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The Quest for Precision Medicine: Unmeasured Patient Factors and Mortality After Congenital Heart Surgery

Sara K. Pasquali, MD, MHS, **Michael Gaies, MD, MPH**, **Mousumi Banerjee, PhD**, **Wenying Zhang, MS**, **Janet Donohue, MPH**, **Mark Russell, MD**, **J. William Gaynor, MD**

Division of Cardiology, Department of Pediatrics and Communicable Diseases, University of Michigan C.S. Mott Children's Hospital, Ann Arbor, Michigan; Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; and Department of Surgery, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Abstract

Background.—Emerging data across many fields suggest that unique patient characteristics can impact disease manifestation and response to therapy, supporting "precision medicine" approaches and more individualized and targeted therapeutic strategies. In children undergoing congenital heart surgery, current risk models primarily focus on the population level, and their utility in understanding precise characteristics that place individual patients at risk for poor outcome remains unclear.

Methods.—We analyzed index surgeries in the Pediatric Cardiac Critical Care Consortium (PC^4) registry (August 2014 to May 2016) and utilized a previously constructed model containing patient factors typically included in in-hospital mortality risk models (age, weight, prematurity, chromosomal anomalies/syndromes, preoperative factors, The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery score). Partitioned variances based on a hierarchical generalized linear model were used to estimate the proportion of variation in mortality explained by these factors.

Results.—A total of 8406 operations (22 hospitals) were included. We found that only 30% of the total between-patient variation in mortality in our cohort was explained by the patient factors included in our model. Age, The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery score, and preoperative mechanical ventilation explained the greatest proportion of variation. Of the variation that remained unexplained, 95% was attributable to unmeasured patient factors. In stratified analyses, these results were consistent across patient subgroups.

Conclusions.—Patient factors typically included in congenital heart surgery risk models explain only a small portion of total variation in mortality. A better understanding of other underrecognized factors is critical in further defining risk profiles and in developing more individualized and tailored therapeutic strategies.

Precision medicine involves tailored, individualized therapeutic strategies for patients based on understanding their unique characteristics and risk profiles.[1] Despite significant

Address correspondence to Dr Pasquali, University of Michigan C.S. Mott Children's Hospital, 1540 E Hospital Dr, Ann Arbor, MI 48105; pasquali@med.umich.edu.

improvements in early survival after congenital heart surgery (CHS), patients still encounter significant short-term and long-term morbidity and mortality. Precision medicine approaches could provide insight to elucidate the best option for an individual given their risk profile, mitigating adverse events and optimizing survival and quality of life.

However, to develop more individualized and tailored strategies, it is necessary to further our knowledge of the unique factors that place a patient at risk for morbidity and mortality after CHS. Our current understanding of patient characteristics associated with poor outcomes comes in large part from efforts that have focused on developing population-level risk models to account for differences in baseline severity of illness or case-mix across hospitals to support benchmarking efforts.[2-4] For example, variables such as age, presence of genetic syndromes, and operative complexity have been found to consistently associate with morbidity and mortality after CHS.[2-4] It remains unclear how such population-level models and these traditional risk factors perform in understanding the precise characteristics that place individual patients at risk for poor outcome. Emerging data suggest that additional factors not traditionally incorporated into current risk models may have an important impact on outcomes after CHS, including, for example, abnormalities in the maternal-fetal environment or the presence of certain nonsyndromic genetic variation.[5-11]

In this context, we performed an analysis within the Pediatric Cardiac Critical Care Consortium (PC^4) clinical registry to determine the extent to which measured patient factors included in traditional risk models explain variability in mortality after CHS. Our hypothesis was that these factors explain a relatively small proportion of variation in mortality at the patient level, and that this unexplained variation highlights the need to explore additional patient factors impacting outcomes if we are to move toward precision medicine approaches for patients requiring CHS.

