

Serum Periostin Levels at Birth as a Predictor for Bronchopulmonary Dysplasia in Premature Infants.

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Abstract

Background: Bronchopulmonary dysplasia (BPD) is the most common morbidity complicating preterm birth and affects long-term respiratory outcomes. Periostin plays an important role in the development of various disease such as allergic and pulmonary diseases. The objectives of this study were to evaluate the perinatal factors affecting serum periostin levels at birth and to establish whether serum periostin at birth, day of life (DOL) 28 and corrected 36 week's gestational age could be potential biomarkers for BPD.

Methods: A total of 139 preterm (n=98) and healthy (n=41) infants were included in this study. Among of them, 98 infants born < 32 weeks were divided into BPD (n=44) and non-BPD infants (n=54). Serum periostin levels were measured using an enzyme-linked immunosorbent assay.

Results: The median serum periostin levels at birth in preterm infants born < 32 weeks were significantly higher than those in healthy infants. Furthermore, there were significant inverse correlations between gestational age, birth weight, and serum periostin levels at birth among all 139 preterm and healthy infants. Among preterm infants born < 32 weeks, with BPD and without BPD infants, the median serum periostin levels at birth were higher with BPD than without (345.0 ng/mL vs 278.0 ng/mL, $P=0.002$). Multivariate analysis revealed that serum periostin levels at birth was significantly associated with BPD ($P=0.032$). Receiver operating characteristic analysis for serum periostin levels at birth in infants with and without BPD revealed that the area under the curve were 0.725 (95% CI 0.627- 0.822, $P=0.0001$). Serum periostin levels at birth with moderate/severe BPD were significantly higher than those with non-BPD/mild BPD (338.5 ng/mL vs 283.5 ng/mL, $P=0.0032$).

Conclusions: Serum periostin levels at birth were significantly correlated with BW and GA. Furthermore, serum periostin levels at birth could serve as a biomarker for predicting BPD.

Background

Bronchopulmonary dysplasia (BPD) is the most common morbidity complicating preterm birth and affects neurodevelopmental impairment and long-term respiratory outcomes such as childhood wheezing and asthma (1, 2). BPD results from various perinatal factors including maternal inflammation, surfactant deficiency, ventilation and oxygen toxicity (3, 4). Premature infants are often exposed to positive pressure ventilation, and supplemental oxygen, contributing to the development of BPD. An important pathophysiological feature of infants affected with BPD is developmental arrest of alveolarization (4). Such structural alterations are accompanied by characteristic inflammatory changes and extensive remodeling of the extracellular matrix (ECM), together with increased smooth muscle mass in small pulmonary arteries and airways (5). Periostin is characterized as both a matricellular protein as well as ECM protein belonging to the fasciclin family (6, 7).

Periostin plays an important role in the development of allergic, pulmonary, and the other diseases (7, 8). Lung periostin is expressed in human lung fibroblasts and human bronchial epithelial cells (9). Since periostin is regulated by interleukin (IL)-4 and IL-13 and is involved in pathogenesis of fibrosis and allergy

in various diseases, many studies reported that serum and plasma periostin levels were a potential biomarker for various disease such as idiopathic lung fibrosis in adults and asthma (7, 10, 11, 12). Furthermore, various factors such as transforming growth factor-beta (TGF- β), IL-4, IL-13, mechanical stress, and connective tissue growth factor upregulate periostin (13). In the pathogenesis of BPD, TGF- β is involved in lung vascular development. Periostin are associated with TGF- β mediated fibrosis and lung development exposed to hyperoxia (8, 14). TGF- β , in turn, is associated with the pathogenesis of BPD during lung vascular development. Although periostin expression is increased in autopsy lungs of preterm neonates with BPD (14), few reports have been suggesting the relationship between serum periostin levels at birth and BPD. Although Ahlfeld et al reported that elevated plasma periostin levels in BPD patients on day 28 of life (DOL28) compared with that's' of non-BPD patients, their study had several limitations, such as a low sample number and their choice of sampling times (DOL7 and DOL28) (15).

While some studies propose reference intervals for serum periostin in children (16, 17), reports correlating serum periostin levels in term and preterm births with other perinatal factors are lacking.

