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A New Approach for Classifying Fetal Growth Restriction

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Background: Fetal growth restriction is commonly defined using small for gestational age (SGA) birth (birthweight < 10th percentile) as a proxy, but this approach is problematic because most SGA infants are small but healthy. In this proof-of-concept study, we sought to develop a new approach for identifying fetal growth restriction at birth that combines information on multiple, imperfect measures of fetal growth restriction in a probabilistic manner.

Methods: We combined information on birthweight, placental weight, placental malperfusion lesions, maternal disease, and fetal acidemia using latent profile analysis to classify fetal growth in births at the Royal Victoria Hospital in Montreal, Canada, 2001–2009. We examined the clinical characteristics and health outcomes of infants classified as growth-restricted and nongrowth-restricted by our model, and among the subgroup of growth-restricted infants who had a birthweight ≥10th percentile (i.e., would have been missed by the conventional SGA proxy).

Results: Among 26,077 births, 345 (1.3%) were classified as growth-restricted by our latent profile model. Growth-restricted infants were more likely than nongrowth-restricted infants to have an Apgar score <7 (10% vs. 2%), have hypoglycemia at birth (17% vs. 3%), require neonatal intensive care unit admission (59% vs. 6%), die in the perinatal period (3.8% vs. 0.2%), and require an emergency cesarean delivery (42% vs. 15%). Risks remained elevated in growth-restricted infants who were not SGA, suggesting our model identified at-risk infants not detected using the SGA proxy.

Conclusions: Latent profile analysis is a promising strategy for classifying growth restriction at birth in fetal growth restriction research.

Keywords: Fetal growth; Fetal growth restriction, Small for gestational age birth, Latent class analysis

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Fetal growth restriction, an important cause of perinatal death, occurs when a fetus' growth is pathologically restricted in utero. The most common cause of fetal growth restriction is uteroplacental insufficiency or placental dysfunction, in which an abnormally implanted placenta or placental injury impairs delivery of oxygen and nutrients to the fetus.[1]

Despite extensive research, the tools for screening and diagnosing fetal growth restriction remain poor.[2] An important barrier to identifying new screening and diagnostic modalities has been that the field lacks an accurate case definition for fetal growth restriction. Fetal growth restriction at birth has conventionally been classified using the proxy of "small for gestational age" (SGA) birth, defined as a weight <10th percentile for gestational age.[3] This statistically derived definition of growth restriction is problematic, however, because infants can be in the smallest 10% of their peers but also be healthy (i.e., constitutionally small). Conversely, infants can weigh more than the 10th percentile but fail to reach their individual growth potential due to pathological growth restriction.[4,5] One obstetrics textbook estimates that "approximately 70% of infants with a birthweight below the 10th percentile are normally grown (i.e., constitutionally small) and are not at risk for adverse outcomes because they present one end of the normal spectrum for fetal size."[6] That is, the conventional definition for fetal growth restriction is believed to capture more infants without the disease than with the disease.

Without an accurate outcome definition, we cannot establish if a new diagnostic or screening test or tool is performing poorly because of inherent limitations of the test or because it is being evaluated using an outcome definition that does not capture the true disease of interest. Alternatively, we may overestimate the performance of markers that identify small fetal size rather than true growth restriction. A recent expert review identified a number of promising but still

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Study data cannot be shared due to the conditions under which data were released to the researchers. Individuals seeking access should contact the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Royal Victoria Hospital, Montreal, Quebec. Statistical code for the analyses in provided as Supplementary material.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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unproven biomarkers for improved detection of fetal growth restriction.[7] These include markers of placental insufficiency routinely collected as part of prenatal screening such as pregnancy-associated plasma protein and novel markers of angiogenesis such as placental growth factor.[7] An accurate case definition for fetal growth restriction is needed to adequately evaluate these biomarkers. Likewise, three new high-quality fetal growth charts have recently been created,[8–10] but work to establish the optimal percentile thresholds on the charts for identifying fetal growth restriction has been hindered by the lack of an accurate case definition.

