Simultaneous Prediction of New Morbidity, Mortality, and Survival Without New Morbidity From Pediatric Intensive Care: A New Paradigm for Outcomes Assessment

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Drs. Pollack and Holubkov had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Objectives: Assessments of care including quality assessments adjusted for physiological status should include the development of new morbidities as well as mortalities. We hypothesized that morbidity, like mortality, is associated with physiological dysfunction and could be predicted simultaneously with mortality.

Design: Prospective cohort study from December 4, 2011, to April 7, 2013.

Setting: General and cardiac/cardiovascular PICUs at seven sites.

Patients: Randomly selected PICU patients from their first PICU admission.

Interventions: None.

Measurements and Main Results: Among 10,078 admissions, the unadjusted morbidity rates (measured with the Functional Status Scale and defined as an increase of ≥ 3 from preillness to hospital discharge) were 4.6% (site range, 2.6–7.7%) and unadjusted mortality rates were 2.7% (site range, 1.3–5.0%). Morbidity and mortality were significantly ($p < 0.001$) associated with physiological instability (measured with the Pediatric Risk of Mortality III score) in dichotomous (survival and death) and trichotomous (survival without new morbidity, survival with new morbidity, and death) models without covariate adjustments. Morbidity risk increased with increasing Pediatric Risk of Mortality III scores and then decreased at the highest Pediatric Risk of Mortality III values as potential morbidities became mortalities. The trichotomous model with covariate adjustments included age, admission source, diagnostic factors, baseline Functional Status Scale, and the Pediatric Risk of Mortality III score. The three-level goodness-of-fit test indicated satisfactory performance for the derivation and validation sets ($p > 0.20$). Predictive ability assessed with the volume under the surface was 0.50 ± 0.019 (derivation) and 0.50 ± 0.034 (validation) (vs chance performance = 0.17). Site-level standardized morbidity ratios were more variable than standardized mortality ratios.

Conclusions: New morbidities were associated with physiological status and can be modeled simultaneously with mortality. Trichotomous outcome models including both morbidity and mortality based on physiological status are suitable for research studies and quality and other outcome assessments. This approach may be applicable to other assessments presently based only on mortality. (*Crit Care Med* 2015; XX:00–00)

Key Words: critical care; functional status; functional status score; intensive care; morbidity; outcome prediction; pediatric critical care; pediatric intensive care; pediatrics; severity of illness

Mortality adjusted for physiological status and other case mix factors has been the core methodology of adult, pediatric, and neonatal intensive care assessments for decades. Users of these methods have been early proponents of standardized mortality ratios for quantitative, unit-based quality assessments for both internal and external benchmarking (1–9). Case-mix adjusted survival and death rates are primary outcomes for national databases beyond critical care medicine (10–15). For example, the Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid publish hospital mortality rates for common conditions, including acute myocardial infarction, stroke, congestive heart failure, pneumonia, hip fractures, and gastrointestinal hemorrhage (16–19).

Mortality for most pediatric critical illnesses has decreased since these methods were developed, and medical therapies are increasingly focused on reducing morbidity in survivors (20, 21). Therapeutic initiatives, such as hypothermia, prevention of secondary injury following head trauma, rapid resuscitation of shock, and early thrombolysis therapy, are aimed at reducing survivors' morbidity as well as improving survival rates (22–28). However, most quantitative outcome assessment methods continue to focus on the dichotomous outcome of survival versus death. We hypothesized that morbidity affecting functional status, like mortality, is significantly associated with physiological dysfunction in PICU patients and could be predicted simultaneously with mortality to provide quantitative outcome prediction for morbidity, mortality, and survival without new morbidity (intact survival). This article describes the development and validation of a prediction model from 10,078 patients in the Trichotomous Outcomes in Pediatric Critical Care (TOPICC) study.

METHODOLOGY

This investigation was performed in the Collaborative Pediatric Critical Care Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (29). Patients from newborn to less than 18 years were randomly selected and stratified by hospital from December 4, 2011, to April 7, 2013. The study had daily limits on the number of patients enrolled at each center. To ensure that patients enrolled in TOPICC were randomly selected from all eligible PICU admissions, a

random number sequence was generated by the Data Coordinating Center for each calendar day. During enrollment days when a site had more eligible patients than the daily limit, this number sequence was used to randomly select those patients to be enrolled, based on the trailing digits of their medical record number. Patients from both general/medical and cardiac/cardiovascular PICUs were included. There were no separate general surgical or neurological PICUs. Moribund patients (vital signs incompatible with life for the first 2 hr after PICU admission) were excluded. Only the first PICU admission during a hospitalization was included. Researchers, research coordinators, and research assistants were trained in data collection in-person during quarterly network meetings and during biweekly conference calls. All sites had electronic medical records. Data were collected daily although information available in the medical records may have been accessed retrospectively. The protocol was approved by all institutional review boards. Descriptive publications on partial samples have occurred (20, 21, 30).

