphragmatic pleura and the peritoneum, respectively. DTF was calculated as $[(DT_{ins} - DT_{exp})/DT_{exp}] \times 100$ [4, 15, 17]. DE was measured with a 5 MHz low-frequency sectorial probe positioned at the intersection between the midclavear line and the subcostal margin. By M-Mode tracing, DE was measured as the difference in the position of the outer line of the diaphragm at inspiratory and expiratory peak (I-peak and E-peak). For each considered parameter, the average from five subsequent respiratory cycles was reported [15, 17]. From the same position and with the same probe as DE, I-peak and E-peak velocities were measured by Pulsed Wave Tissue Doppler Imaging (PW-TDI) with a 5 mm sample volume placed on the diaphragmatic line [12, 13, 17]. Average from 10 subsequent respiratory cycles was reported [17].

2.3 | Respiratory Management

Resuscitation in the delivery room was performed following the guidelines of the AAP/AAH [22]. In the NICU, noninvasive respiratory support was performed using NCPAP, bi-level NCPAP, or nasal intermittent positive pressure ventilation (NIPPV). Moreover, infants were started on MV when pH was < 7.20 with $PaCO_2 > 65$ mmHg, or $PaO_2 < 50$ mmHg with $FiO_2 \geq 0.50$, after surfactant treatment, or if they had frequent episodes of apnea (> 4 episodes in 1 h, or > 2 episodes requiring bag-and-mask ventilation) despite adequate NCPAP (5–7 cmH_2O) delivery and oxygenation. MV was performed using patient-triggered ventilation with or without volume guarantee or high-frequency ventilation. Respiratory support was set to maintain $PaCO_2$ of 55–65 mmHg and 90%–95% SpO_2.

Infants were treated with surfactant (Curosurf, Chiesi Farmaceutici Spa, Parma, Italy: 200 mg/kg) if they required MV or $FiO_2 > 0.30$ [23] was necessary to maintain an adequate SpO_2. Additional doses of surfactant (100 mg/kg) were given to infants at the discretion of the attending neonatologist. Less invasive surfactant administration (LISA) and INtubation-SURfactant-Extubation (InSURE) procedure were either used in non-intubated patients.

2.4 | Collected Data

For each infant we recorded gestational age, birth weight, sex, Apgar score at 5 min, need of surfactant, need of noninvasive and invasive ventilation, postnatal steroids, patent ductus

arteriosus (PDA) requiring treatment, early and late onset sepsis (EOS, LOS), BPD, intraventricular hemorrhage (IVH) ≥ grade 3, retinopathy of prematurity (ROP) ≥ grade 3, necrotizing enterocolitis (NEC), duration of hospitalization, and death. BPD was defined as the need for oxygen supplementation or any respiratory support at 36 weeks postconceptional age [19]. The adapted classification of Papile et al. was used to classify the severity of IVH [24]. NEC was diagnosed according to Bell's criteria [25]. ROP was evaluated according to the International Classification [26].

Examined maternal variables included antenatal steroids, type of delivery, hypertensive disorders, oligohydramnios, Intrauterine growth restriction, and clinical chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis > 15,000/mm^3, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid) [27]. BSA was calculated by Mosteller equation.

$$[\mathrm{BSA(m^2)} = \sqrt{\mathrm{Weight(kg)} \times \mathrm{Height(cm)}/3600}\,]$$

3 | Primary and Secondary Endpoints

The primary endpoint of our study was to assess the possible correlation between DE/BSA values measured at different time points and the risk of developing BPD. Secondary endpoints were the assessment of the possible correlation between remaining parameters (DT_{ins}/BSA, DT_{exp}/BSA, DTF, E-peak/BSA, I-peak/BSA) of the diaphragmatic ultrasound and the risk for developing BPD.

3.1 | Statistical Analysis

Data were described as mean and SD for continuous parametric variables, median and IQR for non-parametric variables, and rate and percentage for discrete variables. Shapiro–Wilk test was performed to assess distribution of variables. Comparisons between groups were performed with student *t*-test for parametric continuous variables, such as ultrasound diaphragmatic parameters. Mann–Whitney *U*-test was used for continuous nonparametric variables, and Fisher's exact test for categorical variables.

