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Reduced pulmonary oxygen diffusion at 36 weeks of postmenstrual age in small-for-gestational-age preterm infants of less than 32 weeks without bronchopulmonary dysplasia

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Abstract

Background: Small-for-gestational-age (SGA) preterm infants are at increased risk of developing bronchopulmonary dysplasia (BPD). There is limited information on pulmonary oxygen diffusion of SGA preterm infants, particularly in those without BPD.

Objective: To compare the pulmonary oxygen diffusion of SGA to that of appropriate-for-gestational-age (AGA) preterm infants without BPD.

Study Design: Preterm infants with a gestational age (GA) between 24.0 and 31.6 weeks were studied. The oxygen saturation (SpO_2), fraction to inspired oxygen (FiO_2), and the SpO_2 to FiO_2 ratio (SFR) were compared between SGA and AGA infants. The association between SGA and SFR at 36 weeks was assessed using a multiple regression analysis. In the subgroup without BPD, SGA were match-paired for GA and gender with AGA infants.

Results: We analyzed 1189 infants surviving at 36 weeks: 194 (16%) were SGA and 995 (84%) AGA. The incidence of BPD was significantly higher in SGA than AGA infants (32% vs. 13%; $p = .000$). Out of the 995 infants without BPD, 132 (13%) were SGA and 863 (87%) AGA. SGA was negatively associated with the SFR value at 36 weeks, independently from BPD. SGA infants without BPD had significantly higher (better) SFR at birth, but lower (worse) SpO_2 and SFR and from 33 to 36 weeks than their matched AGA counterpart. At 36 weeks, median SpO_2 and SFR values were 97.7 versus 98.4 ($p = .006$) and 465 versus 468 ($p = .010$) in match-paired SGA and AGA, respectively.

Conclusion: Among preterm infants of less than 32 weeks and without BPD, SGA infants had a reduced pulmonary oxygen diffusion at 36 weeks in comparison with AGA infants.

Abbreviations: AGA, appropriate-for-gestational-age; BPD, bronchopulmonary dysplasia; BW, birth weight; EN, enteral nutrition; FiO_2, fraction of inspired oxygen; GA, gestational age; HOL, hours of life; LGA, large for gestational age; NICU, neonatal intensive care unit; PN, parenteral nutrition; SFR, SpO_2 to FiO_2 ratio; SGA, small-for-gestational-age; SpO_2, oxygen saturation; WT, weight.

KEYWORDS
appropriate-for-gestational-age, bronchopulmonary dysplasia, preterm infant, pulmonary oxygen diffusion, small-for-gestational-age

1 | INTRODUCTION

Several studies have shown a clear association between being small-for-gestational-age (SGA) at birth and altered organ development and function from infancy into adulthood.[1] Impaired neurodevelopment, poor growth, reduced cardiopulmonary function as well as an increased mortality have been documented in SGA preterm infants.[2–4]

Studies on the lungs of SGA preterm infants have shown accelerated lung maturation soon after birth,[5] although an increased respiratory morbidity has been reported later on in life.[6–9] SGA preterm infants have much higher risk of developing bronchopulmonary dysplasia (BPD) compared to appropriate-for-gestational-age (AGA) preterm infants.[10–13]

Given the over representation of SGAs in infants with BPD[13] and the variable incidence of BPD in the overall population of small preterm infants in different studies,[12,14–19] it remains challenging to detect the impact of SGA status on lung development independently from BPD.

To date, the results of the pulmonary evaluation in SGA preterm infants without BPD have mainly focused on spirometry and airflow function at school age.[20–23] There is limited information on pulmonary oxygen diffusion in preterm infants before hospital discharge,[24,25] and there is no data in SGA preterm infants without BPD.

The oxygen saturation (SpO_2) to the fraction of inspired oxygen (FiO_2) ratio (SFR) has been shown to better describe pulmonary oxygen diffusion in preterm infants compared with FiO2 alone and is a reliable noninvasive surrogate for the PaO_2 to FiO2 ratio in a variety of clinical settings.[25–27] In the current study, we compared the FiO_2, SpO_2, and SFR from birth to 36 weeks of postmenstrual age between SGA and AGA preterm infants with and without BPD.

