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Being Small for Gestational Age does not Change Short-Term Outcomes for Extremely Low Birth Weight Babies at Townsville University Hospital

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Abstract

Aim To determine whether being small for gestational age (SGA) is associated with increased mortality and short-term morbidity for extremely low birth weight (ELBW) babies at Townsville University Hospital (TUH).

Methods All babies with a birth weight of <1,000 g born at TUH between January 1, 2010 and January 1, 2021 were included. Data from the neonatal unit's NeoDATA database were used to compare mortality and short-term morbidity outcomes for babies categorized as SGA (birth weight <10th centile) or not. Statistical analyses were used to determine associations between being SGA and survival to discharge, intubation for mechanical ventilation, duration of respiratory support, chronic neonatal lung disease (CNLD), home oxygen, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), sepsis, time to full enteral feeds, and duration of admission.

Results Of 461 ELBW babies, 62 (13.4%) were SGA. The SGA babies were significantly smaller at 714 (580–850) versus 810 (700–885) g ($p < 0.001$) and of advanced gestational age at 28.6 (26.6–30.2) versus 25.4 (24.4–26.6) weeks ($p < 0.001$). No significant difference in mortality existed, with 85% of SGA babies and 84% of others surviving. On univariate analysis, being SGA was associated with significant reductions in intubation for mechanical ventilation ($p < 0.001$), duration of respiratory support ($p < 0.001$), intraventricular hemorrhage ($p = 0.002$), NEC ($p = 0.037$), and admission duration ($p = 0.038$). After controlling for confounding factors, no outcomes were independently associated with being SGA. Logistic regression found survival was associated with birth weight ($p = 0.030$), gestational age ($p = 0.007$), and antenatal corticosteroids ($p = 0.008$).

Conclusions Being SGA is not an independent predictor of mortality nor adverse short-term morbidity for ELBW babies.

Keywords
- Small for gestational age
- growth restricted
- extremely low birth weight
- premature
- mortality
- morbidity

Introduction

Predicting outcomes for growth-restricted extremely low birth weight (ELBW) infants remains difficult, even as survival of babies at the "threshold of viability" improves.[1–6] Accurate prognostic information is vital to inform shared decision-making regarding the care of ELBW babies who are also small for gestational age (SGA). Although evidence

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supports that growth restriction is associated with increased mortality and morbidity for term babies,[7] it is unclear whether this holds true for ELBW newborns, who have inherent increased risks.[5] Few studies specifically investigate outcomes for growth-restricted ELBW babies.

Conflicting outcome data for growth restriction in very low birth weight (VLBW) and/or extremely preterm babies confuses informed counseling of expectant parents regarding whether their baby will be at higher risk for mortality and excess morbidity. While some researchers have found growth restriction is associated with increased mortality in preterm babies,[8–19] others have shown that the neonatal mortality rate is no higher.[20–22] Although traditional thinking may be that growth restriction is associated with poorer outcomes at any gestation, contrary evidence suggests that being SGA may not be an important independent prognostic variable for the smallest preterm neonates. Most previous works suggest no increased risk of intraventricular hemorrhage (IVH)[9,11,15,16,21] nor periventricular leukomalacia (PVL)[11,15,16,18,19] in growth-restricted preterm babies. Contradictory findings have been reported.[14] Whether gastrointestinal complications such as necrotizing enterocolitis (NEC) or gastrointestinal perforation are more common[10,14,18,21,22] or not[16,19] for growth-restricted ELBW babies is also unclear. Perhaps most controversially, there has been a debate in the literature regarding the respiratory complications of preterm SGA babies. Controversy remains as to whether respiratory distress syndrome (RDS) is increased[10] or unaffected/lowered[12,13,15,16,20,22] with growth restriction, but most authors agree that growth restriction increases the risk of chronic neonatal lung disease (CNLD).[11,13,14,16,23–25]

