Trends in Bronchopulmonary Dysplasia Among Extremely Preterm Infants in Japan, 2003-2016

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Trends in Bronchopulmonary Dysplasia Among Extremely Preterm Infants in Japan, 2003-2016

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Objective To investigate recent trends in bronchopulmonary dysplasia (BPD) and its risk factors among extremely preterm infants.

Study design Demographic and clinical data were reviewed for 19 370 infants born at 22-27 weeks of gestation registered in the affiliated hospitals of the Neonatal Research Network of Japan between 2003 and 2016. We investigated the overall survival and prevalence of bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age and risk factors for developing BPD among the survivors.

Results Among 19 370 infants, 2244 (11.6%) died by 36 weeks' postmenstrual age. The mortality rate decreased from 19.0% (99% CI, 15.7%-22.8%) in 2003 to 8.0% (99% CI, 6.2%-10.3%) in 2016. Among 17 126 survivors, BPD developed in 7792 (45.5%) infants, and its proportion significantly increased from 41.4% (99% CI, 36.5%-46.4%) in 2003 to 52.0% (99% CI, 48.2%-55.9%) in 2016. A multivariable analysis of the survivors showed a positive association of BPD with ≥4 weeks' supplemental oxygen or invasive ventilation, birth weight <750 g, small for gestational age, ≥4 weeks' noninvasive positive pressure ventilation, chorioamnionitis, <26 weeks' gestational age, <20 cases per year of center patient volume, or treated patent ductus arteriosus. Although the median duration of invasive ventilation was shortened, the proportions of factors associated adversely with BPD generally showed increasing trends over time.

Conclusions The mortality rate of extremely preterm infants has decreased, but the rate of BPD has increased in survivors between 2003 and 2016. Despite the decreasing duration of invasive ventilation over time, increasing rates of BPD suggest that differences in the patient population or other management strategies influence the development of BPD. *(J Pediatr 2021;230:119-25)*.

Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, is one of the most common and serious complications affecting extremely preterm infants (born at 22-27 weeks of gestation).[1] Infants with BPD require prolonged stays in neonatal intensive care units (NICUs). After discharge, many patients require home oxygen therapy and often experience rehospitalizations owing to reactive airway disease and an increased susceptibility to viral infections.[2] BPD gives rise to not only long-term respiratory problems, but also life-long morbidity in preterm infants, including neurodevelopmental impairment.[3,4]

The pathogenesis of BPD is multifactorial, and oxygen toxicity and ventilator-induced lung injury have been recognized as major risk factors for developing BPD.[5-8] A variety of measures, including antenatal steroids, artificial surfactant administration, less invasive ventilation, and lung protective strategies, have thus been introduced in practice and are used worldwide in the respiratory support of extremely preterm infants.[6,9,10]

With recent progress in the respiratory management of preterm infants, there have been significant changes in obstetric practice and neonatal demographics over the past decade. However, information concerning the impact of these changes on the development of BPD is scarce. Therefore, we investigated the recent trends over 14 years in the incidence rate of BPD and its association with risk factors among extremely preterm neonates using a nationwide cohort database in Japan.

Methods

The Neonatal Research Network of Japan database prospectively registered all of the clinical information on infants with a birth weight of ≤1500 g or gestational age <32 weeks' admitted to the 218 participating NICUs (**Appendix**; available at www.jpeds.com), accounting for 53.8% of 405 secondary- and tertiary-level NICUs in Japan.

We retrospectively analyzed infants who were born alive between January 1, 2003, and December 31, 2016. Decisions regarding the pursuit of active treatment or withdrawal of care were made by neonatologists on the basis of

BPD	Bronchopulmonary dysplasia
NICU	Neonatal intensive care unit
NPPV	Noninvasive positive pressure ventilation
PDA	Patent ductus arteriosus
PMA	Postmenstrual age

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the clinical status of the fetus or infant at birth and their communications with the parents. In general, attending neonatologists attempt to save infants at a gestational age of ≥23 weeks, and this principle did not change during the study period. Data on stillbirths and intrapartum deaths were not originally registered in the database. Eligible infants for the study were born between 22 and 27 weeks of gestation (<28 weeks) and observed from birth to death in the NICU or until 36 weeks' postmenstrual age (PMA). We excluded infants who had major anomalies or congenital or inherited disease, those transferred to other hospitals, and those without available records of mortality, a diagnosis of BPD, and respiratory management practices (duration of supplemental oxygen, invasive ventilation, and noninvasive positive pressure ventilation [NPPV]) before 36 weeks' PMA.

This study was approved by the internal review board of Tokyo Women's Medical University and the ethics committees at each institution involved. Written informed consent was obtained from the parents or guardians of infants. All data were fully anonymized before they were accessed by any of the authors.

The primary end point of the study was the survival rate with BPD at 36 weeks' PMA. BPD was defined as requiring oxygen therapy for 28 days after birth and receiving supplemental oxygen or positive pressure at 36 weeks' PMA.[11] The gestational age was calculated based on an ultrasound examination in early pregnancy and the date of the last menstrual period. Chorioamnionitis was diagnosed by clinical findings, including a maternal fever, leukocytosis, and uterine tenderness, or the presence of acute inflammatory changes observed in the tissue samples collected from the amnion, chorion, and parietal deciduas.[12] Antenatal corticosteroid use was defined as the administration of corticosteroids to the mother at any time before delivery. Small for gestational age was defined as a birth weight below the 10th percentile for gestational age.[13] Respiratory distress syndrome was diagnosed by clinical and radiographic findings. Sepsis was defined as symptomatic culture-proven septicemia or bacteremia. Treated patent ductus arteriosus (PDA) was defined as PDA requiring medical or surgical treatment diagnosed based on both echocardiographic and clinical findings. We defined center patient volume as the average number of infants with a gestational age of <28 weeks admitted per year per center, as previously reported.[14] Invasive ventilation referred to conventional mechanical ventilation or high-frequency ventilation via an endotracheal tube. NPPV included bilevel or continuous positive airway pressure equipped with a nasal mask or prongs.

Statistical Analyses

All statistical analyses were performed using the software program JMP 14.0 (SAS Institute) and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing).[15] To assess changes in patient characteristics over time, the Cochran-Armitage and the Jonckheere-Terpstra tests were used for categorical and continuous variables, respectively. The differences in the changes during the study period among the gestational age groups were assessed by fitting linear regression lines, calculating the Spearman correlation coefficient (r), and using the analysis of covariance. A multivariable logistic regression model was used to identify factors associated with BPD. The following variables were examined as potential confounders influencing the development of BPD: gestational age, birth weight, male sex, multiple births, chorioamnionitis, antenatal steroids, cesarean delivery, small for gestational age, Apgar score at 5 minutes, center patient volume, respiratory distress syndrome, sepsis, PDA, and respiratory managements.[14,16-18] We included in the regression model all variables after transforming continuous variables into binary variables. Results with a 2-sided P value of $< .01$ were considered significant.

Results

A total of 22 472 infants were born at 22-27 weeks of gestation between January 1, 2003, and December 31, 2016 (**Figure 1**; available at www.jpeds.com). Of these infants, 3102 were excluded: 869 infants with major congenital anomalies, 564 infants who were transferred to other hospitals, 19 infants without records of the mortality status, and 1185 and 465 infants without available records concerning the diagnosis of BPD and respiratory management practices, respectively. Ultimately, 19 370 infants were enrolled as the study population. These infants were born at a median gestational age of 25.9 weeks (IQR, 24.4-27.0 weeks) and a birth weight of 746 g (IQR, 604 -907 g). Overall, the incidence rate of BPD and mortality rate at 36 weeks PMA were 40.2% ([99% CI, 39.3%-41.1%], 7792 of 19 370 infants) and 11.6% ([99% CI, 11.0%-12.2%], 2244 of 19 370), respectively. Consequently, 17 126 infants survived to 36 weeks' PMA; of these, 7792 infants (45.5% [99% CI, 44.5%-46.5%]) had BPD.