2 | METHODS

2.1 | Study infants

We retrospectively reviewed data of all infants with a GA between 24.0 and 31.6 weeks consecutively admitted to the "G. Salesi" Children's Hospital, Ancona, Italy, between 1 January 2004 and 28 February 2021. Infants who were outborn, had congenital malformations, were large for gestational age (LGA) infants (birth weight [BW] centile equal or greater than 90th) and missing clinical information were excluded. The study was approved by the local ethics committee (ID. 12-0976).

2.2 | Study design

Infants were classified as SGA and AGA and were compared, both including and excluding those with BPD. The association between SGA and SFR at 36 weeks was also assessed after adjusting for confounding factors, such as GA, gender, antenatal corticosteroids, red blood cell transfusion, surgery, surfactant administration, nutritional intakes, and complications of prematurity. In the subgroup of infants without BPD, a case–control analysis (1:1 ratio, without replacement) was performed using GA (±2 days) and gender as matching variables.

2.3 | Data collection

Clinical data were recorded using a dedicated software (Neotools®; Interactive srl). Body weight (WT) was measured daily using a digital infant scale; total length and head circumference were measured at birth and weekly thereafter using a neonatal stadiometer and a flexible nonstretchable tape, respectively. Weight gain ($g\,kg^{-1}\,day^{-1}$) was calculated from birth to 36 weeks, and from regained BW to 36 weeks. Intakes were collected daily, with complete records of amount and type of parenteral nutrition (PN) and enteral nutrition (EN). The detailed neonatal intensive care unit (NICU) nutrition protocol and criteria for surfactant administration have already been published.[24,28] Complications of prematurity were defined according to the Vermont Oxford definitions. SGA was defined as having a BW below the 10th centile, whereas AGA as a BW between the 10th and 90th centile according to the Italian growth charts.[29] The diagnosis of BPD was assigned according to the physiological definition.[30] Brain injury was defined as IVH grades 1–4, cystic PVL or cerebellar hemorrhage. The SpO_2 (preductal) by pulse oximeter (Masimo) and the FiO_2 as indicated by ventilatory support devices when in use, were prospectively recorded hour-by-hour in the medical records. The SFR was calculated at birth (from 3 to 48 h of life; HOL) and then weekly (from 32 to 36 weeks), as the mean of the SFR values recorded during 24 h on the day that each infant reached a given GA (all GA were reported as postmenstrual age). SFR at 4 weeks of age was also calculated using the same method. At least 12 individual SFR values in 24 h were used to calculate the weekly SFR. A slope of SFR (points/week) for each infant was calculated using SFR values from 32 to 36 weeks.

2.4 | Statistical analysis

The primary objective of the study was to compare the SFR at 36 weeks in the SGA versus AGA infants. As secondary objectives, the

study aimed to compare nutrition, growth, selected interventions, complications of prematurity, and respiratory parameters (FiO_2, SpO_2, and SFR) of SGA versus AGA infants. Due to the exploratory nature of the study, no formal sample size calculation was performed. Depending on the distribution, data were expressed as mean ± SD, median |25th percentile 75th percentile| or percentages. Person's correlation tests were used to assess the association between SFR and WT at 34, 35, and 36 weeks in the entire study cohort. Multiple linear regression analysis with the enter method was used to evaluate the association between SGA and SFR at 36 weeks, both including and excluding infants with BPD. The clinical characteristics of the study groups were compared using independent *t*-test, Mann–Whitney *U* test, chi-square or Fisher test (cohort analysis) and paired *t*-test, Wilcoxon test, or McNemar test (case–control analysis), as appropriate. Statistical significance was set at a $p < 0.05$. SPSS software was used for the statistical analyses (v26.0; SPSS Inc.) and case–control matching was performed using the FUZZY extension in SPSS.

3 | RESULTS

From 1 January 2004 to 28 February 2021, all 1615 infants with a GA between 24.0 and 31.6 weeks admitted to the NICU of the only tertiary referral center of the Marche region were screened for the study. Four hundred twenty-six infants were excluded: 226 were outborn, 52 had malformations, 58 were LGA, 80 died before 36 weeks, and 10 had missing clinical information (Figure 1).

