Exploring the relation between patent ductus arteriosus and bronchopulmonary dysplasia: Insights from national inpatient sample

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ABSTRACT

Background : **Bronchopulmonary dysplasia (BPD) poses a challenge in neonatal care. Previous literature recommended a hypothetical role for patent ductus arteriosus (PDA) in the development of BPD. This study explores the possible link between PDA and BPD, aiming to illuminate demographic and clinical factors influencing BPD development within the context of PDA.**

Methods : **This retrospective cohort analysis employed data from the National Inpatient Sample (NIS) spanning from 2016 to 2020. The study focused on patients diagnosed with PDA and BPD, identified through International Classification of Diseases 10th Revision codes Q250 and P271, respectively. Utilizing STATA ×15, descriptive and inferential statistics, encompassing univariate and multivariate regression analyses, were conducted to examine the association between PDA and BPD.**

Results : **A total of 9737 patients were included: 5133 without PDA and 4604 with PDA. The mortality rate was significantly higher among patients with PDA (3.80%) compared to those without PDA (2.53%) ($P < 0.0001$). Univariate and multivariate regression analyses identified a significant association between PDA and BPD, with odds ratios of 14.62 and 2.43, respectively (both $P < 0.0001$). BPD patients with PDA also exhibited a significantly higher prevalence of extremely preterm birth (76.24% vs. 58.31%, $P < 0.0001$) and extremely low birth weight (65.57% vs. 42.70%, $P < 0.0001$) compared to BPD patients without PDA. In addition, significant associations were observed between BPD and factors such as preterm birth category, neonatal sepsis, race, hospital status, and region (all $P < 0.0001$).**

Conclusions : **This research confirms the connection between PDA and BPD, stressing the importance of continued investigation and prospective studies. The findings highlight the need to**

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consider several factors in understanding the etiology of the disease, which could lead to more targeted interventions and improved patient care.

Keywords : National inpatient sample dataset, retrospective cohort analysis, risk factors and prevalence of bronchopulmonary dysplasia

INTRODUCTION

Bronchopulmonary dysplasia (BPD) poses challenges in neonatal care, particularly impacting prematurely born infants.[1] It is notable that approximately 40% of infants delivered before 28-week gestation develop BPD.[2,3] Infants afflicted with BPD not only confront heightened risks of enduring neurodevelopmental impairments but also higher mortality rates.[4]

The multifaceted etiology of BPD involves intricate interactions between various pathophysiological mechanisms, including parenchymal abnormalities, inflammatory processes, and vascular disturbances.[5] Impaired alveolar and bronchial development contribute to the dysplastic changes observed in the lungs of affected neonates.[6,7] Mechanical ventilation, infection, and oxygen toxicity further exacerbate lung injury and impair alveolarization.[8] The presence of patent ductus arteriosus (PDA) poses a significant risk factor for BPD development.[9] The persistence of a PDA, a common cardiovascular anomaly in premature infants, leads to hemodynamic instability, pulmonary overcirculation, and increased risk of pulmonary edema.[10] This hemodynamic burden exacerbates lung injury and contributes to the development and progression of BPD.[11] Strategies aimed at early detection and management of PDA in preterm infants, including pharmacological closure or surgical ligation, are crucial in mitigating the adverse impact of this comorbidity on the course of BPD.[12]

Among the mutual demographic characteristics of PDA and BPD patients, lower gestational age (GA) and birth weight (BW) have consistently emerged as possible confounders.[3,13] The role of PDA in BPD development remains a subject of ongoing debate.[3] Hemodynamically, significant PDA (hsPDA) may serve as a potential risk factor for the development of BPD in recent cohorts.[9,14]

In a meta-analysis published in 2023 by Villamor *et al.*, notable limitations were observed within the included studies, which consequently affected the overall analysis.[3] A significant challenge arose in assessing both exposure to PDA and the outcome of BPD, particularly BPD associated with pulmonary hypertension (BPD-PH).[3] This difficulty substantially contributed to the observed high heterogeneity in specific analyses. In terms of exposure assessment, the majority of the studies reviewed were retrospective and lacked detailed information on the timing of PDA diagnosis or treatment, as well as the potential risk factors contributing to BPD development in PDA patients.[3]

In this article, our aim is to investigate the relationship between PDA and BPD using data from the National Inpatient Sample (NIS). We aim to illuminate the demographics and clinical factors influencing the development of BPD within the context of PDA. By clarifying these connections, we aim to explore this link for targeted interventions and enhanced management strategies for infants at risk of BPD, thereby improving long-term outcomes for this population.