Figure 2 shows the annual number of infants who survived with and without BPD and who had died by 36 weeks' PMA during the study period. Among the survivors, the proportion of BPD increased between 2003 (41.4% [99% CI, 36.5%-46.4%], 273 of 660) and 2016 (52.0% [99% CI, 48.2%-55.9%], 584 of 1122, P for trend $< .001$). The mortality rate decreased between 2003 (19.0% [99% CI, 15.7%-22.8%], 155 of 815) and 2016 (8.0% [99% CI, 6.2%-10.3%], 98 of 1220, P for trend $< .001$). We then investigated these trends according to the gestational age groups (**Figure 3**, **Table I**; available at www.jpeds.com). As with the overall trend, the proportion of BPD among survivors increased for all gestational age groups from 2003 to 2016, whereas the mortality rates decreased for all gestational age groups.

We investigated the clinical characteristics and their trends over time for the 17 126 survivors at 36 weeks' PMA (**Table II** and **Table III** [available at www.jpeds.com]). The median gestational age and birth weight significantly decreased from 2003 to 2016. Study participants were 53.1% male, with similar proportions during the study period. The proportions of chorioamnionitis, antenatal corticosteroid use, cesarean delivery, small for gestational age, and low Apgar scores increased from 2003 to 2016. The proportion of multiple births and center patient volume decreased from 2003 to 2016. All of the morbidities, including BPD, increased in

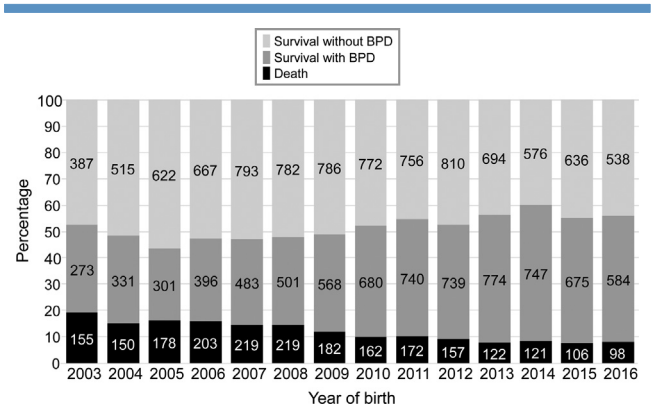

Figure 2. Trends in BPD and mortality at 36 weeks' PMA. The numbers in the bars represent the number of infants. Black, thick gray, and thin gray bars indicate the rate of death, survival with BPD, and survival without BPD, respectively.

proportion from 2003 to 2016 among survivors. The duration of invasive ventilation decreased, whereas the rate of intubation at birth and the duration of NPPV and oxygen therapy increased significantly.

To assess the impact of risk factors on the development of BPD, we used multivariable logistic regression. BPD was significantly associated with supplemental oxygen ≥4 weeks, invasive ventilation ≥4 weeks, birth weight of <750 g, small for gestational age, NPPV ≥4 weeks, chorioamnionitis, gestational age of <26 weeks, center patient volume of <20 cases per year, and treated PDA (**Table IV**). Except for invasive ventilation ≥4 weeks and gestational age <26 weeks, these proportions of variables associated adversely with BPD showed increasing trends during the study period.

In the study population, the combined incidence of BPD and death increased between 2003 (52.5% [99% CI, 48.0%-57.0%], 428 of 815) and 2016 (55.9% [99% CI, 52.2%-59.5%], 682 of 1220, *P* for trend < .001) (**Figure 2**). The combined incidence of BPD and death significantly increased in infants with a gestational age of 24-25 weeks (58.8% [177 of 301] to 61.8% [254 of 411], *P* for trend < .001) and in those with a gestational age of 26-27 weeks (38.2% [146 of 382] to 41.7% [245 of 587], *P* for trend < .001). In those with a gestational age of 22-23 weeks, it tended to increase, but the change did not reach statistical significance (79.5% [105 of 132] to 82.4% [183 of 222], *P* for trend = .012) (**Figure 3**).

To assess the relationship between the incidence of BPD and mortality at 36 weeks' PMA among extremely preterm infants, we compared the changing rates in BPD among survivors (**Figure 4**, A) and mortality (**Figure 4**, B) during the study period according to the gestational age groups (**Table I**). The gradients of regression lines in the rate of BPD did not differ between any 2 gestational age groups. In contrast, the gradients of regression lines in the mortality rate differed significantly among gestational age groups.

We further investigated the changing rates of factors associated with BPD during the study period among gestational age groups (**Figure 5** and **Table V**; available at www.jpeds.com). The proportion of invasive ventilation ≥4 weeks decreased in infants with gestational ages of 24-25 and 26-27 weeks (both *P* for trend < .001), but not in those with a gestational age of 22-23 weeks (*P* for trend = .11) from

Table II. Trends in the characteristics of extremely preterm infants who remained alive at 36 weeks' PMA during the study period

Characteristics	All survivors n = 17 126	2003 n = 660	2016 n = 1122	*P* value for trend
Perinatal characteristics				
Gestational age, weeks	26.0 (24.7-27.0)	26.0 (25.0-27.0)	26.0 (24.6-27.0)	**<.001**
Birth weight, g	768 (628-922)	791 (644-932)	743 (596-901)	**<.001**
Male sex	9097/17 118 (53.1)	377/659 (57.2)	607/1122 (54.1)	.22
Multiple births	3255/17 126 (19.0)	137/660 (20.8)	216/1122 (19.3)	**<.001**
Chorioamnionitis	7053/16 987 (41.5)	213/660 (32.3)	472/1091 (43.3)	**<.001**
Antenatal corticosteroid use	9461/17 014 (55.6)	270/660 (40.9)	769/1100 (69.9)	**<.001**
Cesarean delivery	12 785/17 092 (74.8)	421/660 (63.8)	885/1119 (79.1)	**<.001**
Small for gestational age	3463/17 104 (20.2)	111/660 (16.8)	245/1105 (22.2)	**<.001**
Apgar score <4 points at 5 min	1529/16 828 (9.1)	53/635 (8.4)	127/1116 (11.4)	**<.001**
Center patient volume,* cases per year	20.0 (13.4-28.3)	26.0 (18.8-34.0)	17.0 (11.3-25.0)	**<.001**
Morbidities				
Respiratory distress syndrome	13 236/17 076 (77.5)	464/660 (70.3)	931/1100 (84.6)	**<.001**
Sepsis	2133/17 076 (12.5)	61/660 (9.2)	126/1118 (11.3)	**<.001**
Treated PDA	9410/17 095 (55.0)	285/660 (43.2)	628/1118 (56.2)	**<.001**
BPD	7792/17 126 (45.5)	273/660 (41.4)	584/1122 (52.0)	**<.001**
Respiratory managements				
Intubation at birth	14 627/17 081 (85.6)	499/660 (75.6)	1004/1119 (89.7)	**<.001**
Invasive ventilation,† weeks	5.4 (2.6-8.1)	6.4 (3.0-9.0)	4.7 (1.9-7.4)	**<.001**
NPPV,† weeks	3.7 (1.3-5.9)	0.1 (0.0-2.7)	5.1 (3.0-7.1)	**<.001**
Supplemental oxygen,† weeks	8.9 (6.3-10.7)	9.0 (6.9-10.6)	9.1 (6.4-11.0)	**<.001**

Data are presented as the number/number with available information (percentage) or as the median (IQR). Values in bold are statistically significant.
The *P* values for trend between 2003 and 2016 were obtained using the Cochran-Armitage test for categorical variables and the Jonckheere-Terpstra test for continuous variables. See **Table III** for all the study period between 2003 and 2016.
*Center patient volume was calculated as the average number of infants admitted per year per center.
†Durations of respiratory managements until 36 weeks' PMA.

