REVIEW ARTICLE

Risk Prediction for Stillbirth and Neonatal Mortality in Low-resource Settings

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Abstract

High stillbirth and neonatal mortality are major public health problems, particularly in low-resource settings in low- and middle-income countries (LMIC). Despite sustained efforts by national and international organizations over the last several decades, quality intrapartum and neonatal care is not universally available, especially in these low-resource settings. A few studies identify risk factors for adverse perinatal outcomes in low-resource settings in LMICs. This review highlights the evidence of risk prediction for stillbirth and neonatal death. Evidence using advanced machine-learning statistical models built on data from low-resource settings in LMICs suggests that the predictive accuracy for intrapartum stillbirth and neonatal mortality using prenatal and pre-delivery data is low. Models with delivery and post-delivery data have good predictive accuracy of the risk for neonatal mortality. Birth weight is the most important predictor of neonatal mortality. Further validation and testing of the models in other low-resource settings and subsequent development and testing of possible interventions could advance the field.

Keywords: Low- and middle-income countries, Mortality fetal, Mortality neonatal, Neonatal, Newborn infant, Preterm infants, Perinatal mortality, Resuscitation, Stillbirth.

Newborn (2022): 10.5005/jp-journals-11002-0034

Introduction

Advances in perinatal and neonatal care, including the implementation of programs directed at improving perinatal care, have decreased stillbirth and neonatal mortality globally.[1] However, global stillbirth and neonatal mortality rates remain high with an increasing proportion of the under-5 child mortality.[2,3] Stillbirth and neonatal mortality are concentrated in low-resource settings of LMICs.[4,5] Approximately 98% of all stillbirths and neonatal deaths occur in these low-resource settings,[6] despite the sustained focus of many local or global public health organizations over the last few decades.[7]

A large number of deliveries occur at home in the absence of trained birth attendants that can provide an appropriate level of care.[7,8] Inadequate access to appropriate health care at delivery[9–11] is one of the leading factors responsible for preventable stillbirth and neonatal mortality.[12] Lack of optimal resources combined with varying social issues, cultural practices, and health literacy lead to wide healthcare disparities. The barriers to healthcare at different stages[13] and available resources vary between sites[14–16] making universal access to quality perinatal health care at delivery a difficult aim to achieve.

Timely identification of at-risk pregnancies and neonates is critical for reducing stillbirth and neonatal mortality in low-resource settings. It has been estimated that 0.8 million stillbirths and 1.9 million neonatal deaths per year could be prevented by optimizing the coverage and quality of prenatal, intrapartum, and neonatal care.[10] Unfortunately, studies focused on the quantification of stillbirth risk have been hampered by small event rates, a limited range of predictors that typically exclude obstetric history, lack of validation, and restriction to a single classifier (logistic regression). Consequently, predictive performance remains low, and risk quantification has not been adopted into antenatal practice.[17] Improved risk stratification and triaging of pregnancies and neonates at higher risk of mortality could lead to optimal resource utilization, ensuring an appropriate level of care for at-risk pregnancies and neonates. Analyses of data of pregnancies and neonates with a higher risk of stillbirth or neonatal mortality can inform the field and lead to improved resource allocation to improve care. A recently published study suggests that models that include delivery and post-delivery variables had good predictive accuracy for the risk of neonatal mortality and that birth weight was the most important predictor for neonatal mortality.[18] The current review highlights the available evidence for stillbirth and neonatal mortality risk prediction and identifies possible future research and implementation directions.

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How to cite this article: Shukla VV, Carlo WA. Risk Prediction for Stillbirth and Neonatal Mortality in Low-resource Settings. Newborn 2022;1(2):215–218.

Source of support: We would like to thank the NIH (Grant Number: UG1HD078437), Perinatal Health and Human Development Research Program of the University of Alabama at Birmingham and the children of Alabama Centennial Scholar Fund for supporting this project.