Recent efforts to develop an improved case definition have focused on algorithm-based definitions, which combine information on multiple indicators of fetal growth restriction in a deterministic manner.[5,11,12] A 2018 international Delphi consensus panel of 57 fetal growth experts proposed that fetal growth restriction at birth be defined as a birth weight <3rd percentile or any three of: birth weight <10th percentile; head circumference <10th percentile, length <10th percentile, prenatal diagnosis of growth restriction, and maternal comorbidity.[11] This algorithm-based definition may reduce the high false positive rate of the conventional definition, but its reliance on percentile thresholds fails to overcome the obstacle that not all small infants are growth-restricted, and infants above a given percentile threshold may still have failed to reach their own growth potential. Furthermore, it relies on experts' ability to reach consensus rather than objective criteria.[13]

In fields such as infectious diseases, the lack of a single, accurate diagnostic test to identify disease cases has been overcome with latent class analysis.[14] Latent class analysis is a statistical approach that can be used to identify underlying disease status when multiple diagnostic tests exist, but each imperfectly diagnose the disease.[15] The approach is similar to an algorithm-based definition in that it combines information on multiple, imperfect indicators of disease status. It improves on the algorithmic approach, however, because it does not require any single indicator (such as weight less than 10th percentile) to be present, but rather estimates the probability of disease based on each individual's particular constellation of characteristics or test results. Furthermore, a type of latent class analysis known as latent profile analysis does not require continuous variables (such as birthweight percentiles) to be dichotomized. We hypothesized that latent profile analysis could provide an improved approach for identifying placentally mediated fetal growth restriction at birth in the research setting.

The objective of this proof-of-concept study was to identify fetal growth restriction at birth by combining information on multiple, imperfect indicators of fetal growth restriction through latent profile analysis. Our secondary objective was to compare the clinical characteristics and health outcomes of infants identified as growth-restricted versus nongrowth-restricted by our new approach.

METHODS

Study Population

We drew our study population from singleton, nonanomalous births at the Royal Victoria Hospital in Montreal, Canada, 2001–2009, where the obstetrical and neonatal medical records of all deliveries are abstracted into a clinically detailed, quality-controlled database, the McGill Obstetric and Neonatal Database.[16] We restricted analyses to births ≥28 weeks' gestation, as this age range is most relevant to the diagnosis and management of fetal growth restriction. This study was approved by the University of British Columbia Children's & Women's Research Ethics Board (H14-02809; H20-00964), who provided a waiver of consent.

Measures of Fetal Growth Restriction

We considered seven measures of fetal growth restriction at birth for inclusion. The measures were chosen based on a recent Delphi consensus definition of fetal growth restriction at birth,[11] and adapted based on clinical opinion to include information on placental health to account for the central role of uteroplacental insufficiency in the etiology of placentally mediated fetal growth restriction (1). They included:

1. Birthweight z-score. We used Hadlock's estimated fetal weight-for-gestational-age chart[17] to standardize birthweight (g) for gestational age
2. Birth length z-score. We standardized length at birth (cm) using an internal sex- and gestational age-specific reference derived from infants with an ultrasound-based estimate of gestational age.
3. Head circumference z-score. We standardized head circumference at birth (cm) using an internal sex- and gestational age-specific reference of infants with an ultrasound-based estimate of gestational age.
4. Maternal comorbidities. Maternal comorbidities linked with increased risk of placentally mediated growth restriction included the presence of chronic hypertension, hypertensive disorder of pregnancy (pre-eclampsia superimposed on pre-existing hypertension, pre-eclampsia, hemolysis, elevated liver enzymes, low platelets, or eclampsia) or autoimmune disease (lupus erythematosus or mixed connective tissue disease).
5. Placental malperfusion lesions. We established the presence or absence of lesions associated with maternal and fetal vascular malperfusion that contribute to fetal growth restriction using the Amsterdam Placental Workshop Group's classification.[18–20] We included placental infarctions, accelerated villous maturation, thrombosis and velamentous cord insertion. A sample from all placentas at the Royal Victoria Hospital is sent for pathology examination (unlike many centers, where placentas are only sent for a clinical indication), providing information on placental health for all infants.

6. Placental weight z-score. Placental weight at delivery is measured by nursing staff after the cord had been cut and blood clots removed. Placental weight was standardized into a sex- and gestational age-specific z-score using an internal sex and gestational age-specific reference of infants with an ultrasound-based estimate of gestational age.
7. Metabolic acidosis. We defined metabolic acidosis as a cord pH <7.1.

Because of the high correlation between anthropometric characteristics, we expressed head circumference z-score, birth length z-score, and placental weight z-score as residuals of models regressing each of these characteristics on birthweight z-score.[21] The residuals from these models represent the difference between each infant's actual head circumference, birth length, or placental weight z-score and that expected based on its birthweight z-score. By definition, the residuals are uncorrelated with birthweight z-score, so allow the independent contribution of head circumference, birth length, or placental weight to be isolated.