Yamakawa et al reported that the risk of specific complications is dependent upon the deviation of the birth weight from the mean and that each complication has a different threshold for increased risk[18] suggesting that applying findings from studies of bigger babies to ELBW newborns may not be appropriate. There is a paucity of evidence for the growth-restricted ELBW group, warranting further investigation. Babies born <1,000 g have increased risks of neonatal morbidity and mortality, even when compared to babies in the 1,000 to 1,500 g cohort. In 2017, Hasthi et al reported that ELBW babies had a higher risk than VLBW babies of all studied neonatal morbidities (including a significant increase in continuous positive airway pressure support) and significantly higher neonatal death.[12] Given that ELBW babies are known to have increased complication rates, our study investigated whether growth restriction has an additional detrimental influence on mortality and short-term morbidity for babies born <1,000 g.

The aim of this study was to determine whether growth restriction is associated with increased mortality (primary outcome) and short-term morbidity in babies born <1,000 g and treated at Townsville University Hospital (TUH).

Methods

This study was conducted at TUH, a tertiary perinatal center uniquely positioned to care for most neonates born extremely preterm and with low birth weight in North Queensland. The unit provides care for a region with 10,000 births per year.[26] This paper describes the outcomes for ELBW babies treated between January 1, 2010 and January 1, 2021. The hospital has on-site maternal–fetal-medicine specialists and a level six neonatal intensive care unit. All newborns with birth weight of <1,000 g admitted to the neonatal unit between January 1, 2010 and January 1, 2021were identified for inclusion in this study. Data were collected from the neonatal unit's NeoDATA Microsoft Access database for retrospective analysis. Information is entered into this database contemporaneously during care by the neonatal team. Patient charts and imaging reports were accessed when data were not recorded in the database and to confirm data accuracy for a selection of babies. Only ELBW newborns treated by the neonatal team were included and those with syndromes incompatible with life were excluded.

In line with previous researchers, we have used birth weight below the 10th centile for gestational age to define SGA.[7,27] Fenton Preterm Growth Charts were used[28,29] with birth weight plotted according to gestation (as per obstetric records) and sex. Babies were categorized as SGA or non-SGA (birth weight ≥10th centile). In this manuscript, the term "growth restricted" refers to an infant being SGA.

Neonatal particulars were collected for comparison between the two groups including birth weight, birth gestational age, sex, antenatal steroid administration (one or more doses), and inborn versus retrieved to TUH. The primary outcome variable was survival to discharge. Morbidity outcomes collected (and defined below) were the need for intubation and mechanical ventilation, total duration of respiratory support, CNLD, home oxygen, IVH, PVL, significant retinopathy of prematurity (ROP), NEC, sepsis (including all early and late-onset sepsis), time to full enteral feeds, and total duration of admission.

The need for intubation and positive pressure ventilation was considered an important surrogate marker for the severity of early respiratory disease. The definition of CNLD was any form of respiratory support (supplemental oxygen and/or ventilation) at 36-weeks postmenstrual age, as used by the Australian and New Zealand Neonatal Network (ANZNN).[30] As home oxygen is a significant outcome for families, it was included in analysis. All neonates born <32-weeks gestation routinely receive at least two head ultrasound scans at this center, including an early scan (in the first week of life) and a later scan (at approximately 5 weeks) for all surviving babies. IVH was classified using Papile's description.[31] All grades of IVH were considered significant in this study, and any evidence of PVL was noted. All babies had regular ophthalmology reviews commencing at 30 to 32 weeks corrected age or 28 to 35 days of life. ROP requiring treatment was considered significant. Any clinical, radiological, and/or surgical diagnoses of NEC of any grade[32] were noted as an outcome. Sepsis was defined as babies with a positive blood culture who were managed as infected by the treating team.