3.1 | Cohort analysis

Of the 1189 study infants, 194 (16%) were classified as SGA and 995 (84%) as AGA (Table 1). In the entire study cohort, the incidence of death (14% vs. 5%; $p < .001$), and BPD or death before 36 weeks (41% vs. 17%; $p < 0.001$) were higher in SGA than AGA infants. SGA infants had significantly lower SpO_2 and SFR, and higher FiO2 values from 32 to 36 weeks of postmenstrual age compared to AGA infants (Figure S1, SpO_2: Panel A-B, FiO_2: Panel C, D; SFR: Panel E, F).

Nine hundred ninety-five (84%) of the 1189 study infants were free of respiratory supports and breathing room air at 36 weeks (no BPD): 132 (13%) were SGA and 863 (87%) AGA (Table 1). In the subgroup of infants without BPD, the incidence of mechanical ventilation from birth to Day 7 of life did not differ between SGA and AGA infants (42% vs. 49%; $p = 0.137$, respectively). SpO_2 at 12 and 24 HOL, and SFR at 12, 24, and 48 HOL were higher, whereas FiO_2 at 12, 24, and 48 HOL was lower, in SGA than AGA infants (Figure 2, SpO_2: Panel A; FiO_2: Panel C; SFR: Panel E). SpO_2 and SFR from 34 to 36 weeks of SGA were lower than those of AGA infants (SFR—34 weeks: 461 |455 466| vs. 464 |458 468|, −3 points, $p = 0.001$; 35 weeks: 465 |457 469| vs. 466 |461 470|, −1 points, $p = 0.002$; 36 weeks: 466 |460 469| vs. 468 |463 471|, −2 points, $p = 0.002$; Figure 2, SpO_2: Panel B; FiO_2: Panel D; SFR: Panel F). The SFR slope from 32 to 36 weeks was lower (worse) in SGA than AGA infants (+1.2 |0.2 3.5| vs. +2.3 |0.8 5.6| points/week, $p < 0.001$, respectively).

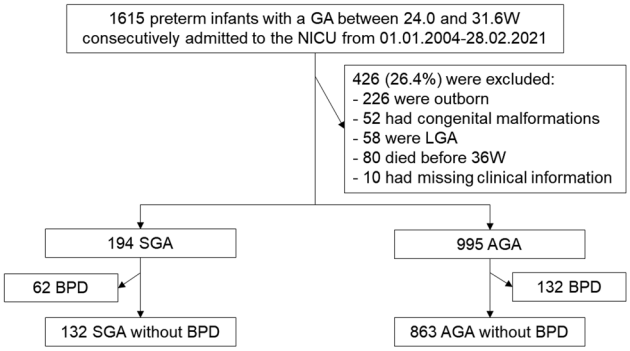

FIGURE 1 Flow diagram of the study infants. AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; GA, gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit; SGA, small-for-gestational-age.

3.2 | Multiple regression analysis

The regression models for the SFR at 36 weeks are shown in Table 2. Being SGA was negatively associated with the SFR at 36 weeks in the entire cohort, after the adjustment for GA, gender, antenatal corticosteroids, surfactant administration, red blood cell transfusions, sepsis, patent ductus arteriosus, BPD, asphyxia, cholestasis, surgery, brain injury, and cumulative PN + EN energy ($kcal\ kg^{-1}\ day^{-1}$) and fluid intakes ($mL\ kg^{-1}\ day^{-1}$) from birth to 36 weeks. This association remained highly significant also in the 995 infants without BPD.

3.3 | Case–control analysis

One hundred thirty-two case–control matched pairs of SGA and AGA without BPD were obtained using GA and gender as matching variables. The results of the case–control comparison were similar to those of the study cohort (data not shown). SFR from 33 to 36 weeks (33 weeks: 462 |453 467| vs. 463 |457 468|, −1 point, $Z = -2.093$, $p = .036$; 34 weeks: 462 |455 466| vs. 465 |459 469|, −3 points, $Z = -2.261$, $p = .024$; 35 weeks: 465 |459 469| vs. 467 |463 470|, −2 points, $Z = -2.719$, $p = .007$; 36 weeks: 465 |459 469| vs. 468 |464 471|, −3 points, $Z = -2.593$, $p = .010$) were lower in SGA than AGA infants. SFR at 24 HOL (452 |413 461| vs. 430 |383 458|, +21 points, $Z = -3.398$, $p = .002$) was higher, whereas SFR at 4 weeks of age (462 |452 468| vs. 465 |458 469|, −3 points, $Z = -2.686$, $p = .005$, respectively) and the individual SFR changes between 4 weeks and birth (+12.1 |0.7 34.4| vs. +33.7 |9.2 85.4|, −21.6 points, $Z = -4.401$, $p < 0.001$, respectively) were lower in SGA than AGA (Figure 3).

