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Original Article

Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia in preterm infants: a retrospective cross-sectional study of the prolonged invasive mechanical ventilation pathway

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Abstract: Background: Bronchopulmonary dysplasia (BPD) remains the dominant chronic morbidity of preterm birth, and hemodynamically significant patent ductus arteriosus (hsPDA) is a frequently invoked but contested correlate. Whether the hsPDA and BPD relationship is statistically concentrated in infants who accrue a prolonged invasive mechanical ventilation (IMV) history has rarely been quantified at a single fixed assessment point. Methods: This record-based retrospective cross-sectional study included 520 infants born at 24+0 to 31+6 weeks admitted between March 2020 and August 2023. All variables were abstracted as statuses or cumulative histories at one fixed index assessment at 36+0 weeks postmenstrual age (PMA). The exposure status was documented hsPDA, the pathway status was cumulative IMV exceeding 7 days, and the outcome status was BPD at the index assessment. Four sequential logistic regression models were fitted. A g-computation decomposition with 2000 bootstrap resamples partitioned the association into components with and without the ventilation pathway. Subgroup, secondary-outcome and eight sensitivity analyses were prespecified. Results: hsPDA was documented in 166 infants (31.9%), prolonged IMV in 208 (40.0%) and BPD in 184 (35.4%). hsPDA was associated with BPD status in the unadjusted model (OR 5.29, 95% CI 3.55-7.87) and after full adjustment (OR 2.17, 95% CI 1.35-3.49, P = 0.001; c-statistic 0.836). hsPDA was associated with prolonged IMV status (OR 2.20, 95% CI 1.36-3.55), and prolonged IMV was associated with BPD status (OR 5.71, 95% CI 3.44-9.50). Decomposition yielded a direct component OR of 1.43 (95% CI 1.03-2.01) and an indirect component OR of 1.21 (95% CI 1.06-1.42), with 34.8% (95% CI 13.4-84.5) of the total association represented by the ventilation pathway. hsPDA was also associated with moderate-to-severe BPD (OR 1.91, 95% CI 1.19-3.07) and ordinal BPD severity (common OR 2.02, 95% CI 1.32-3.09). No subgroup interaction reached significance, and all eight sensitivity analyses were directionally concordant (E-value 2.31). Conclusions: In this retrospective cross-sectional study, hsPDA status was associated with BPD status independent of maturity, perinatal and illness-severity covariates, and approximately one third of that association was statistically represented by a prolonged invasive ventilation history. These findings position cumulative ventilator exposure as a quantitatively important correlate along the observed hsPDA and BPD relationship.

Keywords: Patent ductus arteriosus, bronchopulmonary dysplasia, invasive mechanical ventilation, preterm infant, cross-sectional study

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic complication of preterm birth and carries a durable burden of respiratory, cardiovascular and neurodevelopmental morbidity extending well beyond the neonatal period [1]. Its reported occurrence varies widely across settings and definitions. A multicentre cross-sectional survey of 1,044 infants born before 32 weeks of gestation in 37 Chinese neonatal units found a BPD prevalence of 78.2% under the 2001 National Institute of Child Health and Human Development criteria,

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with point prevalence and severity differing across definitions and the lowest prevalence observed under the 2018 definition [2]. Efforts to standardize ascertainment have converged on severity grading anchored to the mode of respiratory support at 36 weeks PMA. In an analysis of 2,677 infants born before 32 weeks across 18 centers, the definition that best predicted death or serious respiratory morbidity through 18 to 26 months of corrected age classified disease by respiratory support mode at 36 weeks PMA, regardless of prior or concurrent oxygen use, and 683 infants (26%) met that composite endpoint [3]. Application of these severity criteria to 17,793 infants born before 32 weeks across the Chinese Neonatal Network classified 15.5%, 14.8%, and 1.2% as grade 1, 2 and 3 disease, respectively, and found that more than 40% of very preterm infants either died before 36 weeks postmenstrual age (PMA) or developed BPD, with a correspondingly large healthcare burden [4]. Despite three decades of intervention research, no preventive strategy has reliably reduced the burden, and attention has shifted toward identifying the modifiable exposures that lie along the path between prematurity and established lung disease.

Patent ductus arteriosus (PDA) is the exposure most persistently implicated in that path. Hemodynamically significant PDA (hsPDA) produces left-to-right shunting, pulmonary overcirculation and interstitial edema in a lung that is simultaneously undergoing saccular and early alveolar development, a combination that is mechanistically plausible as a contributor to arrested alveolarization. Observational evidence has repeatedly supported an association. In a multicenter cohort of very low birth weight infants, PDA of any grade, including ductal shunts that did not meet hemodynamic significance criteria, correlated with an excess of BPD, necrotizing enterocolitis and intraventricular hemorrhage [5]. In an earlier retrospective evaluation of 242 infants at or below 28 weeks of gestation, of whom 105 (43.3%) developed BPD or died, infants reaching the composite endpoint had been exposed to a hemodynamically significant duct for a longer period than those who did not, 4.8 versus 2.3 days [6]. Yet the interventional evidence points in a different direction. A multicenter noninferiority trial in extremely preterm infants with echocardiographically confirmed PDA found expectant management noninferior to early ibuprofen for the composite of necrotizing enterocolitis, moderate-to-severe BPD or death at 36 weeks PMA [7], and a subsequent large masked placebo-controlled trial of selective early ibuprofen for a large duct found no reduction in death or moderate or severe BPD [8]. An overview of Cochrane systematic reviews summarizing the accumulated randomized evidence likewise concluded that pharmacologic ductal closure has not translated into improvement in these clinically important respiratory outcomes [9]. The resulting discrepancy between a consistent association and a null treatment effect is the central unresolved question in this field.

One explanation for the discrepancy is that hsPDA does not act on the lung in isolation but is entangled with the intensity and duration of respiratory support that infants with a significant shunt receive. Duration of invasive mechanical ventilation (IMV) is among the strongest and most reproducible correlates of BPD. In a prospective multicenter study of 6,538 very preterm infants across 47 neonatal intensive care units, the median duration of initial IMV was 26 days among infants with moderate-to-severe BPD compared with 6 days among those with no or mild disease [10]. More directly, a secondary analysis of a randomized trial of PDA management reported that persistent moderate-to-large ductal shunts, even when they lasted several weeks, were not associated with increased BPD in infants who required intubation for fewer than 10 days, whereas prolonged ductal exposure was associated with an increased occurrence of moderate or severe BPD in those intubated for 10 days or longer [11]. Independent risk-factor modeling in extremely preterm infants has identified prolonged IMV (OR 1.10, 95% CI 1.03-1.17) and hsPDA (OR 2.27, 95% CI 1.22-4.20) as concurrent independent correlates of BPD [12]. These observations converge on the hypothesis that ventilator exposure is not merely a confounder of the hsPDA and BPD relationship but a quantitatively substantial part of it.

Formal quantification of that contribution remains scarce. Contemporary syntheses confirm that pharmacologic agents can achieve

ductal closure, with ibuprofen generally preferred for its safety profile [13], and a Bayesian model-averaged meta-analysis of 32 studies comprising 8,513 infants found that both surgically treated and prolonged PDA were associated with BPD-associated pulmonary hypertension [14], but neither line of evidence partitions the hsPDA and BPD association into the portion that travels with a prolonged ventilation history and the portion that does not. Most available analyses are also longitudinal in structure, which introduces variable follow-up, competing risk of death before 36 weeks and heterogeneous exposure windows into the estimate. A design that fixes all three variables at one common assessment point removes that heterogeneity and permits a transparent statistical partition, at the acknowledged cost of temporal ordering. We therefore conducted a record-based retrospective cross-sectional study in which hsPDA status, cumulative invasive ventilation history and BPD status were all ascertained at a single fixed index assessment at 36+0 weeks PMA, with the aim of quantifying the cross-sectional association between hsPDA and BPD and the proportion of that association statistically represented by a prolonged invasive ventilation pathway.

Materials and methods

Study design and setting

We conducted a single-center, record-based, retrospective cross-sectional observational study in the Department of Neonatology (neonatal intensive care unit) of Handan First Hospital, Handan, Hebei, China. Eligible admissions occurred between 12 March 2020 and 31 August 2023. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting recommendations for cross-sectional studies. The design is strictly cross-sectional: every analytic variable was abstracted as a status or as a cumulative history at one fixed index assessment, and each infant contributed exactly one analytic record. Accordingly, all estimates are reported as prevalence and cross-sectional odds rather than incidence, and no follow-up time, time-to-event or hazard model was fitted.

Ethics

The study protocol was reviewed and approved by the Ethics Committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine, Hebei Province (approval No. CZX2023084). The requirement for individual informed consent was waived because the dataset was de-identified before analysis and the study involved no intervention. All procedures were consistent with the Declaration of Helsinki. All clinical care and all data collection described in this report took place in the Department of Neonatology of Handan First Hospital, which is the implementing unit. Ethical review was carried out by the Ethics Committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine.

Index assessment

The fixed index assessment was defined a priori as 36+0 weeks PMA. This single time point served three functions simultaneously. It was the point at which exposure status was determined, the point at which the cumulative ventilation history was summarized, and the point at which outcome status was recorded. Because the exposure, the pathway variable and the outcome share one common ascertainment point, the analysis characterizes a contemporaneous cross-sectional structure and does not establish temporal ordering among the three.