Patients and Methods

Data Source

The PC^4 is a quality improvement collaborative that collects data on all patients with primary cardiac disease admitted to the cardiac intensive care unit of participating hospitals.[12] The PC^4 maintains a clinical registry to support research and quality improvement initiatives.

Each participating center has a trained data manager who has completed a certification exam. The data managers collect and enter data in accordance with the standardized PC^4 Data Definitions Manual. The PC^4 registry shares common terminology and definitions with applicable data points from the International Pediatric and Congenital Cardiac Code, The Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database, and American College of Cardiology Improving Pediatric and Adult Congenital Treatment Registry, as previously described.[12] Participating centers are audited on a regular schedule and audit results suggest complete, accurate, and timely submission of data across centers, with the most recent published results demonstrating a major discrepancy rate of 0.6% across 29,476 fields.[13] The University of Michigan Institutional Review Board provides oversight for the

PC[4] Data Coordinating Center; this study was reviewed and approved with waiver of informed consent.

Study Population

The episode of the analysis was the surgical hospitalization associated with any index cardiovascular operation. We included all hospitalizations between August 2014 and May 2016. Hospitalizations were excluded where the primary operation was ligation of patent ductus arteriosus in a neonate less than 2.5 kg or if it could not be classified according to the STS–European Association for Cardio-Thoracic Surgery (STAT) Mortality Categories.[14] We also excluded 1 hospital who had recently joined the consortium and had accrued only a small number of cases to date (<50).

Model, Outcome, and Predictor Variables

We utilized a previously constructed model to assess in-hospital mortality. This model is currently used to provide case mix–adjusted benchmark data to hospitals participating in PC[4], and was constructed using a similar modeling strategy to that described previously for intensive care unit mortality.[4] Predictor variables included patient factors traditionally utilized and previously validated for the purpose of population-level models used for case mix adjustment in the field.[2-4] Age, weight, prematurity, chromosomal anomalies or syndromes, preoperative mechanical ventilation, preoperative shock, preoperative mechanical circulatory support, other STS-defined preoperative factors, and STAT score were included in the final model (Table 1). Note, prior cardiac surgery, extracardiac anomalies, preoperative renal failure, and preoperative neurologic deficit were not significant in the final model and not included. The bias-corrected C-statistic of this model was 0.88, similar to other similar models widely used in the field, such as the STS model (C-statistic = 0.86).[2] It is important to note that the C-statistic does not convey information regarding the amount of variation explained by the model, but rather it assesses discrimination and whether a randomly selected patient who had the outcome event of interest was assigned a higher risk score by the model than a patient who did not.

Variation Explained

To assess the amount of variation in mortality explained by the variables in our analysis, we used a previously described statistical approach known as partitioned variances.[15-17] This approach allows us to assess the proportion of variation in the cohort “explained” by factors included in the statistical model (both hospital-related and patient-related factors) as well as the proportion of variation that is “unexplained.” Specifically, a hierarchical logistic regression model (ie, generalized linear mixed model) with a hospital-specific random effect term was used. The total variance in mortality is the sum of 3 variance components: (1) variance due to the hospital random effect, (2) variance due to measured patient factors (fixed effects) included in the model, and (3) variance due to unmeasured patient factors. In this context, *unmeasured* refers to factors not included in the model. The variance components above were estimated based on the hierarchical logistic regression model. This allowed us to assess the relative importance of each component. The residual intraclass correlation coefficient was calculated based on the fully adjusted model and represents the

percentage of variation attributable to unmeasured hospital factors after adjustment for patient variables.

We further evaluated the proportion of variation explained by specific individual patient characteristics by constructing a series of adjusted models as described previously in which only 1 of the patient factors was included in the models at a time in addition to the hospital-specific random effect, and the variance partitioning analysis was repeated. In addition, we performed a stratified evaluation to assess whether results differed across specific strata, and repeated the analyses within STAT categories 1-3 and 4-5 as well as within the neonate vs nonneonate groups.

Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) or STATA Version 14 (Stata Corp, College Station, TX), with statistical significance at a *P* value of less than .05.

Results

Study Population

The study cohort included 8406 operations from 22 hospitals (Table 1). Hospitals' average annual volume of index surgical cases ranged from 205 to 726 cases/year. The overall in-hospital mortality rate was 2.8% and ranged from 0.5% to 5.5% across hospitals. The study cohort included 20.4% neonates and 12.8% with a chromosomal anomaly or syndrome. Patient distribution across STAT categories was 29% STAT 1, 33% STAT 2, 13% STAT 3, 21% STAT 4, and 4% STAT 5.

Variation in Mortality Explained—Overall

Patient factors included in the analysis are displayed in Table 1. Results from our evaluation of the proportion of variation in mortality explained by these patient factors are summarized in Table 2. Overall, 30% of the total variation in mortality in our cohort was explained by these patient factors, while 4% was related to hospital. Of the variation that remained unexplained, 95% was at the patient level.

Variation in Mortality Explained—Specific Patient Factors

We further evaluated the proportion of variation explained by specific individual patient factors (Table 3). We found that the variable that explained the greatest variation was age or prematurity status (17.5%), followed by STAT score (13.4%), and preoperative mechanical ventilation (12.0%). Each of the other variables explained less than 10% of the variation in mortality.

Variation in Mortality Explained—Stratified Analyses

In addition, we performed stratified analyses to understand whether the proportion of variation in mortality explained by patient factors included in our analysis varied across certain subgroups of patients. These included the subgroups of STAT 1-3 vs 4-5 and neonates vs non-neonates. We found fairly consistent findings, with the proportion of

variation in mortality explained by patient factors ranging from 22% to 27% across all of the subgroups examined.

Comment

In this analysis, we found that measured patient factors typically included in traditional CHS risk models explain a relatively small proportion of between-patient variation in mortality. This finding does not indict the usefulness of existing models, as they were developed primarily for population-level assessments. However, our analysis suggests that for the purposes of risk prediction at the patient level and the design of more precise and tailored therapeutic strategies, further efforts are needed to better understand additional important patient factors that impact clinical outcomes.

The ultimate goal of improved patient-level risk prediction is in matching therapeutic strategies to an individual patient's risk profile, or practicing "precision medicine." For example, consider a full-term infant with tetralogy of Fallot who requires an intervention in the newborn period. This patient may be eligible for a number of surgical or catheter-based interventions, as well as various perioperative monitoring strategies and care protocols. By our current risk models, this patient may be considered relatively low risk aside from their age. However, emerging data suggest that an infant with the same diagnosis who also has specific nonsyndromic genetic anomalies, or was born to a mother with placental dysfunction, may have a completely different risk profile that would not be identified by our current models.[5-11] These as yet unaccounted for individual vulnerabilities may, for example, render the patient less tolerant of cardiopulmonary bypass, increasing the benefit of alternative treatment options or certain postoperative monitoring or therapeutic strategies. A more comprehensive understanding of the precise factors impacting risk could result in more patient-specific strategies for intervention and monitoring and therapies to mitigate this risk.

To realize the potential of precision medicine approaches several additional steps are necessary. First, we must determine the key unmeasured or underrecognized patient factors that predict risk for adverse events, or response to various therapies and treatment strategies. The list of potential variables remains infinite, but candidates come from some specific emerging domains such as the maternal-fetal environment, sociodemographic factors, genetic variation, and other biologic indicators such as various omic data.