Table IV. Multivariate logistic regression model for BPD among survivors at 36 weeks' PMA

Variables	Total, n	BPD, n (%)	Crude OR, *P value	aOR, *P value	2003-2016, n = 17 126 (%)	2003, n = 660 (%)	2016, n = 1122 (%)	P value for trend†
Supplemental oxygen ≥4 weeks								
Yes	14 514	7534 (51.9)	9.85 (8.27-11.72)	6.98 (5.80-8.41)	14 514/17 126	560/660	960/1122	**<.001**
No	2612	258 (9.9)	**<.001**	**<.001**	(84.7)	(84.8)	(85.6)	
Invasive ventilation ≥4 weeks								
Yes	11 091	6444 (58.1)	4.82 (4.39-5.30)	3.42 (3.04-3.86)	11 091/17 126	464/660	645/1122	**<.001**
No	6035	1348 (22.3)	**<.001**	**<.001**	(64.8)	(70.3)	(57.5)	
Birth weight <750 g								
Yes	7980	4813 (60.3)	3.14 (2.90-3.41)	1.62 (1.43-1.84)	7980/17 108	289/660	561/1105	**<.001**
No	9128	2974 (32.6)	**<.001**	**<.001**	(46.6)	(43.8)	(50.8)	
Small for gestational age								
Yes	3463	1951 (56.3)	1.73 (1.56-1.91)	1.40 (1.22-1.61)	3463/17 104	111/660	245/1105	**<.001**
No	13 641	5834 (42.8)	**<.001**	**<.001**	(20.2)	(16.8)	(22.2)	
NPPV ≥4 weeks								
Yes	8006	3754 (46.9)	1.11 (1.03-1.20)	1.38 (1.25-1.52)	8006/17 126	92/660	725/1122	**<.001**
No	9120	4038 (44.3)	**<0.001**	**<0.001**	(46.7)	(13.9)	(64.6)	
Chorioamnionitis								
Yes	7053	3501 (49.6)	1.34 (1.23-1.45)	1.29 (1.17-1.43)	7053/16 987	213/660	472/1091	**<.001**
No	9934	4217 (42.5)	**<.001**	**<.001**	(41.5)	(32.3)	(43.3)	
Gestational age <26 weeks								
Yes	8119	4719 (58.1)	2.68 (2.47-2.91)	1.18 (1.04-1.33)	8119/17 126	317/660	554/1122	.10
No	9007	3073 (34.1)	**<.001**	**<.001**	(47.4)	(48.0)	(49.4)	
Center patient volume <20 cases per year								
Yes	8520	3997 (46.9)	1.12 (1.04-1.21)	1.16 (1.06-1.27)	8520/17 126	232/660	677/1122	**<.001**
No	8606	3795 (44.1)	**<.001**	**<.001**	(49.7)	(35.2)	(60.3)	
Treated PDA								
Yes	9410	4557 (48.4)	1.30 (1.20-1.41)	1.12 (1.02-1.23)	9410/17 095	285/660	628/1118	**<.001**
No	7685	3217 (41.9)	**<.001**	**.002**	(55.0)	(43.2)	(56.2)	
Sepsis								
Yes	2133	1158 (54.3)	1.50 (1.33-1.69)	1.10 (0.96-1.27)				
No	14 943	6608 (44.2)	**<.001**	.07				
Intubation at birth								
Yes	14 627	6964 (47.6)	1.84 (1.64-2.07)	1.03 (0.89-1.18)				
No	2454	811 (33.1)	**<.001**	.65				
Respiratory distress syndrome								
Yes	13 236	6177 (46.7)	1.24 (1.13-1.37)	0.91 (0.81-1.02)				
No	3840	1586 (41.3)	**<.001**	.04				

Values in bold are statistically significant.
*ORs (99% CI) and *P* values were obtained from logistic regression analysis. Adjusted values were obtained from a logistic regression analysis after adjusting for male sex, multiple births, antenatal corticosteroid use, cesarean delivery, Apgar score of <4 points at 5 minutes, and all variables listed in this table.
†The *P* values for trend between 2003 and 2016 were obtained using the Cochran-Armitage test.

2003 to 2016, and the gradients of regression lines differed between a gestational age of 22-23 weeks ($P < .001$) or 24-25 weeks ($P = .009$) and a gestational age of 26-27 weeks (Figure 5, B). The proportion of infants with a birth weight of <750 g did not change among gestational age groups from 2003 to 2016 (all P for trend $> .01$), although the gradients of regression lines differed between the patients with a gestational age of 24-25 weeks ($P = .002$) and 26-27 weeks ($P = .003$) or a gestational age of 22-23 weeks. The proportion of small for gestational age increased in all gestational age groups from 2003 to 2016 (all P for trend $< .001$), and the gradients of regression lines differed between the patients with a gestational age of 24-25 and 26-27 weeks ($P = .008$) (Figure 5, C). The proportion of treated PDA increased in infants with a gestational age of 26-27 weeks (P for trend $< .001$) but did not in those with a gestational age of 22-23 weeks ($P = .97$) or 24-25 weeks ($P = .12$). The regression gradients in the rate of treated PDA did not differ among gestational age groups (Figure 5, G). The other factors associated with BPD (Figure 5, A, D-F and Table V) and BPD (Figure 4, A and Table I) showed similar trends in all gestational age groups during the study period.

Discussion

From 2003 to 2016 in Japan, the incidence of BPD increased, whereas in-hospital mortality decreased among extremely preterm infants. Despite the shortened duration of invasive ventilation, the proportions of factors associated adversely with BPD generally increased during the study period. Advanced NICU care improved mortality, but was accompanied by an increase in survivors with BPD, which may be partly explained by the increasing prevalence of other risk factors for BPD among extremely preterm infants in Japan.

Recent studies have reported decreasing, unchanged, or increasing rates of BPD among preterm infants compared with previous decades.[19-24] The increased incidence of BPD may be due to the increased survival of extremely preterm infants.[23] However, the present study showed that the combined incidence of BPD and death increased especially in infants at 24-27 weeks of gestation (Figure 3). These results may imply

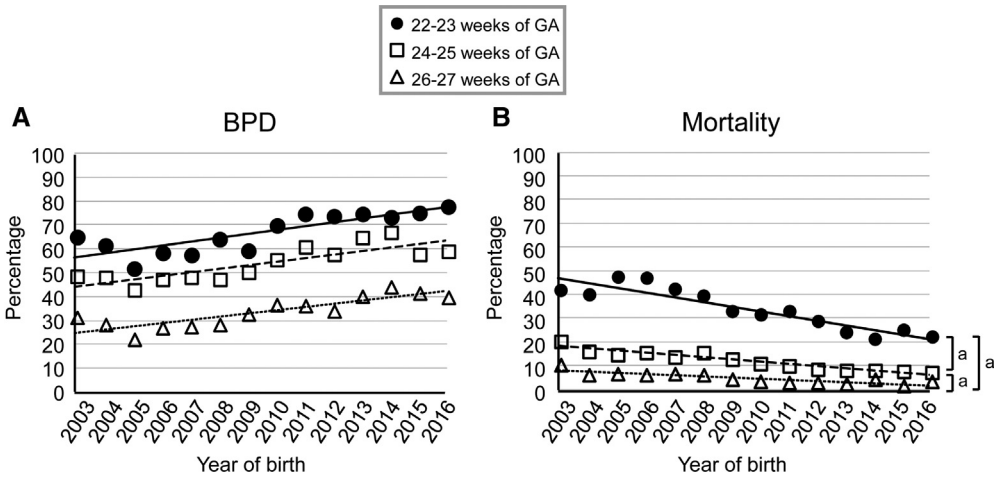

Figure 4. The changing rates of BPD among survivors and mortality at 36 weeks' PMA according to the gestational age groups. **A,** BPD; **B,** mortality. ●, 22-23 weeks; □, 24-25 weeks; △, 26-27 weeks. The solid line (22-23 weeks), long dashed line (24-25 weeks), and dotted line (26-27 weeks) represent the regression lines. [a] $P < .001$ for comparison between GA groups by analysis of covariance. *GA*, gestational age.

that the improved survival is accompanied by an increase in survivors with BPD and a decrease in survivors without BPD. The mortality rate exhibited the most significant decreasing trend in infants with a gestational age of 24-25 weeks ($r = -0.98$) and the incidence of BPD showed similar increasing trends for all gestational age groups (**Figure 4**, A and B). These results indicate that other factors beyond the infant survival might be associated with the increased incidence of BPD in extremely preterm infants.