Participants and eligibility

Source records comprised all preterm infants identified in the neonatal intensive care unit electronic record system during the study window. Inclusion required a gestational age at birth between 24+0 and 31+6 completed weeks, an evaluable index assessment at 36+0 weeks PMA, echocardiographic and clinical documentation sufficient to classify hsPDA status, ventilation records sufficient to determine whether cumulative invasive ventilation exceeded 7 days, and available BPD status together with the prespecified core covariates. Of 812 potentially eligible records, 36 were removed as duplicate or repeat eligible admissions (so that one index record was retained per infant), 78 fell outside the prespecified gestational age range, 46 had a major congenital anomaly, chromosomal syndrome, major congenital heart disease other than isolated PDA or a major pulmonary or airway malformation, 42 lacked an evaluable index assessment because of death or transfer before 36+0 weeks

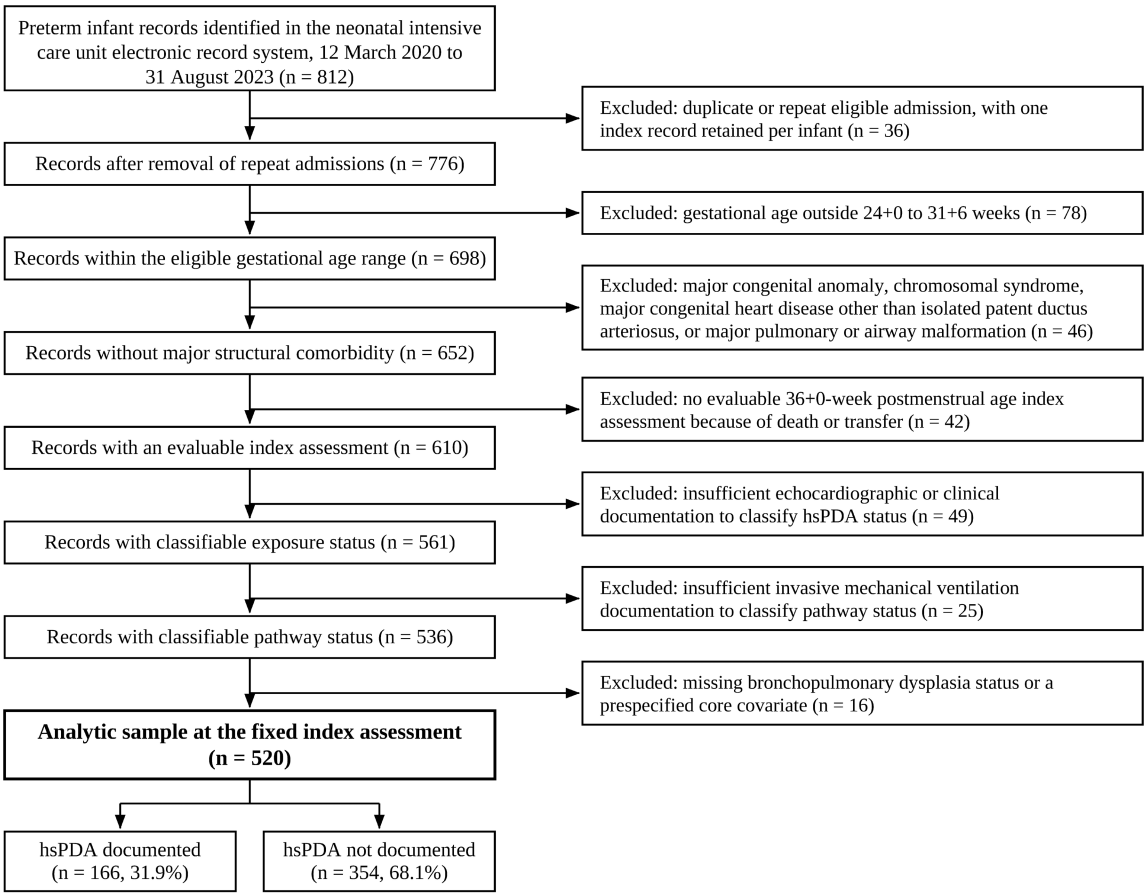


Figure 1. Flow of records through the retrospective cross-sectional study. Records were screened from the neonatal intensive care unit electronic record system for admissions between 12 March 2020 and 31 August 2023. One index record was retained per infant, and eligibility required a gestational age of 24+0 to 31+6 weeks, an evaluable index assessment at 36+0 weeks postmenstrual age, classifiable exposure and pathway statuses, and complete outcome and core covariate data. The final analytic sample comprised 520 infants, of whom 166 had a documented hsPDA at the index assessment. hsPDA, hemodynamically significant patent ductus arteriosus.

PMA, 49 had insufficient echocardiographic or clinical documentation to classify hsPDA status, 25 had insufficient ventilation documentation, and 16 were missing BPD status or a prespecified core covariate. The final analytic sample comprised 520 infants. The stepwise selection sequence is shown in **Figure 1**.

Exposure status

hsPDA status was the primary exposure-status variable and was coded as documented or not documented by the index assessment. Classification followed the combined clinical and echocardiographic criteria used in routine practice at the study unit, comprising demonstration of a transductal left-to-right shunt together with supporting markers of hemodynamic significance including ductal diameter, left atrial-to-aortic root (LA:Ao) ratio and disturbed diastolic flow, interpreted alongside the clinical respiratory and circulatory status recorded in the chart. The most relevant ductal diameter available from echocardiography and the corresponding LA:Ao ratio were retained as continuous descriptors. PDA management was abstracted as none or conservative, pharmacologic, or surgical or transcatheter closure, and was treated as a descriptive and sensitivity variable rather than an adjustment covariate, since management is a consequence of exposure status rather than a confounder of it. Echocardiographic studies were obtained and interpreted as part of routine clinical care rather than under a standardized research acquisition and reading protocol, no independent blinded re-reading was undertaken, and the

source records did not contain the date of first documentation or the cumulative duration of ductal patency, so hsPDA could be represented only as a binary status at the index assessment. Two further features of the exposure definition require explicit statement. First, the source records did not contain the calendar date of the first echocardiographic report meeting the hemodynamic significance criteria, the date on which the shunt was documented to have closed, or the cumulative number of days for which a significant shunt persisted. It was therefore not possible to stratify the exposure by the time window of first documentation, that is, within 7 days, 8 to 28 days, or beyond 28 days of life, to report the duration of significant shunting or the time point of closure, or to perform the sensitivity analysis restricted to infants first diagnosed within the first week after birth. The binary exposure status consequently assigns the same value to an infant whose duct was documented on the third day and closed pharmacologically on the fifth and to an infant who shunted continuously for several weeks, and every estimate reported here should be read with that aggregation in mind. Second, echocardiography was not performed under a fixed screening protocol applied to every admission; studies were requested by the attending team on clinical grounds and the resulting reports were retained in the record. Because eligibility for the present analysis required documentation sufficient to classify hsPDA status, all 520 analyzed infants had an evaluable ductal measurement, including the 354 classified as not having a hemodynamically significant duct, in whom the median ductal diameter was 0.67 mm; the 49 records excluded for insufficient echocardiographic or clinical documentation are infants in whom no such study was available. If echocardiography was preferentially requested in infants with greater respiratory instability, this workup pattern would enrich both comparison groups for sicker infants and could bias the observed association in either direction, and we therefore regard workup bias as an unquantified source of uncertainty rather than one we can exclude. Hemodynamic significance was therefore judged from echocardiographic descriptors alone. Neither circulating natriuretic peptides, that is B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, nor a lung ultrasound interstitial edema score was available in the source records for the study period, so the exposure does not incorporate these neonatal-specific markers of the hemodynamic burden imposed by the duct.

Pathway status

The primary statistical pathway variable was a binary summary of the cumulative invasive ventilation history accrued from birth through the same index assessment, dichotomized at more than 7 days versus 0 to 7 days. Cumulative invasive ventilation days and cumulative supplemental oxygen or respiratory support days were retained as continuous descriptors. Cumulative ventilation days were additionally categorized as 0, 1 to 7, 8 to 14 and more than 14 days for graded analysis.

Outcome status

The primary outcome-status variable was BPD recorded at the 36+0-week PMA index assessment. BPD severity was abstracted on the four-level ordinal scale of none, mild, moderate and severe. Prespecified secondary outcome statuses were moderate-to-severe BPD, defined as severity grade moderate or severe; prolonged invasive ventilation status; necrotizing enterocolitis of Bell stage II or higher; and severe intraventricular hemorrhage of grade 3 or 4.

Covariates

Covariates were specified in advance and entered in four nested blocks. The core maturity block comprised gestational age at birth in completed weeks, birth weight in grams and infant sex. The perinatal block added completed antenatal corticosteroid course, maternal hypertensive disorder, chorioamnionitis and cesarean delivery. The illness-severity block added moderate-to-severe respiratory distress syndrome, early-onset sepsis and late-onset sepsis. Five-minute Apgar score, any surfactant treatment, multiple gestation and calendar year of admission were reserved for sensitivity analysis. The dataset contained no missing values for any analytic variable, so no imputation was required and all models were fitted on the complete analytic sample of 520 infants. Several variables that are recognized correlates of both ductal outcome and bronchopulmonary dysplasia were not retrievable

from the source records and therefore could not be entered into any model, specifically the cumulative postnatal corticosteroid dose, the cumulative fluid load, the cumulative volume of transfused blood products and the lung ultrasound interstitial edema score.

Statistical analysis

Continuous variables are summarized as mean with standard deviation or as median with interquartile range according to distribution, and were compared between exposure groups using the Welch t test or the Mann-Whitney U test. Categorical variables are summarized as counts with percentages and compared using the chi-square test. All reported percentages are prevalences at the index assessment. The value of each test statistic is reported alongside the corresponding *P* value in the tables, as the t statistic for the Welch t test, the Z statistic for the Mann-Whitney U test, the chi-square statistic for contingency table comparisons and the Wald chi-square statistic for regression coefficients.