For example, Kim and associates[10] recently investigated the impact of genetic variation in oxidative stress management and vascular regulation pathways on mortality after cardiac surgery in nonsyndromic children undergoing CHS. Variants in the *VEGFA* gene and *SOD2* gene were evaluated and genotypes were grouped to form a risk score reflecting the cumulative number of risk alleles. The total burden of risk alleles was found to be additive, and after adjustment for common clinical factors included in our current models, patients with the highest risk score had an adjusted hazard ratio of 15.64 for worse transplant-free survival.[10]

Additionally, Kim and colleagues[18] demonstrated that the presence of a copy number variant (CNV) was also associated with significantly decreased transplant-free survival after CHS.[18] CNVs are duplications or deletions of genomic regions, and previous studies have shown that large CNVs are potentially pathogenic and are overrepresented in children with congenital heart disease.

Another recent example of previously underrecognized risk factors relates to the maternal-fetal environment and factors associated with placental dysfunction. It has been shown that pregnancies in which the fetus has congenital heart disease have an increased prevalence of preeclampsia, small for gestational age, and preterm birth, all of which are evidence of impairments in the maternal-fetal environment. Gaynor and colleagues[5] found that an impaired maternal-fetal environment was identified in up to 30% of neonates undergoing complex CHS, and was associated with significantly lower survival at 36 months of age. Importantly, these findings do not appear to be completely mediated by birth weight or gestational age (factors currently included in our traditional models). In Gaynor and colleagues'[5] study, the most common factor associated with an impaired maternal-fetal environment was fetal growth restriction, which is not necessarily equivalent to either low birth weight or preterm birth. For example, a neonate may have a birth weight greater than 2.5 kg and yet still have fetal growth restriction; conversely, neonates born before 37 weeks may show appropriate growth.

In addition to the impact of individual risk factors, there is also emerging evidence that there may a cumulative effect of an increasing number of risk factors (accumulating deficits), and an individual's risk can be thought of as an aggregate of risk factors across multiple domains.[19] Such models have been developed to evaluate risk of death after pediatric heart transplantation. In a recent study, overall mortality was 7.1% in patients with no risk factors, 13% in those with 3 risk factors, and 71.4% in patients with 4 risk factors.[19] Further analysis in this area in a broader CHS population may provide additional understanding regarding the impact of not only individual factors, but also the cumulative impact of multiple factors.

A second concept key to recognizing the potential of precision medicine approaches is the need to move away from procedure-based and episode-based analysis and take a more patient-centered, disease-based approach. This includes measurement of long-term outcomes outside of hospitalizations. For example, understanding how specific risk factors impact not only in-hospital outcomes associated with the Norwood procedure, but also 5-year survival in those with hypoplastic left heart syndrome whether undergoing a Norwood operation, hybrid palliation, or transplant. This will require a transition from our current data infrastructure in the field to a more comprehensive and integrated system.[20] Last, it is important to note that future discoveries that enable to us to better define longer-term outcomes and associated risk factors hold the potential to not only improve patient-level risk prediction, but also further augment population-level models used for hospital quality assurance and benchmarking activities.

Limitations

The primary limitation of our analysis results from the scope of our database. The PC[4] clinical registry is a detailed source of clinical data on patient characteristics, therapies, and

outcomes, but by design it includes data easily extractable from the medical record. Similar to other existing registries, it does not regularly capture more detailed variables that are likely needed to more precisely understand and predict patient-level outcomes. The recent integration of the dataset with real-time streams of physiologic data from the intensive care unit and future plans to integrate with genetic or biomarker data and maternal-fetal data may foster these types of analyses moving forward. Further, the recent launch of a longitudinal patient reported outcomes module linked with the PC^4 dataset, and integration of the registry with others in the field to form a "network of networks" known as Cardiac Networks United will support future assessment of outcomes beyond the intensive care unit and in-hospital period.[20,21] In addition, certain rare patient factors (eg, preoperative renal failure) that have been shown to have an association with mortality in other models were not statistically significant or retained in the model we utilized, but might have an important role in predicting patient-level outcomes. The overall similarity of the variables included in our model and our model performance compared with other similar models widely used in the field suggest that our findings are likely generalizable.[2,3] Our sample size also prohibited evaluation of specific patient populations; future analyses may focus on the differential impact of certain patient factors across subgroups, and we anticipate that some factors may be more important in some patient groups than in others. In addition, the PC^4 registry includes primarily medium-volume and large-volume hospitals. It is possible that analysis of a broader group of hospitals or the addition of other hospital factors in the models such as surgical volume may result in an increase in the proportion of variation in mortality explained by hospital. However, given the substantial variability in mortality across hospitals seen even in the cohort we analyzed, we do not believe that our conclusions would be significantly altered. Last, we limited our analysis to evaluation of preoperative and operative variables. Some of the unexplained variation in mortality is likely to be explained with inclusion of factors such as postoperative complications. However, these types of variables are not as useful for the purpose of predicting patient outcomes at the time of preintervention decision making and early perioperative care period, the point at which precision medicine approaches would often be applied. Certain types of unmeasured patient factors such as complications are also likely influenced by hospital-specific practices and variability as well, and further understanding of these relationships is also necessary.