The pathogenesis of BPD is closely associated with oxygen toxicity and barotrauma/volutrauma to the premature lung during prolonged mechanical ventilation.[5,8,16] Avoiding intubation, higher target ranges of oxygen saturation, and invasive respiratory support seem to decrease the risk of BPD in extremely preterm infants.[9,25,26] However, the present study showed that the rate of survivors with BPD increased during the period of a shortened duration of invasive ventilation and prolonged duration of NPPV and oxygen therapy. We speculate that the decreasing use of invasive ventilation may contribute to prolonged oxygen therapy and an increased use of NPPV. A recent study also showed the tendency to use NPPV and prolonged oxygen therapy in extremely preterm infants and suggested that increased use of NPPV over time had not been accompanied by substantial improvements in BPD rates or childhood lung function among survivors.[3] These findings are inconsistent with those of other studies demonstrating a beneficial effect of less invasive respiratory care on the development of BPD compared with invasive care for preterm infants.[6,20,27] Although the present study does not prove a causal relationship between the development of BPD and respiratory management practice, merely avoiding invasive ventilation and replacing it with NPPV and/or supplemental oxygen therapy may have less of an impact on the prevention of BPD than the control of other risk factors. Identifying the best indication and ideal timing for respiratory care in individual infants is a challenge to be addressed in the future.

Other individual risk factors for the development of BPD included lower birth weight, small for gestational age, chorioamnionitis, lower gestational age, lower patient volume, and treated PDA, all of which increased over the 14-year study period. These factors are consistent with the findings of previous reports on risk factors for BPD.[14,28-34] Furthermore, these factors are also associated with the mortality of extremely preterm infants.[14,22,35-37] Considering the improved survival of these infants, the increase in the incidence of BPD may be related to improvements in the early survival rate of infants who would have otherwise died before they reached 36 weeks' PMA. Interestingly, we found that the incidence of BPD and the proportion of small for gestational age or treated PDA showed different increasing patterns of longitudinal changes during the study period (**Figure 4**, A, **Figure 5**, C and G, and **Table V**). There might be additional factors contributing to the development of BPD in survivors who previously would have died before 36 weeks' PMA, which minimized the individual benefits of less invasive respiratory care in extremely preterm infants. To prevent BPD in extremely preterm infants, further studies are needed not only to improve respiratory care for these infants, but also to manage known risk factors for BPD that could be modifiable. For example, identifying how and when to treat PDA might be beneficial in the prevention of BPD because of the relatively high incidence and the increasing trend of treated PDA in our cohort. Additionally, the centralization of perinatal care for high-risk pregnant women and newborns might be important for preventing BPD because of the decreasing trend of the number of infants admitted per center in our cohort. Further identification of genetic or environmental factors associated with BPD in this patient population will lend insight into therapeutic targets for prevention of BPD.

Several limitations associated with the present study warrant mention. Japan has a relatively homogenous racial and ethnic background with universal access to the health care system for

all the eligible newborns, irrespective of socioeconomic status. This factor may limit the generalization of the study findings to other populations or those with variable access to health care. There is insufficient information on specific respiratory support strategies such as primary application of noninvasive support, oxygen saturation targets, and other approaches to mitigate the risk of BPD, such as early nutritional support and administration of corticosteroids, caffeine, and vitamin A.[25,26] The rate of BPD may be overestimated because there are no data on whether the oxygen therapy requirements were determined by the oxygen reduction test.[38] Finally, we evaluated the risk factors for BPD among survivors and did not assess the detailed causes of death in each infant who might have developed BPD if they survived to 36 weeks' PMA. This approach may produce selection bias owing to the competing risk of death with the study outcomes.

In conclusion, the overall incidence of BPD increased significantly among extremely preterm infants between 2003 and 2016 in Japan. This trend was accompanied by increases in survival and the many risk factors associated with BPD among survivors at 36 weeks' PMA, despite a decrease in the duration of invasive ventilation. To decrease the incidence of BPD, further studies are required to promote global improvements in prenatal care of high-risk pregnancies and intensive care of neonates that encourage lung growth and attenuate inflammation and oxidative stress in the preterm lung. ■

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References

1. Siffel C, Kistler KD, Lewis JFM, Sarda SP. Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review. J Matern Fetal Neonatal Med 20191-11.
2. Davidson LM, Berkelhamer SK. Bronchopulmonary dysplasia: chronic lung disease of infancy and long-term pulmonary outcomes. J Clin Med 2017;6:4.
3. Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. N Engl J Med 2017;377:329-37.
4. Malavolti AM, Bassler D, Arlettaz-Mieth R, Faldella G, Latal B, Natalucci G. Bronchopulmonary dysplasia-impact of severity and timing of diagnosis on neurodevelopment of preterm infants: a retrospective cohort study. BMJ Paediatr Open 2018;2:e000165.
5. Wai KC, Kohn MA, Ballard RA, Truog WE, Black DM, Asselin JM, et al. Early cumulative supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. J Pediatr 2016;177:97-102.e2.
6. Fischer HS, Buhrer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. Pediatrics 2013;132:e1351-60.
7. Laughon M, Allred EN, Bose C, O'Shea TM, Van Marter LJ, Ehrenkranz RA, et al. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. Pediatrics 2009;123:1124-31.
8. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med 2011;183:1715-22.
9. Dumpa V, Bhandari V. Surfactant, steroids and non-invasive ventilation in the prevention of BPD. Semin Perinatol 2018;42:444-52.
10. Greenough A, Ahmed N. Perinatal prevention of bronchopulmonary dysplasia. J Perinat Med 2013;41:119-26.
11. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
12. Redline RW. Inflammatory responses in the placenta and umbilical cord. Semin Fetal Neonatal Med 2006;11:296-301.
13. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatr Int 2014;56:702-8.
14. Spotswood N, Orsini F, Dargaville P. Australian and New Zealand Neonatal Network. Association of center-specific patient volumes and early respiratory management practices with death and bronchopulmonary dysplasia in preterm infants. J Pediatr 2019;210:63-8.e2.
15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8.
16. Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. Respir Med 2017;132:170-7.
17. Morrow LA, Wagner BD, Ingram DA, Poindexter BB, Schibler K, Cotten CM, et al. Antenatal determinants of bronchopulmonary dysplasia and late respiratory disease in preterm infants. Am J Respir Crit Care Med 2017;196:364-74.
18. Landry JS, Menzies D. Occurrence and severity of bronchopulmonary dysplasia and respiratory distress syndrome after a preterm birth. Paediatr Child Health 2011;16:399-403.
19. Botet F, Figueras-Aloy J, Miracle-Echegoyen X, Rodriguez-Miguelez JM, Salvia-Roiges MD, Carbonell-Estrany X. Trends in survival among extremely-low-birth-weight infants (less than 1000 g) without significant bronchopulmonary dysplasia. BMC Pediatr 2012;12:63.
20. Vendettuoli V, Bellu R, Zanini R, Mosca F, Gagliardi L , Italian Neonatal Network. Changes in ventilator strategies and outcomes in preterm infants. Arch Dis Child Fetal Neonatal Ed 2014;99:F321-4.
21. Ancel PY, Goffinet F, Group E-W, Kuhn P, Langer B, Matis J, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA Pediatr 2015;169:230-8.
22. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443-56.
23. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
24. Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants. Pediatrics 2009;124:673-9.
25. Poets CF, Lorenz L. Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence. Arch Dis Child Fetal Neonatal Ed 2018;103:F285-91.
26. Hwang JS, Rehan VK. Recent advances in bronchopulmonary dysplasia: pathophysiology, prevention, and treatment. Lung 2018;196:129-38.
27. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980.
28. Bose C, Van Marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, et al. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. Pediatrics 2009;124:e450-8.
29. Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2012;97:F8-17.