TABLE 1 Clinical data of the study SGA and AGA preterm infants.

	All infants			Infants without BPD		
	SGA (*N* = 194)	AGA (*N* = 995)	*p* Value[a]	SGA (*N* = 132)	AGA (*N* = 863)	*p* Value[a]
Prenatal data and characteristics [birth]						
GA (days)	207 ± 12	205 ± 14	.115	210 ± 10	207 ± 13	.003
BW (g)	831 ± 194	1252 ± 328	.000	888 ± 183	1296 ± 314	.000
BW SDS	−1.8 ± 0.4	−0.0 ± 0.6	.000	−1.8 ± 0.4	−0.0 ± 0.6	.000
TL at birth (cm)	34.2 ± 3.1	38.4 ± 3.5	.000	35.1 ± 2.9	38.9 ± 3.2	.000
TL at birth SDS	−1.56 ± 0.74	0.01 ± 0.69	.000	−1.52 ± 0.73	0.02 ± 0.68	.000
HC at birth (cm)	24.9 ± 1.8	26.9 ± 2.3	.000	25.4 ± 1.6	27.2 ± 2.2	.000
HC at birth SDS	−1.36 ± 0.70	0.10 ± 0.79	.000	−1.38 ± 0.70	0.11 ± 0.80	.000
Males (%)	49	52	.387	40	51	.022
Singleton birth (%)	74	65	.014	73	64	.034
Apgar at 5 min (no.)	8 |7 9|	8 |8 9|	.315	8 |8 9|	8 |8 9|	.899
Antenatal corticosteroids (%)	94	95	.536	96	96	.787
Cesarean section (%)	100	90	.000	100	91	.000
Hypertension in pregnancy (%)	58	20	.000	59	19	.000
Early postnatal growth [birth 36 weeks]						
WT at nadir (g)	755 ± 175	1112 ± 315	.000	803 ± 166	1153 ± 303	.000
Age at nadir (days)	4 |3 4|	4 |3 5|	.000	4 |3 4|	4 |3 5|	.000
PWL (%)	10 |7 12|	11 |8 14|	.000	10 |7 12|	11 |8 14|	.000
Time to regain BW (days)	9 |7 11|	12 |9 15|	.000	9 |7 11|	12 |9 15|	.000
WT 36 weeks (g)	1546 ± 235	2136 ± 304	.000	1569 ± 228	2153 ± 300	.000
WT 36 weeks SDS	−2.70 ± 0.58	−1.23 ± 0.74	.000	−2.62 ± 0.55	−1.18 ± 0.73	.000
TL 36 weeks (cm)	40.3 ± 2.1	44.4 ± 1.9	.000	40.7 ± 1.9	44.6 ± 1.8	.000
TL 36 weeks SDS	−2.79 ± 0.81	−1.18 ± 0.75	.000	−2.63 ± 0.74	−1.11 ± 0.71	.000
HC 36 weeks (cm)	29.5 ± 1.3	31.3 ± 1.3	.000	29.8 ± 1.1	31.5 ± 1.3	.000
HC 36 weeks SDS	−2.32 ± 0.89	−1.02 ± 0.93	.000	−2.07 ± 0.74	−0.92 ± 0.87	.000
WT gain BW 36 weeks ($g\,kg^{-1}\,d^{-1}$)	16.4 ± 2.8	14.5 ± 3.0	.000	16.6 ± 2.7	14.4 ± 3.1	.000
WT gain regained BW 36 weeks ($g\,kg^{-1}\,d^{-1}$)	17.3 ± 3.2	16.3 ± 3.0	.000	17.5 ± 2.9	16.3 ± 3.1	.000
Selected interventions [birth 36 weeks]						
Intubated birth 24 h (%)	55	53	.632	37	48	.023
Need of surfactant (%)	50	50	.990	30	45	.001
Need of RBC transfusion (%)	53	34	.000	39	27	.003
Need of PN (%)	99	59	.000	99	54	.000
Need of amines (%)	23	16	.017	11	11	.800
Need of postnatal corticosteroids (%)	10	5	.005	1	1	1.000
Need of oxygen (%)	73	75	.521	61	72	.008
Oxygen duration (h)	458 |78 1186|	157 |32 846|	.001	114 |16 448|	106 |21 425|	.996
Need of CPAP (%)	89	87	.335	85	85	.951
CPAP duration (h)	380 |104 879|	200 |66 702|	.002	163|60 590|	148 |56 571|	.658