In this study, we hypothesized that serum periostin at birth might increase in BPD patients, and could serve as biomarkers of BPD. The objectives of the present study were to evaluate the perinatal factors affecting serum periostin levels at birth in preterm and healthy infants and to validate whether serum periostin at birth, DOL28 and corrected 36 week's gestational age could be potential biomarkers for BPD.

Materials And Methods

Ethics approval and compliance

This research was approved by the Institutional Review Board of Fukushima Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. As our human subjects were neonates, informed consent was solicited from parents or other legal guardians, and documented in writing.

NICU Patients

Blood samples were obtained from mechanically ventilated or oxygenated patients with parental consent in the neonatal intensive care unit (NICU) of Fukushima Medical University from November 2014 to July 2020. We examined cord blood at birth and venous blood at 36 weeks postmenstrual age and DOL28. Newborns with congenital anomalies or those who died prior to postnatal day 28 were excluded. Data for analysis included gestational age, phenotypic sex, body weight at birth, invasive mechanical ventilation at DOL28, supplemental oxygen at DOL14, respiratory distress syndrome (RDS), being small for gestational age (SGA), patent ductus arteriosus (PDA), Apgar scores and maternal complications: chorioamnionitis (CAM), premature rupture of membrane (PROM), hypertensive disorders of pregnancy (HDP) were recorded. BPD was defined in accordance with the National Institutes of Health consensus definition for infants (18). At a postmenstrual age of 36 weeks, the infants were classified into the following groups: mild BPD was defined as the need for supplemental oxygen at ≥ 28 days but not at 36 weeks

postmenstrual age; moderate BPD was defined as the need for supplemental oxygen at 28 d, in addition to supplemental oxygen at FiO_2 (fraction of inspired oxygen) ≤ 0.30 at 36 weeks postmenstrual age; and criteria for severe BPD included the need for supplemental oxygen at 28 days and, at 36 weeks postmenstrual age, the need for mechanical ventilation and/or FiO_2 (fraction of inspired oxygen) > 0.30 (18). SGA was defined as a birth weight of < -1.5 standard deviations that was corrected for the gestational age and sex in accordance with the criteria from previous study (19).

Healthy neonatal subjects

Healthy neonates who were born from 36.6 weeks to term in our hospital were included if informed consent was obtained from parents and/or legal guardians and documented in writing.

Serum periostin measurements

Serum samples were obtained from neonates at birth, DOL 28, and corrected 36 weeks. Using serum samples stored at -80°C until assay, serum periostin levels were measured using an enzyme-linked immunosorbent assays (ELISA) at Shino-Test (Kanagawa, Japan), as previously described (20, 21, 22).

Statistical analysis

All data are presented as the medians. The Mann–Whitney U -test was used to compare continuous variables, and χ^2 test was used for nominal variables. To evaluate the correlation between two parameters, Pearson's correlation coefficient was calculated. We performed multivariate analyses to determine factors significantly associated with serum periostin levels at birth as BW, GA, RDS, BPD, oxygen supplementation at DOL 14, invasive mechanical ventilation at DOL 28, and Apgar score at 1 min < 3 in premature infants born at less than 32 weeks. Next, we also performed multivariate analyses to determine factors significantly associated with BPD as potential confounding factors such as BW, GA, invasive mechanical ventilation at DOL 28, Apgar Score at 1 min < 3 , oxygen supplementation at DOL 14 and serum periostin levels at birth in premature infants born at less than 32 weeks. The accuracy of diagnosing or classifying BPD was evaluated by receiver operating characteristics (ROC) curves with area under the curve (AUC) use to quantify the sensitivity of independent risks for BPD. The levels of significance were set 0.05 ($P < 0.05$). Data analysis was performed with SPSS (version 21.0) and GraphPad Prism version 8 software.

Results

Clinical characteristics and Serum periostin levels at birth in preterm and term infants.

A total of 139 preterm ($n = 98$) and healthy ($n = 41$) infants were included in this study. The clinical characteristics of preterm infants born at less than 32 weeks and healthy control are summarized in Table 1. Figure 1 shows the serum periostin levels at birth in preterm and term infants. The median serum periostin levels at birth among preterm infants born at less than 32 weeks was significantly higher than those among healthy infants (292.0 ng/mL vs 142.0 ng/mL, $P < 0.0001$) (Fig. 1A). Furthermore, there were

significant inverse correlations between BW ($r=-0.672$, $P < 0.0001$), GA ($r=-0.640$, $P < 0.0001$), and serum periostin levels at birth in 139 preterm and term infants (Fig. 1B and C).

