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ORIGINAL ARTICLE

The Impact of Small-for-gestational-age on Neonatal Outcome Among Very-low-birth-weight Infants

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Background: This study aimed to evaluate the impact of small-for-gestational-age (SGA) on mortality and morbidity in very-low-birth-weight (VLBW) infants.
Methods: We conducted a retrospective cohort study on VLBW infants registered at the Premature Baby Foundation of Taiwan between 2007 and 2011. All 21 neonatal departments in Taiwan participated in the data collection, and a total of 4636 VLBW infants were registered during the study period. The SGA group ($n = 560$) was selected from the database on the basis of birth weight below the 10th percentile for gestational age, whereas the appropriate-weight-for-gestational-age (AGA) group ($n = 1120$) included infants randomly selected via incidence density sampling with a 2:1 match for each SGA case. The association of SGA with individual outcome variables including mortality, respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity (ROP), intraventricular hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia (BPD) was evaluated after adjustment for potential confounders.
Results: The SGA group was associated with increased risks of mortality [odds ratio (OR) 1.89; 95% confidence interval (CI) 1.39–2.58], severe ROP (OR 1.56; 95% CI 1.13–2.14), and BPD (OR 2.08; 95% CI 1.58–2.75) compared to the AGA group. Further subgroup analysis showed that SGA had significant effects on mortality in the VLBW infants with a gestational age of 24–29

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weeks, as well as on BPD in those with a gestational age of 27—32 weeks. By contrast, the association of SGA with severe ROP was only significant in the VLBW infants with a gestational age of 27—29 weeks.
Conclusion: Our data provide evidence that SGA may be associated with increased risks of neonatal mortality, ROP, and BPD in VLBW infants.

1. Introduction

Small-for-gestational-age (SGA) infants represent a significant percentage of infants admitted to Neonatal Intensive Care Units. SGA is associated with an increased risk of spontaneous and iatrogenic preterm delivery.[1,2] However, its impact on prematurity-associated neonatal morbidity has been disputed due to inconsistent results in the literature. Although some studies showed that SGA was an adverse risk factor of neonatal clinical outcomes,[3,4] others suggested a lower risk for respiratory distress syndrome (RDS) in SGA infants compared to appropriate-weight-for gestational age (AGA) infants.[5—7] Similarly, the reported associations between SGA and risks of intracranial hemorrhage and periventricular leucomalacia (PVL) vary from one study to another.[8,9]

It has been speculated that these discrepancies may be attributed to differences in study methodologies and sample characteristics, such as the definitions of SGA, sample sizes, range of gestational ages, and birth weights of study populations. In addition, AGA comparison groups often differed in either birth weights or gestational age; it was unclear whether the clinical outcome resulted from a shorter gestation period or impaired prenatal growth. To address this issue, some studies have compared the clinical outcomes in SGA infants with those in gestational age-matched AGA infants.[10,11]

To evaluate the association of SGA with neonatal mortality and morbidity accurately, we conducted a matched group study to avoid selection bias and compared the neonatal outcomes in SGA and AGA very-low-birth-weight (VLBW) infants matched for gestational age.

2. Methods

2.1. Ethics statement

Written informed consent was obtained from designated relatives of each infant. The study was approved by the Institutional Review Boards of each participating hospital, including the National Taiwan University Hospital, Chang Gung Memorial Hospital, China Medical University Hospital, National Cheng Kung University Hospital, Tri-Service General Hospital, Chung Shan Medical University Hospital, Shin Kong Wu Ho-Su Memorial Hospital, and Kaohsiung Medical University Chung-Ho Memorial Hospital, as well as the Joint Institutional Review Board of the other hospitals.

2.2. Participants

A total of 4636 VLBW infants born with a birth weight below 1501 g were registered in the database of the Premature Baby Foundation of Taiwan between 2007 and 2011. All 21 hospitals located across the island of Taiwan participated in the data collection. In addition to neonatal histories such as diagnoses, complications during hospitalization, and clinical outcomes from their health records at the time of discharge, the database also included antenatal and perinatal information. Data entry was conducted after death or discharge of infants from hospital. Patient information received by the database coordinator was cross checked with the national birth registry. Exclusion criteria included congenital anomalies and chromosome anomalies.

Gestational age was determined from maternal dates of the last menstrual period and the date of embryo transfer for *in vitro* fertilization. SGA infants were identified as having birth weights below the 10^{th} percentile for gestational age on sex-specific standards,[12] whereas AGA infants were defined as infants' birth weights between the 10^{th} and 90^{th} percentiles (inclusive) for gestational age. SGA—AGA match was carried out and SGA infants with two gestation age-matched AGA cases were selected in our study group. For each SGA case, two gestation age-matched AGA infants were randomly selected using the incidence density sampling approach in a 2:1 match.