METHODS

Study design, population, and data source

This retrospective cohort study utilized data from the NIS database covering the years 2016–2020. The NIS, administered as part of the Healthcare Cost and Utilization Project, serves as the largest publicly accessible inpatient database encompassing various payers, supported by the Agency for Healthcare Research and Quality. It encompasses patient records from U.S. community hospitals, representing over 97% of the country's population, excluding rehabilitation and long-term acute care facilities. The NIS comprises a 20% stratified sample of discharges from U.S. community hospitals, compiling approximately 35 million weighted hospitalizations annually across 47 geographically dispersed states and the District of Columbia. Diagnostic coding was conducted according to the International Classification of Diseases 10th Revision, Clinical Modification (ICD-10-CM). Approval from the Institutional Review Board was not required for this study, as it utilized a publicly available database containing deidentified patient data. Patients diagnosed with PDA and BPD were identified using respective ICD-10-CM codes Q250 and P271, focusing on the pediatric population aged younger than 1 year.

Description of variables

We extracted baseline characteristics data such as age, sex, race, primary payer (Medicare/Medicaid, private insurance, self-pay, and other), hospital location (rural or urban), hospital teaching status (rural, urban nonteaching, and urban teaching), and hospital region (Northeast, Midwest, South, and West). Race was categorized as White, Black, Hispanic, Asian or Pacific Islander, Native American, and others. The other variables of interest used in the multivariable

regression were cesarean delivery, neonatal bacterial sepsis, multiple pregnancies, and chorioamnionitis. BW is also included and is classified by the WHO into four categories: extremely low BW (LBW) (<1000 g), very LBW (1000–1499 g), moderate LBW (1500–2499 g), and normal/high BW (≥2500 g). Neonates under 2500 g are considered LBW. GA is an important confounder and is categorized by WHO into extremely preterm (<28 weeks), very preterm (28–<32 weeks), moderate-to-late preterm (32–<37 weeks), full term (≥37 weeks), and unspecified for those without recorded GA. All codes used are shown in Supplementary Table 1.

Statistical analysis

STATA ×15 was used to conduct our analysis either descriptive or inferential. Descriptive statistics were used to show the numbers of baseline characteristics and percentages in the BPD with PDA versus without. Inferential statistics were used to investigate causality; univariate and multivariate regression analyses were presented in odds ratio (OR) along with their corresponding 95% confidence intervals (CIs). Results are considered significant if $P < 0.05$. We depended on previous literature reviews in selecting our covariates. The Chi-square test (χ^2) was used to assess the statistical significance of difference across the two groups (BPD with vs. without PDA) for categorical variables. The Shapiro–Wilk test assessed data for normality of the continuous variables, age, and LOS. The Mann–Whitney *U* test was used if the data were not normally distributed.

RESULTS

Baseline characteristics

A total of 9737 patients were included in the study, with 5133 individuals without PDA and 4604 with PDA, as shown in Figure 1. The comparison of baseline characteristics reveals significant differences between these groups, highlighting potential risk factors and health outcomes associated with PDA.

Notably, the mortality rate among PDA patients is higher at 3.80% compared to 2.53% among their non-PDA counterparts, with a significant $P < 0.0001$. Furthermore, there is a marked difference in the prevalence of preterm births, particularly in the unspecified preterm category, with PDA patients showing a prevalence of 76.24% compared to 58.31% among non-PDA patients, underscored by a highly significant $P < 0.0001$.

In terms of BW, extremely LBW is significantly more prevalent among PDA patients (65.57%) compared to non-PDA patients (42.70%), with a $P < 0.0001$, indicating the significance of this difference. In addition, the incidence of neonatal sepsis is higher in the PDA group (32.43%) compared to the non-PDA group (18.25%), supported by $P < 0.0001$.