All ultrasound diaphragmatic measurements (except for DTF) were normalized per BSA considering that: (a) enrolled infants had a wide range of birthweight (540–1380 g), (b) patients with BPD had significantly lower birthweight and gestational age, (c) patients were followed up for a 21 days-period, during which weight was expected to increase, (d) previously reported percentiles of I-peak and E-peak in infants > 3 kg showed fluctuating pattern according to birthweight [17].

Variations over time of diaphragmatic function measurements was assessed by analysis of variance (ANOVA) for repeated measures. Receiver operating characteristic (ROC) curves were analyzed for each timing for variables with significant differences between the two groups, namely I-peak/BSA and E-peak/BS. Areas under curve (AUC) and best cut-off values for each timing were calculated.

Logistic regression analyses assessed the possible correlation between ultrasound diaphragmatic measurements and other variables with $p < 0.05$ in univariate analyses and the risk of developing BPD. Thus, logistic regression analysis evaluated the effect of gestational age, ventilation mode, I-peak/BSA, and E-peak/BS on the risk for BPD. I-peak/BSA was not included at T_0 considering the suboptimal discrimination of AUC and mediocre sensitivity and specificity of the calculated cut-off found with ROC analysis. The number of independent variables to predict BPD was limited to a maximum of four basing on the small sample size [28].

To analyze the predictive value of I-peak/BSA and E-peak/BS on the occurrence of BPD, we used ROC (receiver operating characteristic) curve analysis. AUC and the best cut-off value for each timing were calculated.

Data were analyzed with SPSS, version 26.0 (IBM, New York, USA).

4 | Results

We enrolled 36 newborns with gestational age 28.5 ± 2.1 weeks and birth weight 1121 ± 315 g. During the study period, 18 infants with gestational age < 32 weeks were not enrolled in the study, 2 because of death within 3 days of life, 1 because of lack of parental consent, and 15 because of no signs of RDS. Moreover, 4 patients were excluded from the study after enrollment, 3 because of death or transfer to surgical facility before 36 weeks postmenstrual age, and 1 because of incomplete ultrasound measurements. Among enrolled infants, 12/36 (33%) were diagnosed with BPD. Patients who developed BPD had significantly lower gestational age and birth weight, and higher occurrence of PDA and LOS (Table 1). Patients who developed BPD more frequently received MV (Table 1), and a higher proportion of infants who developed BPD was on NIMV or CPAP at all timings of diaphragmatic ultrasound (Table S1).

Unnormalized data are reported in Table S2. No significant differences were found between infants with or without BPD in the primary outcome of DE/BSA and in the secondary outcomes of DT_{ins}/BSA, DT_{exp}/BSA, DTF, and DE/BSA. The secondary outcomes of I-peak/BSA and E-peak/BSA were significantly higher at T_0, T_1, T_2, and T_3 in infants with BPD than without BPD (Table 2). I-peak/BSA was significantly higher in patients on MV in comparison to those on noninvasive support and with no support at T_0 and T_1 and T_2, and in those on noninvasive support in comparison to those with no support at T_2 and T_3 (Table S3); E-peak/BSA was significantly higher in patients on MV in comparison to those with no support at T_0, T_1, and T_2, and in comparison to those on noninvasive support at T_0 (Table S3). I-peak/BSA and E-peak/BSA did not significantly differ between patients with PEEP level < versus ≥ 5 cmH_2O at any considered timing (Table S4). DE/BSA significantly changed over time in infants with BPD ($p = 0.032$), while other measurements did not (Table 2).

Regression analyses showed that, after adjustment for GA and ventilation mode, E-peak/BSA at T_0 ($p = 0.040$) and T_1 ($p = 0.026$) and I-peak/BSA at T_2 ($p = 0.046$) were independently correlated

TABLE 1 | Clinical characteristics of enrolled patients.