2.3. Outcome variables

RDS was defined by clinical diagnosis as requiring surfactant therapy. The extent of intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) was graded according to the classification of Papile et al[13] and Bell et al,[14] respectively. Severe retinopathy of prematurity (ROP) was classified as Stage 3 to Stage 5 according to the international classification.[15] PVL was diagnosed by echolucent areas or persistent echogenicity in periventricular areas on coronal and sagittal views of cranial ultrasounds.[16] Bronchopulmonary dysplasia (BPD) was defined as infants requiring oxygen supplementation at the postconceptional age of 36 weeks.[17]

2.4. Statistical analysis

The Chi-square test and the Student *t* test were used to compare the distributions of categorical variables and continuous variables between two groups, respectively. For

each outcome variable (neonatal death, RDS, BPD, IVH, PVL, ROP, and NEC), separate Chi-square tests were performed to compare SGA and AGA infants. A value of $p < 0.05$ was taken to be significant. Multiple logistic regression analysis adjusted for use of antenatal steroids and sex was performed to relate individual outcome variables including RDS, IVH, PVL, and ROP to SGA (with the AGA group as the reference). With adjustment for antenatal steroids, sex, sepsis, and the number of days of use of intermittent positive pressure ventilation (IPPV), multiple logistic regression was performed to relate BPD to SGA. With adjustment for antenatal steroids, sex, and the Apgar score at 5 minutes after birth, multiple logistic regression was performed to relate neonatal death to SGA. A variable was considered to be significantly associated with outcome if the odds ratio (OR) differed from 1.0 and $p < 0.05$. The association of SGA with outcome variables was further examined in subgroup analysis with stratification according to gestational ages. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

A total of 4448 VLBW infants were enrolled in the study after congenital anomalies and chromosome anomalies ($n = 188$) were excluded. There were 1454 (33.2%) SGA infants within the gestational age range of 22—36 weeks and 2850 (65%) AGA infants within the gestational age range of 21—32 weeks. After the SGA—AGA match, 560 SGA infants were selected and 1120 AGA infants were randomly matched with the SGA group according to the gestational age at birth. The gestational age of the study population ranged from 22 weeks to 32 weeks (Figure 1).

Table 1 shows the characteristics of VLBW infants classified as SGA and AGA. The two groups differed in sex, birth weight, body length, head circumference, and parity. The SGA group also had lower Apgar scores at 5 minutes after birth, higher incidence of neonatal sepsis, and longer duration in use of IPPV. By contrast, no significant differences were observed between the two groups in use of antenatal steroids, multiple births, artificial fertilization, or the incidence of pneumothorax and patent ductus arteriosus.