The primary analysis fitted four sequential binary logistic regression models with BPD status as the dependent variable. Model I was unadjusted. Model II added the core maturity block. Model III added the perinatal block. Model IV, the primary fully adjusted model, added the illness-severity block. Model discrimination was assessed by the c-statistic, calibration by the Hosmer-Lemeshow test across ten risk deciles, and collinearity by the variance inflation factor.

The pathway analysis proceeded in two stages. Component models estimated the adjusted association between hsPDA status and prolonged ventilation status, and between prolonged ventilation status and BPD status, using the Model IV covariate set. A decomposition was then performed by g-computation. A logistic model for the pathway variable given exposure status and covariates was combined with a logistic model for the outcome given exposure status, pathway status and covariates. Marginal outcome probabilities were standardized over the observed covariate distribution under each combination of exposure status and pathway distribution, and were converted to a total component, a direct component and an indirect component on the marginal odds ratio scale. The proportion of the total association represented by the ventilation pathway was computed as the ratio of the log indirect component to the log total component. Percentile confidence intervals were obtained from 2000 nonparametric bootstrap resamples of the full analytic dataset. Following the interpretive rules fixed at the design stage, this procedure is reported as an exploratory cross-sectional statistical decomposition of contemporaneously summarized variables; it is not a causal mediation analysis, and the components are not natural direct or indirect effects. Because the design fixes all three variables at one instant, a directional sensitivity analysis was specified in which the roles of the exposure status and the pathway status were exchanged, so that prolonged invasive ventilation was treated as the exposure and hsPDA as the pathway variable, and the same g-computation decomposition with 2000 bootstrap resamples was repeated. This analysis was included to make explicit that the observed partition is compatible with more than one temporal ordering and cannot by itself distinguish a pathway running from ductal significance to prolonged ventilation from one running from severe lung disease to delayed ductal closure.

Prespecified subgroup analyses refitted the Model IV specification within strata of gestational age, birth weight, sex, antenatal corticosteroid completeness, respiratory distress syndrome severity, delivery mode and plurality, with the stratifying variable removed from the covariate set where it was collinear with the stratum definition. Multiplicative interaction was assessed by a product term in the full sample. Graded analyses examined ductal diameter halves among exposed infants, LA:Ao ratio and cumulative ventilation categories against the corresponding unexposed reference stratum, with linear trend tested across ordered categories. Subgroup analyses were interpreted as exploratory and no formal adjustment for multiplicity was applied to the within-stratum estimates; for reference, a Bonferroni-corrected threshold for the seven interaction tests would correspond to a two-sided alpha of 0.007. No formal power calculation was undertaken for the subgroup comparisons, and strata containing few outcome events were expected to yield unstable estimates.

Table 1. Baseline demographic and perinatal characteristics at the fixed index assessment, by hsPDA status

Characteristic	All infants (n = 520)	hsPDA (n = 166)	No hsPDA (n = 354)	Test statistic	P
Gestational age, weeks, mean ± SD	28.3 ± 1.6	27.3 ± 1.5	28.8 ± 1.4	t = 10.40	<0.001
24+0 to 25+6, n (%)	32 (6.2)	25 (15.1)	7 (2.0)	χ^2 = 86.06	<0.001
26+0 to 27+6, n (%)	172 (33.1)	82 (49.4)	90 (25.4)		
28+0 to 29+6, n (%)	235 (45.2)	55 (33.1)	180 (50.8)		
30+0 to 31+6, n (%)	81 (15.6)	4 (2.4)	77 (21.8)		
Birth weight, g, mean ± SD	1197 ± 251	1056 ± 240	1263 ± 229	t = 9.31	<0.001
<1000, n (%)	103 (19.8)	61 (36.7)	42 (11.9)	χ^2 = 65.30	<0.001
1000 to 1249, n (%)	198 (38.1)	71 (42.8)	127 (35.9)		
1250 to 1499, n (%)	156 (30.0)	28 (16.9)	128 (36.2)		
≥1500, n (%)	63 (12.1)	6 (3.6)	57 (16.1)		
Male sex, n (%)	291 (56.0)	97 (58.4)	194 (54.8)	χ^2 = 0.47	0.495
Multiple gestation, n (%)	115 (22.1)	33 (19.9)	82 (23.2)	χ^2 = 0.53	0.467
Cesarean delivery, n (%)	334 (64.2)	103 (62.0)	231 (65.3)	χ^2 = 0.38	0.540
Complete antenatal corticosteroid course, n (%)	392 (75.4)	123 (74.1)	269 (76.0)	χ^2 = 0.13	0.720
Maternal hypertensive disorder, n (%)	99 (19.0)	32 (19.3)	67 (18.9)	χ^2 = 0.00	1.000
Chorioamnionitis, n (%)	72 (13.8)	28 (16.9)	44 (12.4)	χ^2 = 1.51	0.219
Five-minute Apgar score, median (IQR)	8 (7-9)	7 (7-8)	8 (7-9)	Z = 2.47	0.011
Moderate-to-severe RDS, n (%)	187 (36.0)	100 (60.2)	87 (24.6)	χ^2 = 60.88	<0.001
Any surfactant treatment, n (%)	290 (55.8)	117 (70.5)	173 (48.9)	χ^2 = 20.53	<0.001
Early-onset sepsis, n (%)	39 (7.5)	16 (9.6)	23 (6.5)	χ^2 = 1.19	0.276
Late-onset sepsis, n (%)	117 (22.5)	57 (34.3)	60 (16.9)	χ^2 = 18.61	<0.001
Calendar year of admission, n (%)	520 (100)	166 (100)	354 (100)	χ^2 = 6.66	0.155

hsPDA, hemodynamically significant patent ductus arteriosus; SD, standard deviation; IQR, interquartile range; RDS, respiratory distress syndrome. Continuous variables were compared using the Welch t test or the Mann-Whitney U test and categorical variables using the chi-square test. Percentages are prevalences at the fixed index assessment. The *P* value shown for gestational age and birth weight strata refers to the overall distribution across strata; the *P* value for calendar year of admission refers to the distribution of exposure status across the calendar years spanned by the study period. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

Eight sensitivity analyses were performed: additional adjustment for five-minute Apgar score, surfactant treatment, multiple gestation and calendar year of admission; exclusion of infants with necrotizing enterocolitis of stage II or higher or severe intraventricular hemorrhage; exclusion of infants who underwent surgical or transcatheter ductal closure; restriction to gestational age 24+0 to 29+6 weeks; substitution of moderate-to-severe BPD as the outcome; Firth penalized logistic regression; a modified Poisson model with robust variance yielding a prevalence ratio; and inverse probability of treatment weighting with weights truncated at the first and ninety-ninth percentiles. Robustness to unmeasured confounding was quantified by the E-value. Two-sided *P* values below 0.05 were considered statistically significant. Analyses were performed in Python 3.11 using statsmodels 0.14.6, with the random seed fixed for reproducibility of the bootstrap.

Results

Sample selection and baseline characteristics

The stepwise selection sequence from 812 source records to the 520-infant analytic sample is shown in **Figure 1**. Mean gestational age was 28.3 ± 1.6 weeks and mean birth weight was 1197 ± 251 g. hsPDA was documented at the index assessment in 166 infants (31.9%), a cumulative invasive ventilation history exceeding 7 days was present in 208 (40.0%), and BPD was present in 184

Table 2. Respiratory support, ductal characteristics and outcome status at the fixed index assessment, by hsPDA status

Variable	All infants (n = 520)	hsPDA (n = 166)	No hsPDA (n = 354)	Test statistic	P
Ductal diameter, mm, median (IQR)	1.00 (0.46-1.99)	2.33 (2.03-2.62)	0.67 (0.26-1.02)	Z = 18.30	<0.001
LA:Ao ratio, mean ± SD	1.38 ± 0.25	1.68 ± 0.20	1.24 ± 0.13	t = 25.76	<0.001
PDA management, n (%)				χ^2 = 374.12	<0.001
None or conservative	366 (70.4)	23 (13.9)	343 (96.9)		
Pharmacologic	142 (27.3)	131 (78.9)	11 (3.1)		
Surgical or transcatheter	12 (2.3)	12 (7.2)	0 (0.0)		
Cumulative invasive ventilation, days, median (IQR)	3 (0-13)	13 (3-20)	1 (0-10)	Z = 8.97	<0.001
0 days, n (%)	202 (38.8)	29 (17.5)	173 (48.9)	χ^2 = 89.71	<0.001
1 to 7 days, n (%)	110 (21.2)	26 (15.7)	84 (23.7)		
8 to 14 days, n (%)	100 (19.2)	41 (24.7)	59 (16.7)		
>14 days, n (%)	108 (20.8)	70 (42.2)	38 (10.7)		
Cumulative respiratory support, days, median (IQR)	20 (7-50)	50 (24-63)	13 (4-31)	Z = 10.61	<0.001
Prolonged invasive ventilation >7 days, n (%)	208 (40.0)	111 (66.9)	97 (27.4)	χ^2 = 71.71	<0.001
BPD, n (%)	184 (35.4)	102 (61.4)	82 (23.2)	χ^2 = 70.77	<0.001
BPD severity, n (%)				χ^2 = 73.87	<0.001
None	336 (64.6)	64 (38.6)	272 (76.8)		
Mild	12 (2.3)	7 (4.2)	5 (1.4)		
Moderate	97 (18.7)	50 (30.1)	47 (13.3)		
Severe	75 (14.4)	45 (27.1)	30 (8.5)		
Moderate-to-severe BPD, n (%)	172 (33.1)	95 (57.2)	77 (21.8)	χ^2 = 62.66	<0.001
NEC stage II or higher, n (%)	46 (8.8)	29 (17.5)	17 (4.8)	χ^2 = 20.95	<0.001
Severe IVH grade 3 to 4, n (%)	36 (6.9)	17 (10.2)	19 (5.4)	χ^2 = 3.44	0.063

hsPDA, hemodynamically significant patent ductus arteriosus; IQR, interquartile range; SD, standard deviation; LA:Ao, left atrial-to-aortic root; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage. Percentages are prevalences at the fixed index assessment. *P* values for multi-level variables refer to the overall distribution. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

(35.4%). Moderate-to-severe BPD was present in 172 infants (33.1%).

