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Original Article

Pulmonary hypertension with bronchopulmonary dysplasia: Aichi cohort study

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Abstract

***Background*:** The incidence of pulmonary hypertension (PH) associated with bronchopulmonary dysplasia (BPD) has not been investigated in regional cohorts. The aim of this study was to clarify the incidence of PH associated with BPD in all very low birthweight infants (VLBWIs) born during the study period in Aichi Prefecture, Japan.

***Methods*:** We conducted a retrospective observational cohort study of all VLBWIs born in Aichi Prefecture. The inclusion criteria were VLB, birth between 1 January 2015 and 31 December 2015, and admission to any neonatal intensive care unit in Aichi Prefecture. BPD28d and BPD36w were defined as the need for supplemental oxygen or any respiratory support at 28 days of age or 36 weeks of postmenstrual age (PMA). The primary outcome was the incidence of PH after 36 weeks' PMA (PH36w) in VLBWIs with BPD28d and BPD36w. The secondary outcomes were the clinical factors related to PH36w in BPD36w patients. Mann–Whitney *U*-test and Fisher's exact test were used for univariate analysis. Differences were considered statistically significant at $P < 0.05$. Risk ratio (RR) and 95% confidence interval (CI) were also evaluated.

***Results*:** A total of 441 patients were analyzed. A total of 217 and 131 patients met the definition of BPD28d and BPD36w, respectively. Nine patients were diagnosed with PH36w (4.2% and 6.9% of the BPD28d and BPD36w patients, respectively). The presence of oligohydramnios (RR, 2.71; 95% CI: 1.55–4.73, $P = 0.014$) and sepsis (RR, 3.62; 95% CI: 1.51–8.63, $P = 0.025$) was significant in the PH36w patients.

***Conclusions*:** The incidence of PH36w was 4.2% and 6.9% in the BPD28d and BPD36w patients, respectively. Oligohydramnios and sepsis were significantly associated with PH36w in VLBWIs.

Key words bronchopulmonary dysplasia, oligohydramnios, pulmonary hypertension, sepsis, very low birthweight infant.

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The mortality of very low birthweight infants (VLBWIs) has recently improved with the recent advances in intensive neonatal management.[1,2] However, bronchopulmonary dysplasia (BPD) remains one of the most severe problems for VLBWIs because it is associated with high mortality and neurodevelopmental impairment.[3–5] According to the Neonatal Research Network of Japan (NRNJ) database, the incidence of

BPD at 28 days of age in VLBWIs increased from 27.7% in 2005 to 41.6% in 2014.[6] In addition, pulmonary hypertension (PH) associated with BPD is considered important, because more severe preterm newborns have been saved by the recent advanced intensive neonatal management.[7–9] There have been some studies about PH associated with BPD, but they were based on patient data from a single or small number of institutions.[4,10–15] To determine the actual incidence of PH associated with BPD in VLBWIs, a cohort survey is needed.

In Aichi Prefecture, Japan, there are approximately 65 000 births each year. Almost all VLBWIs born in Aichi Prefecture are hospitalized in neonatal intensive care units (NICUs) of the Tokai Neo Forum, which includes all hospitals with NICUs in Aichi Prefecture. A cohort survey of VLBWIs with BPD admitted to NICUs in the Tokai Neo Forum might contribute to our knowledge of the incidence of PH associated with BPD in more detail. By understanding the background of PH associated with BPD in detail, an appropriate management strategy to prevent it might be established. Thus, we conducted this study to clarify the incidence of PH associated with BPD in all VLBWIs born during the study period in Aichi Prefecture.

Methods

We conducted a retrospective observational cohort study of all VLBWIs born in Aichi Prefecture. The inclusion criteria of this study consisted of VLB, birth between 1 January 2015 and 31 December 2015, and admission to NICUs of the Tokai Neo Forum. To exclude factors other than BPD that could affect PH, we excluded VLBWIs with obvious chromosomal or other congenital anomalies.