	All patients ($n = 36$)	BPD ($n = 12$)	No BPD ($n = 24$)	p
Infants				
Gestational age (weeks)	28.5 ± 2.1	26.7 ± 1.6	29.5 ± 1.7	< 0.0001[a]
Birth weight (g)	1121 ± 315	901 ± 251	1231 ± 288	0.042[a]
Birth weight < 10° percentile	4 (11)	0	4 (17)	0.278
Male	19 (53)	6 (50)	13 (54)	1.000
Apgar score at 5 min	8 (7–8)	8 (7–8)	8 (8–9)	0.337
Early onset sepsis	0 (0)	0 (0)	0 (0)	N/A
Surfactant	17 (47)	9 (75)	7 (29)	0.014[a]
Noninvasive ventilation	33 (92)	12 (100)	21 (87)	0.536
Mechanical ventilation	4 (11)	4 (33)	0 (0)	0.008[a]
Postnatal steroids	5 (14)	5 (42)	0 (0)	0.002[a]
Patent ductus arteriosus	16 (44)	9 (75)	7 (29)	0.014[a]
Late onset sepsis	3 (8)	3 (25)	0 (0)	0.031[a]
Length of stay (days)	57.5 (50–79)	84 (76–117)	52 (43–59)	< 0.001[a]
Death	0 (0)	0 (0)	0 (0)	N/A
Mothers				
Vaginal delivery	10 (28)	5 (42)	5 (21)	0.246
Antenatal steroids	34 (94)	11 (92)	23 (96)	1.000
Hypertensive disorders of pregnancy	5 (14)	2 (17)	3 (12)	1.000
Oligohydramnios	3 (8)	2 (17)	1 (4)	0.252
Clinical chorioamnionitis	2 (6)	2 (17)	0 (0)	0.105
Intrauterine growth restriction	5 (14)	1 (8)	4 (17)	0.646

Note: Mean ± SD, median and (IQR), or rate and (%).
[a]BPD versus no BPD.

with the risk of BPD (Table 3). ROC curves of I-peak/BSA and E-peak/BSA were assessed at all time points. The highest AUC for I-peak/BSA was 0.868 (95% confidence interval [CI] 0.712–1.024) at T_1 and the best calculated cut-off was 18 cm/s/m^2 with sensitivity and specificity of 0.92. The highest AUC for E-peak/BSA was 0 0.938 (95% CI 0.862–1.013) at T_1, and the best calculated cut-off was 17 cm/s/m^2 with a sensitivity of 0.99 and a specificity of 0.79 (Table 4, Figure 1).

5 | Discussion

This is the first study investigating the correlation of diaphragmatic ultrasound parameters with the risk of development of BPD in very preterm infants. We found that in a small cohort of infants < 32 weeks, prospectively studied from 3 to 21 days of life, I-peak/BSA and E-peak/BSA could accurately predict the development of BPD. On the contrary, the primary outcome of DE/BSA did not differ between infants with or without BPD.

I-peak/BSA and E-peak/BSA predict BPD at different timings. Regression analysis demonstrated that I-peak/BSA measured at 14 (T_2) days of life is an independent risk factors for BPD. Moreover, ROC analysis at T_1 demonstrated that a I-peak/BSA > 18 cm/s/m^2 predicts BPD with a sensitivity and specificity of 92%. Consistently, regression analysis demonstrated that E-peak/BSA measured at 3 (T_0), and 7 (T_1) days of life is an independent risk factors for BPD. This correlation was confirmed by the ROC analysis at T_1 which showed that an E-peak/BSA > 17.1 cm/s/m^2 can predict BPD with a sensitivity of 99% and specificity of 79%. Therefore, E-peak/BSA might predict BPD earlier than I-peak/BSA. Previous studies investigating diaphragmatic ultrasound in infants with BPD did not measure I-peak and E-peak [15, 16]. However, values of I-peak and E-peak not normalized for BSA found in our study are comparable to those previously reported in preterm infants with RDS [12, 13], supporting the reliability of our measurements. Our study suggests that I-peak and E-peak not normalized for BSA are higher from 3 days of life onward in comparison to those obtained in more mature patients with RDS within 72 h of life (1.5–1.9 vs. 1.3–1.4 cm/s, and 1.6–1.7 vs. 1.1–1.4 cm/s, respectively) [12]. This result might be interpreted as an increase in diaphragmatic velocities occurring after the acute restrictive phase of RDS, reflecting the establishment of proper lung volumes [20]. Moreover, the higher values of I-peak and E-peak observed in our study might have also been influenced by the lower gestational age of enrolled patients (median gestational age 26–29 vs. 30–31 weeks) [12], and explained as an effort to compensate for more severe pulmonary disease.

