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SHORT REPORT

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Association between newborn screening analyte profiles and infant mortality

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ABSTRACT

Objective: To assess whether newborn screening analytes could be utilized beyond their traditional application to identify infants at high risk of mortality within the first 6 months of life.

Methods: We linked a province-wide newborn screening registry with health administrative databases to identify infant deaths within 6 months in a source population of live-born infants between 2010 and 2014. We used a nested case-control study design, in which all infant deaths between 7 days and 6 months of age were included as cases, and a random sample of infants from the source population were selected as controls and were matched to cases at a ratio of 10:1. We examined the association between mortality and screening analytes (acylcarnitines, amino acids, fetal-to-adult hemoglobin ratio, endocrine markers, and enzymes) using lasso regression to fit multivariable models.

Results: Among 350 infant deaths between 7 days and 6 months of age, and 3498 matched controls with complete data, our multivariable model demonstrated only modest ability to identify infant deaths (optimism-corrected *c*-statistic: 0.61, 95% confidence interval: 0.50–0.71).

Conclusion: We did not find newborn screening analytes to be strongly predictive of infant mortality between 7 days and 6 months of age in the general population of newborns. Future studies should investigate whether predictive modeling within more homogeneous cause-of-death categories could lead to improved predictive ability for infant mortality.

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Introduction

A growing body of research has assessed associations between routinely-measured newborn screening analytes and specific neonatal complications [1–3]. One recent study of early neonatal death among extremely preterm infants reported strong associations between screening analytes and surviving the first week after birth [4]. Another that examined metabolic profiles of infants who died of sudden infant death syndrome (SIDS) [5] found significant associations with lower levels of several acyl-carnitines, which are associated with disruptions in fatty acid metabolism and energy production [6,7].

Given these emerging observations, we postulated that screening analytes could be useful for identifying infants at higher risk of mortality beyond the early neonatal period. Our primary aim was to assess the association between newborn screening analyte profiles and infant mortality between 7 days and 6 months.

Materials and methods

We conducted a nested case-control study using data from a source population of all live-born infants born in Ontario between 1 January 2010 and 31 December 2014 with complete newborn screening data. We excluded infants who screened positive for any disorders on the newborn screening panel, had unsatisfactory blood sample quality, were transfused prior to blood spot collection, were a twin or higher-order multiple, had missing gestational age information, or

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Supplemental data for this article can be accessed here.

