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ORIGINAL ARTICLE

Screening Echocardiography Identifies Risk Factors for Pulmonary Hypertension at Discharge in Premature Infants with Bronchopulmonary Dysplasia

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Abstract

Hypothesis Premature infants with bronchopulmonary dysplasia (BPD) are at increased risk of secondary pulmonary hypertension (BPD-PH). Prior studies yielded mixed results on the utility of echocardiographic screening at 36 weeks post-menstrual age (PMA). We present our experience using echocardiographic screening at the time of BPD diagnosis to identify infants at highest risk of BPD-PH at discharge.

Materials and Methods Retrospective cohort analysis of clinical/ demographic data and screening echocardiograms in patients with BPD. Discharge echocardiograms identified infants with or without BPD-PH at discharge. 36 weeks PMA screening echocardiograms and clinical data were then reviewed to identify which factors were associated with increased odds of BPD-PH at discharge. Associations between echocardiographic findings were evaluated with 2- and 3-variable models to predict increased risk of BPD-PH at discharge.

Results In our cohort of 64 infants with severe BPD, BPD-PH was present in 22/64 (34%) infants at discharge. There were no clinical differences at time of 36 weeks PMA screening evaluation (mean PMA 36.6 ± 2.9 weeks). PH at screening was poorly predictive of PH at discharge as PH at screening resolved in 49% of patients. However, having an ASD, RV dilation, hypertrophy, or reduced function on screening, especially in combination, were associated with BPD-PH at discharge.

Conclusion In our cohort of premature infants with BPD, 36 weeks PMA screening echocardiogram identified patients at increased risk for BPD-PH at discharge when ASD, RVH, or impaired RV function were present. Larger prospective studies are indicated to validate these findings.

Keywords Neonate · Bronchopulmonary dysplasia · Pulmonary hypertension · Echocardiogram · Screening

Neonatal care and outcomes have steadily improved over recent decades, with average survival-to-discharge rates improving to 62% for infants born at 24 weeks post-menstrual age (PMA) and to 92% at 28 weeks PMA [1]. Concurrently, the incidence of bronchopulmonary dysplasia (BPD) has risen, with up to 68% of infants born before 29 weeks PMA diagnosed with BPD prior to discharge from the neonatal intensive care unit (NICU) [1]. Of particular concern in patients with BPD is the development of secondary pulmonary hypertension (BPD-PH), which has been described in 18–30% in recent reports [2–6] and associated with a 16% in-NICU and 40% 2-year mortality rate in a recent meta-analysis [7]. Furthermore, recent studies have demonstrated worse neurodevelopmental outcomes in premature infants with BPD-PH compared to their peers with BPD but no PH [8, 9].

Recent screening guidelines of premature infants with BPD for PH have been published by the American Heart Association/American Thoracic Society (AHA/ATS) and Pediatric Pulmonary Hypertension Network (PPHNet). The predominant recommendations are to obtain

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echocardiograms focused on evidence of PH and related dysfunction at 36 weeks PMA when BPD is diagnosed, or sooner in patients with prolonged ventilator need or recurrent hypoxia [10, 11]. Echocardiographic assessment of RV function in premature infants with BPD has identified several measures, including tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RV FAC), and left ventricular eccentricity index in systole, which correlate with worse outcomes in premature infants with BPD and PH [12–15]. Despite these guidelines, regimented screening has not been widely implemented; a survey of neonatologists in 2017 found only 38% had routine institutional screening protocols for PH in premature infants with BPD [16].

While multiple studies have examined the BPD population for predictive risk factors for BPD-PH, it is not entirely clear what besides severity of BPD predisposes patients to BPD-PH [3, 17–20]. We evaluated our institution's experience with screening premature infants with BPD. Given varied findings in scientific literature, we evaluated whether clinical factors or echocardiographic data present at BPD diagnosis could identify patients at the highest risk of BPD-PH at time of death or NICU discharge.

