EMERGING TECHNOLOGY REVIEWS

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Genotype Assessment as a Tool for Improved Risk Prediction in Cardiac Surgery

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PREDICTION OF PERIOPERATIVE mortality and morbidity risks remains an important issue in adult cardiac surgery for both the patient and the physician. One objective method to estimate the perioperative risk involves the use of risk prediction models (RPMs). These statistical tools have been utilized for more than 30 years and primarily are based on the correlations that exist among a patient's preoperative health condition, the type of surgical procedure, and the frequency of postoperative complications that result from surgery.[1-3] One of the major limitations of current RPMs is their relative lack of accuracy. In fact, the calculated perioperative risk of death during adult cardiac surgery may be incorrect in 1 of every 5 patients and even higher in high-risk groups.[3,4] Over the past decade, linkages have been identified between inherited genetic information and many chronic pathologies (eg, cardiovascular diseases, diabetes mellitus, cerebrovascular diseases) that increase the risks of postoperative complications and mortality following cardiac surgery.[4-6] These linkages raise the question of whether information about a patient's genome could improve the predictive capability of existing RPMs. The present review addresses this question.

OUTCOME MEASUREMENT AND RISK PREDICTION IN CARDIAC SURGERY

As perioperative risks simply reflect the expected proportions of outcomes from a surgery, specific outcomes must be measured before perioperative risks can be predicted. Treatment outcomes can be measured in many different ways, including patient satisfaction, symptom relief, the fulfillment of specific medical criteria for curing a disease, the occurrence of complications, or death.[7] The classification of these outcomes into at least 2 defined categories allows for the determination of associations between the phenomena that occur during treatment and the outcomes of the treatment in question. Inferences from these observations form the background for generating assumptions about the rules that govern future events.[7,8] However, predicting the risk of perioperative complications is a difficult and somewhat uncertain task.[9] This process requires both basic and complex knowledge that can be simplified into the 3 questions of what, why, and how risks can be predicted and the consideration of the possible pitfalls of these predictions.

WHAT RISKS CAN BE PREDICTED?

Traditionally, the eventual outcomes of medical procedures, such as the mortality or morbidity of a defined illness, are measured as dichotomous categoric data.[3,7,8] Mortality is used likely because it is a robust and reliable outcome measure. However, the search for improvements in cardiac surgical treatment procedures has led to research on major postoperative morbidities that clearly influence postoperative mortality, such as acute kidney injury, acute lung injury, infection, and neurologic sequelae.[6,10-13] The identification of factors that increase the probability of major adverse events can stimulate further research initiatives that strive for the prevention of these events or their early treatment.

WHY PREDICT THE PERIOPERATIVE RISKS OF COMPLICATIONS?

Outcome measure models allow for the stratification of patients with respect to their observed or predicted risk of death or specific morbidity. This ability is indispensable for the research and validation of new drugs and treatment methods.[14] Also, this stratification is useful for educational purposes.[15] However, the use of poor outcome data for hospital quality control studies, particularly with respect to mortality analyses, has produced many controversies.[7,14,16] Accurate data and appropriate adjustments for patient risk factors are indispensable aspects of quality comparison and control.[17] RPMs also may be used directly to provide information to individual patients for decision-making purposes; however, this function of RPMs remains complicated and a controversial issue.[7,9]

HOW TO CALCULATE THE PERIOPERATIVE RISKS?

Estimating the existing perioperative risk in a cardiac surgical patient is a process consisting of data collection, data validation, and the application of an algorithm or formula that calculates the risk, typically displayed as a percentage. It is noteworthy that no approved standards exist for perioperative risk measurement, and several methods are used for its estimation.

In addition to risk scales based on expert judgments, the following 3 statistical methods have been used to construct

multivariate RPMs: logistic regression, Bayesian modeling, and neural network models.[1,4,8,18-20] All of these methods are based on the concepts of calculating risk, which is computed typically in terms of an odds ratio, and incorporate several factors that may increase risk, which are referred to as "predictors", into the analysis. The first RPMs were developed using logistic regression, and the prediction accuracy of these models varied between 70% and 74%.[1,16]