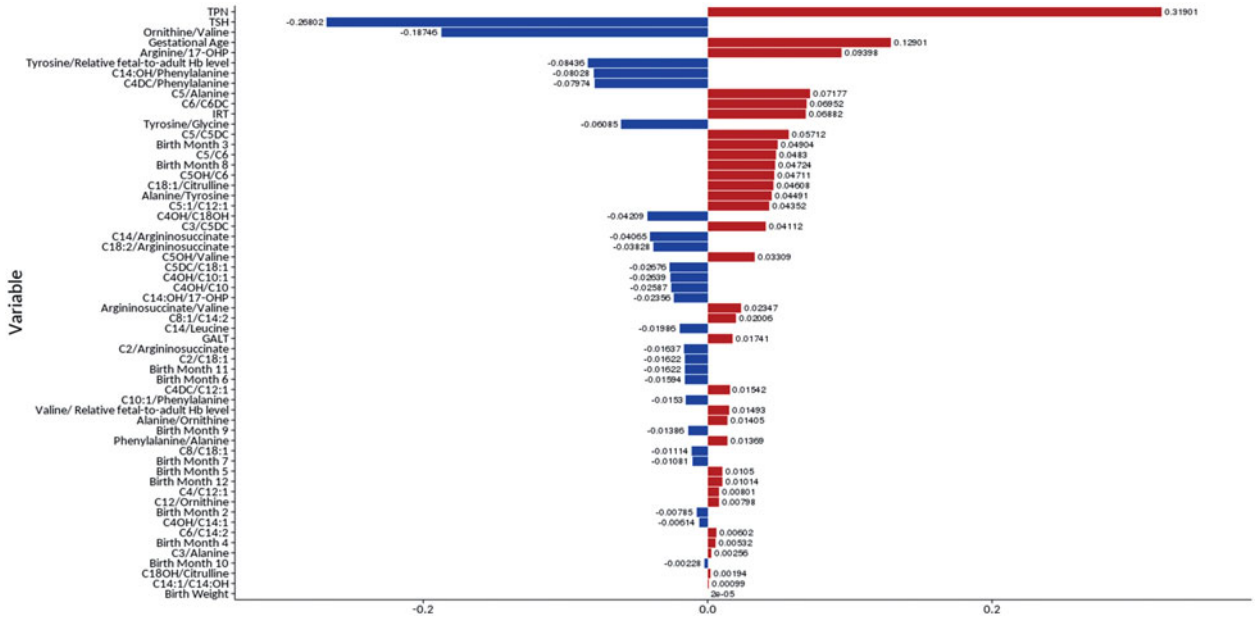

Figure 1. LASSO estimates for final model predicting infant mortality between 7 and 180 days after birth. *C*-statistic: 0.71 (95% CI: 0.68–0.74); optimism-corrected *c*-statistic: 0.61 (95% CI: 0.50–0.71). Three hundred fifty cases and 3498 controls were included in the LASSO model, as those with missing data were excluded.

were not continuously eligible for publicly-funded health care until the end of follow-up (until death for cases and until 6 months of age for controls).

We linked the source population to vital statistics death registrations to identify cases of infant death between 7 and 180 days after birth. Deaths in the early neonatal period (i.e. <7 days) were excluded since the likelihood of receiving newborn screening testing would be highly correlated with length of survival. Additionally, we excluded infant deaths due to external causes (e.g. trauma) since associations with newborn screening analytes would not be biologically plausible (Supplementary Table 1). For each case, we randomly selected 10 control infants matched on gestational age at birth (in completed weeks), birthweight *z*-score (computed according to Canadian sex- and gestational age-specific growth curves [8]), and month of birth.

Each infant's electronic newborn screening record contained information on 48 individual analytes (Supplementary Table 2) as well as information on biological sex, gestational age (completed weeks), mode of feeding, and timing of blood spot collection. We also derived variables representing ratio combinations ($n = 1128$) to capture the relative balance/imbalance between individual analytes. We described the baseline characteristics of cases and controls using frequency distributions and descriptive statistics. Given the high-dimensional nature of the data, we used a technique known as lasso [9,10] (least absolute shrinkage and selection operator) regression to select those variables that were most predictive of infant death, while avoiding model overfitting. The *c*-statistic and receiver-operating characteristic (ROC) curve were used to measure model fit and predictive performance, and we performed cross-validation to provide some protection from overfitting and to generate an optimism-corrected *c*-statistic. Additional details on the analyses are provided in Supplementary Appendix 1. We also conducted a sensitivity analysis to assess whether our model might perform better when limited to term births (i.e. ≥37 weeks' gestation). Finally, we carried out secondary analyses in which we refit models within more homogeneous cause-of-death categories. However, for these secondary analyses, we included deaths between 7 and 365 days of age in order to increase the sample size within the cause-of-death groupings (Supplementary Table 3).