Data included descriptive and demographic information (**Table 1**). Interventions included surgery and interventional catheterization. Cardiac arrest included closed chest massage within 24 hours prior to hospitalization or after hospital admission but prior to PICU admission. Admission source was classified as emergency department, inpatient unit, or postintervention unit from the same hospital or another institution. Diagnosis was classified by system of primary dysfunction based on the reason for PICU admission; cardiovascular conditions were classified as congenital or acquired. Potential predictors of morbidity and/or mortality were identified a priori and included gender, age, admission source, admission status (elective vs emergency), postintervention status and type of intervention, cardiac arrest, diagnosis, baseline functional status, and physiological status.

Outcomes

Morbidity, mortality, and survival without new morbidity were assessed at hospital discharge. Morbidity affecting a significant decrement in functional status was assessed with the Functional Status Scale (FSS) and was recorded for the preacute illness (baseline) and at hospital discharge (31). The FSS is an age-independent assessment of pediatric functional status suitable for large studies. It was developed specifically for this project as well as to provide a new functional status assessment instrument suitable for large pediatric outcome studies. The domains, domain items, and data collection process were designed to be used in this study and the validation process was constructed to be similar to the data collection process used in this study. It is composed of six domains (mental status, sensory, communication, motor function, feeding, and respiratory), with domain scores ranging from 1 (normal) to 5 (very severe dysfunction). The operational definitions and manual for the classifications have been published (31). It was determined from the medical records and/or discussions with the healthcare providers. Newborns never achieving a stable baseline were assigned an FSS score of 6; this was operationalized by assigning an FSS of 6 to admissions to the study sites from 0 to 2 days old and to transfers from another facility from 3 to 6 days old. Baseline FSS scores were categorized as 6–7 (good), 8–9 (mildly abnormal), 10–15 (moderately abnormal), 16–21 (severely abnormal), and more than 21 (very severely abnormal) (20). New morbidity was defined as an increase in the FSS score of greater than or equal to 3 points from baseline to hospital discharge; changes of this magnitude indicate very significant worsening of functioning. Previous analysis on those children with FSS score changes of greater than or equal to 3 points revealed that over 95% of these children had a change of two or more points in a single domain, a clearly significant functional change (20, 21, 31). Morbidity occurs in essentially all ages and types of patients, in relatively equal proportions, and involves all FSS domains (21).

Measurement of Physiological Status

Physiological status was measured with the Pediatric Risk of Mortality (PRISM) III score with a shortened time interval (2 hr prior to admission to 4 hr after admission for laboratory data and the first 4 hr of PICU care for other physiological variables) (5, 30). For model building, the PRISM components were separated into cardiovascular (heart rate, systolic blood pressure, temperature), neurological (pupillary reactivity, mental status), respiratory (arterial P_{O_2}, pH, P_{CO_2}, total bicarbonate), chemical (glucose, potassium, blood urea nitrogen, creatinine), and hematological (WBC count, platelet count, prothrombin, and partial thromboplastin time) components, and the total PRISM III was also separated into neurological and nonneurological components.

Congenital Cardiac Conditions

The timing interval for assessing PRISM III data was modified for cardiac patients less than 91 days old because some institutions admit infants to the PICU prior to a cardiac intervention to "optimize" the clinical status but not for intensive care; in these cases, the postintervention period more accurately reflects intensive care (5). However, in other infants for whom the cardiac intervention is delayed after PICU admission, the intervention is a therapy required due to failed medical management of the acute condition; in these infants, the routine PRISM data collection time interval is an appropriate reflection of critical illness. Therefore, while blinded to outcome status, we identified infants for whom it would be more appropriate to use data from the 4 hours after the cardiac intervention (postintervention time interval) and those for whom using the admission time interval was more appropriate. We operationalized this decision on the conditions likely to present within the first 90 days, the time period when the vast majority of these conditions present. This is shown in **Table 2**.

Statistical Methods

Statistical analyses used SAS 9.2 (SAS Institute Inc., Cary, NC) for descriptive statistics, model development, and fit assessment and R 3.0.2 (The R Foundation for Statistical Computing,

