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Estimating mortality risk of pediatric critical illness: A worthy obsession

Hector R. Wong, MD

Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center and Cincinnati Children's Research Foundation. Department of Pediatrics, University of Cincinnati College of Medicine.

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Our field seems obsessed with predicting critical illness-related mortality. Pediatric Risk of Mortality (PRISM) and Pediatric Index of Mortality (PIM) are established severity of illness measures to estimate the risk of mortality in general populations of critically ill children, based on physiologic and laboratory variables [1, 2]. PRISM is now in its fourth iteration (PRISM-IV), reflecting contemporary practice patterns and a broader patient population, and is now an open source algorithm[3]. Both PRISM and PIM are effective for benchmarking outcomes and for considering the confounding effects of illness severity when analyzing clinical data.

Benchmarking and the ability to account for illness severity are sufficient to support our obsession with predicting critical illness-related mortality. There are other reasons supporting this obsession if one accepts the premise that knowing baseline risk of mortality is fundamental to clinical practice and research. One reason surrounds the concept of *situational awareness*, which involves the perception and understanding of environmental factors in a given time and space, and how those factors and our actions influence goals and objectives. Situational awareness is particularly important for decision making in complex, dynamic areas where information flow is high and poor decisions might lead to serious consequences, such as in the pediatric intensive care unit. Having a reliable estimate of risk can enhance situational awareness in pediatric medicine and potentially improve outcomes [4]. Whether knowing baseline mortality risk *per se* enhances situational awareness in the pediatric intensive care unit and improves outcomes requires formal testing.

High-risk therapies and interventions are inherent to caring for critically ill patients. Optimizing the risk to benefit ratio of high-risk therapies allows for patient care that is more rational and potentially more effective. It follows that knowing baseline mortality risk provides an opportunity for identifying which patients stand to benefit most from high-risk therapies, and which patients should receive standard care. The oncology field embraces this

concept, whereby mortality risk estimates inform decision making amongst multiple therapeutic protocols. Related to this concept, knowing baseline mortality risk can enable allocation of limited intensive care unit resources.

The concept of *enrichment* might be the most impactful reason to estimate baseline mortality risk, because enrichment strategies can improve the design of interventional clinical trials. *Enrichment* refers to the use of any patient characteristic to select a population in which a drug or intervention effect is more likely than in an unselected population. *Prognostic enrichment* refers to the selection of a population having a higher likelihood of a disease-related event, such as mortality. Enrichment strategies are particularly effective when selecting patients for treatment trials in highly heterogeneous syndromes, such as those encountered in the pediatric intensive care unit[5]. By selecting a patient population with a higher event rate, prognostic enrichment strategies can reduce the number of subjects needed for a clinical trial. Indeed, prognostic enrichment may represent a solution to the perception that mortality is not a feasible outcome measure for clinical trials involving critically ill children [6].

Mortality risk scores such as PRISM and PIM are not intended for, and are therefore not appropriate, for individual patient decision-making or selection of patients for clinical trials [7]. In addition, mortality risk scores tend to perform less well when applied to distinct forms of critical illness, such as sepsis[8]. This creates a need for the development of alternative outcome prediction tools. Biomarkers have the potential to meet this need [5, 8–11].

There are several ideal characteristics of a robust, biomarker-based outcome prediction tool. The biomarker(s) should have biological plausibility with regard to pathophysiology and outcome. Biomarker data should reflect an early time point in illness trajectory and should be rapidly available. The latter is particularly important given the time-sensitive demands inherent to decision making in the intensive care unit[12]. The biomarker-based prediction tool should add information to existing tools; this is the concept of *value added*. Finally, it is imperative to test the prediction tool in separate validation cohorts with decision rules defined *a priori*.

In this issue of *Pediatric Critical Care Medicine*, Wilson et al. report on the test characteristics of admission troponin I levels to estimate the risk of mortality in a general population of critically ill patients [13]. The study meets some of the aforementioned criteria for a robust outcome prediction tool. As an established biomarker of myocardial injury, it is certainly biologically plausible that increased troponin I concentrations are associated with increased risk of mortality in pediatric critical illness. The troponin I measurements were conducted within 24 hours of presentation to the pediatric intensive care unit. This represents an optimal time to estimate mortality risk, as it could potentially inform decision-making. Finally, it is entirely clinically feasible to generate troponin I data to meet the time sensitive demands of decision-making in the pediatric intensive care unit.

The study by Wilson et al. does not meet all of the aforementioned criteria. Notably, the investigators applied a different troponin I decision rule to the second cohort, relative to the

first cohort. It would have been informative to apply the decision rule generated during the analysis of the first cohort to the second cohort, *a priori*, and determine the test characteristics based on that decision rule. The test characteristics of troponin I were not superior to that of PIM2 for estimating the risk of mortality. Accordingly, depending on the intended use of troponin I for estimating the risk of mortality, one could argue that troponin I has no value added relative to what already exists.

Nonetheless, Wilson et al. provide us with a rationale to pursue further troponin I as candidate biomarker to estimate the risk of mortality in critically ill children. The fact that troponin I measurements are readily available provides an opportunity for direct clinical translation, without the need to develop, validate, and obtain approval for a new clinical assay. Significant challenges remain to establish troponin I as a prognostic biomarker for pediatric critical care. The available data provides an opportunity to establish *a priori* decision rules for prospective testing in a formal validation cohort. Ideally, the validation cohort includes a heterogeneous patient cohort from more than one center, reflecting the diversity of pediatric critical illness and practice patterns. Testing in relatively homogenous patient cohorts, such as those with sepsis, is another consideration. If feasible, troponin I performance is compared to existing prognostic tools in order to assess the important concept of value added. Combining troponin I with other candidate prognostic biomarkers is another consideration. Finally, the design of prospective studies should account for the intended use of troponin I as a prognostic biomarker.

Our obsession with predicting mortality in critically ill children is worthy and Wilson et al. fuel this obsession effectively. The development of a reliable, biomarker-based prognostic tool for pediatric critical care, that meets the time sensitive demands of decision-making in the pediatric intensive care unit, holds the promise of transforming clinical care and research. This embodies the concept of precision pediatric critical care medicine.

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