Table 1
Characteristics of subjects

	Healthy control (N = 41)		Preterm Infants < 32 weeks (N = 98)	
Gestational age, median (IQR), weeks	38.7	(37.7–39.9)	26.0	(24.2–28.2)
Birth weight, median (IQR), g	2948	(2588–3122)	743	(621–1068)
Male gender, n (%)	18	(43.9)	48	(49.0)
CAM, n (%)	NA		43	(43.9)
Antenatal steroid, n (%)	0	(0)	90	(91.8)
PROM, n (%)	0	(0)	26	(26.5)
HDP, n (%)	0	(0)	8	(8.2)
RDS, n (%)	NA		71	(72.4)
SGA, n (%)	0	(0)	15	(15.3)
PDA, n (%)	NA		55	(56.1)
BPD, n (%)	NA		44	(44.9)
Oxygen supplementation at DOL14, n (%)	NA		51	(52.0)
Invasive Mechanical ventilation at DOL28, n (%)	NA		61	(62.2)
Apgar score at 1 min < 3, n (%)	0	(0)	26	(26.5)
Apgar score at 5 min < 3, n (%)	0	(0)	10	(10.2)

IQR: interquartile range, NA: not applicable, CAM: chorioamnionitis, PROM: premature rupture of membrane, HDP: hypertensive disorders of pregnancy, ROP: retinopathy of prematurity, SGA: small for gestational age, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus.

Perinatal factors and serum periostin levels at birth in preterm infants born at less than 32 weeks.

Next, among preterm infants born less than 32 weeks, we correlated serum periostin levels at birth with perinatal factors (Table 2). GA and BW were negatively correlated with serum periostin levels at birth. Additionally, serum periostin levels at birth were significantly higher in RDS, BPD, invasive mechanical ventilation at DOL 28, and Apgar score at 1 min < 3. In particular, the median serum periostin levels at

birth were higher with BPD than without (345.0 ng/mL vs 278.0 ng/mL, $P = 0.002$). Multivariate analysis revealed that serum periostin levels at birth was significantly associated with BPD ($P = 0.032$).

Table 2

Associations between serum periostin levels at birth and perinatal factors in preterm infants born < 32 weeks

	Serum periostin levels at birth (ng/mL)	coefficient	Univariate analysis (P-value)	Multivariate analysis (P-value)
Gestational age	-	-0.265	0.008	0.588
Birth weight	-	-0.326	0.001	0.396
Male vs Female	306.5 vs 287.5	-	0.234	-
CAM vs non-CAM	289.0 vs 296.5	-	0.994	-
Antenatal steroid vs no antenatal steroid	300.0 vs 266.6	-	0.078	-
PROM vs non-PROM	295.5 vs 291.5	-	0.554	-
HDP vs non-HDP	300.0 vs 266.6	-	0.315	-
RDS vs non-RDS	303.0 vs 256.0	-	0.008	0.081
SGA vs non-SGA	290.0 vs 321.0	-	0.598	-
PDA vs non-PDA	299.0 vs 291.0	-	0.155	-
BPD vs non-BPD	345.0 vs 278.0	-	0.002	0.032
Oxygen supplementation at DOL14 vs no oxygen supplementation at DOL14	303.0 vs 284.0	-	0.188	-
Invasive mechanical ventilation at DOL28 vs no invasive mechanical ventilation at DOL28	305.0 vs 252.0	-	0.002	0.845
Apgar score at 1 min < 3 vs no Apgar score at 1 min < 3	326.5 vs 283.0	-	0.022	0.364
Apgar Sscore at 5 min < 3 vs no Apgar score at 5 min < 3	300.0 vs 291.5	-	0.469	-
NA: not applicable, CAM: chorioamnionitis, PROM: premature rupture of membrane, HDP: hypertensive disorders of pregnancy, SGA: small for gestational age, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus.				

