RESEARCH ARTICLE

Customized compared to population-based centiles for detecting term small for gestational age infants in Greece

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Abstract

Background: Applying customized centiles may improve the accuracy of detecting small for gestational age (SGA) infants; however, the evidence is inconclusive whether adjusted centiles are more sensitive in identifying infants at increased risk of morbidity. We aimed to examine the validity of customized centiles in a Greek cohort and evaluate their performance compared to population-based centiles in predicting infants at risk of increased morbidity.

Methods: We prospectively recorded the neonatal and maternal characteristics of singleton, low-risk, term infants over a year. Infants were defined as SGA if their birth weight was under the tenth centile, classified both by population-based centiles and customized centiles, adjusted for maternal and innate factors. We performed a comparative analysis utilizing linear regression analysis and calculating the receiver operating characteristics (ROC) curves.

Results: Overall 657 infants were identified. Population-based centiles detected 42 (6 %) SGA infants, while customized centiles 80 (12 %). Perinatal morbidity was associated with an odds ratio of 1.02 with customized centiles [95 % confidence interval (CI): 1.01-1.04] and with an odds ratio of 1.02 with population-based centiles (95 % CI: 1.02-1.02). In predicting perinatal morbidity, no significant difference was detected between customized centiles [area under the ROC curve 0.773 (95 % CI: 0.699-0.847)] and population-based centiles [area under the ROC curve 0.737 (95 % CI: 0.662-0.813)] (p =0.272).

Conclusions: Customized centiles provided increased accuracy in comparison to the population-based centiles in detecting SGA term infants. However, customized centiles had no better impact on predicting a poor perinatal outcome. HIPPOKRATIA 2020, 24(3): 133-137.

Keywords: Customized centiles, population-based centiles, small for gestational age infants

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Introduction

Infants born small for gestational age (SGA) represent a heterogeneous group that consists of growth-restricted and potentially vulnerable infants and constitutionally but otherwise healthy infants[1]. Whereas growth-restricted infants do not reach their genetic growth potential, constitutional SGA infants represent the one end of the usual spectrum of size[1]. Regarding SGA infants, the most popular definition is based on birth weight below the tenth percentile, adjusted for gender and gestational age using appropriate reference data[2]. The population-based centiles that have been traditionally used are adjusted for gender and gestational age but do not account for any other growth modifying factors[3]. Customized models, on the contrary, have been adjusted for maternal and innate factors such as maternal weight, height, ethnicity, or parity[4].

The customized charts have been introduced into the clinical practice in several countries to assess the neonatal growth in the term and preterm population so far[1,4-10]. Studies have suggested that customized centiles may be more precise in detecting SGA infants at increased risk of perinatal morbidity than population-based centiles[1,4-10]. However, the theoretical advantage of customization may be of limited value when applied in term infants. Furthermore, evidence suggests that data regarding the prediction of perinatal morbidity may have been overestimated[11,12]. Hence, the evidence about the validity of customized growth centiles compared to population-based centiles is scarce to draw any conclusions[13,14].

The current study aimed to evaluate whether customized centiles applied in a population of term infants in Greece would be better than population-based centiles in detecting SGA infants. Also, we aimed to evaluate the performance of customized compared to population-based centiles in predicting SGA infants at risk of increased perinatal morbidity.

Methods

The study was conducted from January 2014 to January 2015 in a tertiary Neonatal Unit of a University

Hospital. During the study period, we prospectively enrolled all Greek origin infants born at term, at 37 to 42 weeks' gestation, by a singleton, low-risk pregnancy as described below. We excluded infants who were of non-Greek origin, part of multiple births, delivered preterm, whose pregnancy had been complicated with congenital anomalies, or terminated for maternal or fetal reasons to consort with the methodology described in the previous studies[4,6,9,15]. The Ethical Committee of the Papageorgiou Hospital approved the study (decision No 895) and data were anonymously recorded.

For each infant, we recorded the gestation, the gender, the birth weight measured in the delivery room with an electronic scale, the height, and the head circumference measured within the first 24 hours of age. We also recorded the maternal characteristics, including the ethnicity, the age, the weight as measured at the first antenatal visit, the weight gain during the pregnancy as extracted by the initial and the last trimester weight, the height based on maternal recall. The body mass index (BMI) was extracted from the weight and height according to the formula $BMI = weight/height^2$ (kg/cm^2). We recorded the parity, determined the gestational age by ultrasound examination during pregnancy's first trimester and factors associated with low birth weight, such as gestational diabetes and hypertension. Finally, the computed perinatal morbidity was defined by the need for admission to the nursery due to hypothermia, hypoglycemia, or feeding difficulty.