Finally, the mode of respiratory support might affect observed diaphragmatic velocities. I-peak/BSA and E-peak/BSA at

TABLE 2 | Diaphragmatic ultrasound parameters measured at the different data points of the study.

	BPD ($n = 12$)	No BPD ($n = 24$)	p-value
DT_{ins}/BSA (mm/m^2)			
T_0	12.6 ± 3.1	10.8 ± 2.7	0.081
T_1	12.6 ± 3.0	11.0 ± 2.1	0.071
T_2	12.3 ± 3.1	10.6 ± 1.8	0.059
T_3	12.0 ± 3.2	10.5 ± 1.9	0.080
p-value	0.555	0.119	
DT_{exp}/BSA (mm/m^2)			
T_0	8.8 ± 2.5	7.7 ± 1.9	0.147
T_1	9.0 ± 1.8	8.8 ± 1.4	0.689
T_2	9.1 ± 2.0	7.9 ± 1.4	0.059
T_3	8.3 ± 1.7	7.5 ± 1.4	0.132
p-value	0.311	0.059	
DTF (%)			
T_0	46.4 ± 12.0	43.1 ± 11.3	0.320
T_1	41.0 ± 13.3	39.2 ± 11.5	0.631
T_2	34.3 ± 14.1	41.0 ± 15.0	0.186
T_3	45.4 ± 15.7	44.9 ± 19.2	0.875
p-value	0.189	0.682	
DE/BSA (mm/m^2)			
T_0	29.9 ± 6.9	30.6 ± 6.0	0.757
T_1	33.4 ± 8.9	32.9 ± 8.2	0.866
T_2	27.9 ± 8.1	31.8 ± 9.5	0.248
T_3	37.5 ± 7.5	37.1 ± 11.3	0.918
p-value	0.032	0.288	
I-peak/BSA ($cm/s/m^2$)			
T_0	17.7 ± 3.2	15.7 ± 2.2	0.034
T_1	20.5 ± 4.4	14.6 ± 3.0	< 0.001
T_2	20.0 ± 3.8	15.1 ± 3.3	< 0.001
T_3	19.5 ± 4.1	14.0 ± 3.5	< 0.001
p-value	0.531	0.393	
E-peak/BSA ($cm/s/m^2$)			
T_0	18.1 ± 4.2	15.1 ± 2.9	0.017
T_1	19.2 ± 4.1	15.0 ± 3.5	0.003
T_2	18.4 ± 4.4	14.8 ± 3.5	0.012
T_3	17.1 ± 4.6	11.4 ± 4.9	0.002
p-value	0.556	0.041	

Note: All values are normalized for body surface area (BSA). Mean ± SD. DT_{ins}: diaphragmatic thickness at end of inspiration; DT_{exp}: diaphragmatic thickness at end of expiration; DTF: diaphragmatic thickness fraction; DE: diaphragmatic excursion; E-peak: expiratory peak velocitiy; I-peak: inspiratory peak velocity.

