

Morbidity

Changing the Outcome Paradigm for Pediatric Critical Care



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KEYWORDS

- Morbidity • Functional status • Quality • Outcomes • Outcomes research
- Critical care • Pediatric critical care • Pediatric intensive care

KEY POINTS

- Morbidity is an important outcome that can be measured even for large studies. There are many measures of morbidity that can be selected based on the context of the study.
- In pediatric critical care, functional status is an “intermediate” outcome on the pathway to death that is significantly associated with physiologic instability (measured by the Pediatric Risk of Mortality [PRISM] score).
- Morbidity risk in pediatric critical care can be measured using physiologic profiles (PRISM) and other case-mix factors and used for quality assessment in a manner similar to death.
- New functional status morbidity rates are approximately double mortality rates.
- The Functional Status Scale (FSS) developed by the Collaborative Pediatric Critical Care Research Network is a granular method of measuring functional status and new functional status morbidity that is applicable to large-sample studies.

INTRODUCTION

The primary focus of critical care has evolved from saving lives by monitoring and maintaining physiologic status to placing greater emphasis on the prevention of secondary injuries and preservation of function. Current pediatric ICU (PICU) mortality rates approximate 2.5% to 5%, decreased from 8% to 18% during the early years of pediatric critical care,¹ and it has been suggested that a portion of the reduced mortality rates has been an exchange for higher morbidity rates.²

Pediatric critical care does not have a consensus concept of morbidity. Despite the low mortality rates and changing primary focus of pediatric critical care to include

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morbidity prevention, the primary outcome for many critical care studies and assessments remains mortality. Studies that formerly could be accomplished with mortality as a legitimate and meaningful outcome are now difficult or impossible due to sample size considerations. If mortality is the primary outcome for research, quality, or other studies, the sample size required may be very large and the time required to obtain these samples may be so long as to make the results less meaningful when the study is completed.

This article's aims are

- To review the conceptual framework of morbidity most relevant to pediatric critical care
- Describe the uses of morbidity in research, quality, and other types of studies
- Describe measures of morbidity, especially those that measure functional status
- Review the foundational evidence that strongly supports the use of functional status morbidity as an equivalent or separate outcome to mortality
- Summarize the current pediatric critical care morbidity literature and the methods used to assess morbidity

WHAT IS MORBIDITY?

Morbidity is often difficult to define. Although mortality is simple (alive or dead), morbidity is usually conceptualized as an important deviation from baseline and/or a deviation from the expected result of care. In the context of critical care, morbidity is frequently thought of as the ramifications of both the disease process and the care provided in the ICU. It may encompass events during the inpatient stay, discharge status, or the long-term effects of the disease and the ensuing critical care interventions.

Morbidity during intensive care includes a diverse group of indicators, including the development of multisystem organ dysfunction, need for vasoactive medications, days on the ventilator, length of stay, hospital-acquired infections, and other medically focused outcomes. Morbidity, especially in the surgical literature, has increasingly been focused on inpatient complications or an unexpected hospital course associated with a procedure or its subsequent care, including length of stay, adverse events, and errors. An excellent example of using inpatient complications has been developed by using the congenital heart Society of Thoracic Surgeons Congenital Heart Surgery Database.³ The selected complications of specific interest and relevance to congenital heart surgery patients include renal failure requiring dialysis, neurologic deficits at discharge, atrioventricular block requiring a permanent pacemaker, mechanical circulatory support, phrenic nerve injury or paralyzed diaphragm, and unplanned operation. The result of combining these complications with postoperative length of stay has been standardized for specific operations, resulting in a morbidity index specifically relevant to these patients' inpatient course, and suitable for use as a quality assessment method. Research by Kronman et al used more global measures of inpatient care such as cost.⁴ Contemporary trends, such as patient-centered care and family-centered care and cost, may be may also be converted to morbidity indicators, such as family-related and patient-related changes in stress, mental health, financial status, and family functioning.⁵

Despite the traditional emphasis on inpatient metrics, there is growing recognition that the most important morbidities are decreases in functional status, which persist or develop after the hospital stay. These may be general, such as changes to activities of daily living, or organ-specific changes measured by functional tests, such as maximum oxygen consumption after cardiac surgery or pulmonary function tests after thoracic disease. Both types of morbidities are important. A recent review found that

new functional impairment at the time of ICU discharge was reported from 10% to 36% of discharges depending on the methodology used.⁶ Evidence detailed in this article indicates that changes to functional status in critically ill children are tightly linked to physiologic dysfunction (severity of illness).

THE RELATIONSHIP OF PHYSIOLOGIC DYSFUNCTION TO MORBIDITY

Morbidity often represents an intermediate outcome in a critically ill patient's progression toward death and is likely the result of the same physiologic dysfunctions that are associated with mortality (Fig. 1). Therefore, the conceptual foundation of intensive care, maintaining physiologic stability to prevent mortality, can be extended to morbidity, indicating that morbidity is a suitable and generalizable outcome measure for critical care quality assessments and research studies.