In the survey we investigated gestational age (GA) in weeks and days, birthweight (BW) in grams, sex, small for gestational age (SGA; defined as birthweight below the 10th percentile for GA in the Japanese population),[16] oligohydramnios, preterm rupture of membranes (PROM), prenatal maternal steroids, intraventricular hemorrhage (IVH), IVH grade ≥3,[17] periventricular leukomalacia (PVL),[18] retinopathy of prematurity (ROP) stage ≥3,[19] auditory screening test failure, necrotizing enterocolitis (NEC),[20] survival at 28 days of age, and BPD28d (defined as the requirement of oxygen or respiratory supportive therapy, including nasal high-flow therapy [NHF], at 28 days of age), for each VLBWI. If BPD28d was present we investigated serum immunoglobulin (Ig)M level (mg/dL) at admission, clinical or histological chorioamnionitis (cCAM or hCAM), respiratory distress syndrome (RDS), pneumothorax, pulmonary hemorrhage, sepsis, Japanese BPD classification based on the presence or absence of RDS, intrauterine infection/inflammation, and chest X-ray findings (Table 1),[21,22] postmenstrual age (PMA) at termination of mechanical ventilation (MV) in weeks, PMA at termination of non-invasive positive pressure ventilation (NIPPV) or NHF in weeks, inhaled nitric oxide (iNO) use up to 7 days after birth, use of indomethacin for patent ductus arteriosus (PDA), surgical treatment for PDA, BPD36w (defined as oxygen use or any respiratory supportive therapy, including NHF, at 36 weeks' PMA), fraction of inspired oxygen (FiO_2) at 36 weeks' PMA, steroid therapy for BPD28d, respiratory care after discharge or at the investigation, and PH36w (defined as PH after 36 weeks' PMA). We also queried which parameter was used for the echocardiographic diagnosis of PH. The queried parameters included tricuspid regurgitation (TR) velocity, systolic flattening of interventricular septum (IVS), ratio of acceleration time to ejection time (AT/ET) of pulmonary artery (PA) flow, right ventricular (RV) wall thickness and PH score. The PH score consists of seven items: ratio of the diameter of the aortic valve to the diameter of the PA valve, ratio of the diameter of the mitral valve to the diameter of the tricuspid valve, thickness of the RV anterior wall at end-diastole and at end-systole, ratio of the length of the left ventricular major axis to minor axis at end-systole on left ventricular short axis view, RV systolic time interval, and AT/ET of PA flow. Each item was scored from 0 to 2 and the total score of all items was evaluated. A total score of 0–1 was defined as no PH, a total score of 2–4 was defined as mild PH, a total score of 5–8 was defined as moderate PH, and a total score of ≥9 was defined as severe PH.[23] Additionally, respiratory therapy and vasodilation agents used for PH36w were investigated. Oxygen therapy, MV and NIPPV or NHF were included as types of respiratory therapy. As vasodilation agents, phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil), endothelin antagonists (bosentan, ambrisentan and macitentan), prostacyclin derivatives (epoprostenol, beraprost and treprostinil), and iNO were investigated.

Table 1 Japanese bronchopulmonary dysplasia classification[21,22]

Type	RDS	Intrauterine infection/ inflammation	Bubbly/ cystic appearance
1	+	−	+
2	+	−	−
3	−	+	+
3'	−	+	−
4	−	ND	+
5	−	−	−
6	Not classified in any of the preceding types		

ND, no data; RDS, respiratory distress syndrome.

The primary outcome measure of this study was the incidence of PH36w in VLBWIs with BPD28d and BPD36w. The secondary outcome measures were the clinical factors related to PH36w in BPD36w patients. To identify clinical factors predicting PH36w in BPD36w patients, we compared clinical factors in the PH36w and non-PH36w patients. All statistical analyses were performed with EZR version 1.31. Mann–Whitney *U*-test and Fisher's exact test were used for univariate analysis. Logistic regression analysis was planned for multivariate analysis. Risk ratio (RR) and 95% confidence interval (CI) were also evaluated. Differences were considered statistically significant at $P < 0.05$.

This study was approved by the ethics committee of Fujita Health University (HM18-273).