Latent Profile Analysis

We fit a latent profile model estimating the probability of each infant's growth restriction status given the observed measures of fetal growth described above.[15] We used maximum likelihood estimation to fit a latent class model with two classes (growth-restricted and nongrowth-restricted).[22] We set up several equations, where the response variables were observed measures of fetal growth, which were modeled using logistic or linear regression depending on the nature of the measures. Most models contained intercept terms only, with separate intercepts estimated according to latent class status (for example, the log-odds of placental malperfusion lesions in the growth-restricted class). We used the expectation-maximization algorithm to iteratively update estimates of the mixture probabilities (the probability of being in the growth-restricted or nongrowth-restricted class) and the estimates of the intercepts across the models until convergence was achieved. The probability of observing a particular combination of measures was a mixture of the two class-specific probability functions. We then estimated every infant's probability of being in either class given their particular combination of fetal growth measures. Infants were classified as growth-restricted if their posterior probability of growth restriction was greater than their posterior probability of being nongrowth-restricted. We also examined the distribution of the posterior probability as a continuous variable.

Model development was a subjective, iterative process informed by clinical expertise, plausibility of results, and ability to achieve model convergence. We did not use fit statistics like the Akaike information criterion to assess model performance, since it is not comparable across models when response variables (observed measures of growth restriction) are added or removed. We began with a model containing birthweight z-score only, then added pathological variables (placental lesions, maternal comorbidity, and acidemia), following by anthropometric variables (placental weight, head circumference, and birth length z-scores). As recommended, we fit our final model with different starting values to help ensure estimates reflected a global maximum.[23] Missing data were assumed to be missing at random. Because latent class analysis estimates each regression equation separately based on all available data for that measure, a predictive probability can still be estimated for infants with missing measures by "borrowing" information on conditional probabilities from observations with complete profiles.[23] That is, each individual contributes to the estimation of all equations for which they have data, and estimation of each individual's posterior probability of growth restriction is derived from the equations for which they have available data. Our models were estimated using the "gsem" command in Stata 16 (College Station, TX); see eAppendix 1; http://links.lww.com/EDE/B833 for statistical code. Greater details on the methods and underlying assumptions are available elsewhere.[24,25]

Establishing Face Validity

As is standard in the field, we evaluated the model's credibility by assessing the face validity of its results. We compared maternal characteristics of infants identified as growth-restricted versus nongrowth-restricted by our model, and examined perinatal health outcomes such as Apgar scores and neonatal intensive care unit (NICU) admission, as well as use of obstetrical interventions such as labor induction and emergency cesarean delivery.

Although we expected growth-restricted infants to be more likely to be born preterm (as the only treatment for prenatally detected growth restriction is an iatrogenic early delivery), we conducted sensitivity analyses restricting model validation to term infants (37–41 weeks) to ensure that our latent profile model was not simply picking up adverse outcomes caused by preterm delivery that were unrelated to fetal growth restriction (e.g., following an iatrogenic preterm delivery due to deteriorating maternal condition with pre-eclampsia). We examined the characteristics and clinical outcomes of infants who were identified as growth-restricted by our model, but had birthweights ≥10th percentile (i.e., growth-restricted but not SGA), and infants with a birthweight <10th percentile but not classified as growth-restricted by our model (i.e., SGA but not growth-restricted). Finally, we examined pregnancy outcomes according to categories of posterior probability (<0.10, 0.10–0.39, 0.40–0.69, and ≥0.70).

We compared the characteristics and clinical outcomes of infants classified as growth-restricted by our model to those identified as growth-restricted using criteria included in a recent Delphi consensus definition of fetal growth restriction at birth.[11] However, as data were unavailable on one of the six criteria included in the Delphi consensus definition ("prenatal suspicion of growth-restriction"), results should be viewed as

exploratory only, and do not provide a definitive comparison of the two definitions.

RESULTS

There were 30,597 births at the Royal Victoria Hospital during our study period. We excluded 1900 twins and higher order multiples, 2411 births with congenital anomalies, and 209 births <28 weeks, leaving 26,077 births for analysis. This included two infants (0.01%) with missing birthweight (0.01%), 564 (2.2%) with missing placental weight, 1,390 (5.3%) with missing birth length, and 1,397 (5.4%) with missing head circumference data.