Although it has been well known for decades that physiologic dysfunction early in the PICU course is strongly associated with mortality risk, the association of physiologic dysfunction with morbidity has only recently been evaluated.⁷ The Collaborative Pediatric Critical Care Research Network (CPCCRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development assessed the relationship of physiologic profiles measured within the first 4 hours of admission to the ICU to both mortality and the development of significant, new functional status morbidity at hospital discharge. This study is the Trichotomous Outcome Prediction in Critical Care (TOPICC) study. The measure of physiologic profiles is the Pediatric Risk of Mortality (PRISM) score and the measure of morbidity is the Functional Status Scale (FSS [discussed later]).^{8,9}

The CPCCRN study first identified a similar relationship between physiologic profiles and the development of new functional status morbidities as the relationship between physiologic profiles and mortality. As the physiologic instability increased, there was an increasing risk of both morbidity and mortality (Fig. 2A, B). Next, the TOPICC study determined the factors associated with the development of morbidity and mortality for critically ill children. Table 1 compares the univariate odds ratios of developing either morbidity or mortality given the descriptive or physiologic factors. In

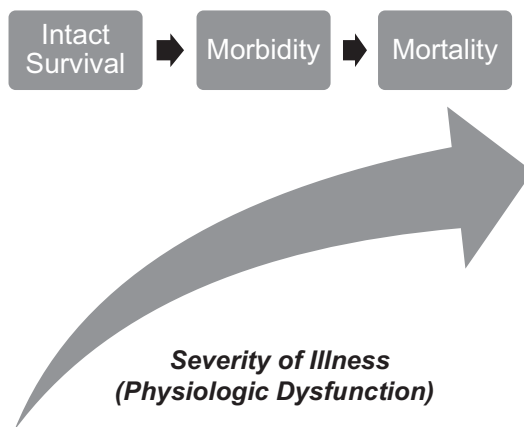


Fig. 1. The conceptual framework for critical care functional morbidity. The risks of both morbidity and mortality increase as severity of illness (physiologic profiles) increases. In this conceptual framework, morbidity is an intermediate outcome on the pathway to mortality.

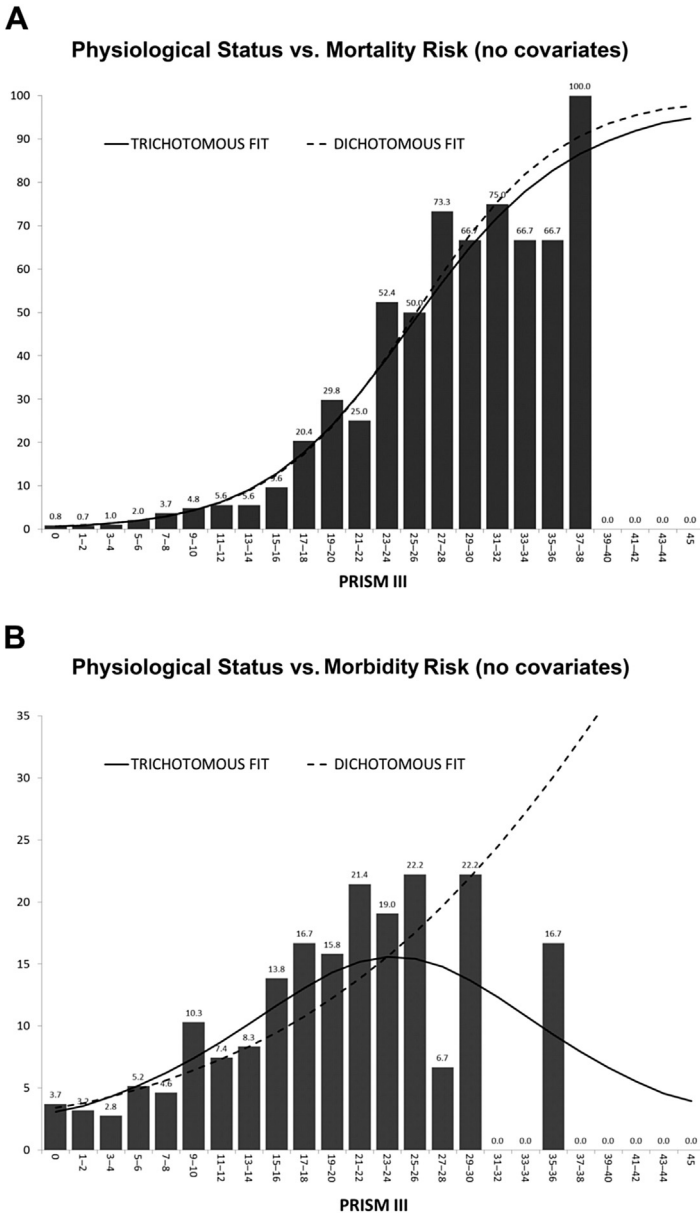


Fig. 2. The association of morbidity and mortality risk with physiologic profiles (PRISM). (A) Illustrates the relationship of PRISM with mortality risk and this relationship changes little when the prediction model is dichotomous (survival/death) or trichotomous (functional status morbidity/intact survival/death). (B) Illustrates the association of functional status morbidity with PRISM. In the dichotomous model (functional status morbidity/other), the relationship of morbidity risk to PRISM is similar to mortality risk. With the trichotomous model, however, morbidity risk increases until morbidity risk decreases as patients with high risks die. (From Pollack MM, Holubkov R, Funai T, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. Crit Care Med 2015;43[8]:1699–1709.)