Infants with a birth weight below the tenth centile were defined as SGA[16]. The population-based birthweight centiles were based on the revised Fenton's growth charts adjusted for gestation and gender[16]. We used the customized birth weight centiles based on the Gestation Related Optimal Weight centile calculator (available at www.gestation.net). The bulk calculator that has been developed by Gardosi et al[15,17] utilizes the maternal height, weight at the first antenatal visit, parity, and ethnicity, in a regression analysis model to derive the adjusted for the gender optimal average weight of the fetus at 40 weeks. Additionally, we used Hadlock's formula to calculate the coefficient of variation and derive the growth centiles at each gestation[18]. Therefore, the following groups were identified: customised only SGA, population only SGA, customised and population SGA, and non-SGA infants.

Statistical analysis

The data were analyzed using the IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). We calculated descriptive statistics for maternal and neonatal characteristics. Continuous variables are presented as means ± standard deviation, while categorical variables as numbers with percentages in brackets. The Kolmogorov-Smirnov test assessed the normality of continuous variables' distributions. We performed comparisons of continuous variables utilizing one-way ANOVA with Bonferroni posthoc analysis. We utilized the Pearson's chi-square test or Fisher's exact test to compare categorical variables, as appropriate. The linear regression analysis was conducted to evaluate the association of population-based and customized centile charts (continuous variables) with perinatal morbidity. We investigated for each chart how accurately categories of less than the tenth centile (SGA infants) detected infants with perinatal morbidity by calculating the sensitivity and the specificity. The receiver operating characteristic (ROC) curve analyses were conducted, estimating the area under the curve to determine which model better predicted perinatal morbidity. All performed tests were two-sided, and we considered statistically significant p values less than 0.05 (alpha 0.05).

Results

During the study period, a total of 657 infants of term, low-risk pregnancies were identified. Customised only SGA were 38 (6 %) infants, population only SGA was none, customised and population SGA were 42 (6 %) infants, and non-SGA infants were 577 (88 %) infants. Using the customized centiles, a total of 80 (12 %) SGA infants were detected (42 of whom had been also detected with the population centiles), whereas using the population centiles 42 (6 %) SGA were identified (all of whom had been also detected with the customized centiles).

The maternal characteristics of the study population and the infants classified as SGA by either method compared to non-SGA infants are depicted in Table 1. Maternal BMI was normal in 67 %, and pregnancy was nulliparous in 45 % of the cases. No significant differences were found in maternal characteristics between customized SGA, both customized and population-based SGA, and non-SGA infants (Table 1).

Overall, the mean gestation of infants was 38.3 weeks, and the mean birth weight 3,152 grams. Neonatal morbidity was significantly higher in SGA than non-SGA infants, classified by either centile. The overall morbidity was estimated at 8 %, based on the predefined criteria (Table 2).

Perinatal morbidity was associated with an odds ratio of 1.02 with customized centiles [95 % confidence interval (CI): 1.01-1.04] and with an odds ratio of 1.02 with population-based centiles (95 % CI: 1.02-1.02) per centile decrease of birth weight. The accuracy of population-based and customized centiles in recognizing infants with perinatal morbidity is depicted in Table 3. At less than the tenth centile threshold, the sensitivity and specificity were calculated as 0.36 and 0.96 for customized centiles, while 0.30 and 0.93 for population centiles, respectively. Finally, model discrimination for both customized and population-based centiles is depicted in Figure 1. The area under the ROC curve was 0.773 (95 % CI: 0.699-0.847) for customized centiles and 0.737 (95 % CI: 0.662-0.813) for population-based centiles, with no significance detected between the ROC curves (p =0.272).

Discussion

The current study's findings suggest that the utilization of customized instead of population-based centiles may

Table 1: Maternal characteristics of the entire study population, the customised only small for gestational age (SGA), the customised and population SGA, and the non-SGA infants.