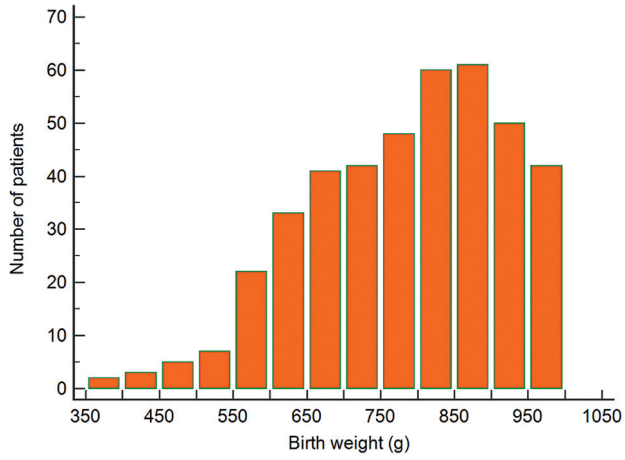
The Townsville Hospital and Health Service Human Research Ethics Committee (reference HREC/QTHS/74970) and

the Research Governance Officer provided ethical approval for this study, including a waiver of consent. Analysis was performed using MedCalc Version 18.11.6. Babies were separated into two groups: SGA versus non-SGA. Normally distributed variables are expressed as mean (standard deviation), nonnormally distributed data have been expressed as median (interquartile range), and categorical data are presented as a number and percentage. Chi-square analysis was performed for categorical variables and Mann–Whitney u-test for continuous variables, to determine significant associations between SGA and studied outcomes. Regression analysis was used to identify whether SGA was independently associated with mortality and each short-term morbidity outcome. Potential confounding factors included in the analysis were birth weight, gestational age, sex, antenatal corticosteroids, and birth at this center. The impact of being SGA on each categorical and continuous outcome has been reported as the odds ratio and beta coefficient, respectively, with 95% confidence interval. An association was considered significant when $p < 0.05$. The analysis was repeated for the subgroup of babies born less than 28-weeks gestation.

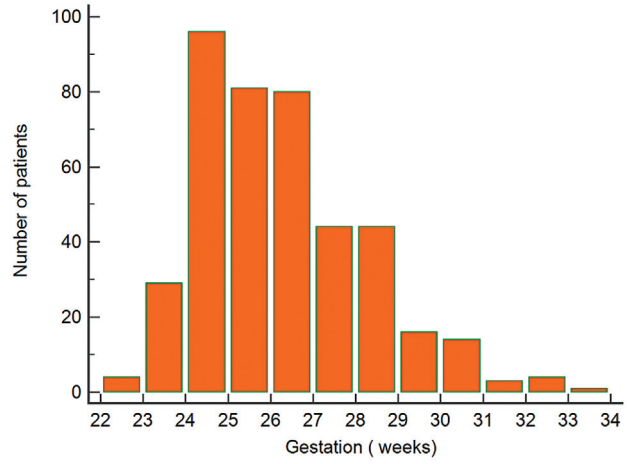
Results

A total of 461 ELBW babies met the study inclusion criteria, of whom 62 were SGA and 354 were not. Group demographics are shown in ►**Table 1**. The overall median birth weight was 800 (684 to 880) g (**Graph 1**) and median gestation 25.6 (24.5 to 27.2) weeks (**Graph 2**). There were comparable numbers of male and female babies in each group. Babies in the SGA group were significantly smaller than those in non-SGA group: 714 (580 to 850) versus 810 (700 to 885) g ($p < 0.001$). Conversely, the gestational age at birth for the SGA babies was higher: 28.6 (26.6 to 30.2) versus 25.4 (24.4 to 26.6) weeks ($p < 0.001$). Antenatal steroid administration of 95% of SGA and 89% of non-SGA babies was not significantly different ($p = 0.124$).

There was no significant difference in mortality when the two groups were compared, with 85% of SGA and 84% of non-SGA babies surviving until discharge (►**Table 2**). The most common causes of death in order of decreasing frequency were extreme prematurity, NEC, IVH, respiratory failure/CNLD, sepsis, hypoxic-ischaemic encephalopathy, multiorgan failure, intractable seizures, and one death from rhinovirus infection with neurological and respiratory comorbidities (►**Table 3**). Some had more than one cause attributed.



Graph 1 Birth weight.



Graph 2 Gestational age at birth.

