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Mortality and morbidity risks vary with birth weight standard deviation score in growth restricted extremely preterm infants

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ABSTRACT

Objective: To assess whether the mortality and morbidity risks vary with birth weight standard deviation score (BWSDS) in growth restricted extremely preterm infants.
Study design: This was a multicenter retrospective cohort study using the database of the Neonatal Research Network of Japan and including 9149 infants born between 2003 and 2010 at <28 weeks gestation. According to the BWSDSs, the infants were classified as: <− 2.0, − 2.0 to − 1.5, − 1.5 to − 1.0, − 1.0 to − 0.5, and ≥ − 0.5. Infants with BWSDS ≥ − 0.5 were defined as non-growth restricted group.
Results: After adjusting for covariates, the risks of mortality and some morbidities were different among the BWSDS groups. Compared with non-growth restricted group, the adjusted odds ratio (aOR) for mortality [aOR, 1.69; 95% confidence interval (CI), 1.35–2.12] and chronic lung disease (CLD) (aOR, 1.28; 95% CI, 1.07–1.54) were higher among the infants with BWSDS − 1.5 to <− 1.0. The aOR for severe retinopathy of prematurity (ROP) (aOR, 1.36; 95% CI, 1.09–1.71) and sepsis (aOR, 1.72; 95% CI, 1.32–2.24) were higher among the infants with BWSDS − 2.0 to <− 1.5. The aOR for necrotizing enterocolitis (NEC) (aOR, 2.41; 95% CI, 1.64–3.55) was increased at a BWSDS < − 2.0.
Conclusion: Being growth restricted extremely preterm infants confer additional risks for mortality and morbidities such as CLD, ROP, sepsis and NEC, and these risks may vary with BWSDS.

1. Introduction

Recent advances in perinatal medicine have made the survival of extremely low-birth-weight (ELBW) infants (birth weight < 1000 g) or extremely preterm infants born at <28 weeks gestation possible. A national survey of mortality conducted in Japan identified a mortality rate of 17.0% in ELBW infants born in 2005 [1]. In this survey, the mortality rate for extremely preterm infants was 20.1%; however, because this study focused on the birth weight rather than gestational age, the influence of an unfavorable intrauterine environment as the cause of small for gestational age (SGA) infants was not clarified in terms of its impact on the mortality rate of extremely preterm infants.

Preterm SGA or growth-restricted infants are known to be at risk of adverse outcomes resulting from immaturity and intrauterine growth restriction [2], such as respiratory distress syndrome (RDS) [3–7], intraventricular hemorrhage (IVH) [3,7], necrotizing enterocolitis (NEC) [8–10], chronic lung disease (CLD) [8–10,12,13] and retinopathy of prematurity (ROP) [7–11]. However, there are several conflicting reports, with some indicating that the risk of RDS was unchanged [9] or decreased [10], or that the risk of IVH was unchanged [8–10] in growth-restricted preterm infants compared with appropriate for gestational age (AGA) infants. These inconsistencies may be partially explained by the differences in the reference growth charts or reference groups used, the subjects being weight-defined versus gestational age-defined, the range of gestational ages, and the confounding factors considered in the analyses.

SGA is a term that is often used as a proxy for restricted growth in utero. However, SGA and fetal growth restriction (FGR) are not synonymous, because SGA refers to both constitutional and pathological growth-restricted infants, while FGR is related to pathologically restricted growth. Additionally, SGA is identified by neonatal anthropometric charts, while FGR is identified by fetal growth charts. However, a recent study suggested that the definition of SGA might well be justified as a proxy for FGR in early preterm gestational age, because the neonatal mortality rates were higher at

Abbreviations: aOR, adjusted odds ratio; AGA, appropriate for gestational age; BWSDS, birth weight standard deviation score; c-PVL, cystic periventricular leukomalacia; CLD, chronic lung disease; ELBW, extremely low birth weight; FGR, fetal growth restriction; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age.

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every preterm gestational age among SGA compared to AGA births [14].

Beyond the issue regarding which reference charts should be used to identify SGA, whether a single cut-off point is sufficient to predict mortality and morbidity risks in growth-restricted extremely preterm infants remains unknown. The aim of our present study was to evaluate the relationship between the birth weight standard deviation score (BWSDS) based on Japanese birth weight charts [15] and mortality and morbidity in a large number of growth-restricted extremely preterm infants based on a database from the Neonatal Research Network of Japan.

2. Study design

2.1. Selection of subjects

A total of 25,052 infants weighing 1500 g or less at birth were listed in the database of the Neonatal Research Network of Japan between January 1, 2003 and December 31, 2010. These very low birth weight infants were admitted to 89 participating neonatal intensive care units (NICUs) in Japan. The gestational period was calculated based on ultrasound examinations in early pregnancy and the date of the last menstrual period. The following infants were excluded from the initial database: 15,433 infants born at less than 22 weeks or more than 28 weeks gestation; 139 infants having no data on gender or gestation, which are necessary to calculate the BWSDS; 108 infants with unidentified outcomes because they were transferred to other hospitals; and 223 infants with major malformations. The BWSDS for the remaining 9149 extremely preterm infants was calculated based on the Japanese neonatal anthropometric chart [15]. According to the BWSDSs, the infants were classified as: <−2.0, −2.0 to −1.5, −1.5 to −1.0, −1.0 to −0.5, and ≥−0.5. Infants with BWSDS ≥ −0.5 were defined as non-growth restricted group.