Serum periostin levels in BPD infants

To investigate whether serum periostin levels were associated with BPD, preterm infants born at less than 32 weeks were divided into BPD neonates (n = 44) and non-BPD neonates (n = 54) (Table 3). The median GA in BPD infants was significantly lower than those in non-BPD neonates (24.4 weeks vs 27.2 weeks, $P < 0.001$). The median BW in BPD neonates was also significantly lower than those in non-BPD infants (638 g vs 952 g, $P < 0.001$). The occurrence of Apgar score at 1 min < 3 (40.9% vs 14.8%, $P < 0.005$) was significantly higher in BPD infants compared with those in non-BPD infants. Furthermore, the incidence of the invasive mechanical ventilation at DOL 28 and oxygen supplementation at DOL14 in BPD infants were significantly higher than those in non-BPD infants. There were no significant differences between BPD and non-BPD infants in terms of phenotypic sex, antenatal steroid usage, SGA, PDA, CAM, HDP and PROM (Table 3). In multivariate analysis of the correlation between serum periostin at birth and clinical parameters, serum periostin levels at birth significantly correlated with BPD ($P = 0.013$) and BW ($P = 0.021$) (Table 3). Receiver operating characteristic analysis for serum periostin levels at birth in infants with and without BPD revealed that the area under the curve were 0.725 (95% CI 0.627–0.822, $P = 0.0001$) (Fig. 2). Using a threshold of serum perisostin > 305 ng/mL at birth identified BPD with 71.7% sensitivity and 63.4% specificity.

Table 3
Characteristics of BPD and non-BPD infants

	Non-BPD (N = 54)	BPD (N = 44)	Univariate analysis P-value	Multivariate analysis P-value
Gestational age, median (IQR), week	27.2 (25.6–29.6)	24.4 (23.7–26.3)	<0.001	0.242
Birth weight, median (IQR), gram	952 (622–1210)	638 (438–734)	<0.001	0.027
Male gender, n (%)	26 (51.8)	22 (46.5)	0.508	-
CAM, n (%)	23 (39.3)	20 (48.8)	0.311	-
Antenatal steroid, n (%)	50 (94.6)	40 (90.7)	0.522	-
PROM, n (%)	13 (24.1)	13 (29.5)	0.647	-
HDP, n (%)	7 (13.0)	1 (2.3)	0.070	-
RDS, n (%)	35 (64.3)	36 (81.4)	0.072	-
SGA, n (%)	6 (12.5)	9 (20.9)	0.262	-
PDA, n (%)	34 (76.7)	21 (53.5)	0.155	-
Oxygen supplementation at DOL14, n (%)	20 (37.0)	31 (70.5)	0.001	0.041
Invasive mechanical ventilation at DOL28, n (%)	21 (66.1)	40 (90.9)	< 0.001	0.391
Apgar score at 1 min < 3, n (%)	8 (14.8)	18 (40.9)	0.005	0.571
Apgar score at 5 min < 3, n (%)	3 (5.6)	7 (15.9)	0.107	-
Serum periostin levels at birth (ng/mL)	345.0	278.0	0.002	0.013
IQR: interquartile range, NA: not applicable, CAM: chorioamnionitis, PROM: premature rupture of membrane, HDP: hypertensive disorders of pregnancy, SGA: small for gestational age, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus. P-value was compared between BPD and non-BPD neonates				

Figure 3 shows the serum periostin levels at birth, DOL 28 and corrected 36-week's postmenstrual age in BPD and non-BPD infants. The median periostin levels on DOL 28 in BPD infants were significantly lower compared with those at birth (345.0 ng.mL vs 281.5 ng/mL, $P = 0.003$). However, the median serum periostin levels on DOL 28 and corrected age of 36-week's gestational were not significantly differed in BPD infants compared with non-BPD infants (DOL 28: 281.0 ng/mL vs 238.5 ng/mL, corrected 36-week's

postmenstrual age: 327.5 ng/mL vs 332.0 ng/mL). Next, we evaluated the relationships between serum periostin at birth and severity of BPD (Fig. 4). Serum periostin levels at birth with moderate/severe BPD were significantly higher than those with non-BPD/mild BPD (338.5 ng/mL vs 283.5 ng/mL, $P = 0.0032$).

