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ORIGINAL ARTICLE

Growth phenotypes of very low birth weight infants for prediction of neonatal outcomes from a Brazilian cohort: comparison with INTERGROWTH

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Abstract
Objective: To assess the predictive value of selected growth phenotypes for neonatal morbidity and mortality in preterm infants < 30 weeks and to compare them with INTERGROWTH-21st (IG21).
Method: Retrospective analysis of data from the Brazilian Neonatal Research Network (BNRN) database for very low birth weight (VLBW) at 20 public tertiary-care university hospitals. Outcome: the composite neonatal morbidity and mortality (CNMM) consisted of in-hospital death, oxygen use at 36 weeks, intraventricular hemorrhage grade 3 or 4, and Bell stage 2 or 3 necrotizing enterocolitis. Selected growth phenotypes: small-for-gestational-age (SGA) defined as being < 3rd (SGA3) or 10th (SGA10) percentiles of BW, and large-for-gestational-age (LGA) as being > 97th percentile of BW. Stunting as being < 3rd percentile of the length and wasting as being < 3rd percentile of BMI. Single and multiple log-binomial regression models were fitted to estimate the relative risks of CNMM, comparing them to IG21.
Results: 4,072 infants were included. The adjusted relative risks of CNMM associated with selected growth phenotypes were (BNRN/IG21): 1.45 (0.92−2.31)/1.60 (1.27−2.02) for SGA; 0.90 (0.55−1.47)/1.05 (0.55−1.99) for LGA; 1.65 (1.08−2.51)/1.58 (1.28−1.96) for stunting; and 1.48 (1.02−2.17) for wasting. Agreement between the two references was variable. The growth phenotypes had good specificity (>95%) and positive predictive value (70-90%), with poor sensitivity and low negative predictive value.
Conclusion: The BNRN phenotypes at birth differed markedly from the IG21 standard and showed poor accuracy in predicting adverse neonatal outcomes.
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Introduction

Preterm birth is the leading cause of perinatal mortality worldwide and is often a consequence of inadequate intrauterine conditions.[1] For decades, newborns have been categorized as small (SGA) or large (LGA) for gestational age (GA), stunted (short length for GA), or wasted (low weight for length or low body mass index [BMI] for GA).[2]

The INTERGROWTH-21st Newborn Size (IG21) standards for infants born at 33 weeks or less of GA were produced with only 408 neonates.[3] This fact limits the reliability and the usefulness of these standards for very low birth weight (VLBW, < 1500 g) preterm infants. In addition, local validation has been recommended by the authors of the IG21 standards and by others.[4−8]

Interestingly, no association has yet been demonstrated between a low weight-to-length (W/L) ratio at birth and major neonatal outcomes. Measures of neonatal morbidity are therefore essential for promoting epidemiological and health service research in order to improve infant health and reduce disparities at birth.[9]

The objective of this study was to assess the predictive value of selected growth phenotypes for a composite neonatal morbidity and mortality (CNMM) indicator in preterm infants < 30 weeks and to compare them with IG21.

Material and methods

Study population

This was a retrospective analysis of data collected prospectively as part of the Brazilian Neonatal Research Network (BNRN) database. The study was approved by a local institutional review board (IRB, CAAE #95153318.0.0000.5440, protocol #2.816.983/2018). Signed informed consent was waived because the database is anonymized.

The BNRN includes 20 public tertiary-care university hospitals from three different Brazilian regions: Northeast, Southeast, and South. These hospitals have collected data on VLBW infants since 1999. In 2014, the database migrated to REDCap (Research Electronic Data Capture),[10] with a real-time data quality check, and was then reviewed by supervisors before annual locking. All data are collected prospectively by each center and included in the database. Patients are followed up to the first outcome (death, discharge, transfer, or first birthday).

BNRN inborn or infants admitted to a BNRN center before 28 days of life with a BW of 401 to 1,499 g or GA between 22 weeks and 29 weeks plus 6 days were included in the database. All records from 2014 to 2019 were eligible; infants with GA < 22 or ≥ 30 weeks were not included in the analysis

because, according to the original inclusion criteria, BW was truncated at 400 and 1500 g at those GAs, respectively. Outborns, twins, infants with congenital infection or malformations, chromosomal abnormality, delivery room death, and missing data were excluded.