30. Peacock JL, Lo JW, D'Costa W, Calvert S, Marlow N, Greenough A. Respiratory morbidity at follow-up of small-for-gestational-age infants born very prematurely. Pediatr Res 2013;73:457-63.
31. Eriksson L, Haglund B, Odlind V, Altman M, Ewald U, Kieler H. Perinatal conditions related to growth restriction and inflammation are associated with an increased risk of bronchopulmonary dysplasia. Acta Paediatr 2015;104:259-63.
32. Metcalfe A, Lisonkova S, Sabr Y, Stritzke A, Joseph KS. Neonatal respiratory morbidity following exposure to chorioamnionitis. BMC Pediatr 2017;17:128.
33. Nobile S, Marchionni P, Carnielli VP. Neonatal outcome of small for gestational age preterm infants. Eur J Pediatr 2017;176:1083-8.
34. Clyman RI. The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia. Semin Perinatol 2013;37:102-7.
35. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Morbidity and mortality in small for gestational age infants at 22 to 29 weeks' gestation. Pediatrics 2018;141:e20172533.
36. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. Pediatrics 2009;123:e138-44.
37. Salas AA, Faye-Petersen OM, Sims B, Peralta-Carcelen M, Reilly SD, McGwin G Jr, et al. Histological characteristics of the fetal inflammatory response associated with neurodevelopmental impairment and death in extremely preterm infants. J Pediatr 2013;163:652-7.e1-2.
38. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics 2004;114:1305-11.

50 Years Ago in *The Journal of Pediatrics*

Sixth Cranial Nerve Palsy in the Neonate

Reisner SH, Perlman M, Ben-Tovim N, Dubrawski C. Transient lateral rectus muscle paresis in the newborn infant. J Pediatr 1971;78:461-5.

In *The Journal* 50 years ago, Reisner et al presented this study on 6360 neonates. The infants were examined at the age of 2-4 days, all with normal neurologic findings apart from unilateral lateral rectus muscle paresis in 35 infants. There were more primipara mothers and more use of oxytocin in the infants with paresis but no signs of birth trauma or a greater rate of instrumental deliveries. By 6 weeks of age, the paresis had resolved in all but 1 child. The authors concluded that the most likely cause was increased intracranial pressure during delivery, causing transient damage to the sixth cranial nerve. De Grauw and Rotteveel in 1983 described identical findings in 3 neonates, but in their study forceps delivery was the hypothesized culprit.[1]

Damage to the sixth cranial nerve can be caused by infections, malignancies, and vascular events; and most commonly in the neonate—by trauma. The prognosis in the neonatal population is good, and in the published cases it resolved within 6 weeks, which is also thought to be the sensitive period for the development of stereopsis and normal visual acuity—meaning that these infants have an excellent prognosis.[2]

Transient lateral rectal muscle palsy after delivery is most likely induced by damage to the sixth cranial nerve due to birth trauma. A current review from 2016 concluded that the majority of cases of strabismus in the neonatal period are benign and resolve without intervention,[3] in line with Reisner's findings 50 years ago. Mansoor et al recommend referral to an ophthalmologist when strabismus remains after 3-6 months for prevention of amblyopia.[3]

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References

1. de Grauw AJ, Rotteveel JJ, Cruysberg JR. Transient sixth cranial nerve paralysis in the newborn infant. Neuropediatrics 1983;14:164-5.
2. Elston JS, Timms C. Clinical evidence for the onset of the sensitive period in infancy. Br J Ophthalmol 1992;76:327-8.
3. Mansoor N, Mansoor T, Ahmed M. Eye pathologies in neonates. Int J Ophthalmol 2016;9:1832-8.

Appendix

The Neonatal Research Network of Japan consisted of the following institutions: Sapporo City General Hospital, Asahikawa Kosei General Hospital, Engaru-Kosei General Hospital, Kushiro Red Cross Hospital, Obihiro-Kosei General Hospital, Tenshi Hospital, NTT Higashinihon Sapporo Hospital, Nikko Memorial Hospital, Nayoro City General Hospital, Sapporo Medical University, Asahikawa Medical University, Aomori Prefectural Central Hospital, Iwate Medical University, Iwate Prefectural Ofunato Hospital, Iwate Prefectural Kuji Hospital, Iwate Prefectural Ninohe Hospital, Sendai Red Cross Hospital, Tohoku University, Akita Red Cross Hospital, Akita University, Tsuruoka Municipal Shonai Hospital, Yamagata University, Yamagata Prefectural Central Hospital, Fukushima Medical University, Takeda General Hospital, Fukushima National Hospital, Tsukuba University, Tsuchiura Kyodo Hospital, Ibaraki Children's Hospital, Dokkyo Medical University, Jichi Medical University, Ashikaga Red Cross Hospital, Gunma Children's Medical Center, Kiryu Kosei General Hospital, Fuji Heavy Industries Health Insurance Society Ota Memorial Hospital, Gunma University, Saitama Medical University, Saitama Children's Medical Center, Nishisaitama-chuo National Hospital, Saitama Medical University Saitama Medical Center, Kawaguchi Municipal Medical Center, Jichi Medical University Saitama Medical Center, Asahi General Hospital, Chiba Kaihin Municipal Hospital, Kameda Medical Center, Tokyo Women's Medical University Yachiyo Medical Center, Juntendo University Urayasu Hospital, Narita Red Cross Hospital, Tokyo Metropolitan Children's Medical Center, Tokyo Women's Medical University, Aiiku Hospital, Nihon University Itabashi Hospital, National Center for Global Health and Medicine, Tokyo Medical University, Teikyo University, Showa University, Japan Red Cross Medical Center, National Center for Child Health and Development, Tokyo Metropolitan Otsuka Hospital, Tokyo University, Toho University, Tokyo Metropolitan Bokuto Hospital, Tokyo Jikei Medical University, Tokyo Medical and Dental University, Saint Luke's International Hospital, Juntendo University, Sanikukai Hospital, Katsushika Red Cross Hospital, Yokohama Rosai Hospital, Yokohama City University Medical Center, St. Marianna University School of Medicine Hospital, Kanagawa Children's Medical Center, Tokai University, Kitazato University, Odawara Municipal Hospital, Nippon Medical School Musashi Kosugi Hospital, Yokohama City Hospital, Saiseikai Yokohamashi Tobu Hospital, National Hospital Organization Yokohama Medical Center, Yamanashi Prefectural Central Hospital, Nagano Children's Hospital, Shinshu University, Iida Municipal Hospital, National Hospital Organization Shinshu Ueda Medical Center, Saku General Hospital, Niigata University, Niigata Prefectural Central Hospital, Niigata Municipal Hospital, Nagaoka Red Cross Hospital, Koseiren Takaoka Hospital, Toyama Prefectural Central Hospital, Toyama University, Ishikawa Medical Center for Maternal and Child Health, Kanazawa Medical University, Kanazawa Medical Center, Fukui Prefectural Hospital, Fukui University, Gifu Prefectural General Medical Center, Oogaki City Hospital, National Hospital Organization Nagara Medical Center, Takayama Red Cross Hospital, Seirei Hamamatsu Hospital, Shizuoka Saiseikai Hospital, Shizuoka Children's Hospital, Hamamatsu Medical University, Numazu Municipal Hospital, Yaizu City Hospital, Fujieda Municipal General Hospital, Nagoya Red Cross Daini Hospital, Nagoya University, Nagoya Red Cross Daiichi Hospital, Toyohashi Municipal Hospital, Nagoya City West Medical Center, Fujita Health University, Anjo Kosei Hospital, Tosei General Hospital, Komaki Municipal Hospital, TOYOTA Memorial Hospital, Okazaki Municipal Hospital, Handa City Hospital, Konan Kosei Hospital, Aichi Medical University, National Mie Central Medical Center, Ise Red Cross Hospital, Yokkaichi Municipal Hospital, Otsu Red Cross Hospital, Shiga University of Medical Science Hospital, Nagahama Red Cross Hospital, Uji Tokushukai Hospital, The Japan Baptist Hospital, Kyoto University, Kyoto Red Cross Daiichi Hospital, National Maizuru Medical Center, Fukuchiyama City Hospital, Kyoto Prefectural University of Medicine Hospital, Kyoto City Hospital, Mitsubishi Kyoto Hospital, Yodogawa Christian Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka University, Takatsuki General Hospital, Kansai Medical University, Osaka City General Hospital, Osaka City Sumiyoshi Hospital, Aizenbashi Hospital, Toyonaka Municipal Hospital, National Cerebral and Cardiovascular Center, Kitano Hospital, Saiseikai Suita Hospital, Chifune Hospital, Bellland General Hospital, Rinku General Medical Center, Osaka Red Cross Hospital, Yao Municipal Hospital, Hannan Central Hospital, Osaka General Medical Center, Osaka City University, Hyogo Prefectural Kobe Children's Hospital, Kobe University, Kakogawa West City Hospital, Saiseikai Hyogoken Hospital, Kobe City Medical Center General Hospital, Hyogo College of Medicine Hospital, Himeji Red Cross Hospital, Toyooka Public Hospital, Hyogo Prefectural Awaji Medical Center, Nara Medical University, Wakayama Medical University, Tottori Prefectural Central Hospital, Tottori University, Shimane Prefectural Central Hospital, Matsue Red Cross Hospital, Kurashiki Central Hospital, Tsuyama Central Hospital, Kawasaki Medical School Hospital, National Hospital Organization Okayama Medical Center, Okayama Red Cross Hospital, Hiroshima City Hiroshima Citizens Hospital, Hiroshima Prefectural Hospital, Hiroshima University, Tsuchiya General Hospital, National Hospital Organization Kure Medical Center, Yamaguchi University, Yamaguchi Grand Medical Center, Tokushima University, Tokushima Municipal Hospital, Kagawa University, Shikoku Medical Center for Children and Adults, Matsuyama Red Cross Hospital, Ehime Prefectural Central Hospital, Kochi Health Science Center, St. Mary's Hospital, National Kyushu Medical Center, Kurume University, Kitakyushu Municipal Medical Center, University of Occupational and Environmental Health, Fukuoka University, Kyushu University, Iizuka Hospital, National Hospital Organization Kokura