Table 1 Population characteristics

Patient characteristics	SGA	Non-SGA	*p*-Value
Total babies	62	354	N/A
Birth weight (g) (median [IQR])	714 (580–850)	810 (700–885)	<0.001
Birth gestational age (weeks) (median [IQR])	28.6 (26.6–30.0)	25.4 (24.4–26.6)	<0.001
Sex Female (*n*, %) Male (*n*, %)	 27, 14% 35, 16%	 168, 86% 186, 84%	0.570
Antenatal corticosteroids (*n*, %)	59, 95%	314, 89%	0.124
Born at TUH (*n*, %)	51, 82%	285, 81%	0.747

Abbreviations: IQR, interquartile range; *n* = number to the abbreviation list; SGA, small for gestational age; TUH, Townsville University Hospital.

Table 2 Incidence of mortality and morbidity outcomes on univariate analysis

Outcomes	SGA	Non-SGA	*p*-Value
Survival to discharge (*n*, %)	53, 85%	296, 84%	0.712
Intubated for mechanical ventilation (*n*, %)	36, 61%	301, 86%	<0.001
Total duration respiratory support (hours) (median [IQR])	699.5 (121–1,171)	1,239 (758–1,628)	<0.001
Chronic neonatal lung disease¶	41, 69%	201, 57%	0.082
Home oxygen (*n*, %)	16, 26%	79, 22%	0.546
Intraventricular hemorrhage (*n*, %)	7, 11%	106, 30%	0.002
Periventricular leukomalacia (*n*, %)	0, 0%	10, 3%	0.181
Significant retinopathy of prematurity (*n*, %)	1, 2%	24, 8%	0.120
Necrotizing enterocolitis (*n*, %)	2, 3%	43, 12%	0.037
Sepsis (*n*, %)	15, 24%	99, 28%	0.773
Time to full enteral feeds (days) (median, IQR)	13.5 (10–20)	16 (11–25)	0.165
Total duration of admission (days) (median, IQR)	82 (60–114)	96 (75–119)	0.038

Abbreviations: IQR, interquartile range; *n* = number to the abbreviation list; SGA, small for gestational age.

Univariate analysis revealed significant associations between growth restriction and five morbidity outcomes (►**Table 2**) and in each instance the morbidity was less frequent in the SGA group. The outcomes less common in SGA babies were requirement for intubation and mechanical ventilation ($p < 0.001$), total duration of respiratory support ($p < 0.001$), IVH ($p = 0.002$), NEC ($p = 0.037$), and total duration of admission ($p = 0.038$). SGA babies also had a significantly shortened period of respiratory support, 699.5 (121 to 1,171) versus 1,239 (758 to 1,628) hours ($p < 0.001$). There were higher rates of CNLD in the SGA (69%) compared to the non-SGA (57%), but this was not statistically significant ($p = 0.082$). There was no difference in home oxygen prescription: SGA group 26% versus non-SGA group 22% ($p = 0.546$). SGA babies had a shorter median duration of admission by 14 days, but the range of admission duration was broad for both groups: SGA 82 (60 to 114) versus non-SGA 96 (75 to 119) days ($p = 0.038$). IVH was less common in the SGA (11 vs. 30%, $p = 0.002$). There was no significant difference in the rates of PVL (0 vs. 3%, $p = 0.181$). Significant ROP, sepsis, and time to full enteral feeds were similar between the SGA and non-SGA groups.

Regression analysis demonstrated no significant association between SGA and any outcome when correcting for birth weight, gestational age, sex, antenatal corticosteroid administration, and inborn status (►**Tables 4** and **5**). Higher birth weight, more advanced gestational age at birth, and receipt of antenatal steroids significantly improved survival (►**Table 6**). When the analysis was repeated for the subgroup of babies born at less than 28-weeks gestation, the results were similar (data not shown).