Materials and Methods

This was a retrospective cohort study of patients admitted to the Neonatal Intensive Care Unit at the University of Virginia Health System Women's and Children's Hospital, a level IV nursery, in Charlottesville, Virginia. This study was approved by the Institutional Review Board at the University of Virginia. As a retrospective cohort study posing minimal risk, consent was waived.

Population

Premature infants < 36 weeks PMA discharged from the University of Virginia Health System NICU between January 1, 2016 and September 1, 2019 with a discharge diagnosis in the medical record of BPD or Chronic Lung Disease (CLD) were considered for study inclusion. BPD was defined using the NIH consensus criteria [20]. Patients were excluded if they did not have both a screening echocardiogram at 36 weeks PMA and a pre-discharge echocardiogram; if they had genetic syndromes potentially contributing to lung disease severity; congenital heart disease beyond atrial septal defect (ASD), small ventricular septal defect (VSD), patent ductus arteriosus (PDA), or single-vein partial anomalous pulmonary venous return (PAPVR); or if they were transferred to another NICU prior to discharge home; as PH status at discharge could not be verified.

Our institutional protocol was to screen infants diagnosed with BPD who had need for supplemental O2 or positive pressure ventilation (moderate or severe BPD by NIH criteria) at 36 weeks PMA. Screening was generally delayed by the NICU team if patients were actively ill, such as during a pneumonia or sepsis requiring antibiotics so as to assess their risk for PH at their baseline. Follow-up screening was planned in protocol-based intervals determined by the results of the initial screening echocardiogram and clinical status. Infants without BPD-PH on 36 weeks PMA screening echocardiogram who were otherwise doing well had repeat screening in 2 months. These patients were generally ready for discharge before that point and were usually discharged without a follow-up echocardiogram with close follow-up. Those with evidence of elevated RV pressures but without signs of RV dysfunction had repeat echocardiograms within a month. If PH and RV dysfunction were present, lung disease was optimized, and pulmonary vasodilators were started with follow-up echocardiogram within a week. Patients with more significant lung disease or who stayed more than 4 weeks after initial screening echocardiogram routinely had a discharge echocardiogram.

Diagnosis of Pulmonary Hypertension

PH was defined as an RV systolic pressure (RVSp) greater than half the systemic systolic pressure (SSp), as determined by a full Doppler envelope of shunting across a PDA or VSD, or by a full Doppler envelope of tricuspid regurgitation, if no shunting could be measured. Patients with right-to-left or bidirectional shunting at any level (ASD, VSD, or PDA) or interventricular septal flattening in systole were also considered to have PH. These definitions were chosen based on prior studies using the same diagnostic criteria [3, 15].

Data Collection

Clinical Data

Antenatal and perinatal data, as well as outcomes of the NICU stay were collected from the University of Virginia Health System electronic medical record and are demonstrated in Table 1 below. BNP levels were obtained at closest planned lab draw to screening echocardiogram. Included in the NICU clinical data were admission temperature and highest base deficit in the first 24 h to calculate a CRIB II score, a standardized risk assessment of mortality for premature infants [21].

Table 1 Demographic and clinical data of PH at discharge and no PH at discharge cohorts