TABLE 1 (Continued)

	All infants			Infants without BPD		
	SGA (*N* = 194)	AGA (*N* = 995)	*p* Value[a]	SGA (*N* = 132)	AGA (*N* = 863)	*p* Value[a]
Need of MV (%)	62	56	.107	45	51	.278
MV duration (h)	91 |20 239|	49 |12 182|	.008	41 |11 94|	24 |10 106|	.760
Complications of prematurity [birth 36 weeks]						
RDS-HMD (%)	75	77	.500	64	74	0.022
BPD (%)	32	13	.000	–	–	–
EOS (%)	5	5	.912	3	4	.641
PDA (presence) (%)	44	40	.285	33	34	.717
Asphyxia (%)	3	2	.684	2	1	1.000
PVL grades 2–4 (%)	2	2	.785	2	2	1.000
CHOLST (>1.0 mg/dL) (%)	20	4	.000	13	3	.000
ROP grades 3–5	0	0.4	1.000	0	0.2	1.000
IVH grades 3–4 (%)	3	3	.592	2	3	.759
LOS (%)	20	11	.001	15	7	.002
NEC grades 2–3 (%)	2	3	1.000	1	3	.353
Surgery (any) (%)	13	9	.069	8	6	.603

Note: Square brackets "[]" were used to specify the time interval for calculating the incidence, median, and mean values. The incidence calculation considered at least one event occurring at any time during the specified interval.

Abbreviations: BW, birth weight; CHOLST, cholestasis; CPAP, continuous positive airway pressure; EOS, early onset sepsis; GA, gestational age; HC, head circumference; IVH: intraventricular hemorrhage; LOS: late onset sepsis; MV, mechanical ventilation; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PN, parenteral nutrition; PVL, periventricular leukomalacia; PWL, postnatal weight loss; RBC, red blood cells; ROP, retinopathy of prematurity; SGA, small for gestational age; TL, total length; WT, weight.

[a]Independent *t*-test, Chi-square test, Fisher test, and Mann–Whitney test were used for the statistical analysis.

4 | DISCUSSION

We investigated pulmonary oxygen diffusion in about 1200 preterm infants with a GA from 24.0 to 31.6 weeks, and compared SGA and AGA infants without BPD. We demonstrated that (1) SGA had better oxygen diffusion in the lungs in the first HOL, (2) but worse oxygen diffusion from 33 to 36 weeks. This information is important as it demonstrates reduced pulmonary oxygen diffusion in SGA infants already during the NICU in-hospital stay. We showed these alterations were measurable in infants without BPD, which adds support to the fact that SGA infants are more likely to develop BPD and exhibit some degree of lung underdevelopment. We would like to comment further on these points.

The finding that SGA had better oxygen diffusion in the lungs soon after birth than AGA preterm infants was in contrasts to the lower SFR/oxygen saturation in the first 3 days of life in SGA compared to no-SGA as reported by other studies.[25,31] However, the available literature does not exclude preterm infants with BPD from SGA and AGA groups, making it difficult to draw any conclusions. Notably, in the current study, fewer SGA infants required surfactant administration compared to AGA, which is in line with an accelerated lung maturation in SGA than AGA infants.[32] In addition, in our cohort, we found a lower incidence of RDS in SGA than AGA infants, although the association between SGA and RDS remains controversial. Some studies have reported a reduced,[33] others an increased risk of RDS in SGA infants,[34] and some authors did not find any association between SGA and RDS.[35–37] We speculated that the different respiratory severity at birth (lower surfactant administration/RDS) of SGA than that of AGA infants may explain the difference of pulmonary oxygen diffusion in the first HOL between these groups. To support this hypothesis, we excluded infants receiving surfactant from the case–control groups as secondary analysis, and after that, the statistically significant difference in pulmonary oxygen diffusion immediately after birth was no longer present (data not shown). In our opinion, this suggests that the reduced incidence of RDS in SGA infants may be responsible for the better pulmonary oxygen diffusion than AGA infants soon after birth in our study.