different timings were increased in patients on MV in comparison to those on noninvasive support or with no support, and in patients on noninvasive support in comparison to those with no support. Despite this result must be interpreted with caution given the low numerosity of patients on MV, it might be explained either with influence of the mode of ventilatory support on I-peak/BSA and E-peak/BSA or with persistence of higher diaphragmatic activity and tone in those patients with more severe RDS. The latter hypothesis would be concordant with higher E-peak values previously reported in preterm infants failing noninvasive ventilation in comparison to those not requiring MV [12]. However, in our study E-peak/BSA at T_0 and T_1, and I-peak/BSA at T_2 maintained significant predictivity for BPD after adjustment for ventilation mode, supporting their potential clinical usefulness for the prediction of BPD. Moreover, in our sample, no differences were found in I-peak/BSA and E-peak/BSA in case of PEEP level < or ≥ 5 cm H_2O, suggesting that PEEP likely does not significantly affect such measurements, in contrast to DT_{ins}, DT_{exp}, and DE [29]. Further studies are warranted to specifically assess the impact of ventilatory support on I-peak and E-peak.

Diaphragmatic peak velocities may be helpful to assess the risk of BPD, because changes of diaphragmatic activity can suggest fatigue and increased work of breathing. In fact, an inverse relationship was observed between diaphragmatic strength and its velocity of contraction [12]. In our patients, I-peak/BSA and E-peak/BSA were higher in patients with BPD than in patients without BPD from 3 (T_0) to 14 (T_2) days of life. This time window includes the evolving phase of BPD that runs from the end of the first week of life to the 36th week of gestational age [27]. During this phase, a transition occurs from lung mechanics typical of RDS, characterized by low compliance, relative homogeneity, and normal airway resistance, to mechanics typical of BPD, characterized by high airway resistance, air trapping, low or high compliance, and heterogeneous aeration [30]. These changes cause an increased work of breathing which explains our findings and suggests that in infants who develop BPD the increase of diaphragmatic contraction velocity likely represents a compensation that counteracts the worsening of respiratory function.

In preterm infants, diaphragmatic thicknesses and excursions are positively correlated with the strength of diaphragmatic contraction [13]. Since in our study parameters expressing thickness and excursion did not differ between infants with and without BPD, it can be speculated that during the evolving phase of BPD the increase of I-peak and E-peak might be the earliest or the only possible diaphragmatic compensative mechanisms. We also demonstrated that DE/BSA progressively increases during the study period in patients who develop BPD. These results are in agreement with the study of Yeung et al., who did not measure I-peak and E-peak but found in a population < 32 weeks that infants with established BPD had higher DE/BSA and DTF at the mean postconceptional age of 37.7 weeks in comparison to healthy controls. As a matter of fact, while DE measures general diaphragmatic mobility, I-peak and E-peak more specifically reflect diaphragmatic efficiency in term of contractile activity and relaxation capacity [13]. Therefore, it can be speculated that in infants with evolving BPD the increased work of breathing may be initially compensated by the increase in the velocity of diaphragmatic contraction, and subsequently by the increase in its thickness and excursion.

The strength of this study was the longitudinal assessment of diaphragmatic ultrasounds parameters in preterm infants during

TABLE 3 | Multivariate logistic regression at T_0, T_1 and T_2, and T_3.

Variables	*B*	SE	Wald	Sig.	Exp (*B*)	95% CI Exp (*B*)
T_0						
Gestational age	−0.687	0.351	3.822	0.051	0.503	0.253–1.002
E-peak/BSA	0.608	0.300	4.122	0.040	1.839	1.021–3.312
Ventilation mode	−0.987	1.551	0.405	0.525	0.373	0.018–7.789
Constant	13.134	19.607	0.449	0.503	505,923.888	—
T_1						
Gestational age	−0.530	0.349	2.308	0.129	0.589	0.297–1.166
I-peak/BSA	0.095	0.166	0.330	0.566	1.100	0.794–1.523
E-peak/BSA	0.709	0.318	4.970	0.026	2.031	1.089–3.788
Ventilation mode	−1.102	1.433	0.591	0.442	0.332	0.020–5.512
Constant	0.231	10.936	0.000	0.983	1.260	—
T_2						
Gestational age	−0.446	0.381	1.374	0.244	0.640	0.321–1.391
I-peak/BSA	0.902	0.462	3.829	0.046	2.467	1.001–6.099
E-peak/BSA	−0.393	0.371	1.125	0.289	0.675	0.382–1.400
Ventilation mode	0.087	1.072	0.007	0.935	1.091	0.026–3.896
Constant	1.902	12.653	0.023	0.881	6.698	—
T_3						
Gestational age	−0.672	0.662	1.030	0.310	0.511	0.139–1.870
I-peak/BSA	0.740	0.334	0.050	0.123	1.077	0.560–2.073
E-peak/BSA	0.386	0.299	1.672	0.196	1.471	0.819–2.641
Ventilation mode	3.997	1.966	4.132	0.042	54.452	1.154–2569.603
Constant	8.743	20.262	0.186	0.666	6265.728	—