Medical Center, Fukuoka City Children's Hospital, National Hospital Organization Saga Hospital, Nagasaki University, National Hospital Organization Nagasaki Medical Center, Sasebo City Hospital, Kumamoto City Hospital, Kumamoto University, Oita Prefectural Hospital, Almeida Memorial Hospital, Nakatsu Municipal Hospital, Miyazaki University, National Hospital Organization Miyakonojo Medical Center, Kagoshima City Hospital, Imakiire General Hospital, Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, Okinawa Prefectural Chubu Hospital, Naha City Hospital, Okinawa Red Cross Hospital.

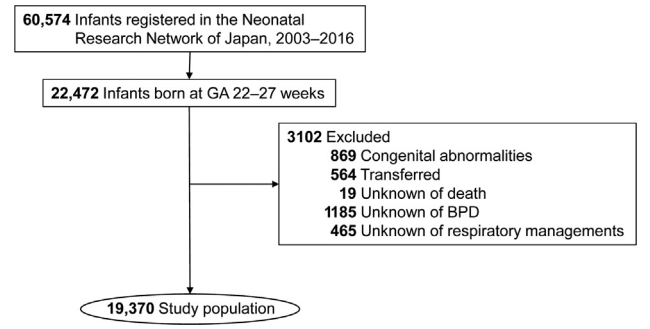

Figure 1. Patient enrollment. *GA*, gestational age.

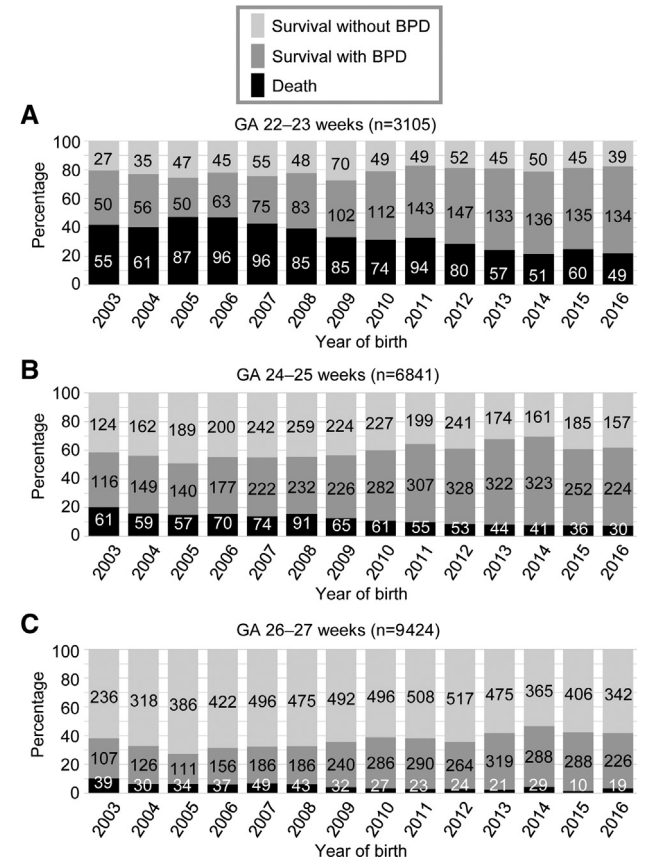

Figure 3. Trends in BPD and mortality at 36 weeks' PMA according to the GA groups. A, B, and C, The 22-23, 24-25, and 26-27 weeks of gestation groups, respectively. The numbers in the bars represent the number of infants. Black, thick gray, and thin gray bars indicate the rate of death, survival with BPD, and survival without BPD, respectively. *GA*, gestational age.

