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Predicting outcomes in congenital diaphragmatic hernia

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ABSTRACT

Identification of CDH infant populations at high risk for mortality postnatally may help to develop targeted care strategies, guide discussions surrounding palliation and contribute to standardizing reporting and benchmarking, so that care strategies at different centers can be compared. Clinical prediction rules are evidence-based tools that combine multiple predictors to estimate the probability that a particular outcome in an individual patient will occur. In CDH, a suitable clinical prediction rule can stratify high- and low-risk populations and provide the ability to tailor management strategies based on severity. The ideal prediction tool for infants born with CDH would be validated in a large population, generalizable, easily applied in a clinical setting and would clearly discriminate patients at the highest and lowest risk of death. To date, 4 postnatal major clinical prediction rules have been published and validated in the North American CDH population. These models contain variables such as birth weight, Apgar score, blood gases, as well as measures of pulmonary hypertension, and associated anomalies. In an era of standardized care plans and population-based strategies, the appropriate selection and application of a generalizable tool to provide an opportunity for benchmarking, policy creation, and centralizing the care of high-risk populations. A well-designed clinical prediction tool remains the most practical and expedient way to achieve these goals.

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Congenital diaphragmatic hernia (CDH) is a condition with variable morbidity and mortality. Large population-based studies suggest the overall mortality from CDH is close to 70% at 1 year.[1–3] Despite advances in knowledge of many facets of this condition, at its core, CDH remains enigmatic.[4] Our understanding of the trajectory of these patients is imperfect and there are multiple complex factors that determine whether a child will have a good or bad outcome. Clinical prediction rules or models can be used to predict the behaviors of populations of infants with CDH.

Clinical prediction rules are evidence-based tools that combine multiple predictors in order to estimate the probability that a certain outcome (e.g., mortality) in an individual patient will occur.[5] A good prediction tool can ideally to be used to guide management and inform prognosis.[6] Clinical prediction rules can be very powerful. They can weigh multiple factors beyond the scope of the bedside clinicians and are not prone to human inconsistencies in application of evidence.[7] Although the concept of an algorithm or formula to predict outcome seems simplistic, the usefulness of a well-constructed clinical predictive rule should not be underestimated. In the case of CDH, a suitable clinical prediction rule can stratify high- and low-risk populations and provide the ability to tailor management strategies based on severity.[8]

Being able to predict high-risk patients *prenatally* can guide conversations about termination and identify fetuses who may be targets for experimental or potentially risky therapies.[3,9–11] Prenatal risk stratification may also identity populations to be considered for delivery at high-volume centers, and guide anticipation of resources that may be required for the infant postnatally.[12] However, identifying infants at high risk for mortality *postnatally* may help to identify groups that might benefit from alternative proactive care strategies, may help guide discussions surrounding palliation and help to standardize reporting and benchmark outcomes so that care strategies at different centers can be compared.[13] As novel strategies are developed to target patients at highest risk of death, reliable means of identifying this high-risk group is a key to the development and evaluation of clinical trials. The higher the risk of the experimental intervention, the more important the reliability of prediction becomes. Multicenter trials require that variables are available at the time of enrollment, are measured in a similar way across centers, and have similar and accurate predictive value. Given the variability in the purpose and timing of prediction models as well as the availability

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and type of information used in these models, several clinical prediction tools have been developed.[8,14–18]

There are limits to the use of clinical prediction rules and the numerous models available for use. In order to understand which models should be used under which circumstances and how, we must consider what a clinical prediction rule is and how it is generated.

Clinical prediction rules are generally created using regression modeling. The model should be derived from a population of patients that is generalizable to the population in which the tool will be used. In a model designed to predict mortality during hospitalization, the relationship between the presumed predictive variables (such as prematurity or presence of a chromosomal anomaly) and mortality is determined by entering the variables into a regression model. A selection algorithm is used to identify each variable that has an independent, significant association with the mortality for inclusion in the final model. The odds ratio or coefficient measure of the variables within the final regression model can be used as measures of prediction when applied to future populations. In the simplest model, the odds ratios can be used to assign a relative point value for each variable. For each risk factor identified in a patient at the time of prediction rule application, the number of points assigned to that factor are applied. These are added up to give a score, which correlates with a defined risk of mortality for that patient.