Clinical characteristics	All patients ($n=64$)	No PH at discharge ($n=42$)	PH at discharge ($n=22$)	p value
Demographic data				
% Female	48%	50%	45%	0.73
Gestational age (weeks)	25.9 ± 2.1	25.6 ± 1.6	26.6 ± 2.9	0.302
Birth data				
Birth weight (kg)	0.76 ± 0.2	0.73 ± 0.2	0.81 ± 0.3	0.408
Birth length (cm)	31.2 ± 4.0	30.9 ± 3.5	31.8 ± 4.9	0.279
Incidence of IUGR	25%	24%	37%	0.761
Incidence of SGA status	27%	21%	36%	0.199
Perinatal data				
Premature ROM	24%	24%	23%	0.883
Placental abruption	17%	17%	17%	0.965
Maternal steroids	88%	93%	77%	0.107
Mean APGAR, 1 min	3.7 ± 2.1	4.0 ± 2.0	3.2 ± 2.1	0.155
Mean APGAR, 5 min	5.7 ± 2.2	5.9 ± 2.3	5.3 ± 2.1	0.167
NICU data				
CRIB II score	12.8 ± 2.9	13.1 ± 2.3	12.1 ± 3.8	0.862
Invasive ventilation, d	83.4 ± 87.1	86.3 ± 83.1	77.7 ± 96.4	0.277
Noninvasive ventilation, d	49.7 ± 33.5	52.8 ± 35.7	43.6 ± 28.4	0.326
Necrotizing enterocolitis	20%	21%	18%	0.759
Culture-positive sepsis	55%	60%	45%	0.283
PDA closure	34%	36%	32%	0.755
Post-pyloric feeds	39%	40%	36%	0.749

IUGR intrauterine growth restriction, *SGA* small for gestational age, *ROM* rupture of membranes, *CRIB II* clinical risk index for babies, *OI* oxygenation index, *DOL* day of life, *PDA* patent ductus arteriosus

Echocardiographic Data

All 36 weeks PMA screening and discharge echocardiograms were reviewed. Echocardiograms were obtained following a specific protocol to assess for pulmonary hypertension. All echocardiographic measures were obtained from the official echocardiographic interpretation by BM. Echocardiograms were obtained on the Philips Epiq platform and stored on a Philips' Xcelera server. Patients were identified based on the discharge diagnosis of BPD. Screening and final echocardiograms were reviewed prior to any medical record data to blind the reviewer to their clinical outcomes. Qualitative assessment of any shunts and right heart appearance and function were included. Quantitative assessment of right ventricular function consistently undertaken included measurement of tricuspid valve regurgitant jets, PDA or VSD shunting, RV FAC, and eccentricity indices in systole and diastole. Pulmonary vein assessment for pulmonary vein stenosis was performed. The data collected within the pulmonary hypertension echocardiogram protocol used changed midway through the study to include several additional validated measures of right ventricular function including tricuspid annular plane systolic excursion (TAPSE) and right ventricular free wall tissue doppler imaging (RV TDI), which was also used to calculate myocardial performance index (MPI). Pulmonary artery acceleration time was a late addition to the protocol and as such, was not collected in this study. As 30–60% of patients had these measurements recorded, these were felt to be inadequately powered in this study and are not included in the data presented.

Statistical Analysis

Demographic, perinatal, NICU, and echocardiographic parameters on 36 weeks PMA screening echocardiogram were compared between those with and without PH at discharge. A power calculation using a conservative assumed BPD-PH incidence of approximately 30% in premature infants with BPD yielded a necessary sample size of $n=46$ patients for $\alpha=0.05$ and 80% power. Categorical values were compared with Chi-squared tests. Continuous variables were compared with the Kruskal–Wallis test. Odds ratios were estimated from univariate logistic regression using Firth's method. Multivariate logistic regression was used to build models of variables from screening echocardiograms that could be used to identify patients with the highest risk of having PH at discharge. Based on the common rule of thumb, 2- and 3-variable models were created so as not to overfit the data [22, 23]. Models were limited to variables

