Initial Metabolic Profiles Are Associated with 7-Day Survival among Infants Born at 22-25 Weeks of Gestation

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Objective To evaluate the association between early metabolic profiles combined with infant characteristics and survival past 7 days of age in infants born at 22-25 weeks of gestation.

Study design This nested case-control consisted of 465 singleton live births in California from 2005 to 2011 at 22-25 weeks of gestation. All infants had newborn metabolic screening data available. Data included linked birth certificate and mother and infant hospital discharge records. Mortality was derived from linked death certificates and death discharge information. Each death within 7 days was matched to 4 surviving controls by gestational age and birth weight z score category, leaving 93 cases and 372 controls. The association between explanatory variables and 7-day survival was modeled via stepwise logistic regression. Infant characteristics, 42 metabolites, and 12 metabolite ratios were considered for model inclusion. Model performance was assessed via area under the curve.

Results The final model included 1 characteristic and 11 metabolites. The model demonstrated a strong association between metabolic patterns and infant survival (area under the curve [AUC] 0.885, 95% CI 0.851-0.920). Furthermore, a model with just the selected metabolites performed better (AUC 0.879, 95% CI 0.841-0.916) than a model with multiple clinical characteristics (AUC 0.685, 95% CI 0.627-0.742).

Conclusions Use of metabolomics significantly strengthens the association with 7-day survival in infants born extremely premature. Physicians may be able to use metabolic profiles at birth to refine mortality risks and inform postnatal counseling for infants born at <26 weeks of gestation. *(J Pediatr 2018;■■:■■-■■).*

Recent improvements in neonatal resuscitation and intensive care have led to an increase in survival among infants born at 22-25 weeks of gestation.[1-3] These neonates suffer high rates of mortality and morbidity, especially at lower gestational ages and birth weights.[4-9] This makes decisions about resuscitation and use of active interventions difficult for clinicians and families.[2,10-13] Compounding the magnitude of clinical decisions regarding infants born extremely preterm is the fact that up to 83% of deaths in infants born at 22-24 weeks of gestation occur in the first week of life.[5]

Given the uncertainty surrounding clinical management of periviable newborns, the American Academy of Pediatrics recommends that decisions regarding care should be individualized and family centered, taking into account conditions and risk factors known to affect outcomes.[14] There are several models to predict survival in this patient population, with the most widely used model being the National Institute of Child Health & Human Development Neonatal Research Network (NRN) Extremely Preterm Birth Outcome calculator, by Tyson et al.[15] However, all of these predictive models rely exclusively on clinical characteristics of the infant.[15-17]

The use of unique sources of data and novel possible predictors may improve survival prediction for infants born at <26 weeks of gestation. One such opportunity is the use of metabolic data measured as part of newborn screening (NBS) for rare inborn errors of metabolism.[18] Our group and others have shown that infants born at term and preterm are metabolically distinct and that metabolic profiles can be used for accurate gestational dating.[19-23] Furthermore, metabolites measured as part of routine NBS have been implicated in neonatal complications, including respiratory distress syndrome, patent ductus arteriosus, and necrotizing enterocolitis.[24,25]

AUC	Area under the curve
IVH	Intraventricular hemorrhage
NBS	Newborn screening
NRN	Neonatal Research Network
ROC	Receiver operating curve
TPN	Total parenteral nutrition

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The objective of this study was to assess the relationship between survival to 7 days of age and metabolic markers in concert with common infant characteristics. We hypothesized that the incorporation of metabolites would strengthen the association with survival beyond the capacity of infant characteristics alone.