Discussion

Growth restriction was not an independent predictor of poor prognosis nor increased mortality for ELBW babies in this series. This supports the findings of recent papers showing no excess mortality for SGA babies born at moderate-to-late

Table 3 Causes of mortality

Cause of death	Total number of cases	Number SGA
Extreme prematurity	30	6
Necrotizing enterocolitis	14	2
Intraventricular hemorrhage/intracerebral bleed	12	0
Respiratory failure/chronic neonatal lung disease	10	6
Sepsis	8	0
Hypoxic ischemic encephalopathy/perinatal asphyxia	3	1
Multiple organ failure	2	0
Intractable seizures	1	0
Viral infection	1	0

Abbreviation: SGA, small for gestational age.
Note: Some babies had more than one cause attributed to their death.

Table 4 Impact of growth restriction (small for gestational age) on morbidity outcomes using multiple logistic regression analysis controlling for birth weight, gestational age, sex, antenatal steroids, and birth place

Outcome	OR	95 CI	*p*-Value
Intubated for mechanical ventilation	0.839	0.250–2.817	0.777
Chronic neonatal lung disease	0.607	0.238–1.552	0.297
Home oxygen	0.502	0.174–1.452	0.204
Intraventricular hemorrhage	1.774	0.533–5.907	0.350
Significant retinopathy of prematurity	3.755	0.258–54.611	0.333
Necrotizing enterocolitis	2.946	0.469–18.496	0.249
Sepsis	1.140	0.410–3.171	0.874

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 5 Impact of growth restriction (small for gestational age) on total duration of respiratory support, time to full enteral feeds and total duration of admission using multivariate linear regression analysis controlling for birth weight, gestational age, sex, antenatal steroids, and birth place

Outcome	β coefficient	95 CI	*p*-Value
Total duration respiratory support (hours)	15.377	−265.281–296.037	0.914
Time to full enteral feeds (days)	1.304	−5.322–7.930	0.699
Total duration of admission (days)	−2.692	−24.043–18.698	0.806

Abbreviation: CI, confidence interval.

Table 6 Factors associated with survival to discharge determined using multiple logistic regression analysis

Variables	OR	95% CI	*p*-Value
Birth weight	1.003	1.000–1.008	0.030
Gestational age at birth	1.522	1.121–2.068	0.007
Sex	1.442	0.792–2.625	0.231
Antenatal corticosteroids	3.005	1.328–6.799	0.008
Birth place (inborn vs. out born)	0.963	0.470–1.974	0.918
Growth restriction (SGA vs. non-SGA)	1.444	0.371–5.615	0.596

Abbreviations: CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

preterm gestations[21,22] and at <30-weeks gestation.[20] After correcting for confounders, there were no significant associations between growth restriction and any measure of neonatal morbidity in our study. On univariate analysis, SGA babies were significantly less likely to need intubation for mechanical ventilation and they had a shorter duration of respiratory support, shorter admission, less IVH, and less NEC. These associations were no longer significant after correcting for birth weight, gestational age, sex, antenatal steroids, and birthplace. Given that demographics between the two study groups were otherwise largely comparable, the most likely explanation is a protective effect from the comparatively advanced gestational age in the SGA group. With increasing gestational age, the proportion of growth-restricted babies increases. This effect has been described by Yamakawa et al although they ultimately concluded that growth-restricted extremely preterm babies had increased mortality and morbidity risks in their cohort.[18] After controlling for the relatively advanced gestational age of our SGA babies, the two groups had comparable outcomes for all neonatal morbidity measures.

The need for intubation and mechanical ventilation and duration of respiratory support was significantly reduced in SGA on univariate analysis. After controlling for known confounding factors, the SGA did not have an increased rate of severe early respiratory disease. Our findings cannot be compared directly to studies reporting lower or unchanged rates of RDS in growth-restricted preterm babies[12,13,15,16,20,22] as the definitions used are different and the patient weights and ages generally higher. Our findings complement previous literature that shows growth restriction is not independently associated with worse early respiratory status in preterm and small babies. The higher incidence of CNLD in the SGA was interesting, but not statistically significant in our population. Importantly, although we have defined CNLD as per the ANZNN, this outcome is analogous to bronchopulmonary dysplasia reported by other researchers. Given the consensus in the