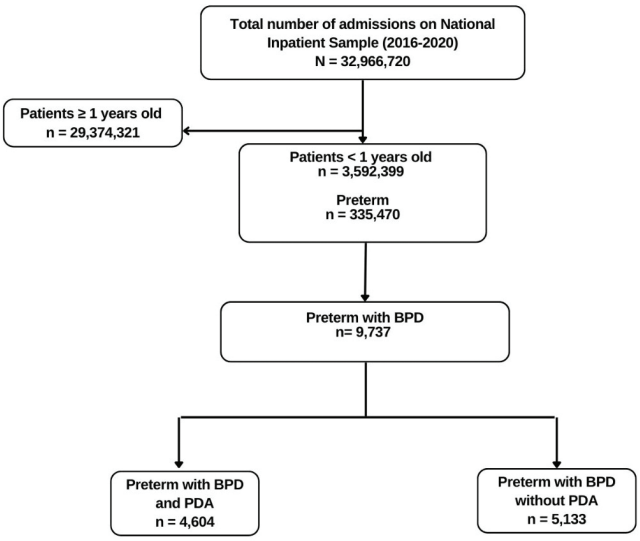

Figure 1: Consort flow diagram for study population selection. BPD: Bronchopulmonary dysplasia, PDA: Patent ductus arteriosus

Sex distribution also differs, with a slightly higher proportion of males (53.32%) among PDA patients compared to females (46.68%), though this difference is less pronounced. The disparities in racial composition are evident between PDA and non-PDA patients ($P < 0.0001$), with the breakdown provided in Table 1.

Association between patent ductus arteriosus and bronchopulmonary dysplasia

The regression analysis underscores the strong association between PDA and the development of BPD. In the univariate model, PDA exhibited an OR of 14.62 ($P < 0.0001$), which remains significant in the multivariate model with an OR of 2.43 ($P < 0.0001$).

Extremely preterm birth emerged as the most critical factor, presenting the highest OR of 169.45 ($P < 0.0001$), significantly amplifying the risk of BPD. Additional risk factors include other preterm categories and LBWs, all of which demonstrated statistically significant associations with BPD (all $P < 0.0001$). Neonatal bacterial sepsis (OR = 1.19, $P < 0.0001$) and multiple pregnancies (OR = 2.01, $P < 0.0001$) were also found to elevate the risk further. In contrast, variables such as chorioamnionitis (OR = 0.92, $P = 0.305$) and cesarean delivery (OR = 0.95, $P = 0.856$) did not achieve statistical significance.

Racial disparities were evident, with Black (OR = 0.9, $P < 0.0001$), Hispanic (OR = 0.95, $P = 0.125$), and Asian/Pacific Islander (OR = 0.8, $P < 0.0001$) groups showing varied odds in relation to BPD development. The analysis also highlighted that treatment in urban teaching hospitals significantly increased the odds of BPD (OR = 6.78, $P < 0.0001$). Moreover, hospital region, financial status, and temporal trends were identified

Table 1. Demographic and health-related variables associated with BPD in patients