TABLE 1. Site and Overall Sample Characteristics

Site	A	B	C	D	E	F	G	Overall
Sample size	1,252	1,404	1,617	1,498	1,347	1,547	1,413	10,078
Median age in yr (IQR)	3.2 (0.7–10.4)	3.5 (0.7–10.9)	3.9 (1.0–10.4)	4.0 (1.0–11.0)	3.9 (1.3–10.9)	4.1 (0.7–11.1)	3.3 (0.6–11.1)	3.7 (0.8–10.8)
Insurance[a]: commercial/ government/ other (%)	25.8/ 72.9/1.3	50.1/ 41.0/8.8	49.9/ 44.2/5.9	41.1/ 54.1/4.9	61.8/ 34.1/4.0	25.9/ 69.7/4.3	34.3/ 61.4/4.2	41.4/ 53.8/4.9
Race: caucasian/ black/other (%)	45.8/ 48.0/6.2	70.5/ 10.5/18.9	47.8/ 27.8/24.4	45.7/ 44.3/10.0	76.8/ 15.7/7.5	44.0/ 6.9/49.1	30.2/ 8.2/61.6	51.2/ 22.8/26.0
Primary system of dysfunction, *n* (%)								
Respiratory	396 (31.6)	422 (30.1)	627 (38.8)	614 (41.0)	580 (43.1)	449 (29.0)	288 (20.4)	3,376 (33.5)
Cardiovascular disease	347 (27.7)	450 (32.1)	321 (19.9)	264 (17.6)	192 (14.3)	316 (20.4)	540 (38.2)	2,430 (24.1)
Neurologic	225 (18.0)	218 (15.5)	348 (21.5)	268 (17.9)	309 (22.9)	373 (24.1)	281 (19.9)	2,022 (20.1)
Other	284 (22.7)	314 (22.4)	321 (19.9)	352 (23.5)	266 (19.7)	409 (26.4)	304 (21.5)	2,250 (22.3)
Admitted for postintervention care, *n* (%)[b]	459 (36.7)	687 (48.9)	580 (35.9)	408 (27.2)	456 (33.9)	504 (32.6)	703 (49.8)	3,797 (37.7)
PICU admission status								
Elective, *n* (%)	417 (33.3)	611 (43.5)	544 (33.6)	443 (29.6)	453 (33.6)	458 (29.6)	741 (52.4)	3,667 (36.4)
Emergency, *n* (%)	835 (66.7)	793 (56.5)	1,073 (66.4)	1,055 (70.4)	894 (66.4)	1,089 (70.4)	672 (47.6)	6,411 (63.6)
Cardiac arrest prior to PICU admission, *n* (%)[c]	27 (2.2)	14 (1.0)	17 (1.1)	24 (1.6)	15 (1.1)	19 (1.2)	26 (1.8)	142 (1.4)
Median (IQR) baseline Functional Status Scale score	6.0 (6.0–8.0)	6.0 (6.0–7.0)	6.0 (6.0–9.0)	6.0 (6.0–9.0)	6.0 (6.0–9.0)	6.0 (6.0–7.0)	6.0 (6.0–8.0)	6.0 (6.0–8.0)
Median (IQR) Pediatric Risk of Mortality score	2.0 (0.0–5.0)	3.0 (0.0–7.0)	0.0 (0.0–4.0)	2.0 (0.0–6.0)	2.0 (0.0–5.0)	0.0 (0.0–4.0)	3.0 (0.0–7.0)	2.0 (0.0–5.0)
Median (IQR) hospital length of stay (d)	5.2 (2.8–10.4)	5.7 (2.9–13.8)	4. 5 (2.3–11.1)	4.7 (2.2–10.7)	4.2 (2.2–8.7)	4.0 (1.9–7.7)	7.0 (3.3–16.8)	4.9 (2.5–11.0)
Outcome at hospital discharge, *n* (%)								
New morbidity[d]	60 (4.8)	47 (3.3)	80 (4.9)	115 (7.7)	35 (2.6)	48 (3.1)	78 (5.5)	463 (4.6)
Death	39 (3.1)	41 (2.9)	37 (2.3)	36 (2.4)	17 (1.3)	34 (2.2)	71 (5.0)	275 (2.7)

IQR = interquartile range.

[a]Other includes unknown.

[b]Interventions included operations and interventional catheterizations.

[c]Cardiac arrest occurring within 24 hr prior to hospital admission or during the hospitalization prior to the PICU admission.

[d]Increase of Functional Status Scale of ≥ 3.

All characteristics except cardiac arrest were significantly different among the sites ($p < 0.001$).

Vienna, Austria; http://www.wu.ac.at/statmath) for analytic and graphical evaluation of predictive ability. Patient characteristics were descriptively compared and evaluated across sites using the Kruskal-Wallis test for continuous variables and the Pearson chi-square test for categorical variables. The statistical analysis was under the direction of R.H.

Model Building

The dataset was randomly divided into a derivation set (75%) for model building and a validation set (25%) stratified by study site.

We tested the hypothesis that both new morbidity and mortality were associated with physiological status by investigating

this relationship in dichotomous and trichotomous (three-outcome) logistic regression models without other covariates. Trichotomous models were constructed using the generalized logit model, which as parametrized simultaneously estimates odds ratios for mortality and for new morbidity versus discharge alive without new morbidity. Separate coefficients were fit for log odds of mortality and of morbidity because assuming proportionality of odds was not tenable. Descriptor variables having significance levels below 0.10 with respect to either morbidity or mortality odds ratios in the univariate trichotomous models were considered candidate predictors for the final trichotomous outcome model. A nonautomated (examined by biostatistician and clinician at each step) backward stepwise selection approach was used to determine factors in the final reported model. Multicategorical factors (e.g., diagnostic categories) had factors combined when appropriate per statistical and clinical criteria. Statistical criteria for factor inclusion and for determining the number of factor categories included the likelihood ratio test for nested models and the Akaike Information Criterion for comparing general models as well as satisfactory overall goodness of fit. Clinician input was included (and paramount) in this process to ensure the model fit overall and within subgroups was relevant and consistent with clinical information. Construction of a clinically relevant, sufficiently predictive model using predictors readily available to the clinician took precedence over inclusion based solely on statistically significance.