Table 1
Significant risk factors for developing new functional status morbidity and mortality

Variable	New Morbidity (%)	Death (%)	Odds Ratios: New Morbidity vs No New Morbidity (Odds Ratio [95% CI])	Odds Ratios: Death vs No New Morbidity (Odds Ratio [95% CI])
Age at PICU admission^a				
0 d to <7 d	7.10	11.30	1.93 (1.12, 3.35)	5.12 (3.09, 8.50)
7 d to <14 d	12.00	9.60	3.40 (1.88, 6.15)	4.53 (2.31, 8.88)
Primary system of dysfunction^b				
Respiratory	4.40	2.20	0.88 (0.55, 1.39)	0.24 (0.16, 0.37)
Cancer	5.70	2.50	1.16 (0.60, 2.23)	0.28 (0.12, 0.63)
Cardiovascular disease — congenital	4.50	4.20	0.92 (0.56, 1.51)	0.47 (0.31, 0.71)
Endocrine	0	0.40	<0.01 (<0.01, >999)	0.04 (0.01, 0.30)
Gastrointestinal disorder	5.70	3.40	1.18 (0.61, 2.31)	0.39 (0.19, 0.81)
Musculoskeletal condition	3.10	0.30	0.61 (0.29, 1.30)	0.03 (0.00, 0.24)
Neurologic	7.10	2.40	1.47 (0.93, 2.34)	0.27 (0.17, 0.43)
Miscellaneous	1.80	1.30	0.34 (0.15, 0.77)	0.14 (0.06, 0.33)
Intervention category^c				
Neurosurgery	3.40	0.80	0.59 (0.36, 0.96)	0.20 (0.07, 0.54)
Orthopedic	2.60	0	0.45 (0.21, 0.97)	<0.01 (<0.01, >999)
Otolaryngology	1.70	0	0.29 (0.14, 0.63)	<0.01 (<0.01, >999)
Miscellaneous	1.60	1.20	0.27 (0.10, 0.74)	0.31 (0.10, 0.98)
Acute (nonprimary) or chronic diagnosis of cancer^d				
Yes	5.90	7.40	1.37 (0.81, 2.30)	2.95 (1.83, 4.76)
Trauma^e				
Trauma	11.90	3.50	3.14 (2.32, 4.24)	1.40 (0.84, 2.32)

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Table 1
(continued)

Variable	New Morbidity (%)	Death (%)	Odds Ratios: New Morbidity vs No New Morbidity (Odds Ratio [95% CI])	Odds Ratios: Death vs No New Morbidity (Odds Ratio [95% CI])
Admission source^f				
Inpatient unit from same hospital	6.60	5.60	2.15 (1.52, 3.02)	3.79 (2.49, 5.76)
Direct admission from referring hospital	7.20	4.90	2.33 (1.75, 3.09)	3.31 (2.27, 4.83)
PICU admission status^g				
Elective (scheduled)	3.20	1.30	0.57 (0.44, 0.72)	0.33 (0.23, 0.48)
Cardiac arrest^h				
Yes	15.40	38.50	6.91 (3.88, 12.3)	33.3 (21.3, 52.0)
4-Hour PRISM scoreⁱ				
PRISM III (total)			1.11 (1.09, 1.13)	1.23 (1.21, 1.25)
PRISM III cardiovascular variables			1.12 (1.06, 1.20)	1.44 (1.37, 1.52)
PRISM III Metabolic Variables			1.16 (1.12, 1.21)	1.35 (1.30, 1.41)
PRISM III chemistry variables			1.14 (1.07, 1.21)	1.46 (1.38, 1.55)
PRISM III Hematological variables			1.16 (1.10, 1.23)	1.39 (1.32, 1.46)
PRISM III neurologic variables			1.17 (1.13, 1.21)	1.30 (1.27, 1.34)

Univariate odds ratios to develop morbidity (N = 351) and mortality (N = 214) based on 7560 PICU admissions. Only statistically significant factors are shown. Nonsignificant factors for both morbidity and mortality within each category are detailed in the footnotes.

^a Reference is age ≥ 144 months. Nonsignificant age categories were 14 days to less than 21 days, 21 days to less than 1 month, 1 month to less than 12 months, 12 months to less than 60 months, and 60 months to less than 144 months.

^b Reference is acquired cardiovascular disease. Nonsignificant systems of dysfunction were hematological and renal.

^c Intervention category. Reference is no intervention. Nonsignificant intervention categories included cardiovascular surgery, interventional catheterization, and general surgery.

^d Cancer. Reference is no acute or chronic cancer.

^e Trauma. Reference is no trauma.

^f Admission source. Reference is operating room or postanesthesia care unit. Nonsignificant categories are admissions from the emergency department of the same hospital.

^g Admission status. Reference is emergency.