Variables	BPD without PDA (*n*=5,133)	BPD with PDA (*n*=4,604)	*P*
Age (Mean±SD)	**2.218±7.016**	**0.073±0.598**	**<0.0001**
Length of Stay (Mean±SD)	**35.961±50.302**	**96.065±57.985**	**<0.0001**
Birth Weight Category			**<0.0001**
Moderate low birth weight	**365 (7.11%)**	**175 (3.80%)**	
Very low birth weight	**1200 (23.38%)**	**841 (18.27%)**	
Extremely low birth weight	**2192 (42.70%)**	**3019 (65.57%)**	
Unspecified low birth weight	**2 (0.04%)**	**0 (0.00%)**	
Preterm Category			**<0.0001**
Moderate to Late Preterm	**188 (3.66%)**	**86 (1.87%)**	
Very Preterm	**1234 (24.04%)**	**539 (11.71%)**	
Extremely Preterm	**718 (13.99%)**	**469 (10.19%)**	
Unspecified Preterm	**2993 (58.31%)**	**3510 (76.24%)**	
Neonatal Bacterial Sepsis			**<0.0001**
No	**4196 (81.75%)**	**3111 (67.57%)**	
Yes	**937 (18.25%)**	**1493 (32.43%)**	
Chorioamnionitis			**<0.0001**
No	**5033 (98.05%)**	**4458 (96.83%)**	
Yes	**100 (1.95%)**	**146 (3.17%)**	
Race			**<0.0001**
White	**2110 (41.11%)**	**1810 (39.31%)**	
Black	**1559 (30.37%)**	**1371 (29.78%)**	
Hispanic	**858 (16.72%)**	**863 (18.74%)**	
Asian/Pacific Islander	**167 (3.25%)**	**177 (3.84%)**	
Native American	**37 (0.72%)**	**18 (0.39%)**	
Other	**402 (7.83%)**	**365 (7.93%)**	
Multiple Pregnancies			**<0.0001**
No	**5043 (98.25%)**	**4509 (97.94%)**	
Yes	**90 (1.75%)**	**95 (2.06%)**	
Primary Expected Payer			**<0.0001**
Medicare	**7 (0.14%)**	**7 (0.15%)**	
Medicaid	**3257 (63.45%)**	**2729 (59.27%)**	
Private Insurance	**1633 (31.81%)**	**1661 (36.08%)**	
Self-pay	**42 (0.82%)**	**38 (0.83%)**	
No Charge	**1 (0.02%)**	**0 (0.00%)**	
Others	**193 (3.76%)**	**169 (3.67%)**	
Calendar Year			**<0.0001**
2016	**751 (14.63%)**	**787 (17.09%)**	
2017	**935 (18.22%)**	**816 (17.72%)**	
2018	**1101 (21.45%)**	**1013 (22.00%)**	
2019	**1234 (24.04%)**	**1003 (21.79%)**	
2020	**1112 (21.66%)**	**985 (21.39%)**	
ZIP Code Income Quartile			0.450
1st–25th	1938 (37.76%)	1692 (36.75%)	
26th–50th	1276 (24.86%)	1170 (25.41%)	
51st–75th	1114 (21.70%)	993 (21.57%)	
76th–100th	805 (15.68%)	749 (16.27%)	
Hospital Bed Size			**<0.0001**
Small	**1061 (20.67%)**	**709 (15.40%)**	
Medium	**1080 (21.04%)**	**961 (20.87%)**	
Large	**2992 (58.29%)**	**2934 (63.73%)**	
Sex			**<0.0001**
Male	**2980 (58.06%)**	**2455 (53.32%)**	
Female	**2153 (41.94%)**	**2149 (46.68%)**	
Region of Hospital			**<0.0001**
Northeast	**983 (19.15%)**	**709 (15.40%)**	
Midwest or North Central	**1410 (27.47%)**	**1142 (24.80%)**	
South	**1958 (38.15%)**	**1955 (42.46%)**	
West	**782 (15.23%)**	**798 (17.33%)**	
Location/Teaching Status			**0.002**
Rural	**24 (0.47%)**	**17 (0.37%)**	
Urban non-teaching	**220 (4.29%)**	**199 (4.32%)**	
Urban Teaching	**4889 (95.25%)**	**4388 (95.31%)**	
Died During Hospitalization			**<0.0001**
No	**5003 (97.47%)**	**4429 (96.20%)**	
Yes	**130 (2.53%)**	**175 (3.80%)**	
Cesarean Delivery			**0.005**
No	**5124 (99.82%)**	**4593 (99.76%)**	
Yes	**9 (0.18%)**	**11 (0.24%)**	

Bold values stand for statistically significant. BPD: Bronchopulmonary dysplasia, PDA: Patent ductus arteriosus,SD: Standard deviation

Table 2: Association between patent ductus arteriosus and development of bronchopulmonary dysplasia