Conclusion

This analysis suggests that patient factors typically included in traditional CHS risk models explain a relatively small proportion of variation in mortality. To develop tools that more precisely predict individual risk, further efforts to better understand and include other underrecognized factors are necessary. Emerging data suggest these may include maternal-fetal, genetic, and other biophysiologic variables. Further work is needed to develop strategies to efficiently integrate these types of data streams with existing clinical data, as well as with critical outcomes beyond the in-hospital period. These efforts may hold the potential to further our ability to develop more individualized and tailored therapeutic strategies for patients undergoing CHS.

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Table 1.

Patient Factors Included in the Model, Distribution, and Associated Mortality Within the Study Population

Variable	Distribution of Patient Factors in the Study Population (N = 8406)	Mortality Rate in Each Subgroup
Age/prematurity status		
Neonate preterm	288 (3.4)	47 (16.3)
Neonate full term	1431 (17.0)	100 (7.0)
Infant	2745 (32.7)	50 (1.8)
Child	3474 (41.3)	31 (0.9)
Adult	468 (5.6)	6 (1.3)
Any chromosomal abnormality/syndrome	1709 (20.3)	69 (4.0)
Weight at surgery		
Underweight	1866 (22.2)	90 (4.8)
Normal weight	6266 (74.5)	142 (2.3)
Overweight	274 (3.3)	2 (0.7)
Preoperative factors		
Mechanical circulatory support	52 (0.6)	11 (21.2)
Shock	80 (1.0)	21 (26.3)
Mechanical ventilation	623 (7.4)	100 (16.1)
Any other	2181 (26.0)	109 (5.0)
STAT		
Score	0.5 (0.3–1.3)	
Category		
1	2464 (29.3)	7 (0.3)
2	2767 (32.9)	37 (1.3)
3	1070 (12.7)	24 (2.2)
4	1787 (21.3)	115 (6.4)
5	318 (3.8)	51 (16.0)

Values are n (%) or median (interquartile range).

STAT, The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

Table 2.

Results of the Variance Partitioning Analysis: Explained and Unexplained Mortality Variation in the Cohort

Mortality Variation	Percentage
Explained	
By patient factors included in the model	30
By hospital	4
Unexplained	66[a]

[a]95% related to unmeasured patient factors, 5% to hospital.

Table 3.

Proportion of Variation in Mortality Explained by Individual Patient Factors Included in the Model

Patient Factor	Variation Explained (%)
Age/prematurity status	17.5
STAT score	13.4
Preoperative mechanical ventilation	12.0
Other preoperative factors	6.8
Weight at surgery	4.2
Preoperative shock	4.2
Any chromosomal abnormality/syndrome	2.7
Preoperative mechanical circulatory support	2.6

Assessed by constructing a series of models as described in the methods in which only 1 of the patient factors was included at a time and the variance partitioning analysis was repeated; for this reason the sum, does not add up to 30%, as in the overall model described in Table 2.

STAT, The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.