Database

The dataset contained selected maternal (demographic, clinical, gestational, and related to delivery) and newborn variables (weight and length at birth, GA, gender, Apgar scores, and main clinical outcomes). The duration of mechanical ventilation and neonatal intensive care unit (NICU) stay were adjusted for competing outcomes (death or transfer before extubation and/or discharge) by replacing the censored value with the largest value within each group plus one day.

Newborn anthropometric measures

The following ratios were calculated for all infants at birth: W/L ratio (kg/m), BMI (kg/m^2), and PI (kg/m^3).

Selected growth phenotypes (according to IG21, for GA and sex)

SGA was defined as being below the 3rd (SGA3) or 10th (SGA10) percentiles of BW, and LGA as being above the 97th percentile of BW. Stunting was defined as being below the 3rd percentile of the length and wasting as being below the 3rd percentile of BMI.

Composite neonatal morbidity and mortality (CNMM)

A composite of adverse perinatal outcomes commonly associated with preterm birth < 30 weeks (i.e., perinatal morbidity/mortality), was defined as the occurrence of any in-hospital death, oxygen use at 36 weeks corrected postnatal age, intraventricular hemorrhage grade 3 or 4, or Bell stage 2 or 3 necrotizing enterocolitis,[11] based on the recommendations of Webbe et al.[12]

Statistical analysis

All variables were summarized as means (standard deviations [SD]), medians (interquartile range [IQR]), or frequencies with percentages, as appropriate.

All infants were randomly allocated to one of two subsets: *training set* (70% of cases, n = 2,900) and *validation set* (30% of cases, n = 1,172) using the sample command of the R software. Infants born at less than 24 weeks of GA were assigned to the training set since the IG21 does not contain references for these GAs. The training set was used to calculate the corresponding centiles for weight, length, W/L ratio, BMI, and PI using fractional polynomial models. In all cases, the fractional polynomial smoothing technique by sex was applied. This new reference for preterm infants < 30 weeks that includes the 3rd, 10th, 50th, and 97th percentiles for selected growth phenotypes was named BNRN (Brazilian Neonatal Research Network).

The following analysis was calculated using the *validation set:*

Single and multiple *log-binomial regression models* were fitted to estimate the relative risks (RR) with 95% confidence intervals (95%CI) of CNMM associated with the growth phenotypes, comparing them to IG21. In the multivariate models, the RRs were adjusted for maternal (skin color, education, hypertension, diabetes, smoking, drinking alcohol, and delivery type) and newborn variables (5' Apgar score < 7).

The *agreement* between BNRN and IG21 growth phenotypes was estimated using the kappa coefficient. According to this coefficient, the strength of agreement was categorized as poor (< 0), slight (0−0.2), fair (0.21−0.4), moderate (0.41−0.6), substantial (0.61−0.8), or almost perfect (0.81−1.0).[13]

The *predictive accuracy* of the BNRN and IG21 growth phenotypes for CNMM was calculated using sensitivity, specificity, positive (PPV), and negative (NPV) predictive values. *Discrimination* of the models was assessed by the areas under the ROC curve (AUC), while *calibration* was assessed by the Hosmer-Lemeshow test (good calibration when p > 0.05). The Brier score was calculated to test de models' *accuracy* (where 0 indicates a perfect model and 0.25 is a non-informative model).[14]

The Stata 14.1 (StataCorp, College Station, USA), SAS 9.4 (SAS, Cary, USA), and R 3.2.4 with GAMLSS framework (https://cran.r-project.org/web/packages/gamlss/index.html) statistical packages were used. A significance level of 0.05 was adopted.

Results

Study population

A cohort of more than 4,000 preterm infants born from 2014 to 2019 was studied (Supplementary Fig. 1). The main differences in maternal and infants' characteristics between the training and validation set are depicted in Supplementary Table 1 and Supplementary Table 2. In short, the training and validation sets were very similar, as expected.