Conflict of interest: None

Risk Prediction for Stillbirth and Neonatal Mortality

Many studies report associations of pregnancy, delivery, and neonatal variables with stillbirth or neonatal mortality.[19,20] Specific variable associations with mortality do not help in identifying individual-level risk assessment. Multivariable risk prediction models provide individual-level risk assessment, which could be helpful for clinical interpretation and intervention.[21,22] Only a few investigators have published studies designed to develop models to predict the risk for stillbirth or neonatal mortality. The majority of the modeling studies for neonatal mortality risk prediction used data from extremely low birth weight neonates (ELBWs) who received intensive care in high-income countries (HIC).[23–27] The prediction models are specific for the type of population and settings from which they are developed, so the models from HICs cannot be extrapolated to low-resource settings of LMICs.

There is a paucity of outcome prediction models for intrapartum stillbirth and neonatal mortality in either HICs or LMICs. A few outcome prediction modeling studies from HICs[23,24] used machine learning-based modeling techniques as they are thought to perform better than conventional models when applied to relatively large data sets because these models may improve the ability to delineate complex relationships and identify novel interactions between variables. However, machine-learning models had not been performed with data from low resource settings of LMICs.[28]

Stillbirth and Neonatal Mortality Risk Prediction in Low-resource Settings in LMICs

Prediction models for intrapartum stillbirth and neonatal mortality in low-resource settings in LMICs have been reported recently.[18] This study had the largest sample size stillbirth or neonatal mortality prediction study to date with 502,648 prospectively enrolled pregnancies over 9 years from six countries in South Asia (India and Pakistan), Africa (Democratic Republic of Congo, Zambia, and Kenya), and Latin America (Guatemala) using a high-quality population-based vital registry (Global Network Maternal Neonatal Health Registry, GN Registry).[19] The investigators reported a comparison of predictive accuracies of conventional and advanced machine learning predictive modeling techniques to identify the best predictive model for intrapartum stillbirth and neonatal mortality in low-resource settings. The availability of a large sample size allowed building models using rigorous modeling techniques with independent training, test, and validation data sets to ensure their generalizability. Using the most important predictive variables and variable interactions from the best-identified model, which was a machine learning model, mortality risk prediction scores were developed. The study also identified important predictors for intrapartum stillbirth and neonatal mortality (Tables 1 and 2). This study determined that models based on prenatal or pre-delivery data have low predictive accuracy for intrapartum stillbirths, whereas neonatal mortality models that include delivery and post-delivery data had a good predictive accuracy of the risk for neonatal mortality. A similar finding of improved predictive accuracy with the addition of delivery and post-delivery variables has been reported in relatively small studies from both HICs[23] and LMICs.[22] Birth weight was identified as the most important predictor of neonatal mortality (Table 2). Birth weight has also been reported in small studies to be associated with the risk for neonatal mortality in studies from HIC,[23,26,29,30] although these studies did not identify that birth weight was the best predictor. An innovative easy to use mortality risk-prediction tool using birth weight as a continuous measure was developed for use by healthcare workers for point of care risk assessment (Fig. 1).

Future Directions for Retrospective or Prospective Assessment of the Risk Score and Tool

The study from the GN Registry[18] was done using a prospectively collected high-quality population-level research database, so the study results are likely to be reproducible in communities in resource-limited regions similar to those of the study settings. However, retrospective and prospective studies could be done to evaluate the predictive accuracy of the risk score and risk assessment tool in communities outside of the GN Registry and adapt them as needed. The score was developed using readily available clinical data; data on stratification of individual risk factors as per illness severity, details of treatments received, laboratory variables, and clinical response were not included for ease of use and because of unavailability of such complex variables. It may be possible to further improve the score predictive accuracy by including complex variables, but such an attempt should be made carefully as that may need model reconfiguration with changes in the variable coefficients.[31] The incremental benefit of such an

Table 1: Top predictors for intrapartum stillbirth and neonatal mortality

Rank	*Predictor*	*AUC*	*AUC increase*
Prenatal			
1	Cluster perinatal mortality	0.6	X
2	Gestational age at enrollment	0.61	0.008
3	Maternal age	0.61	0.003
4	Birth order	0.62	0.008
5	Parity	0.63	0.009
Pre-delivery			
1	Antepartum hemorrhage	0.56	X
2	Cluster perinatal mortality	0.64	0.086
3	Gestational age at enrollment	0.64	0.002
4	Hypertension/pre-eclampsia/ eclampsia	0.66	0.018
5	Maternal age	0.66	0.002