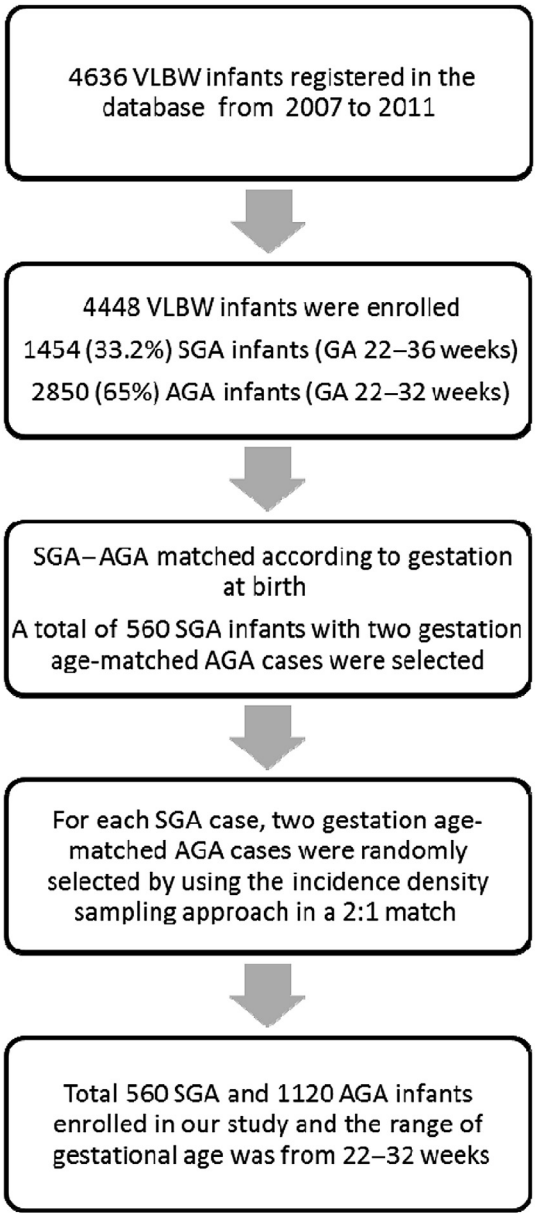

Figure 1 Flowchart of the study populations. Congenital anomalies and chromosome anomalies ($N = 188$) were excluded. AGA = appropriate-weight-for-gestational-age; SGA = small-for-gestational-age; VLBW = very-low-birth-weight.

3.2. Neonatal mortality and morbidity

In our study population, a total of 247 cases died during hospitalization. In the SGA group, the causes of death were RDS (16%), sepsis (7.5%), respiratory failure (60.6%), IVH (4.1%), BPD (4.3%), and undefined reasons (7.5%). In the AGA group, the causes of death were RDS (13.1%), sepsis (9.4%), respiratory failure (55.1%), IVH (8.4%), BPD (2.8%), and undefined reasons (11.2%). The data on the causes of death were missing for 44 out of 247 deaths.

Table 2 shows the effects of SGA on the incidence of various neonatal outcomes including neonatal death, RDS, ROP, IVH, PVL, NEC, and ROP. The risks of neonatal death, BPD, and ROP were higher in the SGA group in comparison to the AGA group. By contrast, there was no statistically significant difference in the risk of RDS, NEC, or PVL between the groups.

Multiple logistic regression analysis was then conducted with adjustments for sex and use of antenatal steroids. Adjusted ORs with a 95% confidence interval (CI) for different neonatal outcomes are illustrated in Table 3. Compared to the AGA infants, the SGA infants were associated with increased risks of neonatal death (OR 1.89; 95% CI 1.39—2.58), severe ROP (OR 1.56; 95% CI 1.13—2.14), and BPD (OR 2.08; 95% CI 1.58—2.75).

Table 4 shows adjusted ORs with a 95% CI for neonatal mortality and morbidity comparing the SGA and AGA groups with stratification according to gestational ages. Our

Table 1 Characteristics of very-low-birth-weight infants classified as small-for-gestational-age (SGA) and appropriate-weight-for-gestational-age (AGA) matched according to gestation.

	SGA $N = 560$	AGA $N = 1120$	p
Infant			
Gestational age at birth (wk), mean (SD)	28.3 (1.9)	28.3 (1.9)	
Sex (% female)	41.3	48.3	0.0062
Birth weight (g), mean (SD)	832.2 (223.4)	1162 (238.5)	<0.0001
Head circumference at birth (cm), mean (SD)	24.11 (2.21)	26.02 (2.1)	<0.0001
Length at birth (cm), mean (SD)	33.36 (3.66)	37.03 (3.39)	<0.0001
Parity (% first born)	62.5	50.1	<0.0001
Multiple birth (%)	30.4	31.0	0.7278
Artificial fertilization (%)	24.1	20.5	0.2164
Antenatal steroid > 2 doses (%)	48.65	48.87	0.9306
Apgar score at 1 minute, median	5	6	
Apgar score at 5 minutes, median	7	8	
≤3 (%)	69 (15.3)	116 (11.9)	0.0018
4–6 (%)	247 (54.8)	476 (48.7)	
>6 (%)	135 (29.9)	385 (49.4)	
Sepsis (%)	106 (19.9)	167 (15.5)	0.02471
Pneumothorax (%)	37 (6.7)	76 (6.8)	0.91981
PDA (%)	227 (44.2)	464 (44.1)	0.97049
IPPV (days of use)	14.8	10.4	0.00015
Mother			
Maternal age at birth (yr), mean (SD)	32.4 (4.7)	32.1 (5.1)	0.1346
Maternal nationality (% non-Taiwan)	4.7	4.4	0.8050
Education level (%)			
Junior high school or below	9.8	8.1	0.1842
Senior high school	30.5	35.0	
University or above	50.7	56.9	

IPPV = intermittent positive pressure ventilation; PDA = patent ductus arteriosus.

subgroup analysis showed significant effects of SGA on mortality in the VLBW infants with a gestational age of 24–29 weeks, as well as on BPD in those with a gestational age of 27–32 weeks. By contrast, the association of SGA and severe ROP was only significant in the VLBW infants with a gestational age of 27–29 weeks.