reliably obtained in most studies, with all included variables observed in at least 62 of 64 cases. A c-index was calculated for each model, with c-indices > 0.8 being considered excellent for discrimination. A p-value of < 0.05 was used for statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Chart review using the discharge diagnoses of BPD or CLD yielded 256 patients, of whom 85 had both screening and discharge echocardiograms. Twenty-one patients were excluded for transfer from the NICU prior to discharge ($n = 3$) or significant congenital heart disease ($n = 18$) (pulmonary valve stenosis (7), tetralogy of Fallot (3), atrioventricular canal defect (2), aortic stenosis (2), coarctation (2), and a large VSD requiring PA banding (2)). In total, 25 of 64 (39%) patients had a PDA or VSD at some point in our study, of which 5 PDAs and one VSD closed, and 3 PDAs were closed percutaneously. Our study population was ultimately comprised sixty-four patients with BPD who had both a screening echocardiogram for BPD-PH at approximately 36 weeks PMA and a separate discharge echocardiogram. Figure 1 describes the breakdown of these 64 patients by their pulmonary hypertension status both at their screening echocardiogram and NICU discharge. Thirty-five patients had PH at screening; in 17 (49%) of them it resolved by discharge. Another 4 patients had no BPD-PH on screening echocardiogram but had it at discharge. The small sizes of individual groups unfortunately precluded significant subgroup analysis due to inadequate power. The diagnosis of PH was made on 59 studies based on PDA in 25, VSD shunting in 4, right-to-left shunting in 4, TR jet in 10, and interventricular septal flattening alone in 16 patients.

Table 1 demonstrates clinical and perinatal data for the entire study population and a comparison between infants with and without PH at discharge. There were no statistically significant differences between the cohorts. The overall study population was extremely premature and approximately 25% were deemed to have SGA and IUGR status. All patients included in the study had severe BPD at the time of their screening echocardiogram by NIH consensus criteria (all had > 30% FiO2 or positive pressure ventilation). The study population required nearly 3 months of invasive positive pressure ventilation and 7 weeks of non-invasive positive pressure ventilation, more than half experienced episodes of culture-positive sepsis, 20% experienced an episode of necrotizing enterocolitis, and a third (34%) had a PDA treated with medication or catheterization-based closure. In total, 4 patients underwent PDA closure and 1 patient underwent ASD closure after their screening echocardiogram. The patient with percutaneous ASD closure and 3 patients with percutaneous PDA closure had BPD-PH at screening; all 4 of these patients had hemodynamic PH prior to shunt closure. The final PDA closure patient had RV systolic pressures approximately 40% of the recorded systemic systolic pressure. BPD-PH resolved prior to discharge in the patient with ASD closure and two patients with PDA closure.

Table 2 is a comparison of outcomes between the groups with and without BPD-PH at discharge. Though infants with BPD-PH at discharge were significantly more likely to be discharged with diuretic therapy, there was no difference in tracheostomy or supplemental oxygen use at discharge. LOS between the two groups was not significantly different when mortalities were excluded (159 ± 79 vs 153 ± 54 days,