Variable	Odds Ratio	*P*	Lower CI	Upper CI
Univariate Regression				
PDA	**14.62**	**<0.0001**	**14.01**	**15.25**
Multivariate Regression				
PDA	**2.43**	**<0.0001**	**2.31**	**2.56**
Preterm Category				
Moderate-to-late preterm	**39.92**	**<0.0001**	**35.08**	**45.43**
Very preterm	**129.02**	**<0.0001**	**112.13**	**148.45**
Extremely preterm	**169.45**	**<0.0001**	**148.78**	**193.01**
Birth Weight Category				
Moderate LBW	**0.25**	**<0.0001**	**0.23**	**0.28**
Very LBW	**0.61**	**<0.0001**	**0.56**	**0.65**
Extremely LBW	**0.81**	**<0.0001**	**0.76**	**0.87**
Unspecified LBW	0.45	0.294	0.1	2
Neonatal Bacterial Sepsis	**1.19**	**<0.0001**	**1.13**	**1.26**
Chorioamnionitis	0.92	0.305	0.79	1.08
Cesarean Delivery	0.95	0.856	0.56	1.63
Multiple Pregnancies	**2.01**	**<0.0001**	**1.66**	**2.42**
Race				
Black	**0.9**	**<0.0001**	**0.84**	**0.95**
Hispanic	0.95	0.125	0.88	1.02
Asian or Pacific Islander	**0.8**	**<0.0001**	**0.7**	**0.91**
Native American	**0.7**	**0.02**	**0.52**	**0.95**
Other	1	0.932	0.91	1.09
Hospital Status				
Urban nonteaching	**2.79**	**<0.0001**	**2.02**	**3.86**
Urban teaching	**6.78**	**<0.0001**	**4.98**	**9.24**
Hospital Region				
Midwest or North Central	**1.09**	**0.021**	**1.01**	**1.18**
South	**0.71**	**<0.0001**	**0.67**	**0.76**
West	**0.63**	**<0.0001**	**0.58**	**0.68**
Primary Expected Payer				
Medicaid	1.3	0.379	0.73	2.32
Private insurance	1.15	0.647	0.64	2.05
Self-pay	**0.31**	**<0.0001**	**0.16**	**0.57**
No charge	0.16	0.085	0.02	1.29
Others	1.2	0.553	0.66	2.16
Year				
2017	**1.13**	**0.003**	**1.04**	**1.22**
2018	**1.44**	**<0.0001**	**1.34**	**1.56**
2019	**1.56**	**<0.0001**	**1.45**	**1.68**
2020	**1.56**	**<0.0001**	**1.44**	**1.68**
ZIP Code Income Quartile				
2nd Quartile	0.94	0.055	0.89	1
3rd Quartile	0.97	0.413	0.91	1.04
4th Quartile	1.01	0.795	0.94	1.09
Hospital Bed Size				
Medium	**0.65**	**<0.0001**	**0.6**	**0.7**
Large	**0.8**	**<0.0001**	**0.75**	**0.85**
Sex (Female)	**0.84**	**<0.0001**	**0.8**	**0.88**

Bold values stand for statistically significant. PDA: Patent ductus arteriosus, LBW: Low BW, CI: Confidence interval

as influential factors in BPD outcomes, with significant *P* values observed across these categories (all $P < 0.0001$). All results are shown in Table 2.

DISCUSSION

The co-occurrence of PDA and BPD poses a challenge, imposing a considerable burden on affected individuals.[1] Recent literature highlights the increased susceptibility of individuals with PDA to developing BPD, a condition characterized by chronic lung disease in premature infants.[9,14] It was observed in a study discussing predictors of BPD or death in premature infants with PDA that death or BPD transpired in 80 cases (43%).[15] Logistic regression analysis revealed that lower GA, an earlier year of birth within the study period, and a larger ductal diameter were the factors associated with a decision to treat PDA.[15] The relationship between PDA and BPD necessitates a comprehensive understanding of the complex relationship between them.

In our study, the logistic regression of the univariate analysis showed that PDA infants have a higher risk of developing BPD than those without PDA (OR: 14.62; 95% CI: 14.01–15.25; $P < 0.0001$). Even after adjusting for potential confounders such as chorioamnionitis, cesarean delivery, BW, and others, this association persisted (OR: 2.4, 95% CI: 2.31–3.56, $P < 0.0001$), reinforcing our conclusion. From the multivariate regression, we also found that extremely preterm birth stands out as a critical factor, boasting the highest OR of 169.45 ($P < 0.0001$), signifying a substantially elevated risk. However, GA was the only variable significantly associated with death or BPD (OR 0.6, 95% CI: 0.5–0.8), as reported in a published article by Chock *et al.*, discussing predictors of BPD or death in premature infants with PDA.[15]

In a case–control study involving 398 preterm infants, conducted by Gentle *et al.* and published in 2023, it was observed that the presence of moderate-to-large PDA was significantly linked to an elevated risk of BPD-PH at the time of discharge.[9] Specifically, infants with PDA exhibited an adjusted OR of 4.29 (95% CI: 1.89–9.77) for developing BPD-PH, whereas infants with moderate-to-large PDA showed an adjusted OR of 4.15 (95% CI: 1.78–9.64).[9] In addition, probit analysis indicated that an increase in the duration of exposure to PDA and hsPDA correlated with a heightened probability of developing the combined outcome of BPD-PH at discharge or mortality. The coefficients were 0.40 ($P < 0.001$) and 0.45 ($P < 0.001$), respectively.[9]