Our final model included birthweight z-score, placental weight z-score, placental malperfusion lesions, maternal comorbidities, and metabolic acidosis. We retained placental malperfusion lesions, maternal comorbidities, and metabolic acidosis because these ensured a plausible rate of fetal growth restriction. Adding placental weight z-score, head circumference z-score, or birth length z-score had minimal impact on the model's classifications (>90% of growth-restricted infants had a concordant status in models including versus excluding these variables, and overall rates were similar). We retained placental weight z-score in our model on substantive grounds given the central role of the placenta in placentally mediated fetal growth restriction, and to ensure our final model included more than one anthropometric characteristic, but excluded the other two anthropometric characteristics (birth length and head circumference z-scores) for parsimony.

Our final model identified 345 infants (1.3%) as growth-restricted. As shown in Table 1, growth-restricted infants were considerably smaller (birthweight z-score of −1.3 vs. 0.3) and had more placental malperfusion lesions (96% vs. 6%), maternal comorbidities (65% vs. 5%), and acidemia (13% vs. 2%) than infants classified as nongrowth-restricted by the model, respectively. Among term births, the proportion of fetal growth restriction decreased to 0.6%, but the higher risk profile (smaller size, higher rates of placental pathology, maternal comorbidities, and acidemia) among growth-restricted infants remained.

Infants identified as growth-restricted by the model exhibited a higher risk profile in terms of their characteristics and clinical outcomes. Mothers of growth-restricted infants were moderately more likely to have smoked in pregnancy (13% vs. 8%), use assisted reproductive technology to conceive (7% vs. 4%), and be nulliparous (64% vs. 46%), but had no meaningful differences in maternal age or prepregnancy body mass index from women with nongrowth-restricted infants (Table 2). Growth-restricted infants had smaller head circumference (−1.0) and birth length z-scores (−1.2) than nongrowth-restricted infants (0.0 for both measures) and were born approximately 3 weeks earlier (36 vs. 39 weeks). Growth-restricted infants were much more likely to be delivered following an emergency cesarean delivery (42% vs. 15% for nongrowth restricted) or induction of labor for a fetal indication (19% vs. 6%), and experience an adverse perinatal outcome (risk of 5-minute Apgar score<7 of 10% vs. 2%; NICU admission 59% vs. 6%; perinatal death 3.8% vs. 0.2%) (Figure 1, data in eTable 1; http://links.lww.com/EDE/B833). Growth-restricted term infants also had a higher risk profile than nongrowth-restricted term births (eTable 2; http://links.lww.com/EDE/B833).

As shown in Figure 2, the birthweight z-scores of infants classified as growth-restricted were systematically smaller than nongrowth-restricted infants. The mean birthweight z-score of growth-restricted infants, −1.3, corresponds to the 9th percentile. Most infants classified as growth-restricted

TABLE 1. Measures of Fetal Growth Restriction Used in Latent Profile Analysis to Classify Fetal Growth Restriction in 26,077 Births at the Royal Victoria Hospital, 2001–2009

	Latent Profile Analysis Classification	
Measure of Fetal Growth Restriction	**Growth Restricted**	**Nongrowth Restricted**
All births	345 (1.3)	25,735 (98.7)
Birthweight z-score, mean ± SD	−1.3 ± 0.8	0.3 ± 1.0
Placental weight z-score, mean ± SD	−1.3 ± 1.1	0.02 ± 1.0
Placental malperfusion lesions, n (%)	331 (96)	1,610 (6.3)
Maternal comorbidity, n (%)	224 (65)	1,218 (4.7)
Acidemia (cord pH < 7.1), n (%)	46 (13)	475 (1.8)
Term births only	147 (0.6)	24,024 (99)
Birthweight z-score, mean ± SD	−1.5 ± 0.8	0.3 ± 1.0
Placental weight z-score, mean ± SD	−1.4 ± 1.1	0.01± 1.0
Placental malperfusion lesions, n (%)	150 (97)	1,128 (4.7)
Maternal comorbidity, n (%)	84 (54)	1,083 (4.5)
Acidemia (cord pH < 7.1), n (%)	18 (12)	441 (1.8)

TABLE 2. Characteristics of 26,077 Births at the Royal Victoria Hospital by Growth restriction Status Derived Through Latent Profile Analysis, 2001–2009