Table 2 Incidence of neonatal morbidity and mortality in very-low-birth-weight infants classified as small-for-gestational-age (SGA) or appropriate-weight-for-gestational-age (AGA) matched according to gestation.

	SGA $N = 560$	AGA $N = 1120$	p
RDS	256 (45.8)	496 (44.3)	0.5575
NEC	30 (5.4)	48 (4.3)	0.3213
ROP (any grade)	255 (57.2)	483 (49)	0.0041
ROP (Grades III–V)	74 (13.29)	100 (8.93)	0.005857
IVH (any grade)	213 (41.3)	387 (36.7)	0.0805
IVH (Grades III, IV)	33 (9.8)	52 (7.5)	0.9488
PVL	22 (4.26)	49 (4.6)	0.7583
BPD	230 (49.4)	306 (30.5)	<0.0001
Neonatal death	119 (21.3)	128 (11.4)	<0.0001

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.

4. Discussion

Our present study provides evidence that SGA may be associated with an increased risk of mortality in VLBW neonates. Previous studies have shown that the mortality of infants with a birth weight below the 10th percentile was higher than that of AGA neonates at all gestational ages up to 36 weeks.[18,19] Similarly, we observed a 1.89-fold increase in mortality in the VLBW infants classified as SGA with a gestational age of 24–32 weeks compared to the AGA infants. Interestingly, Bardin et al[9] did not observe any significant difference in mortality between the SGA and AGA groups; however, their study population was limited to 24–26 weeks' gestation, and therefore they did not represent the complete spectrum of premature infants. Lackman et al[1] also showed in a larger population-based study, that the risk of perinatal death attributed to being born preterm SGA increased significantly only with a birth weight below the third percentile, but no differences were observed in the SGA infants whose birth weights were between the 3rd and the 10th percentiles. This study population included infants from 25 weeks to 40 weeks' gestation, and premature delivery was up to 10.5% in the AGA comparison group. In the present study, we demonstrated that a small size at birth (VLBW infants consisting of birth weights below the 10th percentile for gestational age) may be associated with a significantly increased risk of neonatal death.

Table 3 Multivariate-adjusted odds ratio (95% confidence interval) of outcome variables for the SGA group (the AGA group was the reference).

	OR (95% CI)	*p*
RDS	1.05 (0.86–1.29) *	0.6462
NEC	1.27 (0.80–2.04) *	0.3117
ROP (Stages III–V)	1.56 (1.13–2.14) *	0.0069
IVH (Grades III, IV)	0.98 (0.68–1.42) *	0.9115
PVL	0.92 (0.55–1.55) *	0.7594
BPD	2.08 (1.58–2.75) †	<0.000001
Neonatal death	1.89 (1.39–2.58) ‡	0.000056

AGA = appropriate-weight-for-gestational-age; BPD = bronchopulmonary dysplasia; CI = confidence interval; IPPV = intermittent positive pressure ventilation; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; SGA = small-for-gestational-age.

* ORs of RDS, NEC, ROP, IVH, and PVL with adjustment for sex and antenatal steroids.

† OR of BPD with adjustment for sex, antenatal steroids, sepsis, and number of days of IPPV.

‡ OR of neonatal death with adjustment for sex, antenatal steroids, and Apgar score at 5 minutes after birth.

In addition, our study showed a 2.08-fold increase in the incidence of BPD in the SGA infants. These findings are consistent with previous studies showing premature SGA infants to have an increased incidence of BPD.[19–22] The etiology of BPD is multifactorial, involving factors such as RDS, duration and degree of ventilator support, higher oxygen concentration exposure of the infant, and chronic malnutrition. Experimental studies have suggested that chronic malnutrition induces the deficiency of antioxidants, which might predispose the infant to BPD.[23] Fetal hypoxemia and acidosis caused by restricted growth may be involved in the release of proinflammatory factors such as tumor necrosis factor alpha.[24]

The concept of accelerated lung maturation in response to "stress" was initially proposed in the 1980s and has been supported by some studies.[6,25] However, in this study, we did not find any difference in the incidence of RDS between the SGA and AGA groups. Consistent with our results, several previous studies found no differences in the incidence of RDS between the two groups,[9,26] and some reports even showed an increased incidence and severity of RDS in premature SGA infants.[27,28] Tyson et al[28] emphasized that it is important to compare the outcome of SGA and AGA infants with the same gestational age. In their study, the concept of intrauterine growth retardation on accelerating lung maturation and improving outcome was not supported by the comparison of SGA and AGA with the same gestational age, sex, and race. Interestingly, Zaw and coworkers[29] reported a higher incidence of RDS among SGA infants with use of the fetal growth standard but no difference between SGA and AGA infants with use of the neonatal growth standard. With the restrictions of our database, we could only identify the RDS cases with the use of surfactants and may therefore have lost many RDS cases with mild presentation and no use of surfactants. We speculate that the definition of RDS may be one of the reasons that we did not find any difference in the incidence of RDS between the SGA and AGA groups.