Methods

This was a nested, case-control study within a retrospective cohort of data collected by the California Office of Statewide Health Planning and Development on births from 2005 to 2011 in California. This database contains information from hospital discharge, birth certificate, and death records from birth to 1 year of age. This database was combined with results from NBS using date of birth, hospital of birth, birth weight, and birth time. In California, the Newborn Screening Program (administered by the California Department of Public Health) screens all newborn infants for rare inborn metabolic diseases by measuring markers in a heel-stick blood spot taken between 12 hours and 8 days after birth. The program has been described extensively elsewhere.[26,27]

There were 2 664 595 infants in the source cohort after linkage with vital statistics. Infants were excluded if the birth weight was >4 SDs from the mean for gestational age by sex (to limit potential erroneous data),[28] they were not singletons, they did not have complete NBS metabolic data (this includes infants who died after delivery but before their sample could be analyzed), or if their NBS blood spot was not taken within 72 hours of delivery (**Figure 1**; available at www.jpeds.com). The population was then limited to infants born at <26 weeks of gestation, leaving 1238 infants eligible for analysis. From the final population, infants who died within 7 days were matched to 4 controls by gestational week of birth and birth weight z-score category, which left a final sample of 93 cases and 372 controls (7 infants who died could not be matched to a control).

The outcome of interest for this study was survival past 7 days of age. Henceforth, "survival" in our study will be defined as alive after 7 days and "death" will be defined as deceased at <7 days. Mortality data were obtained from death certificate and death discharge information within the California Office of Statewide Health Planning and Development dataset. Infant and maternal characteristics used in analyses included birth weight, gestational age, sex, delivery type, maternal education, race/ethnicity, Medi-Cal status (California's Medicaid), use of total parenteral nutrition (TPN), birth weight small for gestational age, and any intraventricular hemorrhage (IVH) diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 772.13, 772.14). Criteria for choosing these specific variables included availability, occurrence before NBS, and previous evidence of an association with early infant mortality. Administration of TPN was obtained from the NBS data and was defined as receiving TPN before the blood spot was taken. There were 42 metabolites entered into the model consisting of 12 amino acids, 26 acylcarnitines, free carnitine, 2 hormones, and 1 enzyme (**Table I**; available at www.jpeds.com). In addition, 12 metabolic ratios were considered in the model. We used the same ratios created by NBS to detect known inborn errors of metabolism. No additional ratios were created.

Standardized mass spectrometry (tandem mass spectrometry) was used to measure the amino acids, acylcarnitines, and free carnitine. Thyroid-stimulating hormone and 17-hydroxyprogesterone were measured by high-performance liquid chromatography, and galactose-1-phosphate uridyltransferase was measured with a fluorometric enzyme assay.[26]

Statistical Analyses

All metabolites underwent a natural log transformation before being used in analyses to minimize the skew and influence of outlying observations. Birth weight was transformed into z scores using standardized growth curves[28] and then divided into 10 categories by increments of 0.5. Birth weight small for gestational age was calculated for infants with birth weight <10th percentile from standardized growth curves.[28] Population characteristics of interest and metabolites were summarized by the use of means with SDs and frequencies with proportions for continuous and categorical variables, respectively. Univariate analyses used *t* tests and χ^2 tests for continuous and categorical variables, respectively, to compare infants that survived and those that did not.

Multivariable logistic regression was used to model the association with survival. We used a stepwise regression procedure that consecutively adds explanatory variables based on minimizing *P* value from univariable analyses and then removes any variables with newly recalculated *P* values that eclipse the predetermined threshold. To maximize model performance, all possible explanatory variables had the potential to enter the model, and the criteria for remaining in the model was $P < .10$. In addition, variables with a $P \geq .05$ and $< .10$ were removed if their inclusion raised the Akaike information criterion or had no discernible positive effect on area under the curve (AUC) from a receiver operating characteristic (ROC) curve. If both base metabolites and their ratio were selected for inclusion in the model, severe multicollinearity was assessed and the components were evaluated independently with *P* values and contribution to model AUC and Akaike information criterion. Age at NBS collection and TPN were entered into the model build, as both are well-known to influence values of NBS metabolites,[29-31] and if not selected, a model forcing them in was compared with the original model. In addition, the model was examined in subgroups stratified by TPN and by IVH to compare predictive performance and metabolites of interest.

Performance of the final model was evaluated with AUC, and variables were summarized via OR, 95% CI, and standardized parameter estimates. Cross-validation was applied to assess the model fit, and the final model underwent conditional logistic regression to test for bias due to matching. The final model also was compared (using AUC, 95% CIs, and model contrast tests) to models consisting of metabolites only and clinical characteristics only (sex, IVH diagnosis, race/ethnicity, maternal education, Medi-Cal status, and cesarean

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