When selecting and using prediction models, there are a number of very important considerations:

1. The prediction model should be validated and its discriminatory properties and calibration should be understood. If the model is applied to the exact same patients that were used to generate the model, it will prove to be very accurate in predicting outcomes. In order to see how well a clinical prediction works in real life, the performance of the model should be validated on a different population. In a large dataset, this can be done by developing the prediction model using one segment of the dataset and testing it on another (internal validation). It is even more important to demonstrate that the prediction model will work when it is applied to a different set of relevant patients (external validation). The performance of a model will almost never be as good when tested in a validation population.
   The actual performance of a model can be evaluated based on its calibration and discrimination. Calibration refers to the agreement between predicted and observed outcomes across the entire range of data. There are various measures of calibration that are used to evaluate a model's performance, the Hosmer–Lemeshow test being one of the most common. Calibration can appear falsely poor with large samples. Discrimination is generally the most important property of a prediction model. Discrimination indicates the ability of the model to correctly identify the risk of an outcome for populations at different risk strata. The c statistic or “area under the curve” (AUC) is typically used to report the discrimination of a model; although tables that compare the predicted and actual outcome rates of various risk strata may provide the most intuitive indication of a model's discriminatory properties.
2. The prediction model should be applicable to the population on which it is going to be used and the variables selected should be specific to the time at which the model is to be applied. If a model is created and validated in a patient population within one environment, it may not perform well if applied to different patients in a different environment. In addition, the factors that are entered into a model may be measured differently or not available when it comes time to apply the model elsewhere. The variables within a model determine when the model can be used. A model that contains variables related to the surgical repair of CDH may be very accurate if applied at the time of surgery, but is not an appropriate model to use to determine the risk of death in an infant at the time of birth as operative variables are not available. The predictive abilities of the model will also be compromised as a model derived from a population of patients that survived to surgical repair is likely not generalizable to the preoperative population.
   The importance of variable selection can be seen in models that include clinical outcomes as predictors within a model. For example, episodes of sepsis or the need for ECMO may be excellent predictors of outcome but they are outcomes themselves and directly influenced by care strategies. Moreover, they can occur at varying time points in a patient's care, which makes the tool most valuable when it is applied retrospectively and least valuable when it is applied early in a patient's course of care.
3. A prediction model should be selected that contains variables that most, if not all, patients will have available. This is particularly important when looking at postnatal prediction models that contain prenatal predictors. In a population that receives relatively consistent, standard, prenatal care, a model with prenatal predictors can perform exceedingly well. However, there are many other instances when prenatal data may not be available and the reasons for this missing information can be variable, ranging from maternal socioeconomic barriers, physician practices, and data transfer issues. Models have diminished utility in these situations.
4. Prediction models predict probabilities and not certainties. The model works best when it is used to classify patients according to risk strata. The risk strata can be used within care plans to determine population-level management of patients and can be used to benchmark outcomes between different sites for populations at similar risk strata.

The ideal prediction tool for infants born with CDH would be validated in a large population, generalizable, easily applied in a clinical setting, and would clearly discriminate patients at the highest and lowest risk of death. The population of infants for whom we can most successfully identify high- and low-risk strata are those who assessed at the time of surgery. As mentioned previously, this population already represents a group of patients with improved outcomes, as other patients have not survived to surgery. The defect size at the time of surgery represents one of the best predictors we have of mortality related to pulmonary hypoplasia. Several studies have demonstrated that large defects requiring a patch repair are associated with low survival while defects small enough to undergo a primary repair have an extraordinarily high survival.[19,20] Taking into account potential confounding by treatment bias, the defect size itself, a measure that directly relates to the underlying pathophysiology, predicts a striking difference in outcome.[19,20] This simple measure holds great predictive value but cannot be applied until the time of surgery. Although there is value in being able to stratify by survival at the time of surgery, there is even greater value in predicting adverse outcomes earlier in the treatment path.

Prenatal prediction models are described elsewhere in this issue and have considerable value if the prenatal variables are both available and consistently measured. Although prenatal prediction models are commonly used for decision-making around fetal interventions, postnatal models are less common. Postnatal prediction models can be used by surgeons, intensivists, and neonatologists to develop care plans and can use both prenatal and postnatal predictors. Several postnatal prediction rules for CDH are existing now.

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