literature that CNLD is more common in growth-restricted preterm babies,[11,13,14,16,23–25] it is possible that this association might reach statistical significance if we had a larger sample size. An alternative explanation would be that ELBW babies already have increased CNLD rates compared to the broader population of preterm babies, negating any additional risk from growth restriction in this group. The rate of CNLD in our series would support this alternative explanation. Several explanations for the increased risk of CNLD in growth-restricted babies have been proposed, and animal studies have shown physical changes in the lungs of growth-restricted animals (including altered surfactant quantity and activity, altered alveoli size and number, and interstitial thickening). Long-term implications of newborn growth restriction have been described including increased asthma, bronchiolitis, and worsened lung function at school age.[7,33] Although our data did not show a significant association between growth restriction and CNLD, further investigation of this is warranted. Parents should be reassured, however, that discharge on home oxygen is no more likely for a growth-restricted ELBW baby.

One plausible explanation for why growth restriction is not associated with worse outcomes in ELBW babies is that obstetric management is different for complicated pregnancies. The birth plan, including timing of delivery, is influenced by multiple factors including gestational age and expected fetal growth.[9] A growth-restricted baby is more likely to be semielectively delivered for faltering growth, or deteriorating maternal health, than a well-grown baby unexpectedly born preterm. Zeitlin et al have reported 81.8% of babies <10th centile for weight were born by caesarean section without labor, versus 30.1% of babies in the 50 to 75th centile for weight. The SGA babies had an increased rate of maternal hypertension/growth restriction indicated birth and less prolonged rupture of membranes/hemorrhage. Preterm infants from pregnancies complicated by maternal hypertension have a lower mortality rate.[11] Infection is a likely confounding factor in the birth of appropriately grown preterm babies, who may not have been receiving the intensive obstetric care of their growth-restricted counterparts. Mactier et al recommend a range of interventions to optimize the survival of extremely preterm babies including antenatal steroids, tocolysis, transfer to a tertiary obstetric center, magnesium sulfate, deferred cord clamping, intrapartum fetal heart rate monitoring, and consideration for caesarean section.[1] It is likely that closely monitored growth-restricted babies will have an increased opportunity to receive these interventions, impacting improved outcomes.

The hypothesis that a growth-restricted fetus will have an adaptive stress response, increasing endogenous corticosteroids, thereby accelerating their lung maturation has been proposed.[20,22] This hypothesis has come under intense scrutiny, with multiple authors arguing a lack of evidence.[7,33] Our findings suggest that growth restriction in the ELBW cohort is not associated with worsened early respiratory disease but provides no evidence to support this as the mechanism.

With a retrospective design, our study has intrinsic limitations. It has been assumed that correct diagnoses and recording of clinicians occurred at the time of treatment for each patient, and that this information has been accurately transferred into the neonatal database. In some instances, data were incomplete or missing, which could be explained by the transfer of babies back to referring hospitals or incomplete records. There are differences between authors in how SGA is defined and described,[27,34] which limits the external application of study findings. Zaw et al reported an increased incidence of growth restriction and associations between growth restriction and neonatal complications when fetal growth standards are utilized.[34] Contradictory evidence is provided by Garite et al who reported adverse outcomes were only associated with neonatally diagnosed SGA, rather than antenatally diagnosed growth restriction that was not confirmed after birth.[9] Our study design using postnatal categorization of SGA may underestimate any association between growth restriction and poorer outcomes. The total number of babies included in this study was only 461, despite 11 years of recruitment, and the study may not be powered to detect differences in infrequent outcomes. The scope of our study was limited to short-term outcomes. Previous research suggests that the implications of growth restriction may have longer-term effects,[7,17] and further study is required in this area.

Conclusion

Growth restriction is not associated with excess mortality nor short-term morbidity for ELBW babies at our center. This information should aid antenatal parental counseling for those in the difficult position of expecting an ELBW baby. Clinicians should not be unnecessarily pessimistic regarding survival when ELBW is complicated by growth restriction, and the neonatal journey will not necessarily be more complicated for these babies. This information can reliably inform shared decision-making for the care of SGA ELBW infants.

Conflict of Interest
None declared.

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