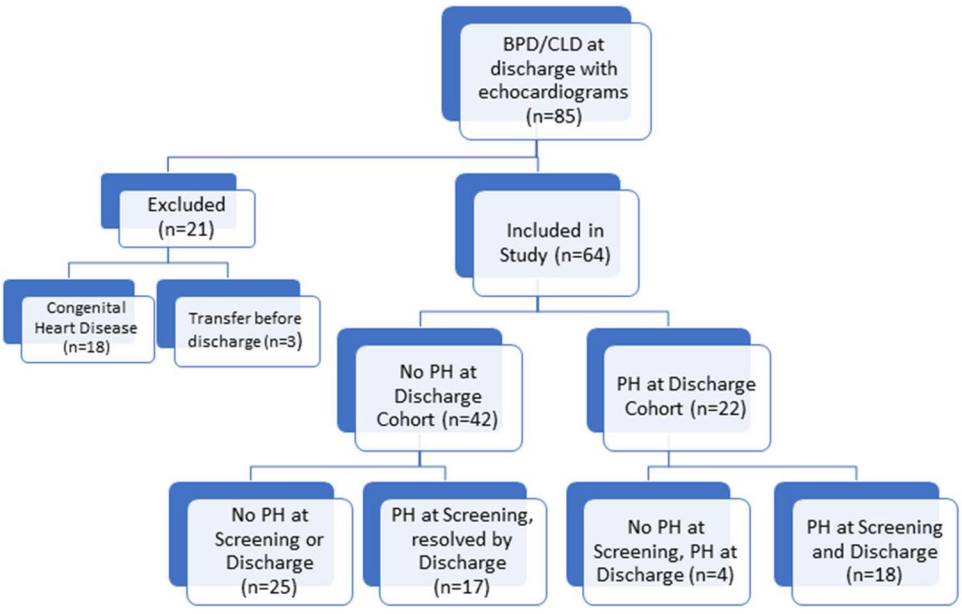

Fig. 1 Cohort organization. *BPD/CLD* bronchopulmonary dysplasia or chronic lung disease, *PH* pulmonary hypertension

Table 2 Outcomes for PH at discharge and No PH at discharge cohorts

Outcomes at discharge	All patients ($n=64$)	No PH at discharge ($n=42$)	PH at discharge ($n=22$)	p-value
LOS, death as competing risk	156.1 ± 70.5	158.9 ± 79.3	153.4 ± 54.4	0.145
Discharged on diuretics	58%	45%	82%	0.005
Discharged on PVDs	9%	0%	27%	0.001
Discharged on O2	81%	81%	82%	0.933
Tracheostomy	25%	26%	23%	0.761
Death	11%	5%	23%	0.029

LOS Length of stay, *PVDs* pulmonary vasodilators, *O2* oxygen

$p=0.145$). Twenty-four patients (39%) had either a small VSD or a PDA at any point in the study; 15 (33%) patients with a PDA or VSD at discharge needed diuretics. Those who died while in the NICU were more likely to have BPD-PH at time of death (5 (23%) vs 2 (5%), $p=0.029$).

Our institutional practice was to optimize lung disease as much as possible and initiate pulmonary vasodilators only in the setting of RV dysfunction causing secondary end-organ dysfunction. Ten total patients were initiated on pulmonary vasodilators in the NICU, including the three patients who improved after ASD or PDA closure. All three of these patients were weaned off pulmonary vasodilators prior to discharge, as was one other patient. Six of the ten patients were discharged on pulmonary vasodilators, all of whom had evidence of PH at discharge. Four patients were on sildenafil monotherapy (2 mg/kg/dose every 6 h; max dose 10 mg every 6 h). Two additional patients were on sildenafil at the above dose and bosentan (2 mg/kg/dose twice daily).

Table 3 demonstrates data from the screening echocardiograms, which were performed at a mean PMA of 36.6 ± 2.9 weeks (range 34 + 5 days–38 + 3 days). Two patients were echoed before 35 weeks PMA, at which time both were over 8 weeks old, receiving invasive positive pressure ventilation and demonstrated acute clinical worsening. As these patients already met NIH criteria for BPD diagnosis, they were included in our cohort. Discharge echocardiograms were undertaken at a median of 5 days (range 1–41 days) prior to discharge. On 36 weeks PMA

Table 3 36 weeks PMA Screening Measurements for those with and without PH at Discharge

Clinical characteristics	No. measured	All patients ($n=64$)	No PH at discharge ($n=42$)	PH at discharge ($n=22$)	p value
Qualitative assessment					
ASD present	64	41%	29%	64%	0.007
RA dilation present	64	30%	29%	32%	0.787
RV dilation present	64	41%	31%	59%	0.009
RV hypertrophy present	64	39%	26%	63%	0.012
Quantitative measurements					
MPA, cm	56	0.79 ± 0.15	0.76 ± 0.13	0.85 ± 0.17	0.078
MPA, Z-score	56	+ 0.4 ± 1.09	+ 0.16 ± 0.95	+ 0.9 ± 1.21	0.048
RV EDA, cm^2	62	3.06 ± 0.93	2.96 ± 0.77	3.24 ± 1.15	0.324
LV EDV, mL	61	3.89 ± 1.69	3.97 ± 1.71	3.72 ± 1.68	0.544
RVSp: SSp	37	0.63 ± 0.21	0.56 ± 0.14	0.75 ± 0.25	0.017
EI, systole	63	0.78 ± 0.13	0.79 ± 0.1	0.72 ± 0.12	0.068
EI, diastole	64	0.84 ± 0.12	0.85 ± 0.11	0.77 ± 0.12	0.017
Functional measurements					
RV FAC	62	0.33 ± 0.09	0.36 ± 0.07	0.27 ± 0.08	< 0.001
BNP measurements					
BNP	46	102 ± 138.8	68.8 ± 73	171.1 ± 208.4	0.035
BNP > 100	46	53%	48%	64%	0.223