In our view, the most interesting finding was that the improvement of oxygen diffusion from 33 to 36 weeks was significantly worse in SGA compared to AGA infants. Of note, in spite of a higher SFR at birth, the SGA infants had a significantly lower SFR already at 4 weeks of age in comparison with AGA infants. These findings remained valid even when infants with sepsis and cholestasis were excluded from the case–control groups as secondary analysis (data not shown). Therefore, in spite of the milder respiratory severity soon

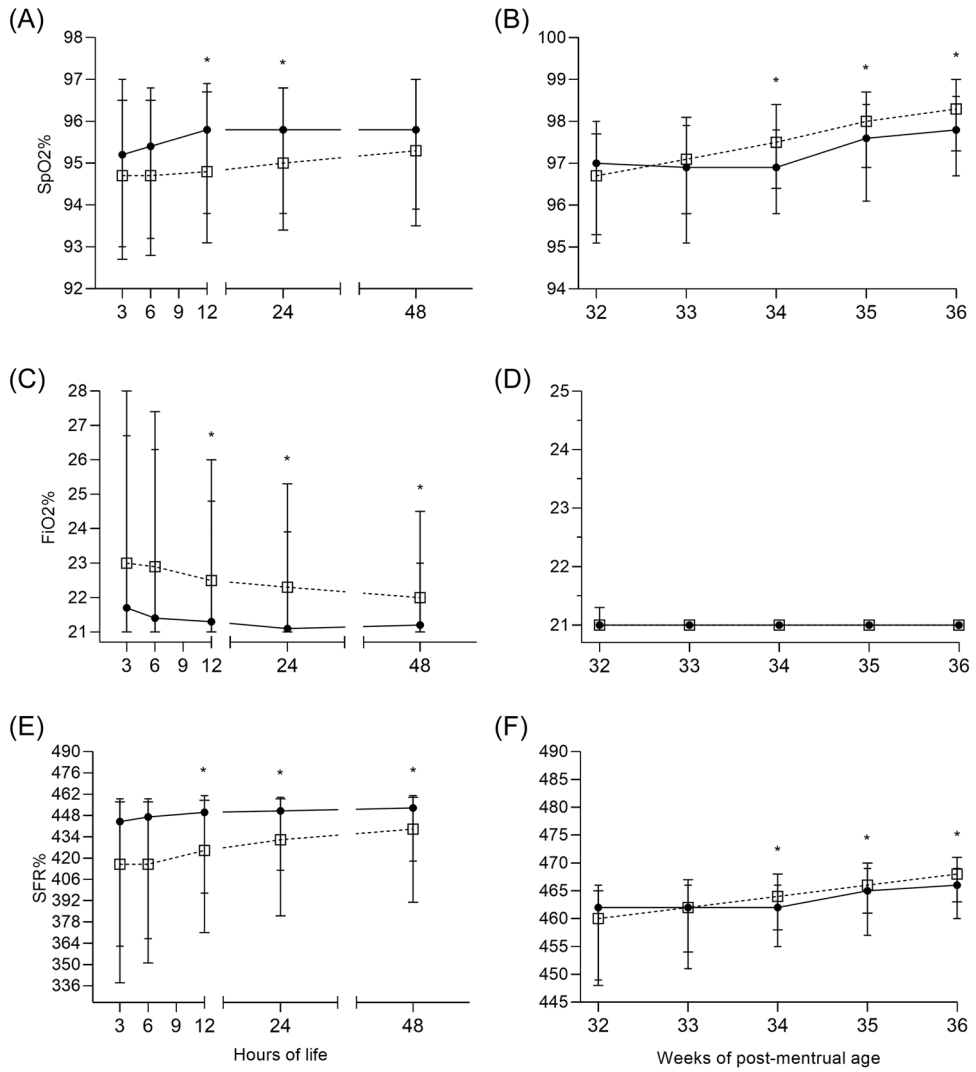

FIGURE 2 Oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), and SpO_2 to FiO_2 ratio (SFR) (%)from 3 to 48 h of life (Panels A, C, and E, respectively) and from 32 to 36 weeks (Panels B, D, and F, respectively) in small-for-gestational-age (SGA) versus appropriate-for-gestational-age (AGA) infants without BPD. SGA were indicated with filled circles and solid lines, whereas AGA with empty boxes and dotted lines. Data are given as medians |25th percentile 75th percentile|. The Mann–Whitney test was used for the statistical analysis ($p < .05$ were indicated by "*").