Baseline demographic and perinatal characteristics by exposure status are presented in **Table 1**. Infants with hsPDA were less mature and smaller at birth, with a mean gestational age of 27.3 ± 1.5 versus 28.8 ± 1.4 weeks and a mean birth weight of 1,056 ± 240 versus 1,263 ± 229 g (both *P*<0.001). They were more likely to have moderate-to-severe respiratory distress syndrome (60.2% versus 24.6%, *P*<0.001), to have received surfactant (70.5% versus 48.9%, *P*<0.001) and to have late-onset sepsis (34.3% versus 16.9%, *P*<0.001), and had a lower five-minute Apgar score (median 7 versus 8, *P* = 0.011). Sex, plurality, delivery mode, antenatal corticosteroid completeness, maternal hypertensive disorder and chorioamnionitis did not differ materially between groups, and the distribution of exposure status across calendar years of admission was stable (*P* = 0.155).

Respiratory support, ductal characteristics and outcome status

Respiratory, echocardiographic and outcome variables by exposure status are shown in **Table 2**. Median ductal diameter was 2.33 mm (interquartile range 2.03-2.62) among infants with hsPDA versus 0.67 mm (0.26-1.02) among those without, and mean LA:Ao ratio was 1.68 ± 0.20 versus 1.24 ± 0.13 (both *P*<0.001), confirming that the exposure classification separated the two groups on the intended hemodynamic axis. Median cumulative invasive ventilation was 13 days (3-20) versus 1 day (0-10), and median cumulative respiratory support was 50 days (24-63) versus 13 days (4-31) (both *P*<0.001). Prolonged invasive ventilation status was present in 66.9% of infants with hsPDA versus 27.4% of those without, and BPD

Table 3. Sequential multivariable logistic regression models for the cross-sectional association between hsPDA status and BPD status (n = 520)

Model	Covariates entered	OR (95% CI)	Test statistic	P
Model I	Unadjusted	5.29 (3.55-7.87)	χ^2 = 67.14	<0.001
Model II	+gestational age, birth weight, sex	2.62 (1.67-4.12)	χ^2 = 17.56	<0.001
Model III	+antenatal corticosteroids, maternal hypertensive disorder, chorioamnionitis, cesarean delivery	2.54 (1.61-4.00)	χ^2 = 16.19	<0.001
Model IV (primary)	+moderate-to-severe RDS, early-onset sepsis, late-onset sepsis	2.17 (1.35-3.49)	χ^2 = 10.27	0.001
Covariate estimates within Model IV				
Gestational age, per week		0.61 (0.47-0.79)	χ^2 = 13.98	<0.001
Birth weight, per g		1.00 (1.00-1.00)	χ^2 = 1.12	0.291
Male sex		1.17 (0.74-1.84)	χ^2 = 0.43	0.510
Complete antenatal corticosteroid course		0.81 (0.49-1.34)	χ^2 = 0.67	0.412
Maternal hypertensive disorder		0.98 (0.55-1.75)	χ^2 = 0.00	0.952
Chorioamnionitis		1.83 (0.97-3.45)	χ^2 = 3.52	0.061
Cesarean delivery		1.12 (0.70-1.80)	χ^2 = 0.24	0.627
Moderate-to-severe RDS		2.09 (1.29-3.39)	χ^2 = 8.92	0.003
Early-onset sepsis		1.46 (0.65-3.26)	χ^2 = 0.86	0.355
Late-onset sepsis		2.48 (1.49-4.12)	χ^2 = 12.16	<0.001

hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia; OR, odds ratio; CI, confidence interval; RDS, respiratory distress syndrome. Model IV c-statistic 0.836; Hosmer-Lemeshow chi-square 3.44, 8 degrees of freedom, P = 0.904; maximum variance inflation factor 3.39. Estimates are cross-sectional odds at the fixed index assessment and are not causal effects. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

was present in 61.4% versus 23.2% (both *P*<0.001). Severity distribution shifted correspondingly, with severe BPD in 27.1% versus 8.5% (*P*<0.001). Necrotizing enterocolitis of stage II or higher was more prevalent among infants with hsPDA (17.5% versus 4.8%, *P*< 0.001), whereas severe intraventricular hemorrhage did not differ significantly (10.2% versus 5.4%, *P* = 0.063).

Primary cross-sectional association

Sequential regression results are presented in **Table 3** and **Figure 2**. The unadjusted association between hsPDA status and BPD status was strong (OR 5.29, 95% CI 3.55-7.87, *P*< 0.001). Adjustment for the core maturity block attenuated the estimate by more than half (OR 2.62, 95% CI 1.67-4.12), consistent with the substantial confounding by gestational age and birth weight evident in **Table 1**. Further adjustment for the perinatal block changed the estimate marginally (OR 2.54, 95% CI 1.61-4.00). In the primary fully adjusted Model IV, hsPDA status remained associated with BPD status (OR 2.17, 95% CI 1.35-3.49, *P* = 0.001). Within Model IV, gestational age (OR = 0.61 per week, 95% CI 0.47-0.79), moderate-to-severe respiratory distress syndrome (OR = 2.09, 95% CI 1.29-3.39), and late-onset sepsis (OR = 2.48, 95% CI 1.49-4.12) were the other independent correlates of BPD status. Model IV showed good discrimination (c-statistic 0.836) and acceptable calibration (Hosmer-Lemeshow chi-square 3.44, 8 degrees of freedom, *P* = 0.904), and the maximum variance inflation factor of 3.39 indicated no problematic collinearity.

Statistical pathway decomposition

Component models and decomposition results are shown in **Table 4** and **Figure 3**. Using the Model IV covariate set, hsPDA status was associated with prolonged invasive ventilation status (OR = 2.20, 95% CI 1.36-3.55, *P* = 0.001), and prolonged invasive ventilation status was strongly associated with BPD status both without (OR = 6.11, 95% CI 3.70-10.10) and with (OR = 5.71, 95% CI 3.44-9.50) additional adjustment for hsPDA status. When the pathway variable was added to the primary model, the hsPDA estimate attenuated from 2.17 to 1.77 (95% CI 1.06-2.94, *P* = 0.028).

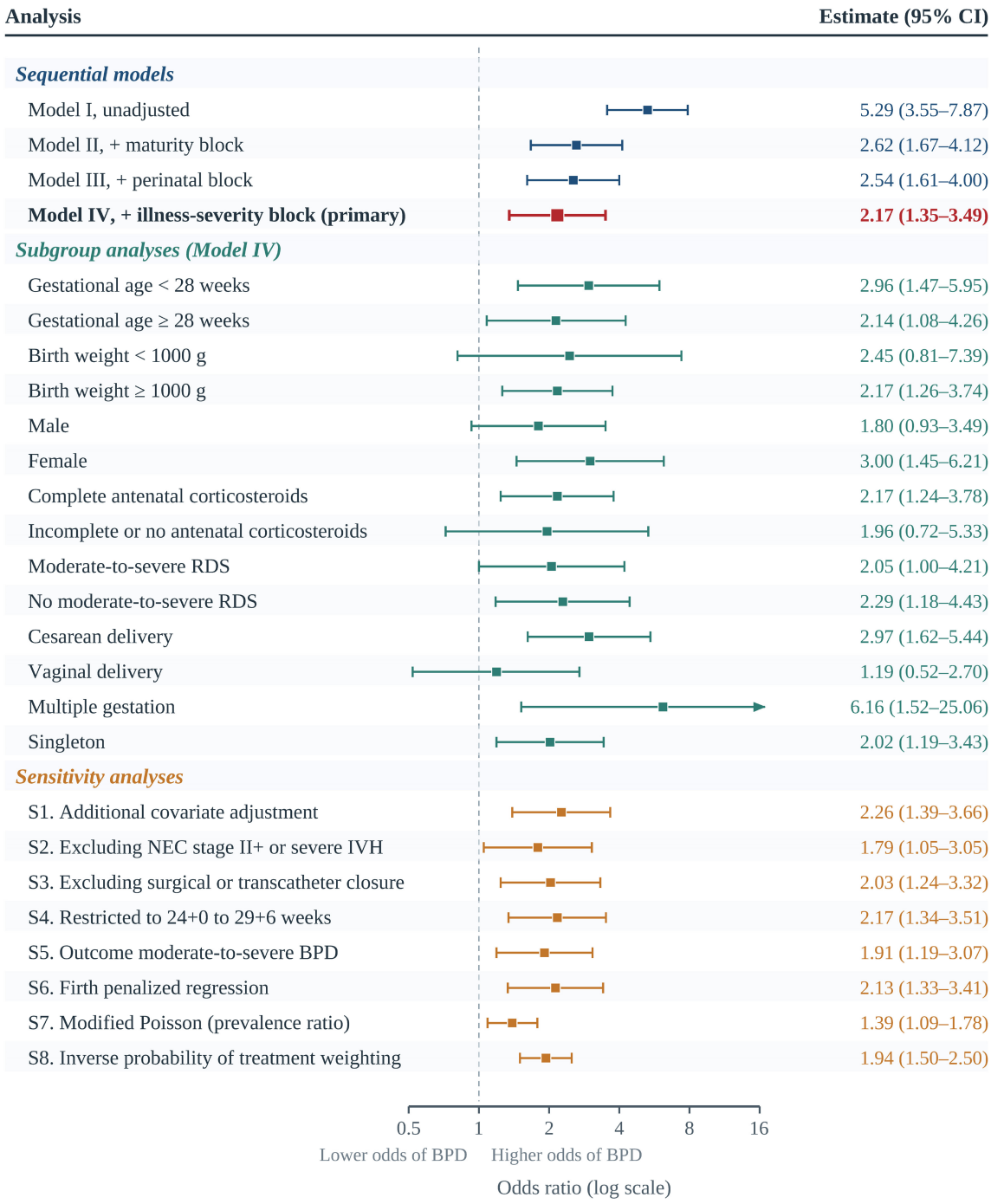


Figure 2. Forest plot of the cross-sectional association between hsPDA status and bronchopulmonary dysplasia status. Squares denote point estimates and horizontal lines denote 95% confidence intervals, plotted on a logarithmic odds ratio scale with the vertical dashed line at the null value of 1.0. The enlarged square marks the primary fully adjusted Model IV estimate. Sequential models correspond to progressive covariate adjustment; subgroup estimates were obtained within each stratum using the Model IV covariate set, excluding the stratifying variable where collinear with the stratum definition; sensitivity analyses correspond to the alternative specifications described in the Materials and methods. The arrowhead in the multiple gestation row indicates a confidence limit extending beyond the plotted axis. The estimate for S7 is a prevalence ratio rather than an odds ratio. BPD, bronchopulmonary dysplasia; CI, confidence interval; hsPDA, hemodynamically significant patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome.