Results

Survey responses were obtained from all 20 facilities in the Tokai Neo Forum. One institution had no admission of VLBWIs. From the 19 other institutions, 468 VLBWIs were included and 27 were excluded. The excluded patients consisted of one patient with atrial septal defect, one patient with ventricular septal defect, four patients lost to follow-up due to transfer to hospitals outside of Aichi Prefecture, and 21 patients who died before the age of 28 days. Of the 441 patients included in the analysis, 217 met the definition of BPD28d (49.2%: 95% CI: 44.4–54.0%). Of the 217 BPDd28 patients, one died before 36 weeks' PMA and 131 patients were classified as having BPD36w. Of the 131 BPD36w patients, nine patients were further classified as having PH36w. There were no PH36w patients in the group of 85 patients who did not have BPD36w (Fig. 1). The characteristics of all included VLBWIs, BPD28d, non-BPD28d and BPD36w patients are listed in Table 2.

Incidence of PH36w in VLBWIs, BPD28d and BPD36w patients

The incidence of PH36w in VLBWIs, BPD28d patients (excluding one patient who died before 36 weeks' PMA), and BPD36w patients was 0.020 (95% CI: 0.009–0.038), 0.042 (95% CI: 0.019–0.078) and 0.069 (95% CI: 0.032–0.126), respectively.

Perinatal factors related to PH36w in BPD36w patients

On univariate analysis a significant difference was seen in the presence of oligohydramnios (RR 2.711; 95% CI: 1.554–4.731, $P = 0.014$) and sepsis (RR 3.615; 95% CI: 1.513–8.634, $P = 0.025$) between the PH36w and non-PH36w patients. Multivariate analysis was not possible because of the small number of PH36w patients (Table 3).

Comparison of characteristics between PH36w and non-PH36w patients

The PMA at termination of MV was not significantly different between PH36w and non-PH36w patients, but the PMA at termination of NIPPV or NHF was significantly longer in PH36w patients. The frequency of any grade of IVH, IVH grade ≥3, PVL and ROP stage ≥3 was not significantly different between the two groups of patients. The composite outcome of respiratory care at the investigation or death after 36 weeks' PMA was significantly more common in the PH36w patients (Table 3, $P < 0.001$).

Characteristics of PH36w patients

PH36w patients were reported from five institutes. PH was diagnosed on echocardiography in all cases (Table 4). The findings of TR velocity, systolic flattening of IVS and PH score were used in five of the nine PH36w patients for PH diagnosis. All patients with systolic flattening of IVS were given a pulmonary vasodilator. At the time of investigation, two patients died, four patients were receiving home oxygen therapy, one patient discharged without any home care and two patients continued hospitalization with NIPPV.

Discussion

This cohort survey is the first regional survey to include all VLBWIs during the survey period, allowing for estimation of the incidence of PH36w in VLBWIs with BPD28d and BPD36w. During the survey period, there were 65 615 births in Aichi Prefecture, Japan, of which 492 involved VLBWIs according to the vital statistics records of Aichi Prefecture.[24]

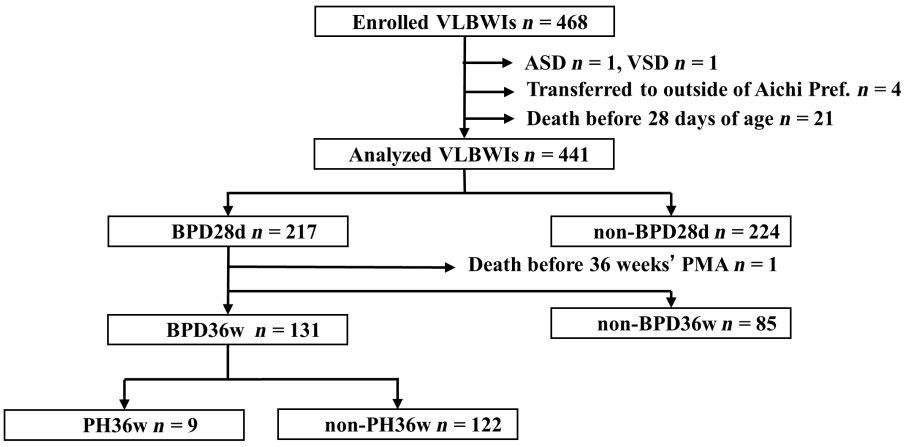

Fig. 1 Study flow chart. ASD, atrial septal defect; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; PMA, postmenstrual age; VLBWI, very low birthweight infant; VSD, ventricular septal defect. BPD28d: defined as oxygen use or any respiratory supportive therapy at 28 days of age; BPD36w: defined as oxygen use or any respiratory supportive therapy at 36 weeks' PMA. PH36w: defined as PH after 36 weeks' PMA.