	Study population (n = 657)	Customized only SGA (n = 38)	Customized and Population-based SGA (n = 42)	Non-SGA (n = 577)	p
Maternal age (years)	30.9 ± 5.8	30.1 ± 6.1	30.2 ± 5.8	31 ± 5.8	0.481
Maternal weight (kg)	67.2 ± 15.5	65 ± 16.5	69.4 ± 27.2	67.1 ± 14.4	0.529
Maternal height (cm)	165.1 ± 6.4	165.5 ± 6.3	163.9 ± 5.1	165.2 ± 6.4	0.505
Maternal BMI	24.6 ± 5.7	23.7 ± 5.8	25.9 ± 11.2	24.6 ± 5.7	0.270
Maternal BMI category					0.160
<18.5	21 (3)	4 (10)	2 (5)	15 (3)	
18.5-24.9	436 (67)	26 (70)	28 (67)	383 (66)	
25-29.9	125 (19)	4 (10)	7 (17)	114 (20)	
>30	75 (11)	4 (10)	5 (11)	66 (11)	
Weight gain during pregnancy, kg	13.9 ± 10.3	15.6 ± 28.2	12.4 ± 5.8	13.9 ± 8.3	0.464
Parity					0.131
Nulliparous	293 (45)	15 (40)	21 (50)	257 (45)	
1	256 (39)	18 (47)	10 (24)	228 (40)	
2	77 (12)	5 (13)	7 (17)	65 (11)	
3+	31 (4)	-	4 (9)	27 (4)	
Gestational diabetes	35 (5)	3 (8)	4 (10)	28 (5)	0.365
Hypertension	15 (2)	-	2 (5)	13 (2)	0.424

Continuous variables are expressed as means ± standard and p value is of one-way ANOVA with Bonferroni posthoc analysis. Categorical variables are expressed as numbers with percentages in brackets and p value is of Pearson's chi-square test or Fisher's exact test. n: number, SGA: small for gestational age, BMI: body mass index. Customized and population only SGA are identical to population SGA infants.

improve the detection of SGA infants. Specifically, in our population, the application of the customized assessment led to the identification of an additional 6 % of SGA infants that had not been detected with the population-based method.

The customized model had been initially proposed by Gardosi et al during the 1990s. After reviewing more than 4,000 pregnancies in the United Kingdom, the authors found that 28 % of the infants that had been traditionally classified as SGA by conventional population-based centiles were, in fact, within normal limits[15,17]. Conversely, 24 % of the infants designated as SGA by customized centiles had not been identified by the standard unadjusted centiles[15,17]. A subsequent study nearly two decades later found that customized growth charts identified five times more SGA infants (13.5 %) than standard charts (2.3 %)[10]. The model has been thereafter applied in several term populations in the developed countries with similar findings[1,4-10]. Several studies also demonstrated that using customized centiles, an additional 7 % to 14 % of SGA infants missed with population-based centiles could be identified[5,9]. Overall, large population cohort studies in France, Spain, and the United States demonstrated that customized centiles were more sensitive in detecting SGA infants[1,6,7]. In line with the previous studies, our findings suggested that the utilization of customized centiles led to detecting a significant number of SGA infants whom the traditionally population-based centiles had missed.

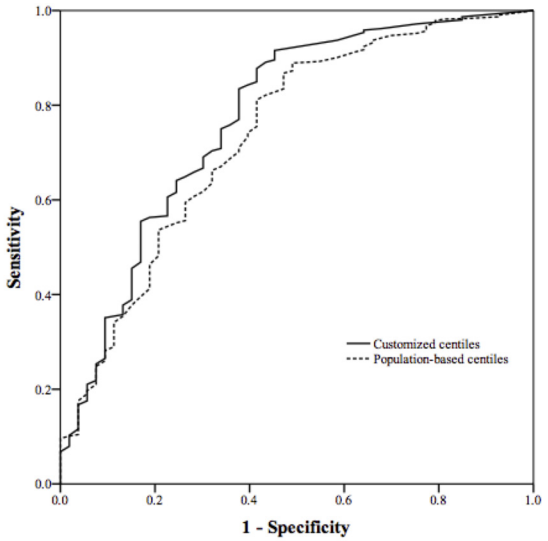

Figure 1: The receiver operating characteristic curve showing how many infants with perinatal morbidity were correctly identified by customized in comparison to population-based centiles.

In the current study, we also assessed whether population-based or customized centiles were more helpful in predicting perinatal morbidity. Although customized centiles have been proven more sensitive in detecting SGA infants, the evidence regarding the related clinical importance remains scarce. The study by Carberry et al demonstrated that the customized reference had a

Table 2: Neonatal characteristics of the entire study population, the customised only small for gestational age (SGA), the customised and population SGA, and the non-SGA infants.