Table 4. Component models and bootstrap statistical pathway decomposition through prolonged invasive mechanical ventilation status (n = 520)

Analysis	Exposure status	Outcome status	OR (95% CI)	Test statistic	P
Component models					
Pathway component	hsPDA	Prolonged IMV >7 days	2.20 (1.36-3.55)	$\chi^2 = 10.31$	0.001
Outcome component	Prolonged IMV >7 days	BPD	6.11 (3.70-10.10)	$\chi^2 = 49.80$	<0.001
Outcome component, hsPDA-adjusted	Prolonged IMV >7 days	BPD	5.71 (3.44-9.50)	$\chi^2 = 45.15$	<0.001
Primary model with pathway variable added	hsPDA	BPD	1.77 (1.06-2.94)	$\chi^2 = 4.83$	0.028
Marginal decomposition (g-computation, 2000 bootstrap resamples)					
Total component	hsPDA	BPD	1.74 (1.22-2.59)	Z = 2.87	0.003
Direct component	hsPDA	BPD	1.43 (1.03-2.01)	Z = 2.11	0.037
Indirect component	hsPDA	BPD	1.21 (1.06-1.42)	Z = 2.63	0.002
Proportion of total association represented, %	hsPDA	BPD	34.8 (13.4-84.5)		

hsPDA, hemodynamically significant patent ductus arteriosus; IMV, invasive mechanical ventilation; BPD, bronchopulmonary dysplasia; OR, odds ratio; CI, confidence interval. All models were adjusted for the Model IV covariate set. Marginal probabilities standardized over the observed covariate distribution were 0.4372, 0.3908 and 0.3092 for the exposed state with the exposed pathway distribution, the exposed state with the unexposed pathway distribution, and the unexposed state, respectively. This decomposition is an exploratory cross-sectional statistical partition of contemporaneously summarized variables; the components are not natural direct or indirect effects and no temporal or causal mediation is implied. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

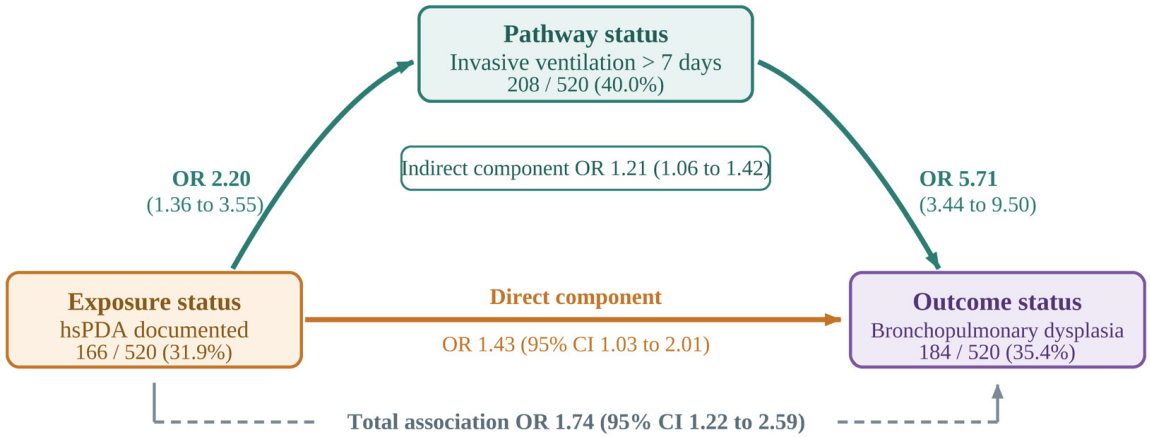


Figure 3. Cross-sectional statistical pathway decomposition through prolonged invasive mechanical ventilation status. The diagram shows the component associations linking hsPDA status, pathway status and outcome status, together with the direct, indirect and total components obtained by g-computation with 2000 bootstrap resamples and the proportion of the total association represented by the pathway. All component models were adjusted for the Model IV covariate set. All estimates are cross-sectional associations at the fixed index assessment; the decomposition is a statistical partition of contemporaneously summarized variables, the components are not natural direct or indirect effects, and no causal mediation is implied. hsPDA, hemodynamically significant patent ductus arteriosus; CI, confidence interval.

The g-computation decomposition returned a total component OR of 1.74 (95% CI 1.22-2.59, P = 0.003), a direct component OR of 1.43 (95% CI 1.03-2.01, P = 0.037) and an indirect component OR of 1.21 (95% CI 1.06-1.42, P = 0.002) on the marginal odds ratio scale. The proportion of the total association represented by the prolonged ventilation pathway was 34.8% (95% CI 13.4-84.5). The point estimate indicates that roughly one third of the observed hsPDA and BPD association is statistically carried by the cumulative ventilation history, while the wide upper bound of the interval reflects the well-known instability of ratio-of-logarithms quantities and should be interpreted with corresponding caution. The joint distribution underlying this partition showed a stepwise gradient: BPD prevalence rose from 10.9% (28/257) among infants with neither hsPDA nor prolonged ventilation, to 29.1% (16/55) with hsPDA alone, to 55.7% (54/97) with prolonged ventilation alone, and to 77.5% (86/111) when both statuses were present. In the directional sensitivity analysis, exchanging the roles of the two variables so that prolonged invasive ventilation was treated as the exposure and hsPDA as the pathway variable produced a total component OR of 4.13 (95% CI 2.75 to 6.83), a direct component OR of 3.87 (95% CI 2.57 to 6.36) and an indirect component OR of 1.07 (95% CI 1.01 to 1.16), with only 4.5% (95% CI 0.4 to 11.0) of that association represented by hsPDA status. The two orderings are therefore not numerically equivalent, but neither can be excluded by these data, because both decompositions are computed from the same contemporaneous cross-sectional summary.

Secondary outcomes and graded analyses

Secondary outcome and graded analyses are shown in **Table 5**. After full adjustment, hsPDA status was associated with moderate-to-severe BPD (OR = 1.91, 95% CI 1.19-3.07, P = 0.008) and with ordinal BPD severity across the four-level scale (common OR = 2.02, 95% CI 1.32-3.09, P = 0.001). It was also associated with necrotizing enterocolitis of stage II or higher (OR = 2.49, 95% CI 1.20-5.18, P = 0.015) but not with severe intraventricular hemorrhage (OR = 1.37, 95% CI 0.62-3.04, P = 0.440). Both halves of the ductal diameter distribution among exposed infants were associated with BPD status relative to the unexposed reference (lower half OR = 2.31, 95% CI 1.25-4.25; upper half OR = 2.14, 95% CI 1.16-3.92). These two

Table 5. Secondary outcome-status associations and graded ductal and ventilation analyses (n = 520)

Analysis	hsPDA, n (%)	No hsPDA, n (%)	Adjusted OR (95% CI)	Test statistic	P
Secondary outcome status					
Moderate-to-severe BPD	95 (57.2)	77 (21.8)	1.91 (1.19-3.07)	$\chi^2 = 7.09$	0.008
Ordinal BPD severity, grades 0 to 3	-	-	2.02 (1.32-3.09)	$\chi^2 = 10.37$	0.001
Prolonged invasive ventilation >7 days	111 (66.9)	97 (27.4)	2.20 (1.36-3.55)	$\chi^2 = 10.31$	0.001
NEC stage II or higher	29 (17.5)	17 (4.8)	2.49 (1.20-5.18)	$\chi^2 = 5.96$	0.015
Severe IVH grade 3 to 4	17 (10.2)	19 (5.4)	1.37 (0.62-3.04)	$\chi^2 = 0.60$	0.440
Graded ductal status, outcome BPD					
Ductal diameter, lower half among exposed	81	354	2.31 (1.25-4.25)	$\chi^2 = 7.15$	0.007
Ductal diameter, upper half among exposed	85	354	2.14 (1.16-3.92)	$\chi^2 = 5.97$	0.015
Ductal diameter, per 0.5-mm increment	-	-	1.20 (1.06-1.35)	$\chi^2 = 8.10$	0.004
LA:Ao ratio, per 0.1-unit increment	-	-	1.12 (1.03-1.22)	$\chi^2 = 6.78$	0.009
Graded ventilation status, outcome BPD					
1 to 7 days versus 0 days	110	202	1.48 (0.68-3.22)	$\chi^2 = 0.99$	0.320
8 to 14 days versus 0 days	100	202	7.91 (3.59-17.42)	$\chi^2 = 26.32$	<0.001
>14 days versus 0 days	108	202	9.82 (4.01-24.04)	$\chi^2 = 25.02$	<0.001
P for trend across ventilation categories	-	-	-	$\chi^2 = 43.05$	<0.001

hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; LA:Ao, left atrial-to-aortic root; OR, odds ratio; CI, confidence interval. All estimates are adjusted for the Model IV covariate set. For the ordinal severity analysis, the estimate is a common odds ratio from a proportional odds model. For graded analyses the two columns give the number of infants in the index category and in the unexposed reference stratum. Denominators for prevalence columns are 166 for hsPDA and 354 for no hsPDA. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

estimates are of essentially the same magnitude and are not ordered, so no trend across the ductal categories is claimed and the previously reported trend test has been withdrawn. Analyzed as a continuous variable across the whole cohort, each 0.5-mm increment in ductal diameter was associated with higher odds of BPD status (OR = 1.20, 95% CI 1.06-1.35, P = 0.004), whereas within the hsPDA group alone ductal diameter carried no additional information (OR = 1.00, 95% CI 0.66-1.52, P = 0.984), indicating that the gradient reflects the contrast between infants with and without a hemodynamically significant duct rather than graded severity among those who have one. Each 0.1-unit increment in LA:Ao ratio was associated with higher odds of BPD status (OR = 1.12, 95% CI 1.03-1.22, *P* = 0.009). Cumulative ventilation categories showed a steep graded pattern relative to infants never invasively ventilated: 1 to 7 days OR 1.48 (95% CI 0.68-3.22), 8 to 14 days OR 7.91 (95% CI 3.59-17.42) and more than 14 days OR 9.82 (95% CI 4.01-24.04), with *P* for trend <0.001.

Subgroup analyses

Subgroup results are shown in **Table 6** and in the corresponding panel of **Figure 2**. The direction of association was positive in every stratum examined. Point estimates were numerically larger among infants below 28 weeks of gestation (OR = 2.96, 95% CI 1.47-5.95) than at or above 28 weeks (OR = 2.14, 95% CI 1.08-4.26), among female infants (OR = 3.00, 95% CI 1.45-6.21) than male infants (OR = 1.80, 95% CI 0.93-3.49), among cesarean deliveries (OR 2.97, 95% CI 1.62-5.44) than vaginal deliveries (OR = 1.19, 95% CI 0.52-2.70), and among multiple gestations (OR = 6.16, 95% CI 1.52-25.06) than singletons (OR = 2.02, 95% CI 1.19-3.43). No test for multiplicative interaction approached statistical significance, with all *P* values for interaction at or above 0.207, so these differences are most reasonably read as sampling variation within strata of unequal size rather than as genuine effect modification. These fourteen within-stratum estimates and seven interaction tests were not corrected for multiplicity, and several strata contained few

Table 6. Subgroup analyses of the adjusted association between hsPDA status and BPD status

Subgroup	n	BPD, n	Adjusted OR (95% CI)	Test statistic	P	P for interaction
Gestational age <28 weeks	204	123	2.96 (1.47-5.95)	$\chi^2 = 9.27$	0.002	0.676
Gestational age ≥28 weeks	316	61	2.14 (1.08-4.26)	$\chi^2 = 4.71$	0.030	
Birth weight <1000 g	103	74	2.45 (0.81-7.39)	$\chi^2 = 2.52$	0.113	0.897
Birth weight ≥1000 g	417	110	2.17 (1.26-3.74)	$\chi^2 = 7.81$	0.005	
Male	291	104	1.80 (0.93-3.49)	$\chi^2 = 3.02$	0.082	0.411
Female	229	80	3.00 (1.45-6.21)	$\chi^2 = 8.71$	0.003	
Complete antenatal corticosteroid course	392	134	2.17 (1.24-3.78)	$\chi^2 = 7.40$	0.007	0.998
Incomplete or no antenatal corticosteroids	128	50	1.96 (0.72-5.33)	$\chi^2 = 1.74$	0.187	
Moderate-to-severe RDS	187	113	2.05 (1.00-4.21)	$\chi^2 = 3.80$	0.051	0.784
No moderate-to-severe RDS	333	71	2.29 (1.18-4.43)	$\chi^2 = 6.04$	0.014	
Cesarean delivery	334	113	2.97 (1.62-5.44)	$\chi^2 = 12.42$	<0.001	0.207
Vaginal delivery	186	71	1.19 (0.52-2.70)	$\chi^2 = 0.16$	0.685	
Multiple gestation	115	47	6.16 (1.52-25.06)	$\chi^2 = 6.45$	0.011	0.245
Singleton	405	137	2.02 (1.19-3.43)	$\chi^2 = 6.79$	0.009	

hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia; OR, odds ratio; CI, confidence interval; RDS, respiratory distress syndrome. Within-stratum models used the Model IV covariate set, with the stratifying variable removed where collinear with the stratum definition. P for interaction was obtained from a multiplicative product term fitted in the full sample. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

Table 7. Sensitivity analyses of the primary cross-sectional association between hsPDA status and BPD status

Analysis	n	Estimate (95% CI)	Test statistic	P
Primary analysis, Model IV	520	OR 2.17 (1.35-3.49)	$\chi^2 = 10.27$	0.001
S1. Additional adjustment for Apgar score, surfactant, plurality and calendar year	520	OR 2.26 (1.39-3.66)	$\chi^2 = 10.95$	<0.001
S2. Excluding NEC stage II or higher or severe IVH	441	OR 1.79 (1.05-3.05)	$\chi^2 = 4.50$	0.034
S3. Excluding surgical or transcatheter ductal closure	508	OR 2.03 (1.24-3.32)	$\chi^2 = 8.03$	0.005
S4. Restricted to gestational age 24+0 to 29+6 weeks	439	OR 2.17 (1.34-3.51)	$\chi^2 = 10.00$	0.002
S5. Outcome redefined as moderate-to-severe BPD	520	OR 1.91 (1.19-3.07)	$\chi^2 = 7.09$	0.008
S6. Firth penalized logistic regression	520	OR 2.13 (1.33-3.41)	$\chi^2 = 9.85$	0.002
S7. Modified Poisson model with robust variance	520	PR 1.39 (1.09-1.78)	$\chi^2 = 6.96$	0.008
S8. Inverse probability of treatment weighting	520	OR 1.94 (1.50-2.50)	$\chi^2 = 25.50$	<0.001
E-value for the point estimate	-	2.31	-	-
E-value for the lower confidence limit	-	1.60	-	-

hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; OR, odds ratio; PR, prevalence ratio; CI, confidence interval. Inverse probability of treatment weights were truncated at the first and ninety-ninth percentiles; the propensity model c-statistic was 0.779 with a propensity score range of 0.027 to 0.922. The E-value expresses the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need with both hsPDA status and BPD status, conditional on the measured covariates, to fully account for the observed association. Test statistics are reported alongside each *P* value: t for the Welch t test, Z for the Mann-Whitney U test, χ^2 for contingency table comparisons, Wald χ^2 for regression coefficients and bootstrap Z for the decomposition components.

outcome events, most notably the multiple gestation stratum with 47 events among 115 infants, so the apparent between-stratum differences should be read as hypothesis generating rather than as evidence of effect modification.

Sensitivity analyses

All eight sensitivity analyses are presented in **Table 7** and in **Figure 2**, and were directionally concordant with the primary estimate. Additional adjustment for five-minute Apgar

score, surfactant treatment, multiple gestation and calendar year of admission slightly strengthened the estimate (OR = 2.26, 95% CI 1.39-3.66). Excluding infants with necrotizing enterocolitis of stage II or higher or severe intraventricular hemorrhage attenuated it modestly (OR = 1.79, 95% CI 1.05-3.05, n = 441), as did excluding the 12 infants who underwent surgical or transcatheter ductal closure (OR = 2.03, 95% CI 1.24-3.32, n = 508). Restriction to gestational age 24+0 to 29+6 weeks reproduced the primary result almost exactly (OR = 2.17, 95% CI 1.34-3.51). Firth penalized regression (OR = 2.13, 95% CI 1.33-3.41), a modified Poisson model on the prevalence ratio scale (PR = 1.39, 95% CI 1.09-1.78) and inverse probability of treatment weighting (OR = 1.94, 95% CI 1.50-2.50) all supported the primary finding; the propensity model showed acceptable discrimination (c-statistic 0.779) with adequate overlap across the propensity score range of 0.027 to 0.922. The E-value for the primary point estimate was 2.31 and for the lower confidence limit 1.60, indicating that an unmeasured confounder would need to be associated with both hsPDA status and BPD status by a risk ratio of at least 2.31, above and beyond the measured covariates, to fully account for the observed association.

Discussion

In this record-based retrospective cross-sectional study of 520 preterm infants assessed at one fixed point of 36+0 weeks PMA, hsPDA status was associated with BPD status after adjustment for maturity, perinatal and illness-severity covariates (OR 2.17, 95% CI 1.35-3.49), and a statistical decomposition indicated that 34.8% (95% CI 13.4-84.5) of that association was represented by a cumulative invasive ventilation history exceeding 7 days. We are not aware of earlier analyses in which the exposure status, the ventilation pathway status and the outcome status are all fixed at one common cross-sectional assessment point and then formally partitioned, rather than being estimated across variable follow-up windows. A graded pattern was present along the ventilation dimension of the association, but not within the ductal dimension, where the two diameter halves gave essentially identical estimates. BPD prevalence rose across the four joint strata of exposure and ventilation status from 10.9% to 77.5%, and with a monotone gradient across cumulative ventilation categories reaching an OR of 9.82 (95% CI 4.01-24.04) beyond 14 days. The association also extended to severity, with a common OR of 2.02 (95% CI 1.32-3.09) across the ordinal grading scale, and proved robust across eight sensitivity analyses with an E-value of 2.31.