Characteristic	**Growth Restricted**	**Nongrowth Restricted**
Birthweight, g, mean ± SD	2,085 ± 624	3,413 ± 511
Gestational age, days, mean ± SD	252 ± 22	275 ± 12
Head circumference z-score, mean ± SD	−1.0 ± 1.0	0.0 ± 1.0
Birth length z-score, mean ± SD	−1.2 ± 1.0	0.0 ± 1.0
Maternal age, years, mean ± SD	31 ± 6	31± 6
Maternal height, cm, mean ± SD	161 ± 7	164 ± 7
Prepregnancy body mass index[a], kg/m^2, mean ± SD	26 ± 6	25 ± 5
Female infant sex, n (%)	173 (50)	12,732 (50)
Nulliparous, n (%)	220 (64)	11,831 (46)
Assisted reproductive technology, n (%)	25 (7.2)	1,097 (4.3)
Smoking in pregnancy, n (%)	44 (13)	2,023 (7.9)

[a]Among 160 and 10,441 women with available BMI data with and without fetal growth restriction, respectively.

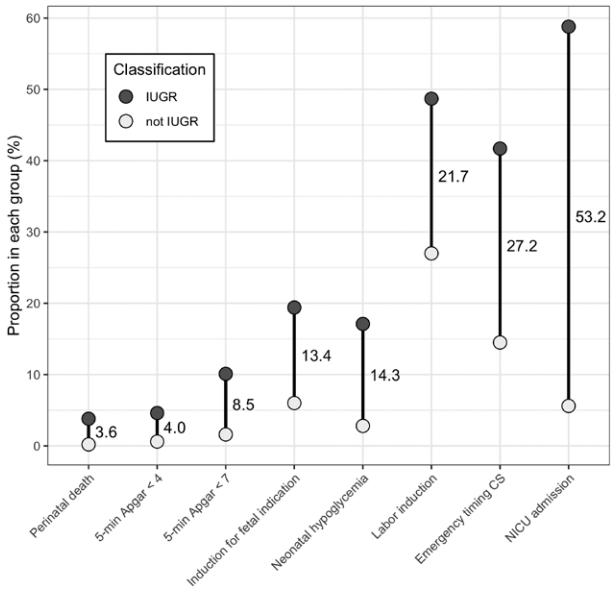

FIGURE 1. Clinical outcomes of 26,077 births at the Royal Victoria Hospital by latent profile analysis-derived growth-restriction status (intrauterine growth restricted, IUGR, vs. non-IUGR), 2001–2009. Vertical black lines indicate the difference between groups in percentage points.

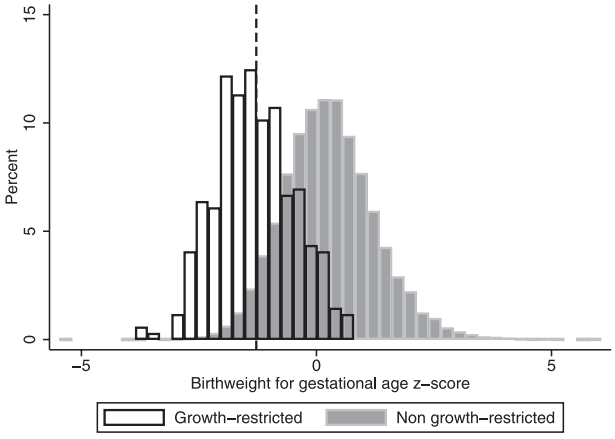

FIGURE 2. Birthweight z-scores of 26,077 infants classified as growth-restricted vs. nongrowth-restricted by latent profile analysis among births at the Royal Victoria Hospital, Montreal, Canada, 2001–2009. Vertical dashed line indicates a z-score of –1.28, corresponding to the 10th percentile.

by our model were small in size (322/345 (93%) of growth-restricted infants had a birthweight z-score below the population 50th percentile), but not necessarily small enough to be below the 10th percentile: approximately one half (n = 159; 46%) of growth-restricted infants had a birthweight z-score above the population 10th percentile. Thus, our definition of fetal growth restriction included a sizeable fraction of infants that would not have been identified using the conventional definition of SGA birth <10th percentile.