Another approach in the development of effective RPMs was the use of the Bayes theory.[20,21] However, logistic regression and Bayesian modeling have an important drawback: both of these models assume that the analyzed relationships are linear.[19] It is important to test risk prediction hypotheses in a model that not only account for simple relationships and risks that are related to single variables but also allow significant interactions and nonlinear relationships to be addressed.[4,19] Neural network approaches were considered to be the best tool for modeling these complex interactions. However, in practice, all 3 of the discussed modeling methods demonstrated discrimination power of approximately 76%.[4,18,19] One of the most likely reasons that the theoretical advantages of neural networks did not increase the predictive ability of the analyzed qualifiers (ie, the RPMs) is the quality of data. It is important to note that all of the statistical models that calculate the odds ratio of an event are only as accurate as the input data used for model construction.[2,14,17] More recent applications of neural network models (which are also known as artificial intelligence approaches) resulted in an increased risk prediction accuracy of up to 81%.[4] This higher accuracy most likely reflects increases in the quality of the input data for these models and the addition of nonlinear associations to the risk prediction algorithm. Currently, the most popular RPMs are based on the results of multiple logistic regressions and data from thousands of patients; these models also have reached a discrimination power of 81%.[3] However, it should be mentioned that the vast majority of published mortality RPMs were developed for mortality risk prediction either after coronary artery bypass graft surgeries or with respect to the general population of cardiac surgical patients.[1-3,20,21] Specific RPMs for patients other than coronary artery bypass graft patients have been published infrequently.[22]

Another evolving problem is the number of predictors that are necessary to estimate the existing risk with sufficient accuracy. An ideal RPM should be as simple (ie, it should consist of the minimal quantity of data that is feasible) and as accurate as possible. Because postoperative complications result from multiple causes, complex RPMs should present theoretically better discrimination power and so, eg, EuroSCORE II consists of 18 variables.[3] However, in more complex models, assuring appropriate data quality becomes more difficult and a simplified model built of reliable, raw, and physiologic data could evince similar accuracy to a more complex one.[23]

Also, it is important to understand the types of predictor variables that constitute actual RPMs in cardiac surgery. The first mortality RPMs, such as acute physiology and chronic health evaluation or simplified acute physiology score, were developed for intensive care purposes.[24,25] In acute pathologies, the mortality of severely ill patients is related partially to the severity of acute organ failure, which is measured by objective physiologic and laboratory parameters.[24,25] For cardiac surgery patients, mortality prediction models primarily are based on variables that reflect the cardiovascular performance of a patient, the type of surgical procedure, and the presence of chronic diseases, which often are defined in an arbitrary manner.[3,4] Few of these variables may be regarded as objective parameters.[23] The objective parameters in the modeling process include the laboratory parameter of serum creatinine level, which is used to gauge kidney function, and the hemodynamic parameters of pulmonary artery systolic pressure and left ventricular ejection fraction.[3,4,22,23] A shift to measuring chronic organ failure with more objective physiologic or laboratory parameters theoretically should improve the accuracy of RPMs in cardiac surgery. However, large patient populations have not been used to assess the efficacy of more objective RPMs, and, thus, the accuracy of these models has not yet been assessed. This delay is due partially to the difficulties that are involved in identifying objective, available, commonly used, and precise parameters of organ function and with conducting great, multicenter, and validation studies.[3]

The outcome of cardiac surgery is a function of the following variables that influence the risk of postoperative complications: (1) patient-related variables (eg, the patient's main disease, physiologic condition, comorbidities, limitations with respect to blood transfusions, among other factors), (2) physician-related variables (the medical plan for diagnosis and treatment), and (3) hospital-related variables (the execution of the physician's medical plan).[4,19] The currently employed RPMs primarily include patient-related and certain physician-related variables.[1,3,21] However, as long as RPMs assess differences in outcomes based only on an analysis of the first 2 types of variables and do not incorporate the measurement of hospital-related variables, the predictions that these RPMs generate will necessarily be imprecise. The most commonly used RPMs include mortality as an outcome measure. Because mortality depends on postoperative morbidity, disease-specific RPMs have been developed to achieve early diagnoses or even prevent severe postoperative clinical events, such as acute kidney injury, postoperative myocardial infarction, infection, or acute respiratory failure.[10-13,26,27] The problem with these tools is that, in contrast to mortality-based RPMs, these disease-specific RPMs are validated rarely against a control population and are even less frequently assessed at multiple centers.[4,13]

FROM RISK FACTORS TO HUMAN GENOME

Preoperatively existing major comorbidities, so-called risk factors (eg, arterial hypertension, diabetes mellitus, obesity, arteriosclerosis), increase the probability of perioperative morbidity and mortality in cardiac surgery.[1,3,18] In the last 20 years, progress in genotyping technology slowly has revealed the genetic background and its interplay with environmental factors in the pathogenesis of these chronic diseases—termed "clinical phenotypes" in genetic studies.[5,28-30] Given the context of the previously described complexity and the long history of the current RPMs in cardiac surgery, certain doubts about the use of genetic associations as potential mortality or morbidity risk predictors inevitably arise. Over the past 2 decades, enormous advancements have been observed in the field of genomics, the