Table 2 Characteristics of all included VLBWIs, BPD28d, non-BPD28d and BPD36w patients

	All (n = 441)	Non-BPD28d (n = 224)	BPD28d (n = 217)	BPD36w (n = 131)
Gestational age (weeks)	29 (26–31)	31 (30–33)	27 (25–28)	26 (25–28)
Birthweight (g)	1,125 (850–1,338)	1,306 (1,166–1,431)	880 (719–1,073)	806 (643–960)
Sex (male)	52.4	50.9	54.4	57.3
Antenatal steroid	58.6	54.8	61.8	66.4
PROM	23.6	14.5	32.3	35.9
Oligohydramnios	19.4	16.9	21.8	27.7
SGA	45.1	62.1	27.6	34.4
Serum IgM >20 mg/dL	–	–	6.0	9.2
cCAM or hCAM	–	–	34.0	33.6
BPD classification				
1 or 2	–	–	63.1	63.4
3 or 3′	–	–	22.6	26.0
4	–	–	4.6	5.4
5	–	–	8.3	3.8
6	–	–	1.4	1.5
RDS	–	–	71.4	71.8
Pneumothorax	–	–	4.1	3.8
Pulmonary hemorrhage	–	–	2.8	3.8
iNO use up to 7 days after birth	–	–	6.9	10.8
Indomethacin for PDA	–	–	47.9	51.1
Surgery for PDA	–	–	8.8	14.5
Sepsis	–	–	11.6	14.5
Termination of MV (weeks)	–	–	30 (29–31)	30 (29–32)
Termination of NIPPV or NHF (weeks)	–	–	35 (34–37)	36 (35–38)
Steroid for BPD	–	–	47.7	66.4
FiO_2 at 36 weeks' PMA	–	–	0.21 (0.21–0.25)	0.23 (0.21–0.25)
IVH	11.3	3.2	18.9	19.8
IVH grade ≥3	3.9	0.9	6.9	6.9
PVL	5	1.8	7.8	10.7
NEC	1.4	0	2.8	2.3
ROP stage ≥3	12.8	3.7	22.2	29.0
AABR test failure	8.9	5.1	12.9	15.1
Respiratory care at the investigation or death after 36 weeks' PMA	–	–	20.3	32.8

Data given as median (interquartile range) or percentage.

BPD28d: defined as the requirement of oxygen or respiratory supportive therapy, including NHF, at 28 days of age.

BPD36w: defined as the requirement of oxygen or any respiratory supportive therapy, including NHF, at 36 weeks' PMA.

AABR, automated auditory brainstem response; BPD, bronchopulmonary dysplasia; cCAM, clinical chorioamnionitis; FiO_2, fraction of inspired O_2; hCAM, histological chorioamnionitis; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NHF, nasal high-flow therapy; NIPPV, non-invasive positive pressure ventilation; PDA, patent ductus arteriosus; PMA, postmenstrual age; PROM, preterm rupture of membranes; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age.

By contrast, this survey included 468 VLBWIs before exclusion criteria were applied. The discrepancy between the prefectural vital statistics records and the number of VLBWIs in our survey might reflect the number of VLBWIs whose address was given as being in Aichi Prefecture but who were born in other prefectures, or whose address was given as being in other prefectures but who were born in Aichi Prefecture.