Discussion

To our knowledge, this is the first study to describe an association between serum periostin levels at birth and perinatal factors in preterm and term infants and the correlation between serum periostin levels at birth and BPD. The present study revealed that higher serum periostin levels at birth in preterm infants born at less than 32 week's gestational age are independent risk factors for BPD and reflects the severity for BPD. Although there are many studies trying to demonstrate an association between serum biomarkers and the risk of BPD, few suggest a correlation between blood periostin levels and BPD. In this study, we also demonstrated that serum periostin levels on DOL28 and corrected 36 week's postmenstrual age could not serve as potential biomarkers for BPD. Ahlfeld et al previously suggested that early elevation of plasma periostin on DOL28 is significantly associated with chronic ventilator-dependent bronchopulmonary dysplasia (15). This may be due to the differences in the type of sample, sample size, and method of analysis. Ahlfeld's study used plasma samples and did not include multivariate or measure periostin levels at birth. In terms of the relationship between periostin and lung disease, previous studies demonstrated that elevated serum periostin levels were associated with various lung disease such as asthma, idiopathic pulmonary fibrosis, and COPD in children and adults (5, 8, 23, 24). Furthermore, the expression of lung periostin was upregulated in patients with idiopathic lung fibrosis (8, 11). Bozyk et al. also reported that periostin expression increased in autopsy lungs of preterm neonates with BPD (14). In a murine model of BPD exposed to hyperoxia, hyperoxia upregulated periostin expression in neonatal mice lung (14). Furthermore, lung periostin levels were also increased during the saccular stage, as previously shown (25). Although the mechanism by which periostin is associated with the pathogenesis of BPD remains poorly understood, we speculate that the linkage of periostin and TGF- β might be associated with the pathogenesis of BPD. Periostin and TGF- β are known to play a critical role in the proliferation of lung fibroblasts (9). Furthermore, many studies in different animal models of BPD confirm elevated TGF- β expression levels and activation of its associated pathways as an important part of lung disease pathophysiology (22, 26, 27). Also, we previously reported that serum TGF- β levels were upregulated in BPD patients (28).

Another new finding in this study was significant correlation of serum periostin levels at birth with BW and GA. Fujitani et al. reported that periostin levels in non-allergic children from 0 years to 15 years were almost 91.9-124.8 ng/mL (29). They also suggested that serum periostin levels gradually increased after age 10 years. Anderson et al also reported that serum periostin levels at ages 2–6 years ranged from 120–150 ng/mL (16). In this study, serum periostin levels of healthy neonates were around 140 ng/mL. Furthermore, serum periostin levels at birth in neonates born at less than 32 week's gestational age was almost 340 ng/mL. On the other hand, a previous study proposed a periostin threshold of 95 ng/mL based on values from healthy adult controls (30). Thus, serum periostin levels in infants were the highest when comparing infants, children, and adult. These developmental changes of serum periostin levels may

be related to metabolic turnover and growth as periostin is a component of the extracellular matrix and regulates serum type I collagen formation, which is essential component of skin, tendon, and bone development (16, 31). Compared with term infants, the cord blood serum procollagen type I C-terminal propeptide (PICP) as bone information in preterm infants was significantly higher and influenced by fetal age (32).

Our study has several limitations. First, it was performed at a single center and the sample size of BPD patients was small. To validate our observations, a larger sample size with multiple centers and different ethnic cohorts would be invaluable. Second, we could not evaluate lung periostin. A previous study demonstrated that lung periostin in BPD infants was higher than in healthy lungs at term (9). Third, we could not detect the cellular sources of periostin. Thus, our next goal is to determine the cell types secreting periostin as well as the mechanism(s) of upregulation of periostin in BPD neonates; this will advance understanding of the pathogenesis of BPD. Lastly, in this study, we did not investigate the correlation between periostin levels and Th2 cytokines such as IL-4 and IL-13. It is noteworthy that upon stimulation by IL-4 and IL-13, periostin could be detected in lung fibroblasts (2). One of the main consequences of BPD is lung fibrosis. Although a previous study suggested that IL-4 and IL-13 levels of tracheal aspirates from premature infants were very low and did not correlate with BPD (29), premature infants born at less than 32 week's gestational age have increased nasal airway IL-4 and IL-13 secretion during rhinovirus infections (30).