Infants who were classified as growth-restricted by our model but were not SGA (i.e., had a birthweight > 10th percentile) had, predictably, high rates of malperfusion lesions, maternal comorbidities, and acidemia (Table 3). Of note, 99.4% of these infants had evidence of placental malperfusion lesions, supporting the likelihood of growth restriction rather than unrelated, acute complications. They also had a high risk of clinical complications: over half (56%) were admitted to the NICU, 10.7% had a 5-minute Apgar score < 7, 11% had hypoglycemia, 46% were delivered by emergency cesarean delivery, and 47% following labor induction (Figure 3). In contrast, infants with a birthweight <10th percentile, but not classified as growth-restricted by our model (i.e., SGA but not growth-restricted) had a risk profile that was closer to those of non-SGA, nongrowth-restricted infants than growth-restricted infants: 7% malperfusion lesions, 6% maternal comorbidities, 3% acidemia, 10% NICU admission, 2% 5-minute Apgar score < 7, 5% hypoglycemia, 12% emergency cesarean delivery, and 35% labor induction.

The distribution of the predicted posterior probability of growth restriction is shown as a continuous variable in eFigure 1; http://links.lww.com/EDE/B833. The growth restriction classification based on a 50% threshold was definitive for most infants: 25,027 (97%) of infants classified as nongrowth-restricted had a posterior probability of <0.1, while among infants classified as growth-restricted 269 infants (78%) had a predicted posterior probability of >0.6, and 239 (70%) were >0.7. Nevertheless, there was a dose-response increase in risk of adverse pregnancy outcomes across categories of posterior probability (eFigure 2; http://links.lww.com/EDE/B833), such that a mild-to-moderate degree of increased risk likely exists in infants with a posterior probability below 0.5.

The characteristics and clinical outcomes of infants classified as growth-restricted by our model versus the Delphi consensus definition are provided in eTable 3; http://links.lww.com/EDE/B833. Although our model appears to be identifying a higher-risk group of infants than those identified using the Delphi consensus definition, results should be interpreted with caution given that data were missing in our cohort on one of the Delphi consensus definition criteria.

DISCUSSION

Main Findings

In this proof-of-concept study, we demonstrated that latent profile analysis can successfully be used to classify fetal growth restriction using multiple, imperfect measures of fetal growth restriction at birth in a probabilistic manner. Infants classified as growth-restricted by our model had a risk profile that was compatible with our current clinical understanding of fetal growth restriction etiology, not only in terms of the measures used to derive the model (e.g., lower birthweight for gestational age and high incidence of placental malperfusion lesions, etc), but also in terms of the clinical characteristics

TABLE 3. Characteristics and Clinical Outcomes of Infants Classified as SGA (<10th Percentile for Sex and Gestational Age) Versus Growth-Restricted (IUGR) Among Nonanomalous Singleton Births at the Royal Victoria Hospital, 2001–2009

	Non-SGA and non-IUGR	IUGR only (non-SGA)	SGA only (non-IUGR)	Both IUGR and SGA
N	24,536	159	1,196	186
Birthweight z-score, mean ± SD	0.4 ± 0.9	−0.6 ± 0.5	−1.6 ± 0.4	−1.9 ± 0.5
Placental weight z-score, mean ± SD	0.1 ± 1.0	−0.8 ± 1.0	−1.2 ± 0.8	−1.8 ± 0.9
Head circumference z-score, mean ± SD	0.1 ± 0.9	−0.5 ± 0.8	−1.2 ± 0.8	−1.5 ± 0.9
Birth length z-score, mean ± SD	0.1 ± 1.0	−0.7 ± 0.7	−1.3 ± 0.9	−1.6 ± 0.9
Maternal comorbidity, n (%)	1,132 (4.6)	144 (91)	86 (7.2)	80 (43)
Placental malperfusion lesions, n (%)	1,537 (6.3)	158 (99)	73 (6.1)	173 (93)
Acidemia (cord pH < 7.1), n (%)	435 (1.8)	24 (15)	40 (3.3)	22 (12)
Gestational age (days), mean ± SD	275 ± 12	247 ± 22	276 ± 10	257 ± 20
Emergency timing cesarean, n (%)	3,592 (15)	73 (46)	141 (12)	71 (38)
Labor induction, n (%)	6,535 (27)	75 (47)	424 (36)	93 (50)
Labor induction for fetal indication, n (%)	1,309 (5.3)	7 (4.4)	241 (20)	60 (32)
Neonatal intensive care unit admission, n (%)	1,331 (5.4)	90 (57)	117 (9.9)	113 (61)
5-minute Apgar < 7, n (%)	384 (1.6)	17 (11)	29 (2.4)	18 (9.7)
5-minute Apgar ≤ 3, n (%)	142 (0.6)	5 (3.1)	17 (1.4)	11 (5.9)
Perinatal death, n (%)	46 (0.2)	2 (1.3)	9 (0.8)	11 (5.9)
Neonatal hypoglycemia, n (%)	662 (2.7)	17 (11)	65 (5.4)	42 (23)

and health outcomes external to the model (e.g., higher risk of adverse perinatal outcomes and obstetric interventions). Importantly, this high-risk profile was also observed in infants classified as growth-restricted by our model, but ≥10th percentile of birthweight (i.e., infants traditionally classified as appropriate-for-gestational-age).