Final Model Evaluation

Final candidate models were evaluated on the derivation and validation sets with respect to consistency of estimated coefficients, predictive ability, and goodness of fit. Predictive ability was assessed by 2D receiver operating characteristic (ROC) curves for dichotomized outcomes) and by 3D volume under the surface (VUS) for the modeled three-level outcome. Overall model goodness of fit was assessed for both the derivation and validation sets using a three-level extension of the Hosmer-Lemeshow test (32). For the entire dataset, goodness of fit with respect to key subgroups was assessed by examining standardized mortality and morbidity ratios for descriptive and diagnostic categories not used in the final model, as well as within the individual study sites. Only categories with at greater than or equal to 10 outcomes in observed and expected cells were used.

Two-dimensional ROC curves were generated, and their variability estimated, using R package pROC (33). Three-dimensional ROC surfaces were constructed by an algorithm varying a grid of two predicted probability cutpoints that gave priority to prediction of deaths, and VUS was estimated using a triplet-classification rule minimizing Euclidean distances (34, 35). The average dichotomized *c*-index (the average of the areas under the curve considered over all possible ordered dichotomizations of the outcome) is reported as an alternate summary measure of multidimensional model discriminatory ability (36). Although asymptotically exact formulas were used to assess SE of 2D areas under the curve, 1,000 bootstrap replications (generated with outcome proportions fixed) were generated to estimate variability of the multidimensional VUS and *c*-index estimates (37).

RESULTS

There were 10,078 patients from the seven sites with each site contributing from 1,252 to 1,617 patients (Table 2). Two patients remained in the hospital after completion of the study and were not included; information on all predictive variables in the model was available for all included patients. The distribution of all patient characteristic except cardiac arrest varied significantly between sites ($p < 0.001$). Overall,

TABLE 2. Pediatric Risk of Mortality III Sampling Intervals for Cardiac Patients Receiving an Intervention

Age at Admission	ICU Length of Stay Prior to Cardiac Intervention	Pediatric Risk of Mortality III Collection Time Interval
< 24 hr	< 12 hr	Admission
	12 hr to 10 d	Postintervention
24 hr to 10 d	0–10 d	Postintervention
	> 10 d	Admission
11–30 d	< 48 hr	Postintervention
	> 48 hr	Admission
31–90 d	< 48 hr	Postintervention if cardiac surgery
		Admission if cardiac catheterization
	> 48 hr	Admission
> 90 d	All	Admission

The admission time interval refers to the period of the 2 hr prior to admission to 4 hr after admission for laboratory data and the first 4 hr of PICU care for other physiological variables. The postintervention time interval refers to the first 4 hr of PICU care after a cardiac intervention (surgery or interventional catheterization, but not diagnostic catheterization).

the median age was 3.7 years, the predominant organ systems of primary dysfunction were respiratory (33.5%), cardiovascular (24.1%), and neurological (20.1%), and most patients were noninterventional (62.3%) and emergency (63.6%) admissions. Of the patients discharged alive, 174 (1.7%) were discharged to other acute care hospitals and 500 (5.0%) were discharged to other inpatient care facilities (rehabilitation, chronic care, skilled nursing, psychiatric). The unadjusted mortality rate was 2.7% (site range, 1.3–5.0%), and the unadjusted new morbidity rate was 4.6% (site range, 2.6–7.7%).

Without covariate adjustments, there was a significant association of morbidity (**Fig. 1*A***) and mortality (**Fig. 1*B***) with physiological instability measured with the PRISM III score ($p < 0.001$ for likelihood ratio test for both outcomes). Increasing PRISM III scores were associated with increasing new morbidity and mortality risks for the dichotomous outcomes. In the trichotomous relationship, the relationship of PRISM III with mortality changes very little after accounting for simultaneous morbidity risk. However, the relationship of morbidity with PRISM III changes substantially after accounting for mortality risk; morbidity risk initially increased with higher PRISM III scores, but then decreased among children with the highest PRISM III scores whose mortality risk is high. The mortality and morbidity univariate odds ratios for the PRISM III score and each of its components of cardiovascular, respiratory, neurological, chemical, and hematologic are also significantly associated with both morbidity and mortality (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B319). Physiological status had a stronger influence on mortality than morbidity as evidenced by the slope in the figures and the significantly different magnitudes of the odds ratios (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/B319; $p < 0.001$ in all instances for Wald tests comparing PRISM coefficients for mortality vs morbidity).