^h Cardiac arrest. Reference is no cardiac arrest.

ⁱ PRISM. Data shown are for each change of 1 PRISM point.

From Pollack MM, Holubkov R, Funai T, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. *Crit Care Med* 2015;43(8):1699–1709.

general, the risk factors for dying are also the risk factors for development of morbidity and when a variable is significant for one outcome, it is often significant for the other. Because the morbidity rate is twice as high as the mortality rate, most of the variables have higher odds ratios for morbidity than mortality. Importantly, physiologic profiles measured by the 4-hour PRISM score were significant for the risk of developing both morbidity and mortality, and they are even a more powerful predictor of morbidity than mortality.

Next, the TOPICC study developed a model to predict the 3 critical care outcomes—intact survival, survival with a functional status morbidity, and death at hospital discharge—simultaneously using multivariate trichotomous logistic regression (see Fig. 2A, B). When the relationships of morbidity and mortality to physiologic profiles measured by the PRISM score are modeled separately, they were similar, with the risk of either mortality or morbidity increasing as physiologic instability increases. But, the relationship changes when both outcomes were considered simultaneously. As physiologic instability increased, both morbidity and mortality risk increased in parallel until mortality risk became dominant and the risk of morbidity decreased as those patients with a high mortality risk die. The association of morbidity risk to physiologic status, when mortality risk is factored in, is an inverted U shape. Morbidity risk first increased in parallel with mortality and then decreased.

This TOPICC study demonstrated that the same relationships underlying the association of mortality to physiologic status strongly influence the development of new, functional status morbidities at hospital discharge, as illustrated in Fig. 1. The implications are important: just as providers have the ability to influence mortality risk by appropriately identifying and treating physiologic dysfunction, they have the ability to influence morbidity through the same mechanisms.

Importantly, this study was also able to develop and validate a predictor of the aforementioned 3 outcomes from critical care simultaneously (Table 2). The relative risks for developing morbidity or mortality are reflected in the coefficients and odds ratios. Therefore, there is the potential to use both morbidity as well as mortality as meaningful ICU outcomes for quality assessments and researching new interventions because morbidity can be adjusted for using physiologic profiles and risk factors in the same way as mortality.

WHY DOES ASSESSING MORBIDITY MATTER FOR PEDIATRIC CRITICAL CARE?

Using morbidity with or without mortality as a critical care outcome presents opportunities. First, morbidity and morbidity plus mortality represent much larger signals for quality assessment and research. New functional status morbidity at hospital discharge, significant enough that parents and health care providers would understand that life has changed at least temporarily for that child and family, is twice as common as mortality. Studies using both outcomes will take less time and be more relevant to ensuring quality of care standards or relevant research outcomes.

The most important potential use for morbidity is as a new measure of quality of care. For almost 3 decades, ICUs have used measures of mortality adjusted for physiologic profiles and/or case-mix variables to assess the quality of care provided within an individual institution over time (internal benchmarking) or across a range of institutions using a known standard (external benchmarking). These methods compare the observed number of outcomes to the expected number of outcomes based on the physiologic and case-mix profiles of the patients (standardized ratios). Low mortality rates limit the utility of mortality as an outcome for quality studies because measuring quality using mortality may require long time periods to acquire a sufficient number

Table 2
Simultaneous prediction of morbidity and mortality

Predictors	Morbidity Coefficients (Standard Error)	Odds Ratios: New Morbidity vs No New Morbidity (95% CI)	Mortality Coefficients (Standard Error)	Odds Ratios: Death vs 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)
Operating room 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				
	Reference	Reference	Reference	Reference
Cardiovascular/respiratory				
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, hematological, 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 FSS 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 neurologic 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 non-neurological score ^d	0.09 (0.01)	1.09 (1.07, 1.12)	0.18 (0.01)	1.19 (1.16, 1.23)

Abbreviation: NA, not applicable.

^a Reference is absence of the factor.

^b Baseline FSS score = 6 or 7.

^c PRISM III neurologic components are pupillary reactions and mental status.

^d For each 1 point change.

From Pollack MM, Holubkov R, Funai T, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. *Crit Care Med* 2015;43(8):1699-1709.

deaths for a reliable quality assessment. Detecting sequential changes over time will be enhanced when the outcomes are both more relevant and more frequent.

A second important and contemporary use of morbidity is for pediatric critical care research trials. Pediatric critical care trials have been stymied by the need for large patient samples or a long enrollment period to capture an adequate number of events. Using mortality as a primary outcome in intervention trials requires very large samples to avoid “fragility,” the concept that represents the number of deaths that, if changed to survivors, would have changed the statistical conclusion of the trial from significant to negative. A recent study noted that the statistical conclusions of more than half of the identified randomized clinical trials could be flipped either by using a more conservative statistical test or just changing the number of deaths to survivors by 2, even in multicentered trials in adult ICUs where mortality rates are approximately 3 to 4 times as high as pediatric units.¹⁰ Critical care in general—especially pediatric critical care, due to the relatively low mortality rate—needs a more frequent outcome than mortality for robust and reliable studies.