Comparison with the Literature

Our use of latent class analysis to identify fetal growth restriction is novel, but the approach is increasingly common in other fields. A 2014 systematic review found 64 studies using latent class models to derive a gold standard diagnostic definition, primarily in infectious diseases.[14] In this field, diseases such as tuberculosis have conventionally relied on microbiology as a gold standard for diagnosis.[14,23,26–29] As many pathogens can be challenging to culture, however, microbiology-based definitions miss many true cases. Alternative measures, such as cytology, will capture most true cases but can be positive due to unrelated conditions (nonspecific). Latent class analysis is used to combine information on multiple tests to estimate an individual's true disease status. The approach has also been used to define other syndromic diseases such as irritable bowel syndrome.[30]

Our approach is intended primarily for use in the research setting, where we believe it can provide a more accurate outcome definition for studies aiming to evaluate new screening or diagnostic tools for fetal growth restriction. An improved outcome definition for fetal growth restriction would also improve studies seeking to identify risk factors for the condition, or understand the longer-term consequences of fetal growth restriction. Although an improved case definition for fetal growth restriction is also urgently needed for obstetrical practice, our approach is not intended for antenatal care, as it is based on measurements that are only available at the time of birth. The contributions of this approach to the clinical management of fetal growth restriction would be indirect only, by supporting the identification of improved tools for diagnosis and screening.

We restricted our measures to variables collected at birth and did not include antenatal tests such as Doppler velocimetry. This restriction was done for two reasons: first, diagnostic or screening tests for fetal growth restriction are conventionally evaluated by comparing to health outcomes at the time of birth (when fetal growth is complete), so our definition mirrors this approach, and second, antenatal tests of fetal growth are usually only available in pregnancies where there is a clinical indication to monitor growth, which would make a definition requiring these tests infeasible for uptake of our approach in large unselected population-based cohort studies.

Strengths and Limitations

Our large cohort with detailed clinical information and routine placental pathology enabled us to assess the feasibility of the approach in an efficient and cost-effective manner. Our study nevertheless leaves outstanding issues. Most notably, we selected our measures of fetal growth restriction based on substantive knowledge, drawing from measures included in a previously published Delphi consensus-based algorithm for fetal growth restriction at birth and supplemented with placental and metabolic variables.[11] We did not conduct an exhaustive examination of which fetal growth measures should or should not be included in a definitive model for fetal growth restriction, as we believe that these decisions should be made using multiple different cohorts, with diverse population