In summary, we conclude that serum periostin levels were significantly correlated with birth weight and gestational age. Furthermore, serum periostin levels at birth could serve as a biomarker for predicting BPD and severity of BPD. The mechanism by which serum periostin is upregulated in BPD infants and inversely correlated with gestational age and birth weight remains to be further elucidated.

Abbreviations

BPD: bronchopulmonary dysplasia

BW: birth weight

GA: gestational age

RDS: respiratory distress syndrome

CAM: chorioamnionitis

PROM: premature rupture of membrane

HDP: hypertensive disorders of pregnancy

SGA: small for gestational age

RDS: respiratory distress syndrome

PDA: patent ductus arteriosus

Declarations

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DISCLOSUREs

Junya Ono is a salaried employee of Shino-Test Co., Ltd., which provided ELISA for periostin without stipulations or influence over the interpretation of test results. The authors have no other potential or actual conflicts of interest pertaining to the contents of this article.

Author Contribution

Hayato Go designed the study, carried out the analyses and drafted the manuscript, and reviewed and revised the manuscript. Hitoshi Ohto, Kenneth Nollet, Satoshi Nunomura, Kenji Izuhara, and Mitsuaki Hosoya reviewed the manuscript. Junya Ono carried out the analyses and reviewed the manuscript. Hajime Maeda, Kei Ogasawara, Maki Sato, Yohei Kume, Hirotaka Ichikawa, Yuji Kanai, Nozomi Kashiwabara, and Kentaro Haneda collected the samples and reviewed the manuscript. All author approved the final manuscript as submitted and agree to accountable for all aspects of the work.

Disclosure statement

The authors have no other potential or actual conflicts of interest pertaining to the contents of this article.