The infants were born to mostly young brown mothers with 8 −11 years of education with a high prevalence of high blood pressure and diabetes and who smoked and consumed alcohol. Most infants were born by cesarean section, at a mean GA of 191 (SD 12) days and with a mean BW of 912 (SD 265) g. The frequencies of abnormal growth phenotypes were very similar, as expected.

Main outcomes

The newborns exhibited significant morbidity (prolonged NICU stay, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and necrotizing enterocolitis) and a high mortality rate, characterizing a high-risk population (Supplementary Table 3). The frequency of CNMM was 58.6% for the whole cohort.

Smoothed centiles for BW, length, W/L ratio, BMI, and PI by sex and GA according to the BNRN reference are shown in Table 1.

Table 2 depicts the comparison and agreement in the frequencies of the selected growth phenotypes between BNRN and IG21. It can be observed that, while the frequencies of all BNRN phenotypes were within the expected limits, those of IG-21 exceeded three to four times the expected values for SGA3, SGA10, and stunting. The opposite was observed

Table 1 Smoothed centiles for birth weight, length, weight-to-length (W/L) ratio, body-mass index (kg/m^2) and ponderal index (PI), by sex and gestational age (GA), from the Brazilian Neonatal Research Network (2014 — 2019, n = 2900).

GA	Weight (kg)							
	Boys				Girls			
	P3	P10	P50	P97	P3	P10	P50	P97
22	0.41	0.47	0.58	0.72	0.40	0.45	0.54	0.66
23	0.40	0.47	0.61	0.79	0.40	0.46	0.58	0.74
24	0.41	0.50	0.67	0.88	0.41	0.48	0.63	0.84
25	0.44	0.55	0.75	1.01	0.42	0.51	0.70	0.95
26	0.48	0.61	0.85	1.14	0.45	0.55	0.78	1.09
27	0.53	0.67	0.95	1.29	0.48	0.61	0.88	1.24
28	0.58	0.75	1.06	1.44	0.53	0.68	0.99	1.41
29	0.64	0.82	1.17	1.60	0.60	0.77	1.13	1.61
GA	Length (cm)							
	Boys				Girls			
	P3	P10	P50	P97	P3	P10	P50	P97
22	24.36	26.21	29.32	32.89	24.39	25.91	28.56	31.70
23	24.95	26.90	30.19	33.95	24.92	26.60	29.53	33.00
24	25.71	27.75	31.19	35.13	25.52	27.34	30.54	34.32
25	26.57	28.69	32.28	36.39	26.18	28.15	31.61	35.69
26	27.50	29.70	33.42	37.69	26.93	29.03	32.73	37.10
27	28.47	30.75	34.59	39.00	27.76	30.00	33.92	38.57
28	29.46	31.81	35.77	40.31	28.68	31.04	35.19	40.09
29	30.46	32.87	36.94	41.60	29.70	32.18	36.53	41.68
GA	Weight-to-length ratio (kg/m)							
	Boys				Girls			
	P3	P10	P50	P97	P3	P10	P50	P97
22	1.50	1.65	1.89	2.28	1.48	1.63	1.97	2.40
23	1.49	1.67	1.97	2.45	1.48	1.65	2.05	2.55
24	1.51	1.74	2.07	2.65	1.52	1.69	2.18	2.76
25	1.55	1.84	2.21	2.88	1.59	1.76	2.34	2.98
26	1.61	1.97	2.37	3.14	1.69	1.86	2.52	3.24
27	1.70	2.11	2.57	3.44	1.80	1.98	2.72	3.52
28	1.83	2.27	2.80	3.77	1.94	2.14	2.94	3.80
29	2.00	2.44	3.06	4.15	2.08	2.34	3.16	4.10
GA	Body-mass index (kg/m^2)							
	Boys				Girls			
	P3	P10	P50	P97	P3	P10	P50	P97
22	4.93	5.53	6.57	8.50	5.33	5.77	6.66	8.51
23	5.06	5.67	6.76	8.76	5.18	5.67	6.63	8.63
24	5.20	5.84	6.97	9.05	5.17	5.69	6.72	8.88
25	5.37	6.04	7.21	9.38	5.26	5.81	6.91	9.20
26	5.56	6.26	7.48	9.74	5.43	6.01	7.18	9.60
27	5.78	6.51	7.79	10.14	5.67	6.28	7.51	10.05
28	6.03	6.79	8.13	10.59	5.96	6.60	7.89	10.55
29	6.31	7.10	8.50	11.09	6.30	6.97	8.31	11.08
GA	Ponderal index (kg/m^3)							
	Boys				Girls			
	P3	P10	P50	P97	P3	P10	P50	P97
22	17.97	19.50	24.02	35.11	20.90	21.97	25.94	36.95
23	9.73	11.48	16.66	29.36	10.77	11.99	16.57	29.25
24	5.03	7.06	13.06	27.80	4.96	6.39	11.74	26.53
25	3.29	5.68	12.73	30.04	2.73	4.41	10.74	28.23
26	3.79	6.64	15.03	35.65	3.13	5.16	12.74	33.72
27	5.71	9.14	19.28	44.18	5.10	7.57	16.80	42.33
28	8.04	12.25	24.67	55.17	7.40	10.44	21.84	53.38
29	9.65	14.89	30.34	68.28	8.59	12.41	26.71	66.30