The univariate odds ratios and CIs of potential predictor variables demonstrated that factors considered were significantly associated with both morbidity and mortality,

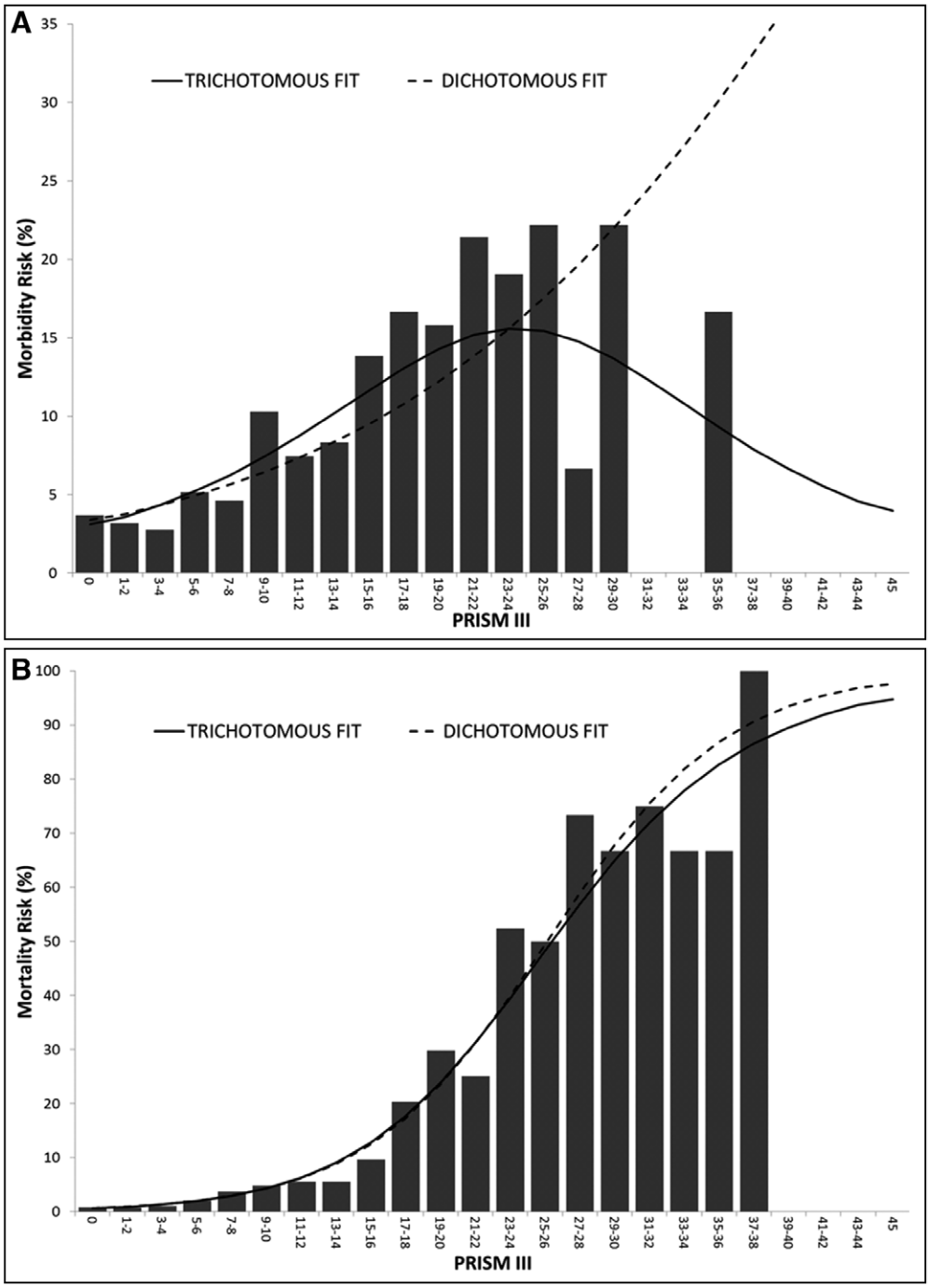

Figure 1. Morbidity (**A**) and mortality (**B**) for dichotomous (*dashed lines*) and trichotomous (*solid lines*) relationships. The graph illustrates the relationships in the development set ($n = 7{,}650$). There were 113 patients with Pediatric Risk of Mortality (PRISM) III scores > 20. There was a significant association of morbidity and mortality with physiological instability measured with the PRISM III score ($p < 0.001$ for likelihood ratio test of significance) for both outcomes.

only one outcome, or neither outcome (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/B319). Potential predictor variables associated with morbidity and/or mortality odds ratios were cardiac arrest status, age, primary system of dysfunction, intervention category, cancer status, trauma status, admission source, baseline FSS, and the PRISM score components.