ASD atrial septal defect, *MPA* main pulmonary artery, *RV EDA* RV end-diastolic area, *LV EDV* LV end-diastolic volume, *SSp* systemic systolic pressure, *RVSp* RV systolic pressure, *EI* eccentricity index, *TAPSE* tricuspid annular plane systolic excursion, *MPI* myocardial performance index, *TV* tricuspid valve, *BNP* B-type natriuretic peptide

echocardiogram, 55% of patients had evidence of BPD-PH. Of those who continued to have PH at discharge, screening echocardiograms demonstrated a higher RV systolic pressure (RVSp; 55.6 vs 42.9 mmHg, $p=0.017$) and RV systolic to systemic pressure ratio (RVSp:SSp; 0.75 ± 0.25 vs 0.56 ± 0.14, $p=0.017$). They were also more likely to have a small or moderate secundum ASD (64% vs 29%, $p=0.007$) and receive qualitative descriptions of RV hypertrophy (63% vs 26%, $p=0.012$), RV dilation (59% vs 31%, $p=0.009$) and impaired RV function (63% vs 26%, $p=0.03$). None of our cohort demonstrated spectral Doppler evidence of pulmonary vein stenosis.

There was more quantitative evidence of RV dysfunction as evidenced by a lower RV fractional area change ($27\%\pm8\%$ vs $36\%\pm8\%$, $p=<0.001$) in patients with BPD-PH at discharge. While main pulmonary artery (MPA) measurements were not significantly different, Z-scores were higher in patients with BPD-PH at discharge ($+0.9\pm1.21$ vs $+0.16\pm0.95$, $z=0.048$). BNP levels at 36 weeks PMA screening were higher in those with PH at discharge (171.1 ± 208.4 vs 68.8 ± 73 pg/mL, $p=0.035$).

As anticipated, (see Supplemental Table 1) the presence of an ASD was associated with RV dilation (35% RV dilation with ASD vs 24% RV dilation without ASD, $p=0.001$). The presence of an ASD was also associated with higher eccentricity index in diastole (1.30 vs 1.12, $p<0.001$). However, there was no association between BNP levels and the presence or absence of an ASD (114 ± 166 vs 94 ± 118, $p=0.76$).

Univariate logistic regression analyses were performed on screening echocardiogram measurements and are displayed in Table 4. Qualitative screening echocardiogram evidence of RV hypertrophy (OR 4.6, CI (1.6–14.0)), RV dilation (OR 3.1, (CI 1.1–9.0)), qualitatively impaired RV function (OR 6.4, (CI 1.2–33.3)) or the presence of an ASD (OR 4.2 (CI 1.4–12.4)) were associated with increased odds of PH at discharge. Any 1% decrease in right ventricular fractional area change was associated with a 1.18 (95% CI 1.08, 1.28, $p<0.001$) increase in the odds of BPD-PH at discharge. This was true across the RV FAC spectrum. A receiver-operator curve was constructed for RV fractional area change with an AUROC of 0.79. A best-fit point of 30.4% yielded a sensitivity of 0.73 and a specificity of 0.82, which is in keeping with previously published data on RV FAC in premature infants [12].