Predictors are added consecutively using the gradient boosted ensemble model; then AUC is calculated. Intrapartum stillbirth was defined as non-macerated stillbirth occurring presumably during labor, and neonatal mortality was defined as mortality from birth to 28 days. Cluster perinatal mortality is the perinatal mortality rate within each distinct geographical area (cluster) of the sites as defined by the GN Registry. Hypertensive disease/severe pre-eclampsia/eclampsia is defined as blood pressure >140/90 mm Hg, proteinuria, and seizures[18]

Table 2: Top predictors for neonatal mortality

Delivery/day 1			
1	Birth weight	0.78	X
2	Bag and mask resuscitation	0.81	0.039
3	Gestational age	0.81	0.003
4	Cluster perinatal mortality	0.82	0.001
5	Maternal age	0.82	0.004
Post-delivery/day 2			
1	Birth weight	0.76	X
2	Neonatal hospitalization	0.81	0.05
3	Neonatal antibiotics	0.84	0.032
4	Gestational age	0.84	0.003
5	Bag and mask resuscitation	0.85	0.01

Predictors are added consecutively using the gradient boosted ensemble model; then AUC is calculated. Neonatal mortality was defined as mortality from birth to 28 days. Cluster perinatal mortality is the perinatal mortality rate within each distinct geographical area (cluster) of the sites as defined by the GN Registry[18]

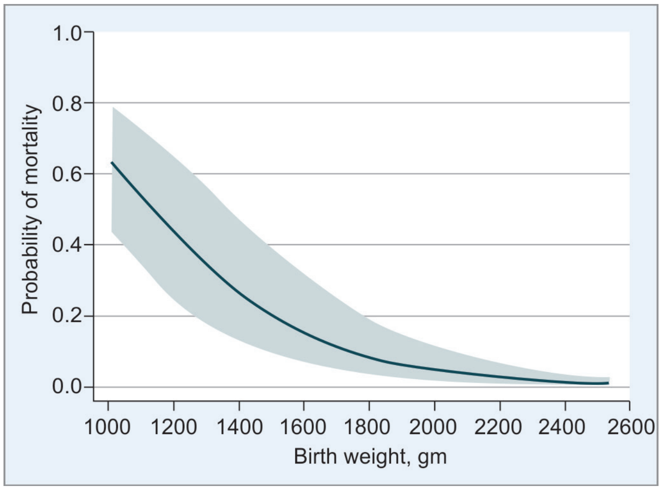

Fig. 1: Probability of mortality as a function of birth weight. The risk for neonatal mortality increased with decreasing birth weight. Birth weight was the most important predictor of neonatal mortality in both the delivery/day 1 and post-delivery/day 2 scenarios and explained a large percentage of the variance of mortality. The probability of neonatal mortality with decreasing in birth weight occurred in both the delivery/day 1 and post-delivery/day 2 scenarios. Reproduced with permission[18]

exercise may not be reasonable as the risk prediction score and tool had good predictive accuracy using readily available clinical variables. After ensuring the applicability of the risk score and risk tool, implementation research assessing mortality risk-based triage, referral, and management for reducing the number of stillbirths and neonatal deaths in low-resource settings of LMICs can be tested. Pre-delivery estimates of birth weight could also be tested as a strategy for pre-delivery triage and referral.

Conclusion

Timely identification of at-risk pregnancies and neonates is critical for the reduction of stillbirth and neonatal mortality in low-resource settings of LMICs. Risk stratification and triage of pregnancies and neonates at higher risk of mortality could help to reduce the burden of stillbirth and neonatal mortality in low-resource settings LMICs. The available risk assessment score and tool can be tested further using retrospectively or prospectively collected data. Implementation research should also be used to assess and improve the utility of these models. A population-based, multi-country, and high-quality database would assist and promote future outcome prediction research in low-resource settings.

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