Considering candidate variables identified in the univariate models, the final multivariate trichotomous outcome model included age, admission source, cardiac arrest, a diagnosis of acute (nonprimary) or chronic cancer, trauma, primary system of dysfunction, baseline FSS, and PRISM III score divided into the neurological and nonneurological components (**Table 3**). All included variables except acute and chronic diagnoses of

TABLE 3. Final Trichotomous Outcome Model for Simultaneous Prediction of Morbidity and Mortality

Predictors	Morbidity Coefficients (SE)	ORs: New Morbidity Versus No New Morbidity (95% CI)	Mortality Coefficients (SE)	ORs: Death Versus No New Morbidity (95% CI)
Intercept	−3.92 (0.17)	NA	−5.51 (0.27)	NA
Age at PICU admission				
0 d to < 14 d	0.80 (0.23)	2.23 (1.43–3.49)	1.64 (0.27)	5.14 (3.00–8.79)
14 d to < 1 mo	0.47 (0.44)	1.61 (0.68–3.79)	1.26 (0.56)	3.53 (1.19–10.50)
1 mo to < 12 mo	0.39 (0.14)	1.48 (1.13–1.93)	0.42 (0.21)	1.52 (1.02–2.28)
> 12 mo	Reference	Reference	Reference	Reference
Admission source				
Direct admission: referral hospital	0.76 (0.15)	2.15 (1.59–2.90)	1.09 (0.24)	2.96 (1.87–4.70)
Inpatient unit: same hospital	0.87 (0.18)	2.38 (1.67–3.39)	1.70 (0.25)	5.46 (3.33–8.95)
Emergency department: same hospital	0.11 (0.16)	1.12 (0.81–1.53)	0.64 (0.25)	1.90 (1.16–3.14)
OR/postanesthesia care unit for postoperative care	Reference	Reference	Reference	Reference
Cardiac arrest[a]	0.97 (0.33)	2.63 (1.38–5.00)	1.52 (0.33)	4.56 (2.40–8.66)
Acute (nonprimary) or chronic diagnosis of cancer[a]	0.25 (0.28)	1.28 (0.74–2.21)	0.89 (0.30)	2.44 (1.36–4.40)
Trauma[a]	1.18 (0.19)	3.26 (2.23–4.77)	0.81 (0.35)	2.26 (1.13–4.51)
Primary system of dysfunction				
Cardiovascular/respiratory	Reference	Reference	Reference	Reference
Cancer	0.73 (0.28)	2.07 (1.20–3.59)	0.90 (0.43)	2.47 (1.06–5.74)
Low risk (diabetic ketoacidosis, hematologic, musculoskeletal, renal)	−0.93 (0.31)	0.39 (0.21–0.72)	−1.69 (0.61)	0.18 (0.06–0.61)
Neurologic	0.38 (0.15)	1.46 (1.08–1.98)	−0.07 (0.25)	0.93 (0.57–1.54)
Other	−0.21 (0.23)	0.81 (0.52–1.28)	0.11 (0.31)	1.11 (0.61–2.03)
Baseline Functional Status Scale score categorized as good[a,b]	−0.23 (0.13)	0.80 (0.61–1.03)	−0.66 (0.19)	0.52 (0.36–0.74)
PRISM III neurological score[c,d]	0.11 (0.02)	1.12 (1.08–1.16)	0.21 (0.02)	1.24 (1.19–1.29)
PRISM III nonneurological score[d]	0.09 (0.01)	1.09 (1.07–1.12)	0.18 (0.01)	1.19 (1.16–1.23)

OR = odds ratio, NA = not applicable, PRISM = Pediatric Risk of Mortality.

[a]Reference is absence of the factor.

[b]Baseline Functional Status Scale score = 6 or 7.

[c]PRISM III neurological components are pupillary reactions and mental status.

[d]For each one point change.

cancer, neurological disease, and the baseline FSS score were significant independent predictors of both morbidity and mortality; cancer diagnoses and baseline FSS score were significant, independent predictors of mortality only, whereas neurological disease was significant for morbidity only. The validation set had 112 morbidities observed and 113.6 morbidities predicted and 61 deaths observed and 67.1 deaths predicted. Trichotomous Hosmer-Lemeshow tests (**Table 4**) found acceptable fit for both the derivation ($p = 0.22$) and validation ($p = 0.32$) sets. **Figure 2** shows the discrimination for the derivation set using the 3D surface of proportions of each outcome correctly simultaneously predicted using varying probability cutpoints. The estimated VUS for this three-way outcome relationship is 0.50 ± 0.019, where 0.019 is the SE of the estimate. For the validation set, the estimated VUS is 0.50 ± 0.034. (VUS chance performance indicated by the shaded area in Fig. 2 is 0.167 [one sixth] in the 3D setting). The area under the curve for the most clinically relevant 2D ROC curves for the derivation and validations sets was 0.89 ± 0.012 and 0.89 ± 0.020 for the survival versus death dichotomy, 0.79 ± 0.011 and 0.80 ± 0.018 for the death or new morbidity versus survival without new morbidity dichotomy, and 0.72 ± 0.014 and 0.74 ± 0.024 for the new morbidity versus death or survival without new morbidity dichotomy (**Supplemental Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/B320). The average dichotomized *c*-index (36) (chance performance = 0.50) achieves values of 0.84 ± 0.009 and 0.85 ± 0.016 for the derivation and validation sets, respectively.