Multivariate logistic regression modeling utilizing impaired RV FAC and presence of an ASD was the strongest 2-variable model predicting BPD-PH at NICU discharge (RV FAC odds ratios 1.17 (CI 1.08–1.28) and ASD odds ratio 4.21 (CI 1.13–15.6); c-index = 0.859). In this model, for every decrease in RV FAC by 1% the odds of PH increased by 1.17. The strongest 3-variable model added the qualitative presence of RVH to RV FAC and ASD (RV FAC odds ratio 1.15 (CI 1.05–1.27), ASD odds ratio 4.33 (CI 1.13–16.6), and RVH odds ratio 2.96 (CI 1.76–11.5); c-index = 0.872). See Supplemental Tables 2 and 3 for these models, and Supplemental Tables 4 and 5 for the strongest 2-variable and 3-variable models.

Table 4 Univariate ODDS RATIOS of PH at discharge for screening echo measurements

Clinical characteristics	Odds ratio	95% CI	*p*-value
Qualitative assessment			
ASD present	4.16	(1.40, 12.38)	0.010
RA dilation present	1.18	(0.39, 3.60)	0.770
RV dilation present	3.11	(1.07, 9.03)	0.037
RV hypertrophy present	4.67	(1.55, 14.05)	0.006
Quantitative measurements			
MPA, cm	1.50	(0.04, 2.13)	0.056
MPA, Z-score	1.90	(1.06, 3.41)	0.032
RV EDA, cm^2	1.36	(0.77, 2.39)	0.285
LV EDV, mL	0.92	(0.66, 1.28)	0.635
RVSp: SSp	1.56	(0.76, 2.23)	0.080
EI, systole	1.27	(0.70, 2.21)	0.060
EI, diastole	1.46	(1.06, 2.10)	0.023
RV FAC	0.85	(0.78, 0.93)	< 0.001
BNP measurements			
BNP	1.005	(0.99, 1.01)	0.101

Discussion

Our retrospective cohort study of premature infants with severe BPD demonstrated that guideline-recommended PH screening protocols can help identify those patients with BPD at greatest risk for PH at discharge. Although neither the perinatal nor clinical courses differed between groups at the time of their 36 weeks PMA evaluations, echocardiographic determinations of pulmonary hypertension, right ventricular dysfunction and hypertrophy or the presence of an ASD were associated with BPD-PH at NICU discharge, which itself was associated with higher use of diuretic medications and higher in-NICU mortality. Using this data, we were able to construct novel models that suggest these factors as particularly high risk for BPD-PH at discharge when in combination. Interestingly, a subset of patients with normal screening echocardiograms later demonstrated PH on their pre-discharge echocardiograms, which is in keeping with a previous natural history study showing a median PMA at diagnosis of 42 weeks [6].

The highly variable clinical progression from BPD to BPD-PH and its associated morbidity and mortality rates underscore the need for ongoing PH screening in premature infants with BPD. Several perinatal risk factors such as

pre-eclampsia, premature rupture of membranes, chorioamnionitis, SGA, prolonged mechanical ventilation, NEC, and sepsis have been associated with the development of PH in premature infants [3, 5, 15], but when focusing on patients with severe BPD (as all our cohort were), none of these factors identified those at greater risk for PH at discharge, consistent with other studies [4, 24]. Further representing the unpredictable nature of BPD-PH was the fact that 18% of our cohort with BPD-PH at discharge had normal 36 weeks PMA screening echocardiograms and that 49% of those with PH at screening had demonstrated resolution by discharge (17/35), which was consistent with previously reported data [6]. These data emphasize the need for regimented, longitudinal PH screening for infants with BPD.