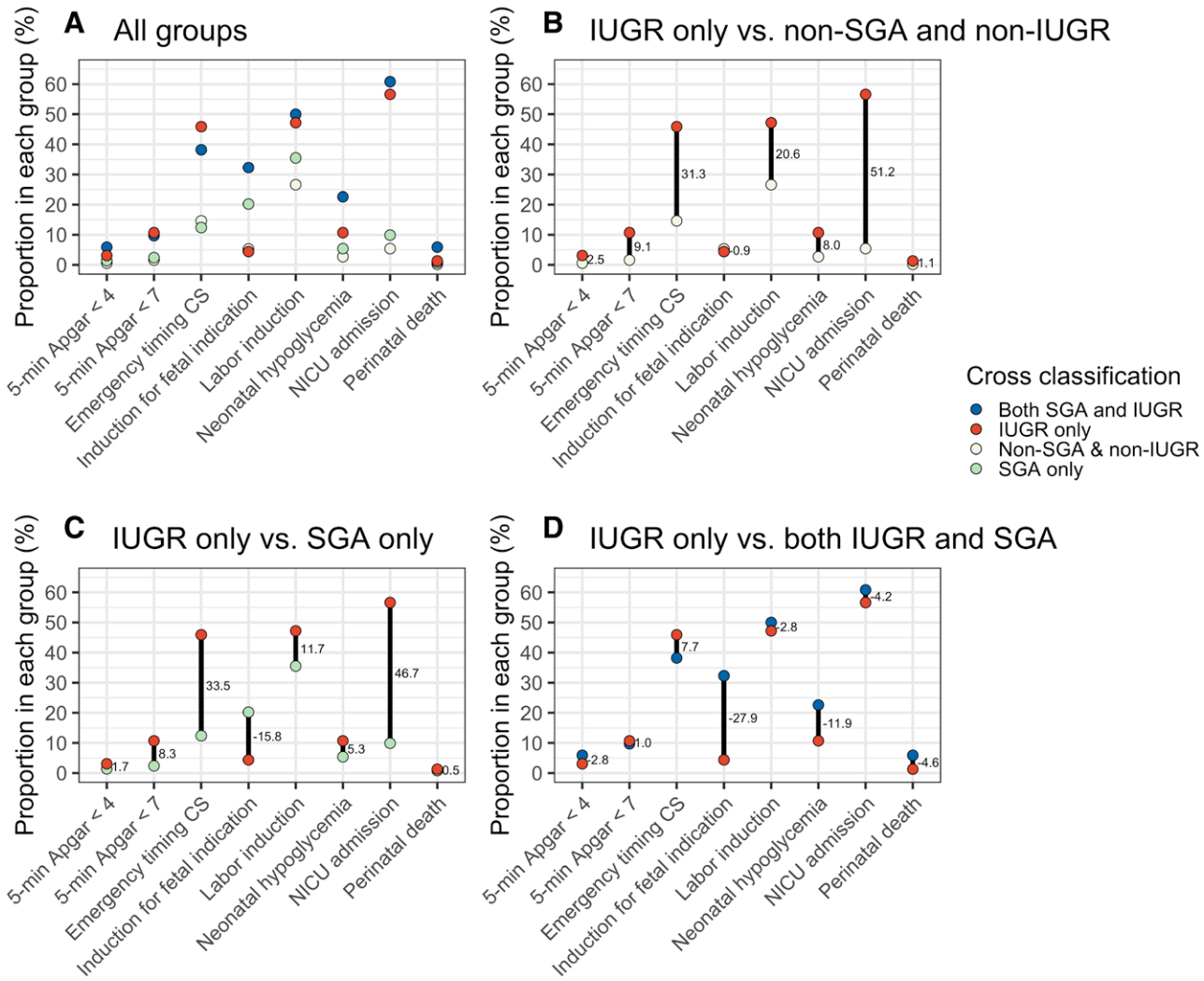

FIGURE 3. Perinatal outcomes of infants classified as (1) SGA (<10th percentile) only, (2) intrauterine growth-restricted (IUGR) only, (3) both SGA and IUGR, and (4) Non-SGA and non-IUGR among singleton births at the Royal Victoria Hospital, 2001–2009. Vertical black lines indicate the difference between groups in percentage points.

characteristics, which was beyond the scope of the current work. Decisions on optimal model specification should also be informed by a detailed chart review of infants whose growth restriction status differed between models to determine which model best matched clinical impressions of the infants' growth restriction status (which was not possible in our de-identified cohort). Individual-level review would also provide a more rigorous evaluation of our model's face validity, such as evaluating cause of death of stillbirths and neonatal deaths, and investigating the extent to which outcomes reflecting clinical processes (such as induction of labor or NICU admission) may have been affected by clinician knowledge of the model's predictors (e.g., metabolic acidosis at birth tipping the balance toward NICU admission), making our model's performance overly optimistic. Examining recurrence of fetal growth restriction, and in particular, discordance between a woman's pregnancies, may also be insightful. Future work to explore the use of multiple growth restriction categories (e.g., mild, moderate, and severe) based on different cut points of the predicted posterior probability, or even use of predicted posterior probability as a continuous variable, would also be worthwhile. Nevertheless, our findings confirm the merits of pursuing such future work. Infants with congenital anomalies were excluded from our study cohort, as the clinical process for diagnosing growth restriction differs in these infants. Thus, if the goal is to establish overall rates of fetal growth restriction in a population, rates of growth restriction due to uteroplacental insufficiency established through latent class analysis should be combined with rates from chromosomal and syndromic causes.

CONCLUSIONS

Although more work is needed to optimize and validate the use of latent class analysis to identify growth-restricted

infants, this proof-of-concept study shows that the approach has the potential to be an important advancement over current approaches for defining fetal growth restriction at birth.

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