Measures of morbidity are already prominent in pediatric critical care research studies. For example, the Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trial investigated whether the intervention of targeted temperature management to hypothermia after cardiac arrest would improve significant changes in adaptive functioning.¹¹ The primary outcome for THAPCA was survival with good functional status as assessed by the Vineland Adaptive Behavior Scale (VABS). The Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT) is using the pediatric version of the Glasgow Outcome Scale–Extended (GOS-E).¹² The potential assessment methods for morbidity following head injury include detailed dissection of neurocognitive function but there is not agreement on the optimal method.¹³ Other studies have assessed neurocognitive outcomes of tight glucose control in critically ill pediatric patients using a range of neuropsychological testing.¹⁴ These studies demonstrate, however, the variability with which morbidity is defined and measured.

MEASURING MORBIDITY

Unlike mortality, which provides a clear dichotomous outcome, morbidity is a continuum of dysfunction. For many studies, documenting morbidity at a specific time point may be sufficient, but for other studies, assessments at a time when the morbidity has stabilized is most relevant. For example, prior work has shown that morbidity after trauma usually plateaus by 6 months postinjury.¹⁵ For the general PICU population, however, recent evidence suggests that the incidence of significant morbidity and mortality determined at hospital discharge may double over the subsequent 3 years.¹⁶

A general method for measuring morbidity after critical care should include a broad range of function and be relevant to large populations in its practicality, specificity, and sensitivity. General measures of morbidity for pediatric critical care, especially if they are to be used for large population studies, such as quality studies requiring a general assessment of functional status should have as many of the following attributes as possible:

- Measure a clinically important outcome state
- Be relevant to long-term outcomes (can be used to project to medium-term and long-term outcomes)
- Can be completed relatively rapidly
- Can be completed without interaction with the family to allow studies to be done without informed consent and efficiently
- Is reliable across the sample even if some individual patients are misclassified

- Is age independent
- Is objective and sufficiently granular to limit subjective assessments
- Has strong inter-rater reliability

Historically, 3 broad categories of methods have been used to assess morbidity in critically ill children: global measurements; health-related quality of life (HRQOL) scales, including health utilities indices; and adaptive behavior scales, including neuropsychological and psychometric testing.⁶ Depending on the method selected, a child's deficits in specific domain(s) (eg, motor ability and communication skills) that are relevant to the context of the study are objectively assessed.

Global Measures of Morbidity

Global outcome scales include the Glasgow Outcome Scale (GOS)¹⁷ and its pediatric versions, the Pediatric Cerebral Performance Category (PCPC) and the Pediatric Overall Performance Category (POPC).¹⁸ These scales assign a single score to classify overall functional level without examining specific domains beyond the PCPC's focus on cognitive performance. The GOS and POPC/PCPC are straightforward to administer but do not have uniformly objective and granular classifications for the assessment, leading to the potential for poor inter-rater reliability and poor precision. The second-generation GOSs are the GOS-E¹⁹ and its pediatric version, the GOS-E Pediatrics (GOS-E Peds).¹² The GOS-E scores use a short structured interview with the patient or family to determine functional status.

The POPC and PCPC are intended to estimate short-term functioning based on a projection by health care providers at hospital discharge. They are widely used after critical illness because of their ease of assessment, face validity due to their similarity to the GOS, and statistically significant (but weak) relationship to long-term neuropsychological tests²⁰ and have been used in large pediatric critical care studies.²¹ The scores include 1 for good, 2 for mild disability, 3 for moderate disability, 4 for severe disability, 5 for vegetative state or coma, and 6 for death. Completion of the POPC/PCPC generally takes only a few minutes and does not require parent/guardian or patient participation for completion. Unfortunately, the PCPC/POPC method lacks both precision and reproducibility. Inter-rater agreement of this system was only 76% to 80% when there was inclusion of a neighboring class.²¹ That is, the agreements were only satisfactory if patients were classified as good to moderate disability, mild to severe disability, or moderate to very severe disability. Lack of precision was evident when the POPC/PCPC was compared with the more objective and granular FSS [discussed later].²²

The GOS-E Peds is primarily used as an outcome for brain injury studies, although it has the potential for outcome assessment for other conditions. It has domains adapted to children (consciousness, independence in the home, independence outside the home, school/work, social and leisure activities, family and friendships, and return to normal life) and separates 2 age groups (younger and older patients) in an attempt to account for developmental stages. The GOS-E Peds was validated in 159 children (average age 81 ± 57 months) at a single site.¹² Overall, the GOS-E Peds was well-correlated with the GOS (correlation >0.8) and reasonably correlated with the composite VABS (correlation >0.6), VABS domains (all correlations >0.45), Bayley (correlation >0.6), and other intelligence scores (correlations >0.55) but less well-correlated with parent ratings scales. The best results were obtained in older children with the worst head injuries. This suggests that it be further validated prior to use in any non-TBI group and in younger children with less severe TBI. The GOS-E Peds has not been assessed for inter-rater reliability (although the adult version has very good

inter-rater reliability and has even been done with a mail questionnaire). Importantly, the validation assessments were done 3 months after the injury as a structured interview with professionals who were not blinded to other results. The GOS-E Peds was used as a secondary outcome in the Cool Kids trial, which was terminated after only 77 patients,²³ and is a primary outcome in the ADAPT.²⁴