Table 2 Comparison and agreement of selected growth phenotypes by BNRN and IG21 (n = 1172).

Growth phenotype	BNRN	IG21	Kappa (95%CI)
Weight-for-GA			
< 3rd centile (SGA)	23 (2.0)	111 (9.5)	0.32 (0.22; 0.42)[a]
< 10th centile (SGA)	126 (10.8)	205 (17.5)	0.72 (0.66; 0.77)[b]
> 97th centile (LGA)	34 (2.9)	16 (1.4)	0.63 (0.48; 0.79)[b]
Length-for-GA			
< 3rd centile (stunted)	27 (2.4)	143 (12.5)	0.28 (0.20; 0.38)[a]
W/L-for-GA			
< 3rd centile	29 (2.5)	9 (0.8)	0.47 (0.27; 0.66)[c]
BMI-for-GA			
< 3rd centile (wasted)	36 (3.2)	N/A	–
PI-for-GA			
< 3rd centile	28 (2.5)	N/A	–

BNRN, Brazilian Neonatal Research Network; IG21, Intergrowth 21st; CI, confidence interval; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age; W/L, weight-to-length ratio (kg/m); BMI body-mass index (kg/m^2); PI, ponderal index (kg/m^3); N/A, not available.
Kappa: [a] fair agreement, [b] substantial agreement, [c] moderate agreement.
Data are expressed as count (percentage).

for LGA and W/L-for-GA. This agrees with the kappa analysis in which agreement between the two references was substantial only for SGA10 and LGA, while a moderate agreement was found for W/L ratio < 3rd percentile and fair agreement for SGA3 and stunting.

Risk of CNMM associated with phenotypes

The adjusted relative risk (aRR) of CNMM associated with BNRN phenotypes (Table 3) showed a higher aRR for stunting and wasting, but a lower aRR for SGA 3 and SGA 10 compared to IG21. No differences were observed for SGA10 or LGA.

Predictive ability, discrimination, calibration, and accuracy of the models

All conditions had an excellent specificity (> 95%) and a good PPV (70-90%), except for LGA, but poor sensitivity and NPV. The highest PPV was observed for W/L ratio < 3rd percentile according to BNRN (93.1%), followed by stunting according to BNRN (92.6%) (Table 4).

The analysis of discrimination, calibration, and accuracy (Brier scores) of the model for CNMM is presented in Supplementary Table 4. Briefly, for both BNRN and IG21, the AUCs were only marginally higher than 0.5 (low discrimination), the Brier scores were very close to 0.25 (not informative), and the Hosmer-Lemeshow test indicated good calibration.

Table 3 Crude and adjusted relative risks of the composite neonatal morbidity and mortality (CNMM) among selected growth phenotypes by BNRN and IG21 (n = 1172).