This study has some limitations. First, there was no standardized protocol for screening echocardiography to identify PH associated with BPD, due to the retrospective nature of the study. The pediatric PH guidelines endorsed by the American Heart Association and American Thoracic Society recommending screening echocardiography for PH in premature infants with moderate to severe BPD were published in 2015. Almost all institutions included in this study did not have protocols to perform screening echocardiography for PH in BPD36w patients. Thus, mild PH in BPD36w patients might have been missed, leading to an underestimation of the incidence of PH36w in BPD36w patients. Altit *et al*. reported that only 38% of institutions had screening protocols for PH associated with BPD according to an electronic survey conducted in 2017.[25] However, circulatory management strategies that included echocardiographic assessment were found to be commonly used by Japanese neonatologists in a national survey about circulatory management for extremely low birthweight infants in 2011. That study showed that echocardiography was performed by neonatologist in all NICUs.[26] Thus, because echocardiographic assessment has been shown to be common in the NICUs, we assumed that evaluation for PH was performed in all units in this study when physicians in the

Table 3 Comparison of characteristics between PH36w and non-PH36w patients

	Non-PH36w (n = 122)	PH36w (n = 9)	P-value
Gestational age (weeks)	26 (25–29)	25 (24–26)	0.150
Birthweight (g)	822 (650–978)	716 (528–893)	0.148
Sex (male)	57.4	55.6	1.000
Antenatal steroid	66.4	66.7	1.000
PROM	35.2	44.4	0.721
Oligohydramnios	24.8	66.7	0.014
SGA	34.4	33.3	1.000
Serum IgM >20 mg/dL	8.3	22.2	0.195
cCAM or hCAM	31.9	55.6	0.162
BPD classification			
1 or 2	64.8	44.4	
3 or 3′	24.6	44.4	
4	4.9	11.1	
5	4.1	0.0	
6	1.6	0.0	
RDS	71.3	77.8	1.000
Pneumothorax	4.1	0.0	1.000
Pulmonary hemorrhage	4.1	0.0	1.000
iNO use up to 7 days after birth	9.0	33.3	0.057
Indomethacin for PDA	51.6	44.4	0.740
Surgery for PDA	15.6	0.0	0.356
Sepsis	12.3	44.4	0.025
Termination of MV (weeks)	30 (29–32)	31 (30–33)	0.294
Termination of NIPPV or NHF (weeks)	36 (35–38)	41 (37–)	0.005
Steroid for BPD	57.9	100.0	0.023
FiO_2 at 36 weeks' PMA	0.23 (0.21–0.25)	0.30 (0.23–0.50)	0.004
IVH	20.5	11.1	0.687
IVH grade ≥3	6.6	11.1	0.484
PVL	10.7	11.1	1.000
NEC	2.5	0.0	1.000
ROP stage ≥3	27.0	55.6	0.120
AABR test failure	15.1	14.3	1.000
Respiratory care at the investigation or death after 36 weeks' PMA	28.7	88.9	<0.001

Data given as median (interquartile range) or percentage. P values were calculated using the Mann–Whitney U-test or the Fisher's exact test.

PH36w: defined as PH after 36 weeks' PMA.

AABR, automated auditory brainstem response; BPD, bronchopulmonary dysplasia; cCAM, clinical chorioamnionitis; FiO_2, fraction of inspired O_2; hCAM, histological chorioamnionitis; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NHF, nasal high-flow therapy; NIPPV, non-invasive positive pressure ventilation; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PMA, postmenstrual age; PROM, preterm rupture of membranes; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age.

institutions considered that a close examination of PH was necessary.

Second, there was no standardized protocol to clarify BPD severity in this survey, such as the oxygen reduction test.[27,28] The definition of BPD36w in this study included any respiratory supportive therapy at 36 weeks' PMA. Respiratory therapy decisions were based on the judgment of each attending physician. However, changes in neonatal respiratory support such as mild respiratory care with NHF made many infants unclassifiable based on current BPD definitions.[2,29,30] With that in mind, we believe that this study was able to evaluate the incidence of BPD as of 2015.

Regarding the incidence of BPD28d and BPD36w in VLBWIs in this study, the incidence of BPD28d was slightly higher in this survey than that according to the NRNJ database in 2014[6] (49.2% vs 41.6%), but the incidence of BPD36w was similar (29.5% vs 29.6%). This means that the BPD severity in the present survey was similar to the BPD severity in the patients included in the NRNJ database. This survey may show the relationship between severe BPD and PH secondary to BPD in Japan.