Our analyses of 36 weeks PMA screening echocardiograms identified several findings associated with increased risk of PH at discharge. Qualitative evidence of RV hypertrophy, dilation, or impaired function, the presence of a secundum ASD, or objective data demonstrating higher BNP, larger MPA Z-scores, higher RV to systemic systolic pressure ratio, and lower RV fractional area change on initial screening echocardiogram were each associated with increased odds of PH at discharge in univariate analyses. Multivariate logistic regression analyses similarly supported these findings with multiple highly discriminatory models. (See supplemental Tables 1–4.) Collectively, these data suggest that regardless of RV pressure, any evidence of RV hypertrophy or dysfunction on a screening echocardiogram may identify which premature infants with BPD are at increased risk for PH at discharge. As previously described by Altit et al. [12], we found RV FAC, readily obtainable on a standard echocardiogram, to be particularly helpful in identifying those at increased odds of PH at discharge. We believe these findings further support the application of a regimented screening protocol for this patient population. They also raise the question whether the presence of an ASD at time of screening should prompt early referral for closure, particularly in patients with severe BPD who have other findings suggestive of RV dysfunction as described above.

This small, single-center study has several limitations. Its retrospective nature limited our ability to obtain all data in some patients. A subset of patients did not have PA acceleration time, TAPSE, or RVFW TDI data, also used to calculate MPI, and this prevented adequate power for statistical significance, but had they been adequately powered, may have demonstrated further useful measurements to evaluate likelihood of BPD-PH at discharge. Further, our practice does not include routine screening of premature infants prior to the diagnosis of BPD, which precludes any assessment of 'early' PH. Some of the measurements which were significantly associated with PH at discharge were closely associated, such as the presence of an ASD with higher EI in diastole and RV dilation. However, this study was inadequately powered to specifically explore the differences between the 17-patient subgroup in whom PH resolved at discharge and the 18 patients in whom PH persisted to discharge. Due to selection bias, our sample of patients was not representative of the full spectrum of BPD patients, as many patients with milder lung disease either did not have BPD as a discharge diagnosis or had mild enough disease to be discharged without repeat echocardiograms. Furthermore, a significant number of patients were excluded because they had more mild disease and did not have a discharge echocardiogram, which may skew results as only the most ill patients who stayed in the NICU long enough for a discharge echocardiogram were included. This selection bias and the fact that we only included screening and discharge echocardiograms limit our ability to draw more robust conclusions about the natural history of BPD-PH. Finally, the small sub-groups of those with PH at discharge limited our ability to identify factors associated with late development of PH. A multicenter prospective study of patients with BPD and regimented screening would be helpful to explore the roles BPD severity plays in risk of BPD-PH at discharge and the natural history of development and resolution of BPD-PH.

In conclusion, we demonstrated that at the time of severe BPD diagnosis in premature infants, neither perinatal nor clinical data were helpful in differentiating between those with or without BPD-PH at the time of NICU discharge, but that concurrent 36 weeks PMA echocardiographic evaluation may help identify those at highest risk based on certain echocardiogram findings. In particular, qualitative evidence of RV dysfunction, hypertrophy, or dilation, the presence of an ASD, or impaired RV FAC were strongly associated with BPD-PH at NICU discharge. These findings support recently published guidelines promoting the use of regimented, longitudinal echocardiographic screening protocols in premature infants with BPD, which is further supported by our findings that nearly 20% of those with BPD-PH at discharge had normal screening studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00246-022-02911-2.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by (BAM), (MAM), and (MRC). The first draft of the manuscript was written by (BAM) and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability All data were obtained retrospectively in a de-identified manner from the medical record of included patients in accordance to guidance provided by the University of Virginia bioethics committee (IRB).

Code Availability Not applicable.

Declarations

Conflict of interest None of the authors have any conflicts of interest to declare relevant to the content in this article.

Consent to Participate This research study was conducted retrospectively from data obtained for clinical purposes. We consulted with the bioethics committee of University of Virginia who determined that consent to participate was not required due to its retrospective nature posing minimal risk to participants.

Consent for Publication This research study was conducted retrospectively from de-identified data obtained for clinical purposes. We consulted with the bioethics committee of University of Virginia who determined that consent for publication was not required.

Ethical Approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University of Virginia approved this study.

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