Growth phenotype	Univariate		Multivariate[a]	
	RR-BNRN (95%CI)	RR-IG21(95%CI)	aRR-BNRN (95%CI)	aRR-IG21(95%CI)
Weight-for-GA				
< 3rd centile (SGA)	1.55 (1.32; 1.83)	1.59 (1.45; 1.76)	1,45 (0,92; 2,31)	1,60 (1,27; 2,02)
< 10th centile (SGA)	1.63 (1.49; 1.79)	1.60 (1.46; 1.75)	1,62 (1,29; 2,03)	1,64 (1,34; 1,99)
> 97th centile (LGA)	0.93 (0.68; 1.29)	1.10 (0.75; 1.62)	0,90 (0,55; 1,47)	1,05 (0,55; 1,99)
Length-for-GA				
< 3rd centile (stunted)	1.68 (1.50; 1.90)	1.60 (1.45; 176)	1,65 (1,08; 2,51)	1.58 (1.28; 1.96)
W/L-for-GA				
< 3rd centile	1.70 (1.52; 1.90)	1.40 (0.98; 1.98)	1,63 (1,09; 2,43)	1,32 (0,62; 2,80)
BMI-for-GA				
< 3rd centile (wasted)	1.46 (1.23; 1.73)	N/A	1,48 (1,02; 2,17)	N/A
PI-for-GA				
< 3rd centile	1.55 (1.32; 1.83)	N/A	1,55 (1,02; 2,34)	N/A

BNRN, Brazilian Neonatal Research Network; IG21, Intergrowth 21st; RR, crude relative risk; CI, confidence interval; aRR, adjusted relative risk; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age; W/L, weight-to-length ratio (kg/m); BMI, body-mass index (kg/m^2); PI, ponderal index (kg/m^3); N/A, not available.
[a] The aRR was adjusted for maternal variables (skin color, education, hypertension, diabetes, smoking, drinking alcohol, and delivery type) and newborn variables (Apgar 5' < 7).

Table 4 Prognostic accuracy of selected growth phenotypes by BNRN and IG21 for the composite neonatal morbidity and mortality (CNMM) (n = 1172).

Growth phenotype	BNRN				IG21			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Weight-for-GA								
<3rd centile (SGA)	3,0%	99,4%	87,0%	44,0%	14,3%	96,9%	85,6%	46,5%
<10th centile (SGA)	16,4%	96,7%	86,5%	47,0%	25,3%	92,7%	82,0%	48,8%
>97th centile (LGA)	2,7%	96,9%	52,9%	43,3%	1,5%	98,8%	62,5%	43,5%
Length-for-GA								
<3rd centile (stunted)	3,9%	99,6%	92,6%	45,0%	18,7%	95,2%	83,2%	48,0%
W/L-for-GA								
<3rd centile	4,2%	99,6%	93,1%	45,1%	1,1%	99,6%	77,8%	44,3%
BMI-for-GA								
<3rd centile (wasted)	4,5%	98,6%	80,6%	44,9%	N/A	N/A	N/A	N/A
PI-for-GA								
<3rd centile	3,8%	99,2%	85,7%	44,9%	N/A	N/A	N/A	N/A

BNRN, Brazilian Neonatal Research Network; IG21, Intergrowth 21st; GA, gestational age; SGA, small for gestational age; LGA, large for gestational age; W/L, weight-to-length ratio (kg/m); BMI, body-mass index (kg/m^2); PI, ponderal index (kg/m^3); N/A, not available.

Discussion

Main findings

This study evaluated several anthropometric measures of preterm infants < 30 weeks at birth and the predictive value of selected growth phenotypes for neonatal morbidity and mortality. In this study, a large cohort of more than 4,000 preterm infants < 30 weeks were randomly allocated to a training or a validation set and percentiles for BW, length, W/L ratio, BMI, and PI by sex and GA were calculated. The results showed that: i) the frequency of all BNRN phenotypes was within the expected limits; ii) the BNRN reference yielded higher aRR than IG21 for length-for-GA and W/L-for-GA, while the opposite was observed for SGA3; iii) both BNRN and IG21 were poor predictors of adverse neonatal outcomes; iv) finally, CNMM showed good calibration but low discrimination.