By contrast, the incidence of PH36w with BPD28d in this cohort of VLBWIs, 4.2%, was lower than the 21.7% reported by Sun *et al*. in a single-institution study with almost the same inclusion criteria.[13] Similarly, Sheth *et al*. reported that the incidence of PH associated with BPD was 26.8% in patients with GA <32 weeks at birth and BW <1,500 g in a single-institution study.[8] The definition of BPD36w in the present study was almost the same as the definition of moderate to severe BPD used by the National Institute of Child Health and Human

Table 4 Characteristics of PH36w patients

Patient ID no.	1	2	3	4	5	6	7	8	9
Institute	A	A	A	B	B	C	C	D	E
Gestational age (weeks/days)	23/0	23/5	27/1	25/3	26/2	26/3	31/1	24/2	25/1
Birthweight (g)	431	435	953	716	946	893	692	528	741
Sex	Female	Male	Female	Female	Female	Male	Male	Male	Male
Antenatal steroid	–	+	+	–	+	+	–	+	+
PROM	–	+	–	+	+	–	–	–	+
Oligohydramnios	–	–	+	+	+	–	+	+	+
SGA	–	+	–	–	–	–	+	+	–
Serum IgM >20 mg/dL	–	–	–	–	+	–	–	+	–
cCAM or hCAM	–	–	–	+	+	+	–	+	+
BPD classification	1	1	1	3	3	2	4	3	3
RDS	+	+	+	+	–	+	–	+	+
Pneumothorax	–	–	–	–	–	–	–	–	–
Pulmonary hemorrhage	–	–	–	–	–	–	–	–	–
iNO use up to 7 days after birth	–	–	+	+	+	–	–	–	–
Indomethacin for PDA	+	+	–	–	+	–	–	+	–
Surgery for PDA	–	–	–	–	–	–	–	–	–
Sepsis	+	–	+	–	+	+	–	–	–
Termination of MV (weeks)	30	31	30	36	32	27	Continued	33	30
Termination of NIPPV or NHF (weeks)	41	41	37	Continued	37	35	NA	Continued	Continued
Steroid therapy for BPD	+	+	+	+	+	+	+	+	+
FiO_2 at 36 weeks' PMA	0.23	0.27	0.23	0.4	0.5	1.0 (nasal cannula)	0.8	0.23	0.3
IVH	–	–	+	–	–	–	–	–	–
IVH grade ≥3	–	–	+	–	–	–	–	–	–
PVL	–	–	–	+	–	–	–	–	–
NEC	–	–	–	–	–	–	–	–	–
ROP stage ≥3	–	+	+	–	–	+	–	+	+
AABR test failure	–	–	–	–	–	–	NA	+	NA
Respiratory care at the investigation or death after 36 weeks' PMA	No home care	HOT	HOT	NIPPV	HOT	HOT	Death	Death	NIPPV
Echocardiographic parameters used for PH diagnosis									
TR velocity	–	–	–	+	+	–	+	+	+
Systolic flattening of IVS	–	–	–	+	–	+	+	+	+
AT/ET in PA flow	+	–	+	+	–	–	–	–	+
RV wall thickness	–	+	–	–	–	–	+	+	–
PH score	+	+	+	+	–	–	–	–	+
Therapy for PH									
O_2 therapy	+	+	+	+	+	+	+	+	+
MV	–	–	–	–	–	–	+	+	–
NIPPV or NHF	–	–	–	+	–	–	NA	+	+
Sildenafil	–	–	–	+	–	+	+	+	+
Bosentan	–	–	–	–	–	+	+	+	+
Ambricentan	–	–	–	–	–	–	–	–	+
Beraprost	–	–	–	–	–	–	+	–	+
Epoprostenol	–	–	–	–	–	–	+	–	–
iNO	–	–	–	–	–	–	+	+	+

BPD28d: defined as the requirement of oxygen or respiratory supportive therapy, including NHF, at 28 days of age.
BPD36w: defined as the requirement of oxygen or any respiratory supportive therapy, including NHF, at 36 weeks' PMA.
AABR, automated auditory brainstem response; AT, acceleration time; BPD, bronchopulmonary dysplasia; cCAM, clinical chorioamnionitis; ET, ejection time; FiO_2, fraction of inspired O_2; hCAM, histological chorioamnionitis; HOT, home oxygen therapy; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; IVS, intraventricular septum; MV, mechanical ventilation; NA, not applicable; NEC, necrotizing enterocolitis; NHF, nasal high-flow therapy; NIPPV, non-invasive positive pressure ventilation; PA, pulmonary artery; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PMA, postmenstrual age; PROM, preterm rupture of membranes; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; RV, right ventricle; SGA, small for gestational age; TR, tricuspid regurgitation.