Note: E-peak: expiratory peak velocity/body surface area; I-peak/BSA: inspiratory peak velocity/body surface area.

TABLE 4 | Area under curve (95% CI), best calculated cut-off values, sensitivity (%), and specificity (%) of inspiratory peak velocity/body surface area (I-peak/BSA) and expiratory peak velocity/body surface area (E-peak/BSA) at the different data points of the study.

	AUC	Cut-off value (cm/s/m^2)	Sensitivity	Specificity
I-peak/BSA				
T_0	0.682 (0.490–0.875)	16.7	75	67
T_1	0.868 (0.712–1.024)	18.0	92	92
T_2	0.938 (0.855–1.020)	19.8	88	92
T_3	0.854 (0.727–0.982)	15.9	85	75
E-peak/BSA				
T_0	0.882 (0.764–1.000)	18.0	92	83
T_1	0.938 (0.862–1.013)	17.1	99	79
T_2	0.837 (0.686–0.988)	16.7	92	75
T_3	0.858 (0.733–0.982)	16.3	75	87

the first weeks of life before and during the evolving phase of BPD, which enabled to evaluate the predictive value of parameters of diaphragmatic function. A limitation of the study was that we did not perform diaphragmatic ultrasounds at 36 weeks of postconceptional age when BPD was established, and this precluded the possibility of comparing our data with those of previous studies [15]. Moreover, the small size of our population did not allow to specifically assess the potential effects of other variables on diaphragmatic function, such as different modes of invasive and noninvasive support. Finally, lung ultrasound score was not performed, not allowing for correlation between diaphragmatic dysfunction and the degree of lung impairment [31].