Characteristics

The apparent differences between BNRN and IG21 can be explained by the present tertiary site cohort that included mothers with a higher risk profile including a high prevalence of hypertension and diabetes, a population not included in the IG21 Project. Similar percentages were found in a study conducted in São Paulo, Brazil (27.4% with hypertension and 17.3% with diabetes),[15] supporting the idea that preterm birth is associated with early abnormal obstetric conditions. Also, this pattern of high-risk mothers is similar to that of the NEOCOSUR South American Network.[16] This sicker population of mothers suggests that BNRN infants were exposed to a suboptimal intrauterine environment and, possibly, to fetal growth restriction (FGR), one of the most important risk factors associated with preterm birth.[1]

Phenotypes according to BNRM and IG21 criteria

Because the birthweight distribution of the BNRM chart was right-shifted (Supplementary Fig. 2), whereas the distribution of the INTERGROWTH chart was shifted to systematically lower values[3] the proportion of BNRN live births classified as SGA by the IG21 criteria was greater than that identified by the BNRN, while the proportion classified as LGA was half under IG21 criteria, according to a previous study conducted in Canada.[7] Importantly, some infants with low or high percentile values are healthy infants who are simply genetically smaller or larger.[17] Comparing the normative IG21 standard, this overall picture suggests that BNRN live births have low rates of growth restriction and high rates of excess growth (Table 2).

Reason for the discrepancies between BNRN and IG21

The discrepancy in the W/L ratio between the BNRN and IG21 populations may be explained by the fact that the latter included mothers of widely varying size (particularly height) and few females with BW in the lower 50th percentile range, which could have led to the greater W/L ratios in the BNRN reference.[18] The kappa agreement was substantial only for SGA10 and LGA.

Selected abnormal growth phenotypes and the risks of CNMM

The risks of CNMM were only slightly different when either BNRN or IG21 was used. Overall, having an abnormal growth phenotype was associated with a 1.5- to 1.7-fold increase in the likelihood of CNMM. BNRN yielded statistically significantly higher aRR than IG21 for stunting and wasting, suggesting that they could have suffered fetal growth restriction due to the high frequency of morbidity during pregnancy. The most important difference was that a W/L ratio < 3rd percentile was significantly associated with CNMM when BNRN but not when IG21 was used, attributable to the prescriptive design of the INTERGROWTH-21st Project.[4]

Differences in neonatal morbidity and mortality rates within centile categories of BNRN and IG21 may be due to differences in the prevalence of phenotypes (Table 2). Although SGA-3 live births identified by the IG21 criteria

represent more severely growth-restricted infants (9.5%), their CNMM risk was similar to that of SGA-3 infants identified by the BNRN criteria (Table 3). This agrees with a recent study in which only prenatal FGR cases with a BW below the 3rd percentile employing the IG21 were at higher risk of adverse postnatal outcomes.[19]

The prognostic value of the selected abnormal growth phenotypes for CNMM showed poor sensitivity and NPV. As a result, many infants would be categorized as false negatives for CNMM. Infants with any of the phenotypes would be more likely to develop CNMM (Table 3), but infants classified as "normal" would still have a 50% risk of developing CNMM.

Comparison with existing literature

The present results are consistent with previous studies. In the RADIUS trial, the abilities of the INTERGROWTH chart to predict adverse perinatal outcomes were similarly poor (AUCs between 0.50 and 0.59).[20] In a study of 3437 fetuses of African-American women, the INTERGROWTH chart poorly detected composite adverse perinatal outcomes at the 10th centile (e.g., AUC 0.55), with a sensitivity of only 22%.[21] Furthermore, in a cohort of 1054 women from the USA, the 10th centile on a customized standard and the INTERGROWTH standard performed poorly to identify adverse neonatal outcomes (AUC 0.51).[19] Finally, in an Argentinean study the sensitivity, positive predictive values, and Youden Index of phenotypes for adverse perinatal outcomes were very low.[22]