The correlation between PDA and BPD is intricate and has yielded contradictory results.[3,16] Animal-based preclinical investigations have demonstrated that exposure to a moderate-to-large PDA for 2 weeks decreased alveolar surface area, thereby exacerbating the arrested alveolar development characteristic of BPD.[17] Interestingly, the abundance of smooth muscle surrounding terminal bronchioles and adjacent pulmonary arteries remained unaltered by exposure to ductal shunts.[17] Certain single-center observational studies support these findings, suggesting that infants with small PDA shunts are not inherently at an elevated risk for developing BPD.[17-22] Rather, the correlation between PDA and BPD becomes evident when moderate-to-large shunts persist beyond 7–14 days.[16,18,20-22] Notably, the

duration of mechanical ventilation plays a pivotal role in this interaction. Research conducted by Clyman and Hills and Clyman *et al.* demonstrated that infants subjected to mechanical ventilation for over 10 days exhibited the most severe manifestations of BPD, particularly when concurrently exposed to a moderate-to-large PDA for at least 7–14 days.[16,23]

The pathophysiological mechanisms driving the development of BPD in patients with PDA entail a complex interplay of factors that significantly impact pulmonary health.[8,24] PDA-induced pulmonary overcirculation imposes a burden on the immature lungs, leading to several detrimental effects.[8,16] The increased blood flow to the lungs results in pulmonary edema, inflammation, and oxidative stress.[8] This inflammatory response is exacerbated by the need for supplemental oxygen therapy in premature infants with PDA, as prolonged exposure to high oxygen levels can induce oxygen toxicity, further aggravating lung injury.[8] Moreover, the requirement for mechanical ventilation in these infants introduces additional insults to the delicate lung tissue, including barotrauma and volutrauma, which contribute to inflammation and impaired lung development.[8,25] This cascade of events disrupts normal alveolar development, leading to decreased gas exchange efficiency and respiratory function.[8] Concurrently, chronic pulmonary overcirculation prompts vascular remodeling in the lungs, characterized by pulmonary hypertension and increased pulmonary vascular resistance, further exacerbating lung injury and contributing to the pathogenesis of BPD.[8,26]

Strengths of utilizing the NIS for investigating the association between PDA and BPD include its large sample size, providing robust statistical power even for rare conditions such as PDA and BPD, and its national representation, offering generalizability to the broader population of patients across the United States. In addition, the longitudinal data available in the NIS enable researchers to assess trends over time and explore changes in the relationship between PDA and BPD across different periods. Moreover, the NIS collects rich clinical information on patient demographics, characteristics, procedures, and outcomes, allowing for comprehensive analyses adjusting for potential confounding factors and examining various aspects of the PDA-BPD relationship. However, limitations such as its retrospective design, reliance on administrative data, lack of detailed clinical information, potential for coding errors, and inability to establish causality must be acknowledged, underscoring the need for cautious interpretation and further research to elucidate underlying mechanisms and inform clinical management strategies.

CONCLUSIONS

Our research enhances the connection between PDA and BPD, as evidenced by our analysis of nationally representative data from the United States NIS. These findings underscore the necessity for continued investigations into this relationship. Moreover, our results emphasize the importance of considering multiple factors when examining the causes of these conditions. Looking ahead, prospective studies are essential for gaining a more thorough understanding and for exploring potential preventive and therapeutic approaches.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: ICD10 codes used for identification of the variables in the study

Variable	Source	ICD-10 code
PDA	I10_DX 1/40	Q250
BPD	I10_DX 1/40	P271
Extremely preterm	I10_DX 1/40	P072
Moderate to late preterm	I10_DX 1/40	P0735, P0736, P0736, P0737, P0738, P0739
Very preterm	I10_DX 1/40	P0731, P0732, P0733, P0734
Unspecified preterm	I10_DX 1/40	P0730
Extremely LBW	I10_DX 1/40	P070
Moderate LBW	I10_DX 1/40	P0716, P0717, P0718
Very LBW	I10_DX 1/40	P0714, P0715
Unspecified LBW	I10_DX 1/40	P0710
Neonatal bacterial sepsis	I10_DX 1/40	P36
Chorioamnionitis	I10_DX 1/40	P027
Caesarean delivery	I10_DX 1/40	P034
Multiple pregnancies	I10_DX 1/40	P015

BPD: Bronchopulmonary dysplasia, PDA: Patent ductus arteriosus, LBW: Low birth weight, ICD: International Classification of Disease