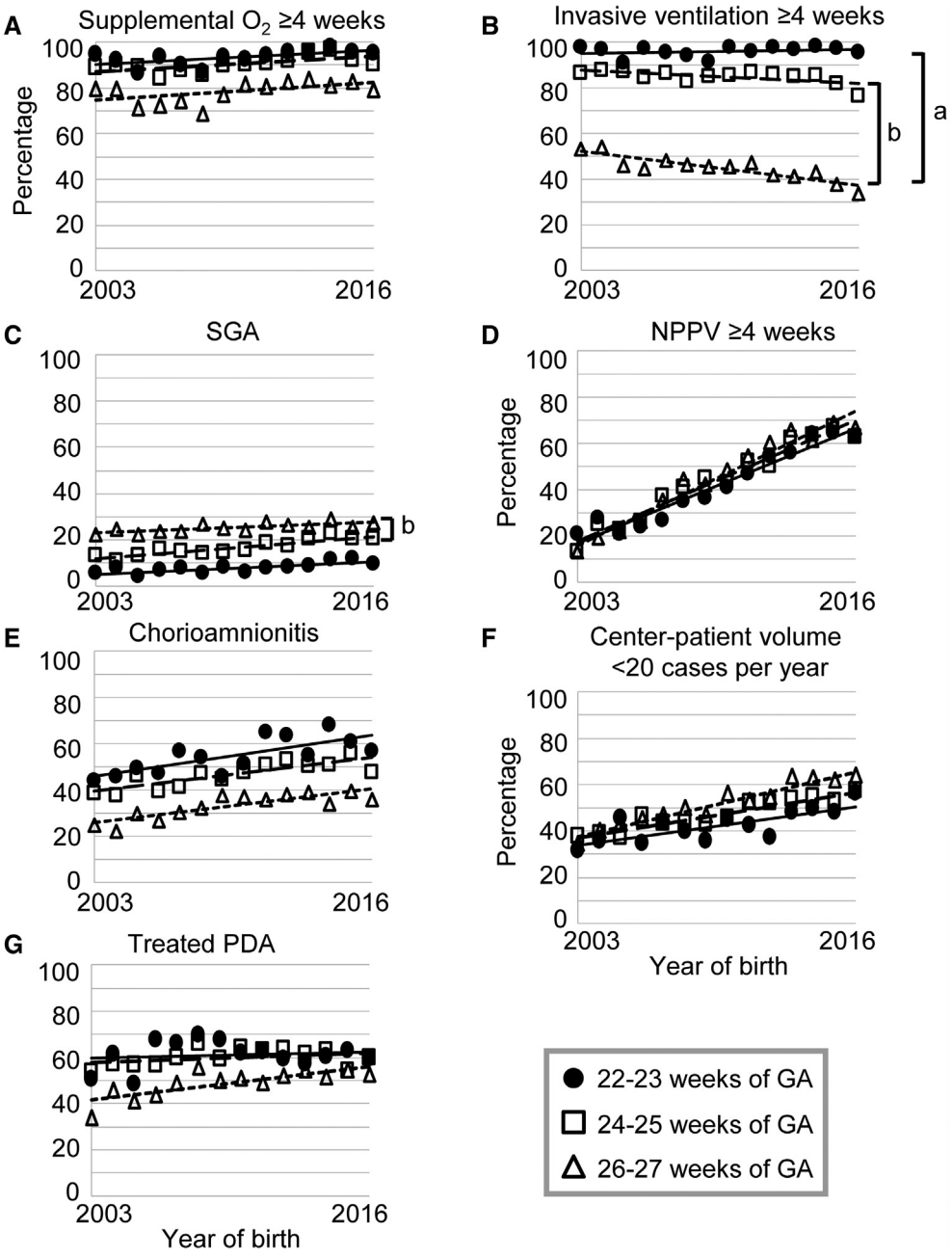

Figure 5. Trends in clinical factors associated with BPD at 36 weeks' PMA according to the GA groups. **A**-**G**, Each clinical factor associated with BPD other than GA and birth weight. **A,** Supplemental oxygen ≥4 weeks. **B,** Invasive ventilation ≥4 weeks. **C,** Small for GA. **D,** NPPV ≥4 weeks. **E,** Chorioamnionitis. **F,** Center patient volume <20 cases per year. **G,** Treated PDA. ●, 22-23 weeks; □, 24-25 weeks; △, 26-27 weeks. The solid line (22-23 weeks), long dashed line (24-25 weeks), and dotted line (26-27 weeks) represent the regression lines. O_2, oxygen. [a] $P < .001$ and [b] $P < .01$ for comparison between GA groups by analysis of covariance. *GA*, gestational age.

Table I. Trends in BPD among survivors and mortality at 36 weeks' PMA according to the gestational age groups

Outcomes	2003-2016	2003	2016	*P* value for trend*	r	*P* value†		
						A	B	C
BPD	n = 17 126‡	n = 660‡	n = 1122‡			.75	.65	.45
22-23 weeks	1419/2075 (68.4)	50/77 (64.9)	134/173 (77.5)	**<.001**	0.82			
24-25 weeks	3300/6044 (54.6)	116/240 (48.3)	224/381 (58.8)	**<.001**	0.81			
26-27 weeks	3073/9007 (34.1)	107/343 (31.2)	226/568 (39.8)	**<.001**	0.84			
Mortality	n = 19 370§	n = 815§	n = 1220§			**<.001**	**<.001**	**<.001**
22-23 weeks	1030/3105 (33.2)	55/132 (41.7)	49/222 (22.1)	**<.001**	−0.91			
24-25 weeks	797/6841 (11.7)	61/301 (20.3)	30/411 (7.3)	**<.001**	−0.98			
26-27 weeks	417/9424 (4.4)	39/382 (10.2)	19/587 (3.2)	**<.001**	−0.83			

Data are presented as the number/number with available information (percentage). Values in bold are statistically significant.
*The *P* values for trend between 2003 and 2016 were obtained using the Cochran-Armitage test.
†The *P* values were obtained using the analysis of covariance. A, 22-23 weeks vs 24-25 weeks; B, 22-23 weeks vs 26-27 weeks; and C, 24-25 weeks vs 26-27 weeks of gestational age.
‡Number of infants who remained alive at 36 weeks' PMA.
§Number of all infants.

Table III. Characteristics of the extremely preterm infants who remained alive at 36 weeks' PMA according to the year of birth

Characteristics	2003 (n = 660)	2004 (n = 846)	2005 (n = 923)	2006 (n = 1063)	2007 (n = 1276)	2008 (n = 1283)	2009 (n = 1354)	2010 (n = 1452)	2011 (n = 1496)	2012 (n = 1549)	2013 (n = 1468)	2014 (n = 1323)	2015 (n = 1311)	2016 (n = 1122)
Perinatal characteristics														
Gestational age, weeks	26.0 (25.0-27.0)	26.0 (24.9-27.0)	26.1 (24.7-27.0)	26.1 (25.0-27.1)	26.0 (24.9-27.0)	26.0 (24.9-27.0)	26.1 (24.7-27.1)	26.1 (24.9-27.0)	26.1 (24.7-27.1)	26.0 (24.7-27.0)	26.0 (24.7-27.1)	25.9 (24.6-27.0)	26.0 (24.7-27.0)	26.0 (24.6-27.0)
Birth weight, g	791 (644-932)	771 (642-930)	788 (634-940)	786 (636-934)	776 (652-912)	769 (640-916)	764 (630-937)	780 (634-926)	764 (642-934)	760 (623-916)	766 (624-922)	746 (602-906)	764 (615-909)	743 (596-901)
Male sex	377/659 (57.2)	423/844 (50.1)	468/923 (50.7)	539/1063 (50.7)	672/1275 (52.7)	676/1283 (52.7)	725/1353 (53.6)	786/1451 (54.2)	832/1496 (55.6)	817/1548 (52.8)	773/1468 (52.7)	692/1323 (52.3)	710/1310 (54.2)	607/1122 (54.1)
Multiple births	137/660 (20.8)	205/846 (24.2)	187/923 (20.3)	253/1063 (23.8)	290/1276 (22.7)	270/1283 (21.0)	217/1354 (16.0)	224/1452 (15.4)	233/1496 (15.6)	280/1549 (18.1)	274/1468 (18.7)	218/1323 (16.5)	251/1311 (19.1)	216/1122 (19.3)
Chorioamnionitis	213/660 (32.3)	259/846 (30.6)	350/923 (37.9)	357/1063 (33.6)	475/1276 (37.2)	518/1283 (40.4)	555/1354 (41.0)	618/1449 (42.7)	667/1492 (44.7)	728/1545 (47.1)	640/1426 (44.9)	585/1296 (45.1)	616/1283 (48.0)	472/1091 (43.3)
Antenatal corticosteroid use	270/660 (40.9)	358/846 (42.3)	374/923 (40.5)	453/1063 (42.6)	597/1276 (46.8)	623/1283 (48.6)	723/1354 (53.4)	806/1445 (55.8)	899/1462 (61.5)	951/1542 (61.7)	935/1453 (64.3)	856/1309 (65.4)	847/1298 (65.3)	769/1100 (69.9)
Cesarean delivery	421/660 (63.8)	608/846 (71.9)	658/923 (71.3)	802/1063 (75.4)	909/1276 (71.2)	928/1283 (72.3)	966/1354 (71.3)	1100/1447 (76.0)	1120/1488 (75.3)	1194/1546 (77.2)	1146/1466 (78.2)	1023/1314 (77.9)	1025/1307 (78.4)	885/1119 (79.1)
Small for gestational age	111/660 (16.8)	150/846 (17.7)	158/923 (17.1)	203/1063 (19.1)	238/1275 (18.7)	252/1283 (19.6)	266/1354 (19.6)	276/1450 (19.0)	326/1496 (21.8)	316/1549 (20.4)	316/1468 (21.5)	320/1321 (24.2)	286/1311 (21.8)	245/1105 (22.2)
Apgar score <4 points at 5 min	53/635 (8.3)	70/815 (8.6)	72/895 (8.0)	88/1031 (8.5)	99/1240 (8.0)	101/1245 (8.1)	84/1319 (6.4)	101/1438 (7.0)	110/1481 (7.4)	169/1537 (11.0)	147/1455 (10.1)	147/1313 (11.2)	161/1308 (12.3)	127/1116 (11.4)
Center patient volume,* cases per year	26.0 (18.8-34.0)	25.3 (16.0-34.0)	23.0 (16.0-34.0)	22.6 (15.8-32.2)	22.0 (15.6-30.6)	20.2 (15.4-30.6)	21.2 (15.6-29.2)	19.0 (13.1-27.0)	19.4 (12.4-27.0)	19.4 (12.4-26.2)	16.5 (10.0-25.0)	17.3 (11.0-25.0)	17.3 (11.0-26.3)	17.0 (11.3-25.0)
Morbidities														
Respiratory distress syndrome	464/660 (70.3)	620/846 (73.3)	612/923 (66.3)	746/1063 (70.2)	933/1276 (73.1)	999/1283 (77.9)	1031/1354 (76.1)	1132/1451 (78.0)	1156/1491 (77.5)	1252/1546 (81.0)	1193/1462 (81.6)	1088/1318 (82.5)	1079/1303 (82.8)	931/1100 (84.6)
Sepsis	61/660 (9.2)	106/846 (12.5)	97/923 (10.5)	124/1063 (11.7)	126/1276 (9.9)	158/1283 (12.3)	188/1354 (13.9)	199/1449 (13.7)	164/1488 (11.0)	209/1543 (13.5)	201/1455 (13.8)	202/1309 (15.4)	172/1309 (13.1)	126/1118 (11.3)
Treated PDA	285/660 (43.2)	438/846 (51.8)	437/923 (47.3)	540/1063 (50.8)	697/1276 (54.6)	784/1283 (61.1)	748/1354 (55.2)	827/1452 (57.0)	827/1493 (55.4)	882/1545 (57.1)	841/1464 (57.4)	750/1317 (56.9)	726/1301 (55.8)	628/1118 (56.2)
BPD	273/660 (41.4)	331/846 (39.1)	301/923 (32.6)	396/1063 (37.3)	483/1276 (37.9)	501/1283 (39.0)	568/1354 (41.9)	680/1452 (46.8)	740/1496 (49.5)	739/1549 (47.7)	774/1468 (52.7)	747/1323 (56.5)	675/1311 (51.5)	584/1122 (52.0)
Respiratory managements														
Intubation at birth	499/660 (75.6)	738/846 (87.2)	773/923 (83.7)	840/1063 (79.0)	1067/1276 (83.6)	1073/1283 (83.6)	1093/1354 (80.7)	1218/1450 (84.0)	1303/1489 (87.5)	1356/1545 (87.8)	1288/1456 (88.5)	1184/1314 (90.1)	1191/1303 (91.4)	1004/1119 (89.7)
Invasive ventilation,† weeks	6.4 (3.0-9.0)	6.0 (3.1-8.9)	5.9 (2.3-8.7)	5.4 (2.1-8.3)	5.7 (2.7-8.3)	5.6 (2.6-8.3)	5.4 (2.4-8.3)	5.4 (2.9-8.1)	5.4 (2.9-7.9)	5.3 (2.7-8.0)	5.1 (2.7-7.7)	5.6 (2.9-8.1)	4.9 (2.3-7.3)	4.7 (1.9-7.4)
NPPV,† weeks	0.1 (0.0-2.7)	0.9 (0.0-3.5)	1.3 (0.0-3.7)	1.6 (0.0-4.0)	2.9 (0.3-4.9)	3.3 (0.9-5.1)	3.4 (1.0-5.4)	3.7 (1.6-5.6)	4.0 (2.1-6.0)	4.3 (2.7-6.1)	4.9 (2.9-6.7)	4.7 (2.9-6.7)	5.0 (3.1-7.0)	5.1 (3.0-7.1)
Supplemental oxygen,† weeks	9.0 (6.9-10.6)	9.0 (6.3-10.4)	8.4 (5.1-10.4)	8.6 (5.1-10.4)	8.7 (5.5-10.6)	8.4 (4.7-10.4)	8.7 (6.0-10.6)	9.0 (6.9-10.7)	9.0 (6.4-10.7)	9.0 (6.7-10.7)	9.0 (7.1-10.6)	9.4 (7.4-11.1)	9.1 (7.1-10.9)	9.1 (6.4-11.0)