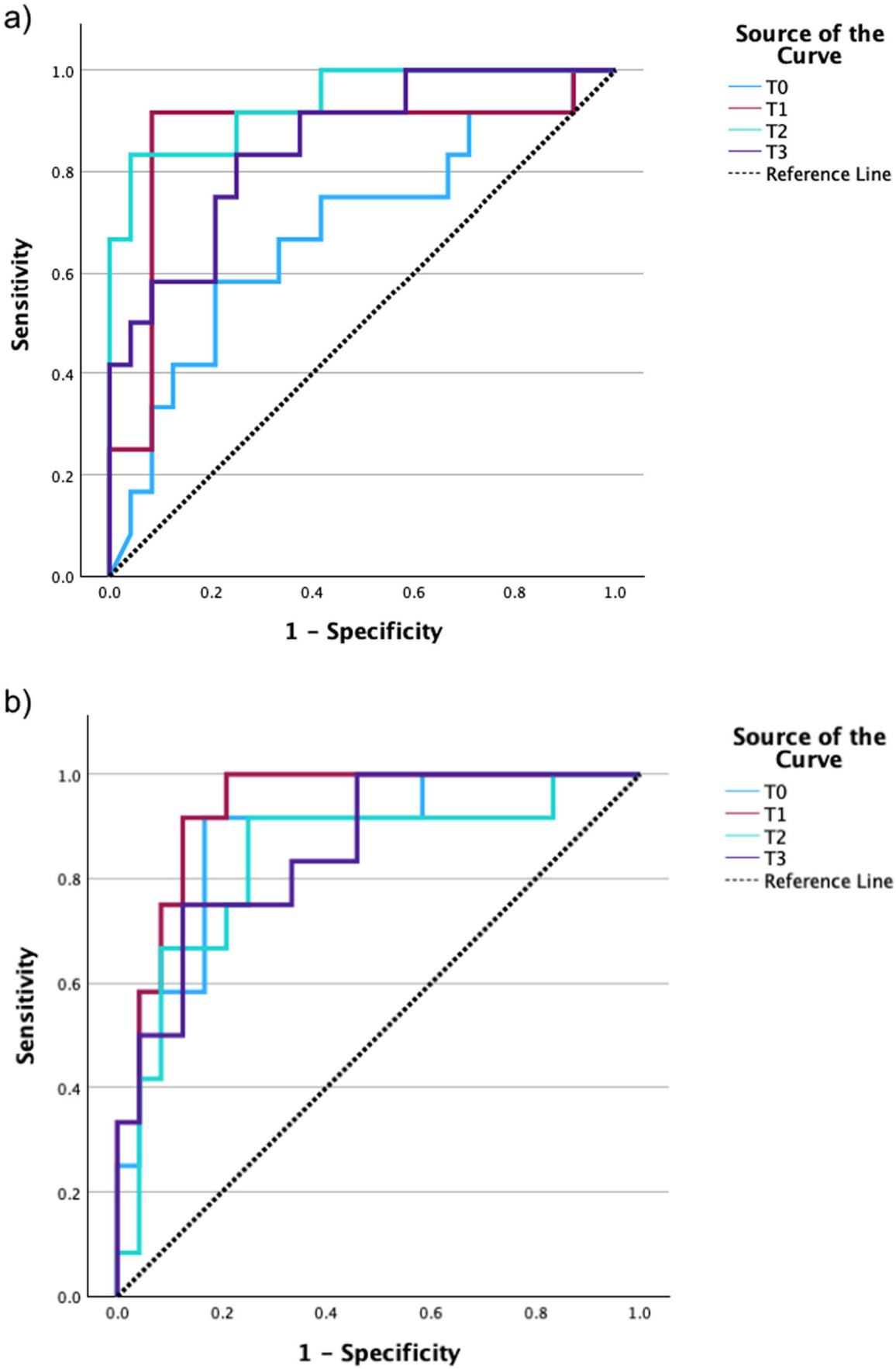

FIGURE 1 | ROC curves of I-peak/BSA (a) and E-peak/BSA (b) at each considered timing. [Color figure can be viewed at wileyonlinelibrary.com]

6 | Conclusions

This study demonstrated for the first time in a small cohort of preterm newborns that ultrasound parameters of peak diaphragmatic velocity, I-peak/BSA and E-peak/BSA, are independent risk factors for the development of BPD. We demonstrated that I-peak/BSA and E-peak/BSA can early and accurately predict the risk of developing BPD in very preterm infants, suggesting their possible clinical usefulness in planning targeted preventive strategies.

Author Contributions

Chiara Poggi: conceptualization, methodology, formal analysis, supervision, data curation, writing – original draft; writing – review and editing, investigation, validation, software, visualization, project administration. **Monica Fusco:** data curation, investigation, writing – review and editing, software, methodology, validation. **Giovanni Sassudelli:** investigation, writing – review and editing, data curation, software. **Iuri Corsini:** investigation, data curation, writing – review and editing, software. **Carlo Dani:** methodology, writing – review and editing, supervision, visualization, validation, conceptualization, project administration.

Ethics Statement

The study was approved prior initiation by the Tuscany Region Ethic Committee for Pediatric Research (Approval #58/2023). Written informed consent was obtained by both parents or legal guardians for each enrolled infants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Table 1: Respiratory support of enrolled infants during the study period. Data are expressed as n and (%), median and (IQR), or range. **Supplementary Table 2:** Diaphragmatic ultrasound measurements for each considered timing. Mean ± SD. **Supplementary Table 3:** Diaphragmatic ultrasound measurements according to respiratory support at T_0, T_1, T_2 and T_3. **Supplementary Table 4:** Values of I-peak/BSA and E-peak/BSA ($cm/s/m^2$) according to different PEEP levels.