It is noteworthy that an increased risk of ROP was found to be associated with SGA in the VLBW infants with a gestational age of 27–32 weeks in this study. The associations between prenatal weight gain and ROP have not been consistent in past studies. Garite et al[3] showed in a large population study that within each gestational age group from 25 weeks to 32 weeks, intrauterine growth restriction was associated with an increased risk of ROP. However, another study indicated that birth weight was not a significant risk factor when including gestational age and serum levels of insulin-like growth factor-I (IGF-I) in

Table 4 Multivariate-adjusted odds ratio (95% confidence interval) of outcome variables for the SGA group (the AGA group was the reference) with stratification according to gestational age.

	GA 30–32 weeks	GA 27–29 weeks	GA 24–26 weeks
SGA (*N*)	178	264	113
AGA (*N*)	356	528	226
RDS *	1.13 (0.71–1.81)	1.31 (0.96–1.77)	0.72 (0.44–1.19)
NEC *	2.2 (0.85–5.67)	1.19 (0.59–2.41)	0.94 (0.37–2.4)
ROP (Stages III–V) *	2.47 (0.83–7.83)	1.71 (1.05–2.79) †	1.71 (0.67–2.13)
IVH (Grades III, IV) *	2.74 (0.07–1.59)	0.81 (0.45–1.46)	1.20 (0.67–2.14)
PVL *	0.33 (0.07–1.59)	1.19 (0.62–2.31)	0.77 (0.27–2.2)
BPD ‡	2.29 (1.28–4.09) †	2.5 (1.69–3.71) §	1.87 (0.87–4.0)
Neonatal death ‖	2.85 (0.84–9.62)	3.21 (1.96–5.25) §	2.05 (1.18–3.55) †

AGA = appropriate-weight-for-gestational-age; BPD = bronchopulmonary dysplasia; GA = gestational age; IPPV = intermittent positive pressure ventilation; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; SGA = small-for-gestational-age.

* ORs of RDS, NEC, ROP, IVH, and PVL with adjustment for sex and antenatal steroids.

† $p < 0.05$.

‡ ORs of BPD with adjustment for sex, antenatal steroid, sepsis, and number of days of IPPV.

§ $p < 0.000005$.

‖ ORs of neonatal death with adjustment for sex, antenatal steroid, and Apgar score at 5 minutes.

multiple regression analyses.[30] Recent evidence suggested that in addition to low gestational ages, both postnatal birth weight gain and serum IGF-I levels during the first weeks/months of life may be the strongest predictor of ROP and correlated with the severity of ROP.[31] Further studies are needed to evaluate the association of poor prenatal weight gain with ROP.

Our results show no evidence that SGA is associated with increased risks of IVH or NEC. Similarly, most previous studies found no differences in the incidence of IVH between SGA and AGA preterm neonates.[22,32,33] However, because several other studies contradict these findings,[34] further research is needed to explore this issue. It is believed that redistribution of blood flow in *in utero* growth restriction leads to a brain sparing effect at the expense of other organs and tissues, such as kidneys, muscles, or intestines.[35,36] Intestinal ischemia could increase the susceptibility of SGA infants to developing NEC. Although our present study found no difference in the incidence of NEC between SGA and AGA infants, the results from previous studies are contradictory, showing either a higher[10,22] or a similar incidence[32] incidence of NEC in SGA infants.

The strength of our present study is that it is a large multicenter cohort study, which allowed us to assess the association between SGA and neonatal outcomes in different gestational subgroups. However, our study has some limitations. First, the reliability of our data depended on the precision of pediatricians and case managers. Second, our study group was limited to the VLBW neonates with a gestational age of 24—32 weeks. Further research is needed to access the impact of SGA on premature infants > 32 weeks. Third, we lacked sufficient prenatal data in the database for the diagnosis of SGA according to the fetal growth standard. Recent studies have emphasized that fetal growth standards more reliably identify increased risks of clinical outcomes among preterm SGA infants compared to neonatal growth standards.[29]

In conclusion, our data provide evidence that SGA may be associated with increased risks of neonatal death, ROP, and BPD in VLBW infants.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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