Data were presented as the number/number with available information (percentage) or as the median (IQR).
*Center patient volume was calculated as the average number of infants admitted per year per center.
†Durations of respiratory managements until 36 weeks' PMA.

Table V. Trends in clinical factors associated with BPD according to the gestational age groups

Variables	2003-2016 (n = 17 126)	2003 (n = 660)	2016 (n = 1122)	*P* value for trend*	r	*P* value† A	*P* value† B	*P* value† C
Supplemental oxygen ≥4 weeks						.81	.64	.78
22-23 weeks	1944/2075 (93.7)	73/77 (94.8)	165/173 (95.4)	**<.001**	0.70			
24-25 weeks	5483/6044 (90.7)	214/240 (89.2)	345/381 (90.6)	**<.001**	0.74			
26-27 weeks	7087/9007 (78.7)	273/343 (79.6)	450/568 (79.2)	**<.001**	0.57			
Invasive ventilation ≥4 weeks						.014	**<.001**	**.009**
22-23 weeks	1989/2075 (95.9)	75/77 (97.4)	165/173 (95.4)	.11	0.20			
24-25 weeks	5114/6044 (84.6)	207/240 (86.3)	290/381 (76.1)	**<.001**	−0.59			
26-27 weeks	3988/9007 (44.3)	182/343 (53.1)	190/568 (33.5)	**<.001**	−0.84			
Birth weight <750 g						**.002**	**.003**	.66
22-23 weeks	2044/2070 (98.7)	76/77 (98.7)	166/168 (98.8)	.26	−0.30			
24-25 weeks	3998/6037 (66.2)	153/240 (63.8)	256/375 (68.3)	.02	0.75			
26-27 weeks	1938/9001 (21.5)	60/343 (17.5)	139/562 (24.7)	.02	0.47			
Small for gestational age						.02	.73	**.008**
22-23 weeks	166/2069 (8.0)	4/77 (5.2)	16/168 (9.5)	**.008**	0.79			
24-25 weeks	1018/6037 (16.9)	31/240 (12.9)	76/375 (20.3)	**<.001**	0.90			
26-27 weeks	2279/8998 (25.3)	76/343 (22.2)	153/562 (27.2)	**.005**	0.77			
NPPV ≥4 weeks						.60	.10	.24
22-23 weeks	936/2075 (45.1)	16/77 (20.8)	108/173 (62.4)	**<.001**	0.95			
24-25 weeks	2771/6044 (45.8)	31/240 (12.9)	239/381 (62.7)	**<.001**	0.97			
26-27 weeks	4299/9007 (47.7)	45/343 (13.1)	378/568 (66.5)	**<.001**	0.99			
Chorioamnionitis						.55	.54	.98
22-23 weeks	1157/2059 (56.2)	34/77 (44.2)	95/167 (56.9)	**<.001**	0.73			
24-25 weeks	2842/5992 (47.4)	93/240 (38.8)	176/367 (48.0)	**<.001**	0.86			
26-27 weeks	3054/8936 (34.2)	86/343 (25.1)	201/557 (36.1)	**<.001**	0.82			
Center patient volume <20 cases per year						.49	.02	.013
22-23 weeks	893/2075 (43.0)	24/77 (31.2)	97/173 (56.1)	**<.001**	0.77			
24-25 weeks	2875/6044 (47.6)	90/240 (37.5)	217/381 (57.0)	**<.001**	0.91			
26-27 weeks	4752/9007 (52.8)	118/343 (34.4)	363/568 (63.9)	**<.001**	0.96			
Treated PDA						.81	.08	.04
22-23 weeks	1274/2072 (61.5)	39/77 (50.6)	102/172 (59.3)	.97	−0.02			
24-25 weeks	3652/6034 (60.5)	129/240 (53.8)	229/381 (60.1)	.12	0.41			
26-27 weeks	4484/8989 (49.9)	117/343 (34.1)	297/565 (52.6)	**<.001**	0.78			

Data are presented as the number/number with available information (percentage). Values in bold are statistically significant.
*The *P* values for trend between 2003 and 2016 were obtained using the Cochran-Armitage test.
†The *P* values were obtained using the analysis of covariance. A, 22-23 weeks vs 24-25 weeks; B, 22-23 weeks vs 26-27 weeks; and C, 24-25 weeks vs 26-27 weeks of gestational age.