In a recent study from Canada the ability of the INTERGROWTH, WHO, and Hadlock charts to predict neonatal risk was poor (AUC = 0.54, for each chart), similar to the present study. At the traditional cut-point of the 10th centile, the sensitivity of the INTERGROWTH chart was 11%, and the positive predictive value was 15%, very low compared with the present study.[23]

Growth phenotypes as screening tools

Although selected growth phenotypes were significantly associated with poor outcomes, they are not useful as screening tools for identifying infants at higher risk using either BNRN or IG21. One possible explanation is that the occurrence of poor outcomes is much more related to postnatal conditions and quality of care than to intrauterine conditions. Another explanation is the choice of the components of the CNMM. Ideally, to be useful as an indicator of neonatal morbidity and mortality, the threshold must have maximum sensitivity but not at the expense of specificity (to minimize unnecessary testing of neonates). A systematic review identified 17 composite neonatal morbidity indicators; however, the heterogeneity of the components and insufficient validation limit their use for benchmarking and meta-analyses.[24]

Strengths and limitations

This study has several *strengths*. To our knowledge, this is the first study conducted in Brazil that developed a reference chart of several anthropometric measures at birth for preterm infants < 30 weeks and assess the predictive ability of selected growth phenotypes for neonatal morbidity and mortality. Another strength is the high quality of the data, which were prospectively collected and audited. In addition, BRNN is a cohort of preterm (< 30 weeks) and very low birth weight (< 1500 g) infants, larger than any other published cohort examining the association between size at birth and perinatal outcomes with validated data from three Brazilian regions collected during routine prenatal care, representing a huge proportion of the Brazilian territory.

On the other hand, the present findings are *limited* by the selected cohort of preterm infants < 30 weeks that were admitted to NICUs of tertiary-care university hospitals, a population that is at higher risk. In addition, since the authors' analysis included 20 public tertiary-care university hospitals from three different Brazilian regions, potential errors concerning gestational age estimates would have affected birth weight-for-gestational age centiles under both the INTERGROWTH and BNRN criteria. Also, there may have been variations in management at each site which could have impacted neonatal morbidity and mortality.

Another limitation is that the W/L ratio quantifies disproportionality between weight and length. As a result, growth restriction or excess resulting in insufficient or excessive weight and length growth may not be correctly identified by the W/L ratio or other weight-for-length ratios.[25] In addition, some important variables such as prenatal steroids, which may be linked to better perinatal outcomes, were not included in this analysis.[26] Finally, there is no gold standard outcome that defines risks associated with preterm birth < 30 weeks;[23] therefore, caution is necessary when generalizing these conclusions to other settings and countries.

The IG21 fetal growth standards might not represent the intrauterine growth of Brazilian fetuses, as does the BNRN cross-sectional growth reference because the latter included a 24 times higher number of preterm infants at less than 30 weeks GA (4,072 infants) and relatively equal numbers of male and female infants.

Conclusions

The BNRN phenotypes at birth differed markedly from the IG21 standards and showed poor accuracy in predicting adverse neonatal outcomes. Taken together, more studies of growth phenotypes in preterm infants < 30 weeks associated with CNMM are still needed before they can be introduced and implemented in clinical practice.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jped.2022.07.007.