	Study population (n =657)	Customized only SGA (n =38)	Customized and Population-based SGA (n =42)	Non-SGA (n =577)	p
Gestational age (weeks)	38.3 ± 1.1	38.3 ± 1.1	38.3 ± 1.4	38.3 ± 1	0.878
Birth weight (g)	3,152 ± 469	2,638 ± 240	2,391 ± 295	3,152 ± 469	<0.001
Head circumference (cm)	34.2 ± 1.5	33.1 ± 1.1	32.3 ± 1.5	34.4 ± 1.5	<0.001
Length (cm)	50.2 ± 2.4	48.9 ± 2	47.4 ± 3	50.5 ± 2.2	<0.001
Gender, male	352 (54)	19 (50)	24 (57)	309 (54)	0.816
Perinatal morbidity	53 (8)	16 (42)	13 (31)	24 (4)	<0.001

Continuous variables are expressed as means ± standard and p value is of one-way ANOVA with Bonferroni posthoc analysis. Categorical variables are expressed as numbers with percentages in brackets and p value is of Pearson's chi-square test or Fisher's exact test. n: number, SGA: small for gestational age. Customized and population only SGA are identical to population SGA infants.

Table 3: The sensitivity, specificity, positive predictive value, and negative predictive value of customized and population centiles.

	Sensitivity	Specificity	Positive Predictive value	Negative Predictive value
Customized centiles				
SGA infants (n =80)	0.36	0.96	0.54	0.91
Population-based centiles				
SGA infants (n =42)	0.30	0.93	0.24	0.95

SGA: small for gestational age.

limited impact on predicting neonatal morbidity among term infants[11]. In accordance, Charkaluk et al suggested that customization did not significantly improve the detection of infants at risk of poor cognitive outcomes[19]. A recent study, including nearly a million infants born over 19 years in Scotland, concluded that partially customized centiles did not identify more infants at risk of death than non-customized centiles[20]. The authors could not fully customize infants due to missing maternal weight and ethnicity data; however, they found that increased risk was evident at term infants with a birth weight lower than the 25th centile, irrespective of whether non-customized or partially customized centiles were used[20]. Moreover, a Swedish population-based cohort study between 2006 and 2015, evaluating term singleton births with population-based and customized charts, recorded an increased proportion of infants below the median using the customized centiles[21]. The authors concluded that an adverse perinatal outcome was differently related to each chart cut-off limit; however, it was similar in the smallest 5 % of the population[21]. In the same aspect, the secondary evaluation of the Generation R study, which included 6,052 participants in the Netherlands, revealed that customized charts were not superior to population charts at identifying SGA newborns at increased risk of adverse outcomes at later age[22]. Finally, a meta-analysis by Chiossi et al evaluating the effectiveness of customization compared to population-based charts for predicting adverse outcomes included 20 observational studies and concluded that both growth charts could identify SGA infants without evidence of the superiority of any method[14]. Our findings were in line with previous studies, suggesting that the customized centiles had no better impact than the population-based centiles in detecting term infants at risk of perinatal morbidity.

The fact that both customized and population-based centiles were of similar prognostic value in detecting perinatal morbidity is particularly important when including only term infants. In general, term infants present low morbidity, and therefore, customization would provide limited benefit. Besides, in preterm infants, the customized model based on ultrasonography-estimated fetal weight presents a substantial difference compared to the population-based reference, while in term infants, those references differ a little[23]. Nonetheless, the pregnancies associated with prematurity should be mostly considered pathological rather than normal, while mostly prematurity is known to be linked with growth restriction and increased morbidity[24,25]. Thus, although the adjustment for the maternal weight, height, or other factors may improve the amount of SGA detected infants, it fails to detect which infants need closer monitoring.

The main strength of our study is that it is novel in evaluating the effectiveness of customized in comparison to population-based centiles in a Greek cohort. The main limitation of the current study arises from its single-center design. Given that our study was conducted in a population with homogenous characteristics, the adjustment for factors with little variation might have a limited effect. Also, our study population was restricted only to term infants, and thus the generalization of our findings is limited. Notably, no population-based only SGA infants were detected in our study. In previous studies, constitutional SGA infants have been reported in 1 % to 12 %[1,4,6].

The limited size of our study sample may have prevented us from detecting any constitutional SGA infants in our cohort. Of note, in our study the maternal anthropometrics were similar between groups, and in fact, not different from the average for Greek population. Thus, the fact that limited women with significant weight or height deviation were included, might also explain that no population SGA infants were detected, given that maternal anthropometrics are a factor that could be associated with constitutional SGA infants.

In conclusion, our study suggested that the utilization of customized in comparison to the population-based centiles provided increased accuracy in detecting term SGA infants; however, using the adjusted for maternal characteristics customized centiles could not improve the detection of infants at risk of poor perinatal outcome. Therefore, further studies are warranted to evaluate the clinical importance of customization regarding the short and long-term neonatal outcomes.

Conflict of interest

Authors declare no conflicts of interest.

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