Health-Related Quality of Life

HRQOL measures attempt to gain an understanding of a child's overall functional status by using the concepts of quality of life. The most popular methods are the PedsQL and the Child Health Questionnaire.^{25–28} Most HRQOL methods assess various combinations of different domains (eg, social, emotional, school functioning, and physical). The responses of children as young as 5 years of age may be used to complete the questionnaires. It is important to recognize that assessments are fundamentally subjective and patient, parent, and health care provider assessments often diverge.²⁹ HRQOL methods have multiple versions that may include interviews, in-person questionnaires/surveys, telephone surveys, long forms, short forms, and disease-specific or condition-specific versions. A recent review found that, overall, there is a significant decrease in HRQOL for PICU patients, although this has been measured by different methods and follow-up periods. This review also examined more than 20 different measures of HRQOL, concluding there are neither HRQOL tools specific to the post-PICU population nor a consensus as to the best method applicable to general post-ICU studies.³⁰

Adaptive Behavior Scales

Adaptive behavior scales are commonly used and currently popular for research and for individual patient assessments. They focus on skill domains considered important to normal functioning and are adjusted for developmental age through evaluation of domains, such as social and cognitive skills. The most commonly used are the VABS and the Adaptive Behavior Assessment System (ABAS).^{31,32} Both methods are available in different formats.

The ABAS is a questionnaire, and is commonly used by schools and in environments where questionnaires are more practical. The VABS is a psychometric instrument that is especially useful in the evaluation of children with intellectual disability, chronic disease, traumatic brain injury (TBI), mental health conditions, and many types of developmental delays as well as part of a battery of neuropsychological tests.

The VABS must be administered by a trained interviewer or psychologist. The VABS assesses personal independence and social responsibility using information relevant to day-to-day activities necessary to take care for oneself and to get along with others. There are multiple versions of the VABS that include short versions that can be administered by telephone. Unfortunately, despite its popularity, the VABS has not been assessed for validity in the peer-reviewed literature in several decades.^{33,34} In general, the VABS is believed to function very well, especially in those with mild and moderate levels of functioning, but it may perform less well in those with severe and profound levels of dysfunction, and it can be logistically difficult to administer to large numbers of patients.

The Functional Status Scale

In an effort to develop a method using the principles of both activities of daily living and adaptive behavior that could be easily and accurately applied to larger patient populations, researchers with the CPCCRN developed the FSS. The FSS was developed by the CPCCRN based on consensus input from pediatricians, pediatric neurologists,

pediatric developmental psychologists, pediatric nurses, pediatric intensivists, and pediatric respiratory therapists from 11 institutions. The FSS (**Table 3**) assesses functioning in the domains of mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status.

Functional status for each domain is categorized from “normal” (1) to “very severe dysfunction” (6), with aggregate scores ranging from 6 (best) to 30 (worst). Construct validity was established by correlating the performance of the FSS with adaptive behavior as measured by the ABAS-II. Adaptive behavior was selected as a similar but not identical measure of function, recognizing that correlation between adaptive behavior scores purporting to measure the same functions is only moderate. Discriminant validity was established by receiver operating characteristic curve analysis. Other patient factors, including age, elective/emergency admission status, operative status, patient type, and study site, were investigated to determine if they were independently associated with FSS after adjusting for the ABAS-II using multivariable linear regression. FSS showed a consistent, moderate to strong association with ABAS-II across these other patient factors. The intraclass correlation of the total FSS was 0.95, indicating overall high reproducibility.

Because the FSS can be determined on admission based on parent recall or medical records, it enables a comparison of preillness with postillness functioning. The FSS was recently used in a CPCCRN study of greater than 10,000 PICU patients and was an excellent metric with sufficient precision and reliability for prediction based on physiologic profiles.⁷ In this study, a new significant functional status change was defined as a change of 3 points or more for 2 major reasons. First, investigators thought that this magnitude of change would be very evident to both parents and providers. Second, 95% of the patients with a change of 3 points or more had a change of at least 2 points in a single FSS domain, indicating that the change had clearly occurred and was unlikely the result of a data collection error. This study established the practical advantages of the FSS for assessing hospitalized children by demonstrating that it can be assessed in less than 5 minutes from the medical record or conversations with health professions caring for the patient. Recently, the FSS was used to assess discharge status in a large pediatric trauma cohort.³⁵

KNOWN MORBIDITY AFTER PEDIATRIC INTENSIVE CARE

Morbidity, including physical, psychosocial, and neurocognitive deficits, is common in intensive care conditions. A recent article found in a general, unselected population of PICU patients that new functional status morbidity assessed with the FSS was 33% higher than mortality at hospital discharge and both the morbidity and mortality rates doubled in the 3 years after initial hospital discharge.¹⁶ Almost as many children demonstrated worsening of their functional status or died (38%) as survived without a change in functional status (44%). Less than 10% of children exhibited functional gains over time. Long-term function was associated with indicators of severity of illness including the need for invasive therapies, such as use of mechanical ventilation and use of vasoactive medications.