Standardized morbidity and mortality ratios for factors not included in the model (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/B321) including PICU type (general medical and cardiac/cardiovascular), elective/emergency admission status, postintervention category including cardiac interventions, and specific diagnoses such as sepsis, respiratory disease, neurological trauma, and congenital heart disease representing over 50% of the sample had standardized ratios not significantly different from unity. Only the commercial payer type but not government payer type had a standardized mortality ratio less than predicted. Model performance within individual study sites revealed significantly more variability (**Fig. 3**). When the standardized ratios are evaluated independently, four sites had standardized morbidity ratios significantly different from unity ($p < 0.05$), three less than 1.0 indicating significantly less morbidity than predicted by the model and one greater than unity. Two sites had standardized mortality ratios different from unity, one below 1.0 and one significantly greater than 1.0. When both standardized ratios were considered simultaneously in an overall assessment of model fit within each site, three sites were significantly different than predicted, one with a higher number of deaths than predicted by the model, a second with a higher number of morbidities and a trend toward fewer deaths than predicted, and a third with number of both mortalities and morbidities significantly lower than predicted.

DISCUSSION

We demonstrated that new morbidities significantly affecting functional status at hospital discharge were associated with many of the same factors as mortality, including physiological status measured by the PRISM III score, age, admission source, and diagnostic factors, and that morbidity can be modeled simultaneously with mortality. Trichotomous modeling

TABLE 4. Trichotomous Hosmer-Lemeshow Goodness-of-Fit Tests for the Development and Validation Sets

	Derivation					Validation				
		Deaths		New Morbidities			Deaths		New Morbidities	
Risk Decile	*n*	Observed	Expected	Observed	Expected	*n*	Observed	Expected	Observed	Expected
1	816	0	1.5	8	9.9	261	0	0.4	4	3.2
2	739	1	2.7	14	13.5	252	0	0.9	2	4.4
3	724	2	3.2	19	16.3	258	0	1	3	5.8
4	745	11	4.6	13	18.7	237	1	1.4	2	5.8
5	763	4	5.6	19	23.4	252	1	1.7	3	7.6
6	750	8	7.8	25	27.1	252	6	2.7	15	8.7
7	829	9	12.0	41	37.4	261	3	3.5	13	11.5
8	704	14	13.5	52	41.7	251	3	4.4	15	14.5
9	735	27	25.8	56	57	244	10	8.3	20	18.3
10	755	138	137.2	104	106.1	250	37	42.8	35	33.8
Total	7,560	214	214.0	351	351	2,518	61	67.1	112	113.6
		Chi-square = 20.0, $p = 0.22$ (16 *df*)					Chi-square = 22.3, $p = 0.32$ (20 *df*)			