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Figures

Figure 1

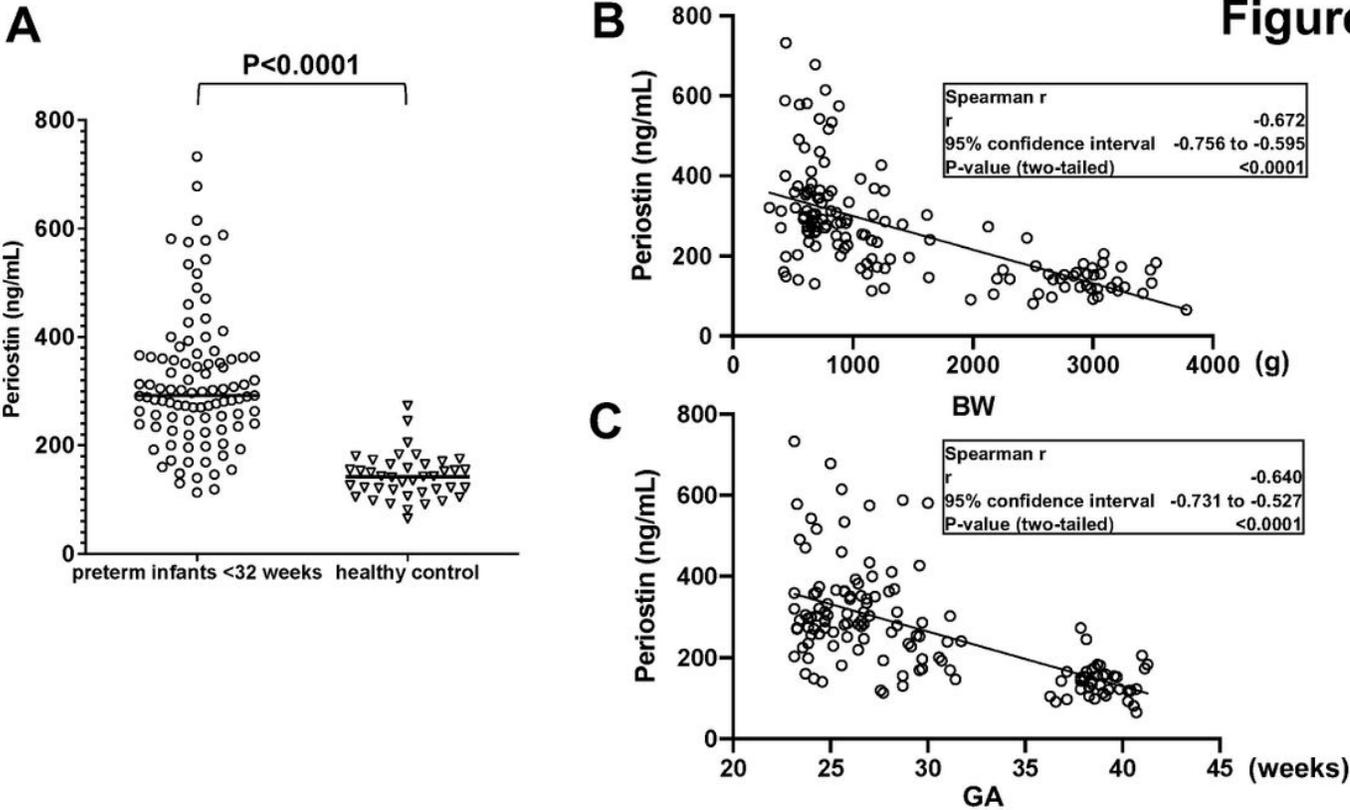


Figure 1

A: Comparing healthy neonates and preterm neonates born at less than 32 week’s gestational age, serum periostin levels at birth were higher in the preterm neonates born at less than 32 week’s gestational age. B-C: Serum periostin levels at birth were significantly correlated with GA (gestational age) and BW (birth weight). Horizontal bars denote the median values in each group of infants.

Figure 2

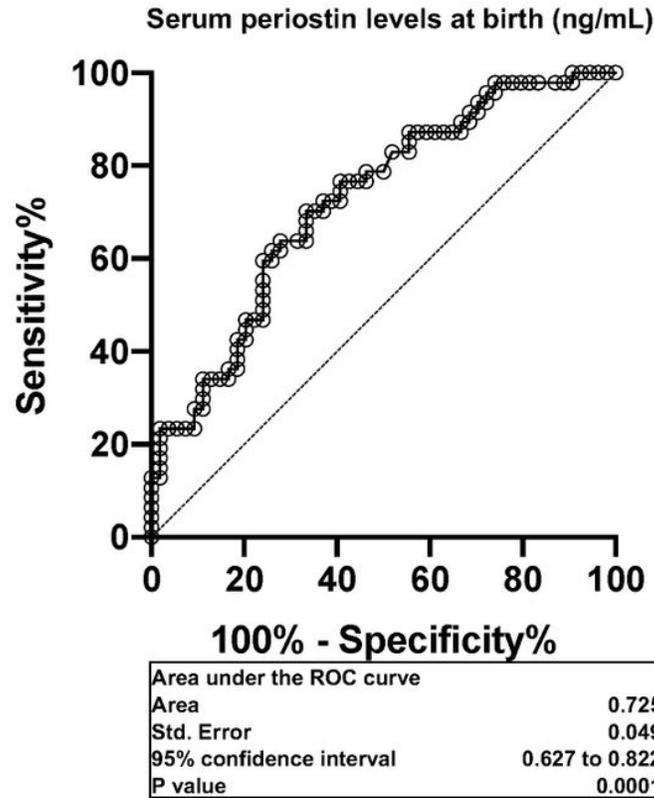


Figure 2

Comparison of receiver operating characteristics curve analyses of serum periostin levels at birth that distinguish infants with and without BPD. ROC: receiver operating characteristics.