References

1. Barros FC, Papageorghiou AT, Victora CG, Noble JA, Pang R, Iams J, et al. The distribution of clinical phenotypes of preterm birth syndrome. JAMA Pediatr. 2015;169:220—9.
2. Victora CG, Villar J, Barros FC, Ismail LC, Chumlea C, Papageorghiou AT, et al. Anthropometric characterization of impaired fetal growth. JAMA Pediatr. 2015;169:e151431.
3. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTERGROWTH-21st very preterm size at birth reference charts. Lancet. 2016;387:844—5.
4. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384:857—68.
5. Pritchard N, Lindquist A, Siqueira ID, Walker SP, Permezel M. INTERGROWTH-21st compared with GROW customized centiles in the detection of adverse perinatal outcomes at term. J Matern Neonatal Med. 2020;33:961—6.
6. Cole TJ, Williams AF, Wright CM. Revised birth centiles for weight, length and head circumference in the UK-WHO growth charts. Ann Hum Biol. 2011;38:7—11.
7. Liu S, Metcalfe A, León JA, Sauve R, Kramer MS, Joseph KS. Evaluation of the INTERGROWTH-21st project newborn standard for use in Canada. PLoS One. 2017;12:e0172910.
8. Godeluck A, Gérardin P, Lenclume V, Mussard C, Robillard PY, Sampériz S, et al. Mortality and severe morbidity of very preterm infants: comparison of two French cohort studies. BMC Pediatr. 2019;19:360—9.
9. Huang J, Zhu T, Qu Y, Mu D. Prenatal, perinatal and neonatal risk factors for intellectual disability: a systemic review and meta-analysis. PLoS One. 2016;11:e0153655.
10. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377—81.
11. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Ann Surg. 1978;187:1—7.
12. Webbe JW, Duffy JM, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105:425—31.
13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159—74.
14. Rufibach K. Use of Brier score to assess binary predictions. J Clin Epidemiol. 2010;63:938—9.
15. Nascente LM, Grandi C, Aragon DC, Cardoso VC. Placental measurements and their association with birth weight in a Brazilian cohort. Rev Bras Epidemiol. 2020;23:e200004.
16. D'Apremont I, Marshall G, Musalem C, Mariani G, Musante G, Bancalari A, et al. Trends in perinatal practices and neonatal outcomes of very low birth weight infants during a 16-year Period at NEOCOSUR Centers. J Pediatr. 2020;225:44—50.
17. Villar J, Restrepo-Méndez MC, McGready R, Barros FC, Victora CG, Munim S, et al. Association between preterm-birth phenotypes and differential morbidity, growth, and neurodevelopment at age 2 years: results from the INTERBIO-21st newborn study. JAMA Pediatr. 2021;175:483—93.
18. Hay Jr. WW. The importance of using local populations to assess fetal and preterm infant growth. J Pediatr (Rio J). 2021;97:582—4.
19. Nwabuobi C, Odibo L, Camisasca-Lopina H, Leavitt K, Tuuli M, Odibo AO. Comparing INTERGROWTH-21st century and Hadlock growth standards to predict small for gestational age and short-term neonatal outcomes. J Matern Neonatal Med. 2020;33:1906—12.
20. Hua X, Shen M, Reddy UM, Buck Louis G, Souza JP, Gülmezoglu AM, et al. Comparison of the INTERGROWTH-21st, National Institute of Child Health and Human Development, and WHO fetal growth standards. Int J Gynecol Obstet. 2018;143:156—63.
21. Kabiri D, Romero R, Gudicha DW, Hernandez-Andrade E, Pacora P, Benshalom-Tirosh N, et al. Prediction of adverse perinatal outcome by fetal biometry: comparison of customized and population-based standards. Ultrasound Obstet Gynecol. 2020;55:177—88.
22. Grandi C, Del Pino M, Casale Aragon D, Dos Santos Rodrigues L, Cunha Cardoso V. Evaluation of the INTERGROWTH-21st project newborn standard for neonatal phenotypes and neonatal morbidity and mortality. Rev Fac Cien Med Univ Nac Cordoba. 2020;77:86—93.
23. Liauw J, Mayer C, Albert A, Fernandez A, Hutcheon JA. Which chart and which cut-point: deciding on the INTERGROWTH, World Health Organization, or Hadlock fetal growth chart. BMC Pregnancy Childbirth. 2022;22:25—36.
24. Lebreton E, Crenn-Hébert C, Menguy C, Howell EA, Gould JB, Dechartres A, et al. Composite neonatal morbidity indicators using hospital discharge data: A systematic review. Paediatr Perinat Epidemiol. 2020;34:350—65.
25. Olsen IE, Louise Lawson M, Nicole Ferguson A, Cantrell R, Grabich SC, Zemel BS, et al. BMI curves for preterm infants. Pediatrics. 2015;135:e572—81.
26. Grandi C, González A, Zubizarreta J. Red Neonatal NEOCOSUR. Perinatal factors associated with neonatal mortality in very low birth weight infants: a multicenter study. Arch Argent Pediatr. 2016;114:426—33.