after birth in SGA versus AGA, the pulmonary oxygen diffusion in SGA was inferior to that of AGA infants as they got close to the NICU discharge. Based on to the SpO_2 versus FiO_2 curve,[38] we estimated that the difference in SpO_2 at 36 weeks between SGA and AGA may correspond up to +10 mmHg of inspired oxygen partial pressure in SGA than AGA infants. The relevance in terms of respiratory function in childhood and adulthood of these small, albeit significant, differences between SGA and AGA infants without BPD soon after birth deserves further investigation. Several studies showed an impaired lung faction of SGA infants from infancy into adulthood.[39,40] However, most follow-up studies during infancy and childhood of very preterm infants did not clearly distinguish between SGA infants with BPD and those without BPD. In our view, this approach hinders the evaluation of the contribution of SGA and BPD on respiratory outcomes in preterm infants.

This retrospective study has limitations and carries the risks of inherent biases. Due to the inconsistent availability of prenatal fetal Doppler velocimetry, we were unable to distinguish constitutional small infants with normal Doppler from those born SGA for severely abnormal Doppler velocimetry. Studies on the validity of using SFR in "healthy" preterm infants are lacking. However, our previous study involving 1005 preterm infants of less than 32 weeks demonstrated an association between the SFR value and respiratory status in preterm infants without BPD.[25] The normal range of SFR is not yet defined in preterm infants making it not possible to define whether the SFR values at 36 weeks of SGA and AGA infants were normal or abnormal. However, the current study was not designed to ascertain it. The ability to find a difference between groups gradually decreased as the infant grew from birth to 36 weeks, due to the upper limit of SFR. However, in the study infants, the difference in

TABLE 2 Linear regression models for the SFR at 36 weeks of postmenstrual age in the study preterm infants.

	All infants ($N = 1189$)[A]		Infants without BPD ($N = 995$)[B]	
	B (95% CI)	*p* Value	B (95% CI)	*p* Value
GA (weeks)	+2.12 (+ 0.76 + 3.66)	.003	+0.94 (+ 0.34 + 1.53)	.002
SGA <10°centile (yes)	−6.47 (−12.1 −0.87)	.024	−5.93 (−8.27 −3.59)	.000
Gender (male)	−1.36 (−5.43 −2.70)	.511	−1.07 (−2.66 + 0.53)	.190
Antenatal corticosteroids (yes)	+0.11 (−9.11 + 9.34)	.981	−0.44 (−4.31 + 3.44)	.825
Surfactant administration for RDS management (yes)	−3.62 (−8.11 + 0.86)	.113	−0.99 (−2.72 + 0.74)	.263
Sepsis (yes)	+2.20 (− 1.79 + 20.5)	.464	−1.23 (−3.83 + 1.37)	.353
PDA (presence) (yes)	+1.21 (−3.63 + 6.06)	.622	−0.89 (−2.81 + 1.03)	.364
Asphyxia (yes)	+5.89 (−7.49 + 19.3)	.388	+2.02 (−4.41 + 8.44)	.538
CHOLST (yes)	+5.84 (−2.90 + 14.6)	.190	+1.33 (−2.63 + 5.30)	.510
Brain injury (yes)	+2.66 (−2.80 + 8.12)	.339	−0.54 (−2.80 + 1.72)	.640
BPD (yes)	−74.7 (−81.0 −68.4)	<.001		
Surgery (yes)	−9.67 (−17.1-2.20)	.011	−2.84 (−6.29 + 0.61)	.107
Blood transfusions (yes)	−4.30 (−9.89 + 1.30)	.132	−3.58 (−5.78 −1.38)	.001
PN + EN energy (birth 36 weeks) (10 kcal kg^{-1} day^{-1})	+4.84 (+ 2.36 + 7.32)	<.001	+0.04 (-0.98 + 1.05)	.945
PN + EN fluids (birth 36 weeks) (10 mL kg^{-1} day^{-1})	+7.42 (+ 4.52 + 10.3)	<.001	+2.41 (+ 1.19 + 3.63)	<.001

Note: A: $R = .745$; B: $R = .561$.