This study was approved by the Institutional Review Board of the Tokyo Women's Medical University (UMIN000006961).

2.2. Outcome variables

The outcome variables included mortality and major morbidity during the NICU stay. The morbidities included RDS, IVH, cystic periventricular leukomalacia (c-PVL), sepsis, NEC, CLD, and severe ROP. The subjects included in the analysis of the CLD and ROP risks were 7817 infants who survived beyond 36 weeks of post-conceptional age. The definitions of these illnesses were in accordance with those used in our previous study [16]. RDS was diagnosed via clinical examinations, chest X-rays, and the stable micro-bubble rating test. CLD was diagnosed in cases in which the respiratory disorder was still present at the corrected gestational age of 36 weeks, in which oxygen or artificial ventilation was required, and the characteristic chest X-ray findings were evident. NEC was determined by the clinical and radiological criteria proposed by Bell et al. [17], and only definite NEC (Bell stages II–III) was included. Severe IVH (grades III–IV) was diagnosed using cranial ultrasound and was graded according to the method reported by Papile et al. [18], and c-PVL was diagnosed using cranial ultrasound or magnetic resonance imaging (MRI). A diagnosis of sepsis was made only in cases with positive blood cultures. These cases also had clinical symptoms. In the present study, the onset of sepsis was impossible to classify in some cases. Therefore, early- and late-onset sepsis were investigated together. Severe ROP was designated as stages III–IV according to the international classification [19] or as patients requiring laser treatment.

2.3. Covariates

The covariates included gestational age, BWSDS groups, parity, sex, plurality, antenatal complete and/or partial administration of steroids, mode of delivery, maternal hypertension (pregnancy-induced hypertension, pre-eclampsia, eclampsia, and HELLP syndrome), and clinical chorioamnionitis based on the diagnostic criteria proposed by Lencki et al. [20]. The definition for pregnancy-induced hypertension was elevated blood pressure (≥140 mm Hg systolic or 90 mm Hg diastolic) occurring after 20 weeks; pre-eclampsia was defined as hypertension with proteinuria (≥300 mg/L protein in a random specimen or an excretion of ≥300 mg/24 h) [21].

2.4. Statistical analysis

Categorical variables were expressed as numbers and percentages. Comparisons of the antenatal factors rates, mortality, and morbidity between non-growth restricted group and other BWSDS groups were analyzed with chi-square test. Continuous variables were expressed as the means and standard deviation. In order to assess whether the BWSDS group had an independent influence on mortality and morbidity due to RDS, CLD, IVH, c-PVL, NEC and ROP, covariates were included, and a multivariable logistic regression analysis was performed.

The IBM SPSS Statistics version 20 software program (IBM Japan, Tokyo, Japan) was used for the statistical analysis of the data in this study. Values of $P < 0.05$ were considered to be statistically significant.

3. Results

The characteristics of the nine BWSDS groups are shown in Table 1. Compared with the non-growth restricted group, the gestational age was significantly higher ($P < 0.001$) and the birth weight was lighter ($P < 0.001$) in the infants with BWSDS < −0.5. Cesarean section delivery, multiple birth, maternal hypertension and antenatal steroid therapy were more frequent, whereas clinical chorioamnionitis and multiparity were less frequently observed in the infants with BWSDS < −0.5 compared with non-restricted group.

The distributions of the BWSDS groups by gestational weeks are shown in Table 2. They were significantly different among the gestational age ($P < 0.001$). As the gestational age was increased, the percentage in growth restricted extremely preterm infants was increased.

The results of chi-square test and multivariable logistic regression analyses for the outcomes are shown in Table 3. Chi-square test showed significantly higher rates of RDS, sepsis, CLD and mortality in the infants with BWSDS < −1.5. The incidence of NEC in the infants with BWSDS < −2.0 was significantly higher. On the other hand, the incidence of severe IVH in the infants with BWSDS < −1.5 to −1.0 and <−2.0 were significantly lower.

To determine the independent effects of BWSDS on these outcomes, multivariable logistic regression analyses were performed after adjusting for gestational age, sex, plurality, multiple births, delivery modes, maternal hypertension, clinical chorioamnionitis, and antenatal steroid use. The mortality and some morbidity risks were different across BWSDS groups; the mortality risk was increased among the infants with BWSDS < −1.0, whereas the risks of CLD, sepsis and severe ROP were increased among those with BWSDS < −1.5. The risk for NEC was significantly higher in the infants with the BWSDS < −2.0. Although the infants with BWSDS < −1.5 had a higher incidence for RDS compared with the reference group by chi-square test, the risk of RDS was significant lower in the infants with BWSDS < −0.5 except for the BWSDS −2.0 to <−1.5. A significant increase in the aOR of severe ROP in the BWSDS < −1.5 group was found after adjusting for covariates, while risks for severe IVH and c-PVL were not significant among the BWSDS groups.