Development in 2001.[31] The incidence of PH36w associated with BPD36w, defined as moderate to severe BPD in the present cohort, was 6.9% and lower than the previously reported incidence from several single-institution studies (22.0%,[14] 27.6%[10] and 28.3%[7]) in which inclusion criteria included GA <28 weeks, <32 weeks, and <29 weeks, respectively. If the

present patients were limited to those with GA <28 weeks, there would have been 88 BPD36w patients and eight PH36w patients, and the incidence of PH associated with moderate to severe BPD would still have been low, at 9.1% in this setting.

One of the factors that led to a low incidence of PH36w with BPD36w in this study is the Japanese respiratory strategy, which tolerates relatively high oxygen saturation (SpO_2) levels. A 2015 national survey of BPD management in Japan found that 54% of units set the upper SpO_2 limit at 95% or more after BPD is diagnosed.[6] This might have been due to the fact that low SpO_2 levels have been shown to be associated with high mortality rates and respiratory complications such as PH.[30,31] As already noted, there was no standardized protocol to screen for PH associated with BPD with echocardiography in this study. Thus, our study might have overlooked mild PH and included only moderate to severe symptomatic PH associated with BPD in the estimation. Du *et al*. reported that the number of patients with mild PH was threefold higher than the number of patients with moderate to severe PH in their study.[12] They also noted that patients with moderate to severe PH accounted for an estimated 5.9% of all patients, similar to the present results.

With regard to the clinical factors associated with PH36w in BPD36w patients, oligohydramnios and sepsis were found to be significant in the present study. Oligohydramnios has been reported as a significant risk factor for PH associated with BPD because of its inhibitive effect on lung development.[32] It is considered that the hypoplastic lung may have elevated pulmonary vascular resistance due to maldevelopment including a decrease in the cross-sectional area and abnormal muscularization of the pulmonary vasculature.[33–35] In contrast, An *et al*. reported that infection during hospitalization is related to PH associated with BPD.[4] In BPD, structural abnormalities of the pulmonary vasculature might cause vessel narrowing and decreased vascular compliance. Decreased angiogenesis as a consequence of BPD might contribute to the smaller vascular cross-sectional area. These factors contribute to elevated pulmonary vascular resistance. In addition, pulmonary vasculogenesis has been shown to be disturbed in a postnatal sepsis model.[36–41] Although SGA has been found to be related to PH associated with BPD[32], a significant association with SGA was not found in the present study. As mentioned earlier, it is possible that cases of mild PH might have been overlooked in the present study. In addition, we were not able to perform multivariate analysis because there were too few PH36w patients.

In conclusion, the incidence of PH36w was 4.2% and 6.9% in VLBWIs with BPD28d and BPD36w, respectively, and the presence of oligohydramnios and sepsis was significant in BPD36w patients with PH36w. This study evaluated the prevalence of PH36w associated with BPD36w in a regional birth cohort without a definitive PH screening protocol. The prevalence of PH36w associated with BPD36w in this study might reflect the prevalence of moderate to severe PH. Although additional studies with more subjects and an established protocol for PH screening are warranted, the present findings imply that VLBWIs with BPD36w, especially when combined with oligohydramnios and sepsis, might need screening for PH.

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Disclosure

The authors declare no conflicts of interest.

Author contributions

Y.Kaw., M.M., M.H., T.T. and Y.Y. contributed to the conception and design of this study. Y.Kaw., M.M., T.T., Y.Y., A.N., Y.Kat., M.Kou., T.K., R.T., K.M., S.Ha., H.Y., K.T., K.I., Y.N., S.Ho., O.S., Y.F., M.Kok. and H.I. collected the data. Y.Kaw. and M.M. analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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