Abbreviations: BPD, bronchopulmonary dysplasia; CHOLST, cholestasis; EN, enteral nutrition; GA, gestational age; PDA, patent ductus arteriosus; PN, parenteral nutrition; RDS, respiratory distress syndrome; SGA, small for gestational age.

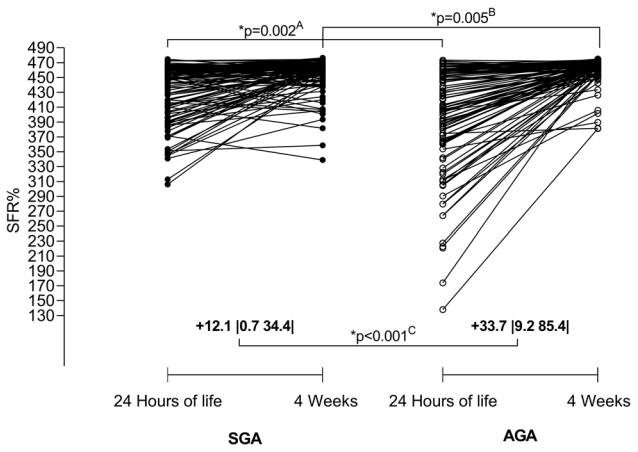

FIGURE 3 Individual SpO_2 to FiO_2 ratio (SFR) changes from 24 h of life (HOL) to 4 weeks of age in 132 small-for-gestational-age (SGA) (-●-) and appropriate-for-gestational-age (AGA) (-○-) matched pairs. [A]Differences in SFR at 24 HOL. [B]Differences in SFR at 4 weeks. [C]Individual SFR changes between 24 HOL and 4 weeks between SGA and AGA matched infant pairs. Wilcoxon test was used for the statistical analysis.

SFR between groups started at 33 weeks and persisted up to 36 weeks, suggesting poorer pulmonary oxygen diffusion in SGA versus AGA, even in the absence of BPD. We used SpO_2 and FiO_2 data that were manually collected on an hourly basis by nurses in the patient medical records during the hospitalization rather than an automatic data entry from cardiomonitor and ventilator supports. However, mean FiO_2, SpO_2, and SFR were calculated from our dataset, which consisted of more than 400,000 datapoints and individual changes as well as group means increased with time. We believe that the increase of SFR over time reflects lung growth (alveolarization) and maturation in rapidly growing infants, despite a relevant contribution of hemodynamic status, and/or blood transfusions on SpO_2 and in turn on SFR values cannot be excluded. The strengths of the study were: (1) the completeness of data, representing all preterm infants of less than 32 weeks in our whole Marche region given that the enrollment was carried out in the only referral center of the Marche region for this type of infant; (2) disease definitions, and institution and local guidelines did not change during the entire study period.

In conclusion, our study reaffirms the over representation of SGAs among BPD infants and, as new finding, we show that pulmonary oxygen diffusion at 36 weeks was significantly poorer in SGA versus AGA infants even without BPD. Our results may trigger additional studies on tracking lung function of SGA infants who do not qualify for the diagnosis of BPD starting from hospital stay.

AUTHOR CONTRIBUTIONS

Alessio Correani: Writing—original draft; methodology; conceptualization. **Lucia Lanciotti:** Data curation; investigation; writing—review and editing. **Chiara Giorgetti:** Data curation; investigation; writing—review and editing. **Maria Laura Palazzi:** Data curation; investigation;

writing—review and editing. **Chiara Monachesi:** Formal analysis; data curation; investigation; writing—review and editing. **Luca Antognoli:** Formal analysis; investigation; writing—review and editing. **Ilaria Burattini:** Data curation; investigation; writing—review and editing. **Paola Cogo:** Data curation; investigation; writing—review and editing; supervision. **Virgilio Carnielli:** Supervision; conceptualization; methodology; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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