Our fully adjusted estimate sits comfortably within the range reported by existing evidence. In a retrospective cohort of 424 preterm infants at or below 1500 g or under 30 weeks of gestation, of whom 204 reached the composite of BPD or death, Bonafiglia et al. estimated the association of hsPDA duration with the composite by logistic regression adjusted for birth weight, five-minute Apgar score, intraventricular hemorrhage and durations of invasive and noninvasive ventilation, and reported an OR of 1.67 (95% CI 1.17-2.56) [15]. Mirza et al., in extremely preterm infants under 29 weeks whose ductal status was confirmed within the first 7 days and who were grouped by duration of significant PDA, found that longer ductal exposure was associated with higher risk of BPD or death on multivariable analysis [16]. Deng et al. examined shunt size and duration in a cohort of infants born before 28 weeks and reported that both dimensions of ductal exposure were associated with death or severe respiratory morbidity [17], a finding that parallels our observation that each 0.1-unit increase in LA:Ao ratio carried an OR of 1.12 (95% CI 1.03-1.22). Independent risk-factor modeling in 468 extremely preterm infants identified hsPDA (OR = 2.27, 95% CI 1.22-4.20) and prolonged invasive ventilation (OR = 1.10, 95% CI 1.03-1.17) as simultaneous independent correlates of BPD [12], a pairing that closely mirrors our component estimates of 2.20 and 5.71. Most directly relevant, Clyman and colleagues reported in a secondary analysis of a multicenter randomized trial that persistent moderate-to-large ductal shunts were not associated with increased BPD among infants requiring fewer than 10 days of intubation, whereas prolonged exposure was associated with moderate or severe BPD among those intubated for 10 days or longer [11]; the same group subsequently replicated this interaction in a secondary analysis of a separate European randomized trial, reporting an OR of 3.00 (95% CI 1.58-5.71) for BPD in association

with prolonged hsPDA shunts among infants intubated for 10 days or more [18], and had earlier shown a duration-dependent relationship between moderate-to-large shunt exposure and BPD or death before 36 weeks [19]. What our study adds is modest and quantitative rather than qualitative. Where prior work established that the hsPDA and BPD association is concentrated among heavily ventilated infants, we report one estimate of the share of that association that travels with the ventilation history, under a design in which all three variables are summarized at the same instant. We do not claim new mechanistic insight, and the width of the interval around the pathway share, from 13.4% to 84.5%, should temper any strong reading of the point estimate.

Several considerations bear on how the pathway result should be read. Mechanistically, a hemodynamically significant left-to-right shunt increases pulmonary blood flow and raises pulmonary interstitial fluid, which reduces compliance and increases the ventilatory support required to maintain gas exchange; that support, once escalated, is itself injurious to a saccular lung through volutrauma, atelectrauma and oxidant stress. On this reading the ventilation history is not a nuisance variable to be adjusted away but a substantive part of the observed relationship, which is precisely what the indirect component of 1.21 (95% CI 1.06-1.42) captures. It also offers a coherent account of why ductal closure trials have been null. If roughly a third of the association operates through accumulated ventilator exposure and the remainder through pathways not addressed by closure timing, then an intervention that shortens ductal patency without changing the trajectory of respiratory support would be expected to yield little improvement in BPD, which is what the randomized evidence has consistently shown [7-9]. At the same time, three cautions are essential. First, the direct component of 1.43 (95% CI 1.03-2.01) remained statistically distinguishable from unity, so ventilation does not account for the whole association and residual pathways, plausibly including pulmonary vascular remodeling, persist. Second, the confidence interval around the proportion extends to 84.5%, so the data are compatible with the ventilation pathway representing anywhere from a modest to a dominant share. Third, and most importantly, the cross-sectional design fixes exposure, pathway and outcome at one instant and therefore cannot establish that hsPDA preceded the accrual of ventilator days. The decomposition is a statistical partition of contemporaneously summarized variables and must not be read as causal mediation; the components are not natural direct or indirect effects, and reverse or bidirectional structures, in which sicker lungs both demand more ventilation and delay ductal closure, remain fully compatible with our data. The directional sensitivity analysis makes this symmetry explicit. When the two variables exchanged roles the pathway share fell from 34.8% to 4.5%. We do not read this contrast as directional evidence. The two decompositions are computed against different total associations, an odds ratio of 1.74 for hsPDA and of 4.13 for prolonged ventilation, and a share expressed against a larger total will be smaller for arithmetic reasons alone; the asymmetry is therefore a consequence of the differing denominators rather than an indication of which ordering holds. The comparison establishes only that the decomposition is not invariant under relabeling, and it is not a demonstration of temporal precedence, and a design recording the date of ductal diagnosis and the daily ventilation trajectory would be required to separate the two competing pathological orderings.

The secondary and subgroup findings warrant separate comment. The association extended to moderate-to-severe disease (OR 1.91, 95% CI 1.19-3.07) and across the ordinal severity scale, which is consistent with evidence linking ductal exposure to the more severe end of the BPD spectrum, including the pulmonary vascular phenotype. A Bayesian model-averaged meta-analysis of 32 studies comprising 8,513 very and extremely preterm infants found associations of BPD-associated pulmonary hypertension with both surgically treated and prolonged PDA [14]. Bjorkman and colleagues, studying 133 preterm infants with BPD who underwent research lung magnetic resonance imaging before 48 weeks PMA, reported that prolonged hsPDA exposure was associated with pulmonary hypertension persisting after resolution of the shunt and with a more severe parenchymal imaging phenotype [20]. Gentle and colleagues similarly reported an association between PDA and the develop-

ment of BPD-associated pulmonary hypertension [21], and Nawaytou et al. found that ductal exposure was associated with pulmonary hypertension risk in this population [22]. Our association with necrotizing enterocolitis of stage II or higher (OR 2.49, 95% CI 1.20-5.18) but not with severe intraventricular hemorrhage (OR 1.37, 95% CI 0.62-3.04) fits the pattern reported in a multicenter cohort of very low birth weight infants, in which ductal patency correlated with a broad but not uniform excess of prematurity-related morbidity [5]. Regarding subgroups, no interaction test approached significance, and the numerically larger estimates among infants below 28 weeks, female infants, cesarean deliveries and multiple gestations should be treated as hypothesis-generating; the multiple-gestation stratum in particular comprised 115 infants with a very wide interval (OR 6.16, 95% CI 1.52-25.06), and subgroup estimates of this kind are notoriously unstable. Evidence that echocardiographic markers of shunt volume correlate with lung ultrasound measures of interstitial edema in very preterm infants [23] is consistent with the continuous ductal diameter association we observed across the whole cohort, an odds ratio of 1.20 per 0.5 mm. We would note, however, that this gradient disappeared when the analysis was confined to infants with a hemodynamically significant duct, so continuous hemodynamic descriptors appear to add information mainly at the boundary between a significant and a non-significant shunt rather than across the range of significant shunts.

The clinical value of these findings lies in where they direct attention. Because the ventilation pathway accounted for a substantial share of the association while ductal closure trials have not improved respiratory outcomes, the modifiable target that our data highlight is cumulative invasive ventilator exposure rather than ductal patency per se. This is consistent with recent meta-analytic evidence from randomized trials that less invasive surfactant administration, which preserves spontaneous breathing on noninvasive support, is associated with lower odds of BPD, death and the composite of death or BPD than intubation-based surfactant delivery [24], and with current clinical guidance, which concludes that the significance, assessment and management of the preterm duct remain unsettled and continue to vary widely in practice [25]. Practically, the four-stratum prevalence gradient observed here offers a simple bedside stratification: infants carrying both hsPDA and a prolonged ventilation history had a BPD prevalence of 77.5%, roughly seven times that of infants with neither, which identifies a group in whom aggressive extubation readiness assessment, lung-protective settings and early transition to noninvasive support may plausibly yield the greatest return. Whether targeted ductal management alters that trajectory remains unresolved and continues to be debated [26].

The mechanistic reading proposed above is supported by experimental evidence, although that evidence was generated in animal models rather than in this cohort. In mechanically ventilated preterm lambs studied with an occluder that allowed ductal patency to be controlled, opening the duct doubled pulmonary blood flow, raised mean pulmonary artery pressure from 24 to 40 torr, and increased lung lymph flow by 68% and lymph protein clearance by 39%, establishing that a left-to-right shunt directly increases fluid filtration across the pulmonary microvasculature [27]. In preterm baboons delivered at 125 days of gestation and ventilated for 14 days, randomization to ibuprofen closure improved the ventilation index and dynamic compliance and increased alveolar surface area relative to animals left with a persistent shunt [28]. A companion experiment in the same model showed that surgical ligation removed the shunt without improving pulmonary mechanics or alveolar surface area, and instead increased expression of genes governing pulmonary inflammation while reducing expression of the epithelial sodium channel that clears alveolar water [29]. Read together these findings support two elements of our interpretation, that ductal overcirculation imposes a fluid and mechanical burden on the immature lung, and that removing the shunt late does not reverse injury already accumulated; they also indicate why the ventilation history matters, since the same immature primate lung develops the histological features of chronic lung disease when it is ventilated for prolonged periods [30]. Our study provides no experimental confirmation of this sequence. We did not undertake a neonatal animal model of unclosed ductal lung injury, nor primary alveolar endothelial or epithelial cell work, so

the association reported here stands as clinical statistical evidence that is consistent with, but does not itself establish, the proposed chain from hsPDA through pulmonary overcirculation and prolonged mechanical ventilation to bronchopulmonary dysplasia.