Although it is not possible to precisely compare morbidity and mortality rates over time because of the different research methods, data from several decades ago demonstrated a PICU mortality rate of 4.6% and a PICU morbidity rate of 3.1% (based on a 2-point or greater POPC change), whereas recent data from the TOPICC study (based on an FSS change of 3 or more points from baseline to hospital discharge) had a reversal of these percentages, with a hospital mortality rate of 2.4% and

Table 3
Functional status scale

	Normal (Score = 1)	Mild Dysfunction (Score = 2)	Moderate Dysfunction (Score = 3)	Severe Dysfunction (Score = 4)	Very Severe Dysfunction (Score = 5)
Mental status	Normal sleep/wake periods; appropriate responsiveness	Sleepy but arousable to noise/touch/movement and/or periods of social nonresponsiveness	Lethargic and/or irritable	Minimal arousal to stimuli (stupor)	Unresponsive, coma, and/or vegetative state
Sensory functioning	Intact hearing and vision and responsive to touch	Suspected hearing or vision loss	Not reactive to auditory stimuli or to visual stimuli	Not reactive to auditory stimuli and to visual stimuli	Abnormal responses to pain or touch
Communication	Appropriate noncrying vocalizations, interactive facial expressiveness, or gestures	Diminished vocalization, facial expression, and/or social responsiveness	Absence of attention-getting behavior	No demonstration of discomfort	Absence of communication
Motor functioning	Coordinated body movements, normal muscle control, and awareness of action and reason	1 limb functionally impaired	≥2 limbs functionally impaired	Poor head control	Diffuse spasticity, paralysis, or decerebrate/decorticate posturing
Feeding	All food taken by mouth with age-appropriate help	Nothing by mouth or need for age-inappropriate help with feeding	Oral and tube feedings	Parenteral nutrition with oral or tube feedings	All parenteral nutrition
Respiratory status	Room air and no artificial support or aids	Oxygen treatment and/or suctioning	Tracheostomy	Continuous positive airway pressure treatment of all or part of the day and/or mechanical ventilatory support for part of the day	Mechanical ventilatory support for all of the day and night

Data from Pollack MM, Holubkov R, Glass P, et al. Functional status scale: new pediatric outcome measure. *Pediatrics* 2009;124(1):e18–28.

morbidity rate of 4.8%.^{2,21} Thus, the “morbidity plus mortality rate” has decreased only from 7.7% to 7.2%, which has been mirrored in other studies.^{2,21,36} These rates are not severity adjusted or risk adjusted, but the potential shift from mortality to morbidity is consistent with the clinical observations of many clinicians.

In the TOPICC study, morbidities affected essentially all types of patients and age groups in relatively equal measure. New morbidities occurred with relatively equal risk in those with all diagnostic groups and all degrees of baseline functional compromise. They also occurred in almost all operative groups, with the highest rates in cardiac surgery and general surgery and in only 3.1% of neurosurgical patients. Importantly, functional morbidity as well as mortality rates differed by more than 300% among the sites, indicating functional morbidity may be used as a robust and relevant measure of quality, effectiveness, and efficacy.

Prior research has used PCPC/POPC to determine risk factors for developing a new morbidity during critical illness. Using the VPS database, Bone and colleagues³⁷ identified children who survived their ICU admission but had worsening of PCPC/POPC scores. New functional or cognitive morbidities were noted in 10.3% and 3.4% of survivors, respectively. Multivariate analysis identified trauma, oncologic, and neurologic diagnoses as particularly high risk. As seen in other studies, patients who required significant invasive support (mechanical ventilation, renal replacement therapy, cardiopulmonary resuscitation, or extracorporeal membrane oxygenation) were also prone to development of new morbidities during admission, consistent with other studies using neuropsychological testing, VABS and HRQOL scales.^{38–40}

In addition to the general knowledge about ICU-generated morbidities, some research has looked at development of new morbidities (or specific types of morbidities) in specific disease states.

Psychological Morbidity and Family Stress

In addition to the physical and cognitive outcomes associated with ICU care, researchers have also examined the psychiatric burden faced by children and families after critical illness. Given the physical and emotional stresses faced by patients and their families in critical care settings, it is unsurprising that there are psychological ramifications of these illnesses. A review by Davydow and colleagues⁴¹ showed a patient incidence of posttraumatic stress disorder symptoms ranging from 10% to 28% and depression symptoms ranging from 7% to 13%. These rates are higher than have been seen in other patient populations, including the pediatric oncology population as well as children sustaining traumatic injury. Factors, such as ICU length of stay and severity of illness at the time of ICU admission, were associated with a higher prevalence of symptoms. This contrasts to studies in the adult population, where evidence is mixed as to whether these factors are associated with worse post-ICU psychiatric morbidity. This may be an instructive reminder as to the limitations of adapting research conducted in adults to the pediatric population.