Results

Among 627,531 live births in the source population, 351 infant deaths met our inclusion criteria and were matched to 3510 control infants (Supplementary Figure 1). Cases were more likely than controls to have had their screening sample taken at >72 h (18.8 versus 13.2%), and to have received Total Parenteral Nutrition (TPN; 8.8 versus 4.2%; Supplementary Table 4). The results from the predictive modeling are summarized in Figure 1. The final lasso model predicting infant mortality between 7 and 180 days of age included 58 variables, and resulted in a *c*-statistic of 0.71 (95% confidence interval [CI]: 0.68–0.74), with an

optimism-corrected *c*-statistic of 0.61 (95% CI: 0.50–0.71). The model ROC curve can be found in Supplementary Figure 2. The newborn screening analytes most strongly associated with 6-month infant mortality were thyroid-stimulating hormone and the ratio of ornithine to valine, each of which was inversely associated with mortality, while the ratio of arginine to 17-hydroxyprogesterone (17-OHP) was most positively associated with mortality (Figure 1). We did not observe any improvement in the model performance in a sensitivity analysis limited to infants born at term gestation (*c*-statistic: 0.65; optimism-corrected *c*-statistic: 0.60). Finally, in our secondary analyses of specific causes of infant death up to 1 year of age, the model for deaths due to congenital anomalies performed similarly to our main analysis (*c*-statistic: 0.76; optimism-corrected *c*-statistic: 0.58), but all other models performed poorly (Supplementary Table 5).

Discussion

In this population-based study, we assessed whether newborn screening analytes could be utilized to identify infants at risk for mortality between 7 days and 6 months of age. Unlike a recent study of early neonatal mortality among very preterm infants [4], our model was only modestly predictive of 6-month infant mortality (optimism-corrected *c*-statistic: 0.61). Although we have previously demonstrated varying degree to which newborn screening analytes can be used to identify infants at risk for neonatal sepsis (optimism-corrected *c*-statistic among term infants: 0.85) or pediatric chronic kidney disease (optimism-corrected *c*-statistic: 0.66) [3,11], the models for both of these specific morbidities performed better than that for mortality observed here. This discordance in predictive ability of our mortality model and our previous studies of specific morbidities may be due to inherent physiological heterogeneity of all-cause infant mortality during the first 6 months of life.

Heterogeneity in causes of death could also partly explain the discordance between our model's modest ability to predict 6-month infant mortality and Oltman and colleagues' strongly predictive model of 7-day infant mortality [4], though different source populations (i.e. general population of births versus extremely preterm births [4]) is another likely explanation. Despite these differences in model performance, both studies found the amino acids alanine (involved in gluconeogenesis [12]) and ornithine (involved in the urea cycle and kidney development [13]) to be among the stronger associations with infant mortality. However, the analyte most strongly associated with infant mortality in our study – thyroid stimulating hormone (TSH) – was not retained in the final model of 7-day infant mortality [4]. TSH plays a role in mediating inflammatory responses to antigen exposure and in preventing infection [14], which may explain its inverse association with mortality in our study.

Given our population-based source population, our results may be generalizable to similar populations. We were unable to partition our data into independent training and validation datasets owing to the small number of infant death events. Although we used cross-validation techniques to adjust for optimism, validation in an external sample would have been preferable. Although we conducted secondary analyses within more homogeneous cause-of-death categories and did not observe any improvements in model performance, the models were unstable owing to the small number of infant deaths within each subgroup. Finally, we were only able to investigate associations for a convenience set of analytes used in newborn screening. A broader, untargeted metabolomic approach may identify additional markers that could improve prediction. However, our results suggest that identifying nonspecific vulnerability, such as death, may be challenging using metabolomic approaches given the heterogeneity of this outcome. Untargeted approaches may be better suited to identification of more specific conditions.

This study contributes to a growing area of research examining the potential utility of routinely-collected newborn screening analytes for identifying neonates at higher risk of morbidity and mortality during the early months of life. Our analyses suggest that newborn screening analytes are not strongly predictive of infant mortality between 7 days and 6 months of age in the general population of newborns. Future studies should investigate whether predictive modeling within larger populations, using a broader set of metabolomic markers and more homogeneous cause-of-death categories.

Disclosure statement

No potential conflict of interest was reported by the authors. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario Ministry of Health or Long-Term Care is intended or should be inferred.

Data availability statement

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification.

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