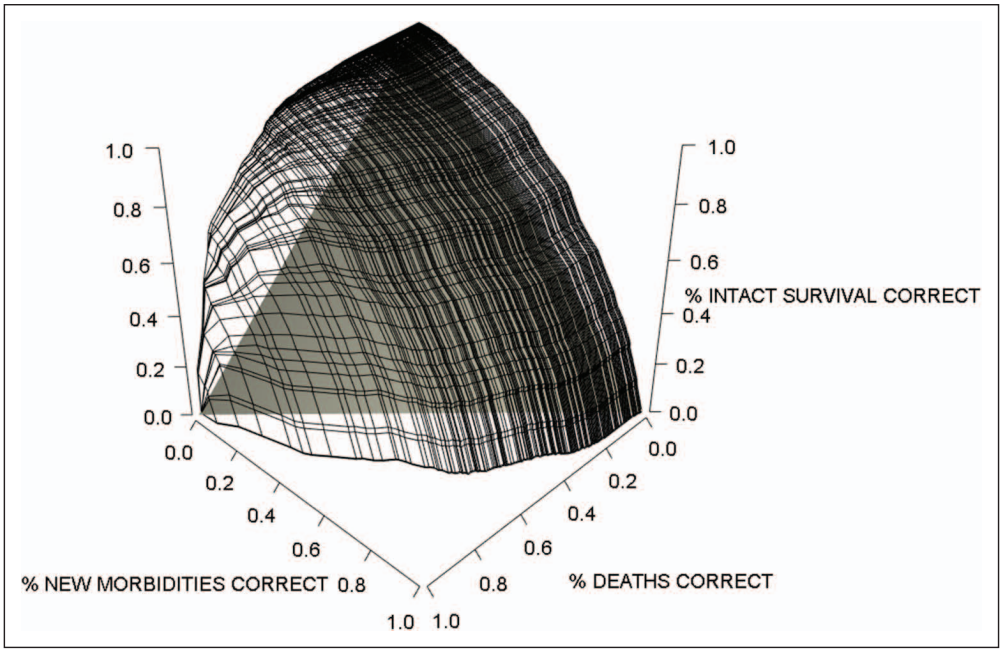

Figure 2. Volume under the surface (VUS) for the trichotomous predictor. Data are shown for the derivation set. The three edges of this surface are the two 2D receiver operating characteristic (ROC) curves for the prediction of each pair of outcomes. In general, vertical "slices" of this surface in any dimension may be viewed as conditional ROC curves showing the ability of the model to predict a pair of outcomes conditional on correctly predicting the third outcome in a given proportion of subjects. Estimated VUS (proportion of the "cube" that is under the prediction surface) was 0.50 ± 0.019 for the derivation set and 0.50 ± 0.034 for the validation set. The *shaded triangular space* indicates chance performance analogous to the diagonal line in a 2D ROC curve which in three dimensions is a VUS of 0.167. Average dichotomized *c*-index (chance performance = 0.50) was 0.84 ± 0.009 and 0.85 ± 0.016 for the derivation and validation sets.

uncovered the phasic association of morbidity risk with physiological status and produced a well-performing model for simultaneous prediction of both morbidity and mortality suitable for risk adjustment in research, quality, and other studies.

We found that the association of new morbidity with physiological status was similar to that of mortality, increasing as physiological dysfunction increased and only decreasing as the physiological dysfunction became sufficiently large to change potential morbidities into mortalities. Critical care mortality is usually associated with physiological abnormalities in the cardiovascular, respiratory, neurological, and hematological systems (5, 38–42). Our findings are consistent with the hypothesis that new morbidity significantly affecting functional status is often an event along the path toward mortality as both outcomes are strongly associated with the degree of physiological alterations. In pediatric critical care, new morbidity assessed by change in functional status is almost twice as common as mortality and could serve as a new, clinically relevant and important outcome for clinical trials and quality studies to supplement the relatively low rate of mortality (21).

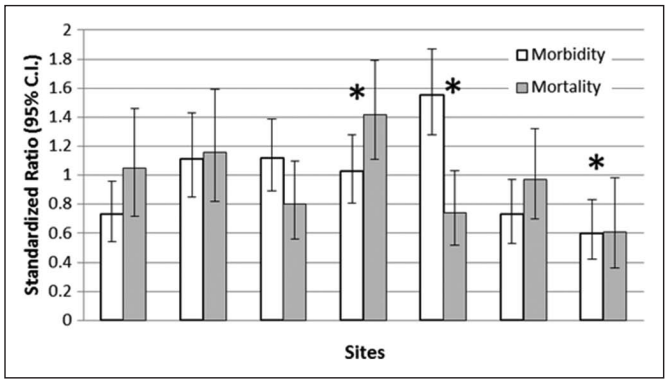

Figure 3. Standardized morbidity (*white bars*) and mortality (*gray bars*) ratios with 95% CIs for the individual sites. Site order does not correspond to Table 2. *$p < 0.05$ for overall model fit at the indicated site.

Our findings have wide implications for research trials and quality programs, especially those currently based on internal or external benchmarking of standardized mortality ratios. First, since pediatric morbidity is more common than mortality and many critical care therapies are aimed at reducing morbidity risk, care assessments that focus on morbidity as well as mortality will have wide appeal and relevance (43–46). Second, although limited in scope, there was more variability among the participating sites in the standardized morbidity ratios than in the standardized mortality ratios. This suggests that quality factors beyond those associated with mortality may influence morbidity and, therefore, the investigation of the variability in standardized morbidity ratios could identify new, important quality factors. Potentially, evaluations of, and improvements in, the structure and process of care analogous to those resulting from the investigations of the variability of standardized mortality ratios could result (46–51). Third, although this study was conducted in PICUs, it is likely that patients in neonatal and adult ICUs have a similar relationship between morbidity and physiological dysfunction, enabling similar models of morbidity and mortality risks based on the physiological dysfunction scores currently available for those patient populations (45, 52, 53). Fourth, non-ICU initiatives that monitor standardized mortality ratios could find relevance and applicability in the simultaneous morbidity and mortality outcome model developed in this study (15–19, 54–56).

The most important limitation to our study is the lack of long-term follow-up to correlate with hospital discharge morbidity. There is continued recovery of function after discharge although the prevalence and severity of long-term morbidity is correlated with the discharge condition (43, 57, 58). We did find that measuring functional status with the FSS as a morbidity

outcome was practical, relevant, and worked well even in this large study. Several other limitations are important. First, the data abstractors were not blinded to the study hypothesis, and this has the potential to introduce bias. Second, although the FSS was designed and validated for this project, we did not formally reassess the accuracy of the data collection.

In conclusion, trichotomous outcome models for pediatric intensive care based on physiological status were developed with performance suitable for use in research trials and quality and other assessments. This approach is likely applicable to other disciplines that are currently dependent on adjusted mortality alone. Given the decreasing PICU mortality rates, the ability to more finely assess outcomes among surviving children in terms of morbidity allows the opportunity to distinguish between different care practices at a more refined level, thereby furthering the opportunity to improve patient outcomes.

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