These considerations bear on which of two candidate translation strategies deserves priority. A duct-targeted strategy seeks to shorten or abolish the shunt by pharmacological or interventional closure. Its appeal is mechanistic directness, and the experimental evidence above shows that early closure can improve compliance and alveolar surface area. Its practical limitations are substantial: randomized evidence has not shown a reduction in bronchopulmonary dysplasia or death for expectant management versus early ibuprofen, for selective early ibuprofen in a large duct, or across the accumulated trial evidence summarized in an overview of systematic reviews [7-9]; late ligation removes the shunt without restoring alveolar growth [29]; most ducts close spontaneously, so the number needed to treat is unfavorable; and pharmacological closure carries renal and gastrointestinal risk. A ventilation-targeted strategy instead seeks to shorten cumulative invasive support whether or not the duct is closed. Its appeal is that the exposure is continuously modifiable at the bedside, that a graded association is observable across the whole range of exposure, with the adjusted odds of bronchopulmonary dysplasia rising from 1.48 at one to seven days to 9.82 beyond 14 days in our data, and that meta-analytic evidence already associates fewer invasive approaches that avoid intubation with lower odds of death or bronchopulmonary dysplasia [24]. Its limitation is confounding by indication, since the sickest lungs both require and least tolerate the support they receive, so an observational gradient cannot establish that shortening ventilation would reduce disease. Our decomposition does not adjudicate between the two strategies. We had previously contrasted the pathway share of the two decompositions, about one third against about one twentieth, but that contrast is uninformative because the two analyses are computed against different total associations and the smaller share follows arithmetically from the larger denominator. What the decomposition does show is more limited: a measurable part of the ductal association, 34.8% with a confidence interval from 13.4% to 84.5%, travelled with the cumulative ventilation history, which is a reason to consider respiratory support alongside ductal management rather than a reason to prefer one over the other. The pragmatic implication is that a trial testing duct-targeted treatment without a co-intervention on respiratory support may be testing the smaller of the two levers, and that factorial designs combining early ductal management with a protocolized extubation and noninvasive support pathway would be more informative than either component alone.

The single-center design has consequences beyond a general statement about generalizability. Thresholds for declaring a duct hemodynamically significant differ appreciably between units, in the ductal diameter cut-off applied, in whether the left atrial-to-aortic root ratio or Doppler flow indices are required, and in whether screening is routine or symptom-driven, so the exposure prevalence of 31.9% observed here would be expected to shift under a different local definition, and any shift in exposure prevalence changes both the marginal association and the share attributed to the ventilation pathway. Respiratory management differs at least as much, in extubation readiness criteria, in the availability and default use of noninvasive modes, and in the threshold for reintubation; because the pathway variable is defined by cumulative invasive ventilation, these differences directly alter the size of the indirect component. The estimates reported here should therefore be read as internally valid for a unit with our practice pattern rather than as transportable coefficients. An informative external validation would be a multicenter retrospective cohort of at least 1500 infants born before 32 weeks, drawn from units with deliberately contrasting ductal screening and respiratory management policies, in which each site records the date of first hemodynamically significant documentation, the cumulative duration of ductal patency, the daily mode and duration of respiratory support, and bronchopulmonary dysplasia graded by respiratory support mode at 36 weeks, so that the decomposition can be refitted within each site, pooled by random effects, and tested for heterogeneity across sites in both the total association and the pathway share.

This study has several strengths. All variables were fixed at one prespecified index assessment, which eliminates the variable exposure windows and differential follow-up that complicate longitudinal analyses of this question, and each infant contributed exactly one record. The dataset was complete for every analytic variable, so no imputation was required and no complete-case selection bias was introduced. The analysis plan was specified in advance with nested covariate blocks, and the primary model showed good discrimination and calibration. Robustness was examined through eight prespecified sensitivity analyses spanning alternative estimands, alternative estimators and alternative populations, and quantified against unmeasured confounding with an E-value of 2.31 [31]. Several limitations must nevertheless temper interpretation. First and foremost, the cross-sectional design cannot establish temporal ordering; the decomposition is a statistical partition and not a causal mediation analysis, and confounding by indication for both ductal treatment and ventilation strategy cannot be excluded. Second, the study is single-center with 520 infants, which limits its generalizability to units with different ductal screening thresholds and respiratory management cultures, and which leaves the subgroup analyses underpowered; the fourteen within-stratum estimates and seven interaction tests were not corrected for multiplicity, and the widest of them, the multiple gestation stratum, rested on 47 events in 115 infants. Third, hsPDA was classified from documentation generated during routine care rather than by a protocolized research echocardiographic scoring system, so exposure misclassification is possible, and the duration of ductal exposure, which prior evidence identifies as important, was not available as a continuous variable. A related limitation is that hemodynamic significance was judged from a binary echocardiographic classification anchored on ductal diameter and the left atrial-to-aortic root ratio, without the neonatal-specific markers that are increasingly used to characterize the hemodynamic burden of the shunt. Current guidance identifies echocardiography as essential for confirming a PDA and assessing its significance [25], comprehensive targeted neonatal echocardiography has been reviewed as a means of assessing the hemodynamic consequences of the shunt in PDA management [32], and the absence of an international consensus on the definition of hemodynamic significance remains a recognized source of heterogeneity between studies [33]. Natriuretic peptides offer a complementary measure of ventricular volume loading: among 102 infants born before 30 weeks, B-type natriuretic peptide discriminated moderate and large from small ducts with an area under the curve of 0.89, rising to 0.93 in the subgroup born before 25 weeks [34], and in a recent prospective dual-center study of infants born before 32 weeks, serum N-terminal pro-B-type natriuretic peptide showed moderate predictive value for BPD or death among infants with a PDA [35]. Lung ultrasound scores, in turn, provide a bedside measure of interstitial oedema and aeration and have been evaluated for the early prediction of BPD in two recent meta-analyses [36, 37] and in a cohort of 160 infants born before 30 weeks [38]. Had these measures been available, exposure could have been graded by hemodynamic burden rather than dichotomized, and they would have provided an independent check on whether the association we observed reflects pulmonary overcirculation specifically; incorporating them into early risk stratification could also help to direct preventive strategies to the infants most likely to benefit [39]. Their absence means that infants with a similar ductal diameter but different degrees of volume loading and pulmonary oedema were treated as equivalent, which would generally be expected to attenuate rather than inflate the association, although this cannot be verified in the present data. Fourth, 42 infants who died or were transferred before 36+0 weeks PMA had no evaluable index assessment and were necessarily excluded, which introduces survivorship selection; because the infants lost in this way are precisely those at highest risk of both a persistent duct and severe respiratory failure, the estimates reported here describe the surviving population and are likely to understate the contribution of hsPDA to the full spectrum of adverse respiratory outcomes, a limitation that a composite of bronchopulmonary dysplasia or death before 36 weeks would avoid but that a fixed cross-sectional index assessment cannot accommodate. Fifth, BPD status was recorded at the index assessment without independent adjudication against a standardized physiologic challenge, and several recognized correlates of both ductal outcome and lung injury

were not retrievable and therefore could not be modelled, specifically the cumulative postnatal corticosteroid dose, the cumulative fluid load, the cumulative transfusion volume and the lung ultrasound interstitial edema score, so residual confounding remains possible and the E-value of 2.31 should be read against that possibility. Prospective multicenter studies with protocolized serial echocardiography, explicit temporal sequencing of ductal and ventilation exposures, and composite outcome definitions are needed to determine whether the partition observed here reflects a modifiable causal structure. Three further limitations deserve explicit statement. The outcome was ascertained only at 36+0 weeks PMA and no post-discharge follow-up was available, so we cannot comment on respiratory readmission, on pulmonary hypertension diagnosed after 40 weeks corrected age, or on neurodevelopment at 6 to 12 months, and the persistence of the association we describe into later infancy is untested. No temporal sensitivity analysis in the conventional sense was possible, because the source records contained neither the date of first hemodynamically significant documentation nor the daily ventilation trajectory, and the directional analysis we substituted addresses the symmetry of the decomposition rather than the sequence of events. Finally, the study contains no in vivo or in vitro component, so the molecular steps linking ductal overcirculation to arrested alveolarization remain inferred from external experimental evidence rather than demonstrated here.

Conclusions

In this record-based retrospective cross-sectional study of preterm infants born at 24+0 to 31+6 weeks and assessed at a single fixed index point of 36+0 weeks postmenstrual age, documented hemodynamically significant patent ductus arteriosus was associated with a consistent pattern of more adverse respiratory status, including higher odds of bronchopulmonary dysplasia after sequential adjustment for maturity, perinatal and illness-severity covariates, higher odds of moderate-to-severe disease, and a graded shift across the ordinal severity scale, together with higher odds of a prolonged invasive mechanical ventilation history and of necrotizing enterocolitis. An exploratory statistical pathway decomposition indicated that approximately one third of the observed exposure and outcome association was represented by cumulative invasive ventilation exceeding 7 days, with a direct component that remained distinguishable from unity, suggesting that ventilator exposure accounts for a measurable but incomplete portion of the relationship alongside additional pathways not captured by the ventilation summary. Independent correlate modeling identified maturity and illness-severity markers as the dominant covariates of bronchopulmonary dysplasia status and showed acceptable discrimination and calibration, supporting the potential utility of pragmatic risk stratification using ductal and ventilation status jointly in routine care. Overall, these findings suggest that cumulative invasive ventilator exposure is a quantitatively important and potentially modifiable correlate lying along the observed relationship between ductal significance and chronic lung disease, and they highlight the need for prospective studies with explicit temporal measurement and standardized phenotyping of both ductal exposure and bronchopulmonary dysplasia to strengthen causal inference and inform implementation.

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Disclosure of conflict of interest

None.

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