Figure 3

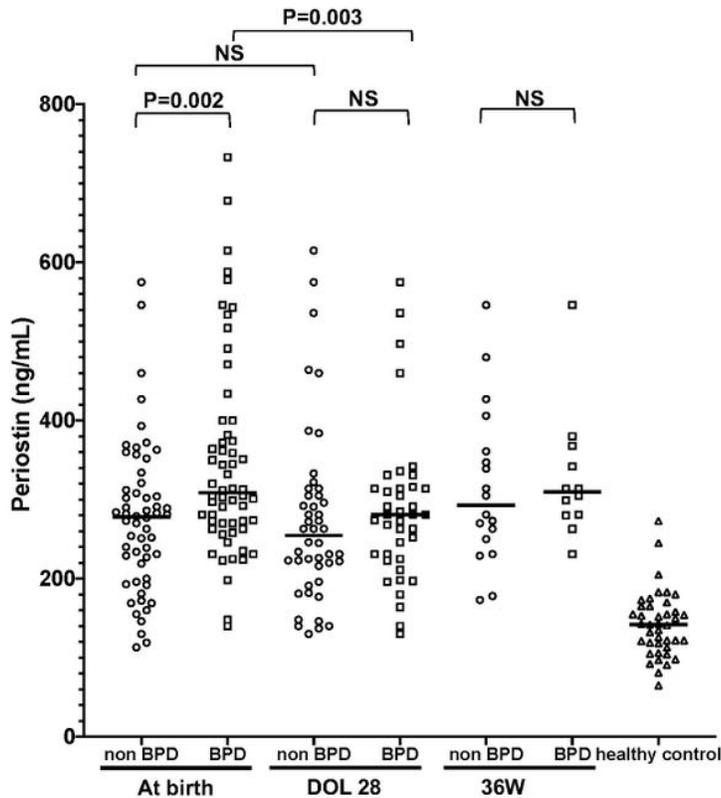


Figure 3

Serum periostin levels at birth were significantly higher in BPD neonates compared with non-BPD neonates. Serum periostin levels on DOL28 and corrected 36 week's postmenstrual age did not differ in infants with or without BPD. Horizontal bars denote the median values in each group of infants. NS: not significant.

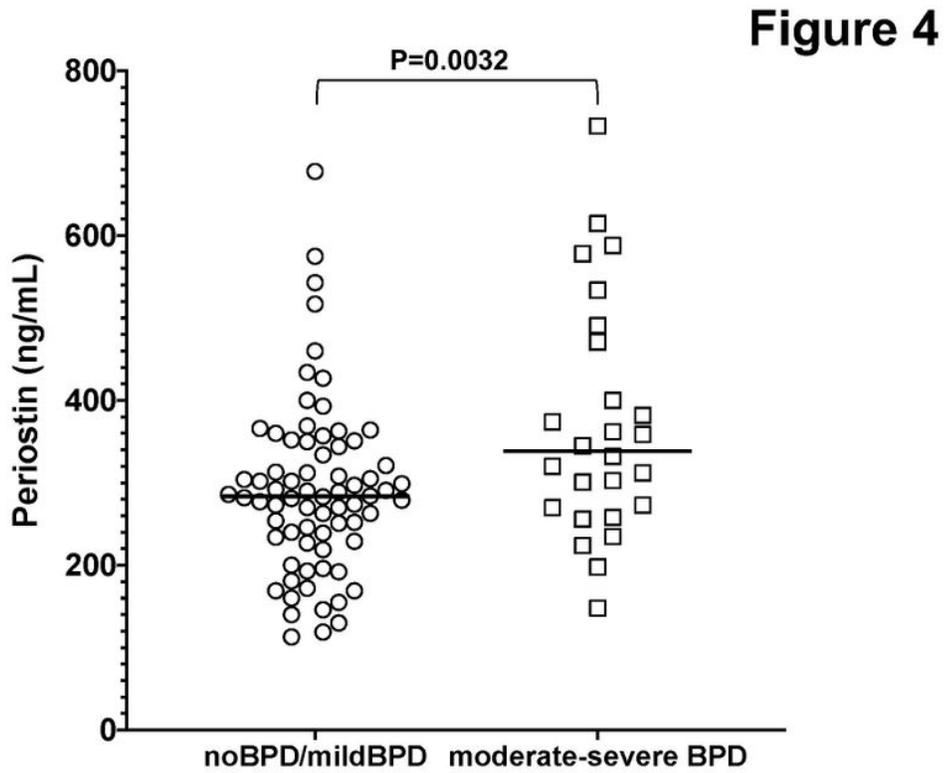


Figure 4

Figure 4

Serum periostin levels at birth were higher in moderate/severe BPD compared with no BPD/mild BPD. Values are the median (no BPD/mild BPD: n=71, moderate/severe BPD: n=27). Horizontal bars denote the median in each group of infants. The other P values were calculated using the Mann-Whitney U test.