Congenital Heart Surgery

Significant functional status morbidity at hospital discharge is approximately 50% greater than mortality for children after pediatric cardiac surgery. Discharge morbidity is associated with the same factors as mortality from congenital heart surgery, including the severity of the anatomic anomaly, the difficulty of the surgical palliation or repair, and the physiologic dysfunction in the immediately postoperative period. The TOPICC performs well predicting morbidity as well as mortality in congenital heart surgery patients as well the general ICU population.⁴²

Trauma

The 2006 Institute of Medicine report, "Emergency Care for Children: Growing Pains," acknowledged the need for better outcomes including functional status at hospital discharge.⁴³ The National Trauma Data Bank, the leading US trauma registry and most commonly used database for injured children from more than 700 facilities, uses only mortality as a hospital discharge outcome for both ICU and non-ICU children even though mortality is substantially less than 3%.⁴⁴ In trauma research, most functional outcome studies have been used only in specific age groups, have been performed only among children with TBI, or have been assessed in a research setting, for example, the Pediatric Evaluation of Disability Inventory,⁴⁵ the Wee Functional Injury Measure For Children (WeeFIM),⁴⁶ and the GOS-E Peds. Few studies have evaluated functional measures of injury outcomes across a range of injury types and severity or have been validated across a wide age range.⁴⁷

SUMMARY

Pediatric critical care has improved mortality rates over time but may have exchanged mortality for the development of new morbidities. Morbidity is linked to the same physiologic factors as mortality in critical illness. A variety of methods have been used to characterize morbidity in the pediatric critical care literature. Consensus on the most appropriate method to assess patient morbidities and integration of such a method into pediatric critical care research (including large database use) will offer the next step forward in caring for critically ill children. The FSS developed by the CPCCRN is a granular, age-independent, and validated method that has been valuable in large-sample critical care studies.

Morbidity assessments should be available from the medical record to ensure they are available for routine studies of quality and available for other large-scale studies. Similarly, databases must incorporate appropriate morbidity measures in their quality and research studies. Currently, large databases, such as those of the Society of Thoracic Surgeons, American College of Surgeons Trauma Registry, and the Pediatric Health Information System do not include a patient-level functional status morbidity assessment.

REFERENCES

1. Pollack MM, Ruttimann UE, Getson PR. Accurate prediction of the outcome of pediatric intensive care. A new quantitative method. *N Engl J Med* 1987;316(3): 134–9.
2. Pollack MM, Holubkov R, Funai T, et al. Pediatric intensive care outcomes: development of new morbidities during pediatric critical care. *Pediatr Crit Care Med* 2014;15(9):821–7.
3. Jacobs ML, O'Brien SM, Jacobs JP, et al. An empirically based tool for analyzing morbidity associated with operations for congenital heart disease. *J Thorac Cardiovasc Surg* 2013;145(4):1046–57.e1.
4. Kronman MP, Hall M, Slonim AD, et al. Charges and lengths of stay attributable to adverse patient-care events using pediatric-specific quality indicators: a multi-center study of freestanding children's hospitals. *Pediatrics* 2008;121(6): e1653–9.
5. Boyd JM, Burton R, Butler BL, et al. Development and validation of quality criteria for providing patient- and family-centered injury care. *Ann Surg* 2016. [Epub ahead of print].

6. Ong C, Lee JH, Leow MK, et al. Functional outcomes and physical impairments in pediatric critical care survivors: a scoping review. *Pediatr Crit Care Med* 2016; 17(5):e247–59.
7. Pollack MM, Holubkov R, Funai T, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. *Crit Care Med* 2015;43(8):1699–709.
8. Pollack MM, Holubkov R, Funai T, et al. The pediatric risk of mortality score: update 2015. *Pediatr Crit Care Med* 2016;17(1):2–9.
9. Pollack MM, Holubkov R, Glass P, et al. Functional status scale: new pediatric outcome measure. *Pediatrics* 2009;124(1):e18–28.
10. Ridgeon EE, Young PJ, Bellomo R, et al. The fragility index in multicenter randomized controlled critical care trials. *Crit Care Med* 2016;44(7):1278–84.
11. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med* 2015;372(20):1898–908.
12. Beers SR, Wisniewski SR, Garcia-Filion P, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. *J Neurotrauma* 2012;29(6):1126–39.
13. McCauley SR, Wilde EA, Anderson VA, et al. Recommendations for the use of common outcome measures in pediatric traumatic brain injury research. *J Neurotrauma* 2012;29(4):678–705.
14. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA* 2012;308(16):1641–50.
15. Polinder S, Meerding WJ, Toet H, et al. Prevalence and prognostic factors of disability after childhood injury. *Pediatrics* 2005;116(6):e810–7.
16. Pinto NP, Rhinesmith EW, Kim TY, et al. Long-term Function after pediatric critical illness: results from the survivor outcomes study. *Pediatr Crit Care Med* 2017; 18(3):e122–30.
17. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480–4.
18. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr* 1992;121: 69–74.
19. Jennett B, Snoek J, Bond MR, et al. Disability after severe head injury: observations on the use of the Glasgow outcome scale. *J Neurol Neurosurg Psychiatry* 1981;44(4):285–93.
20. Fiser DH, Long N, Roberson PK, et al. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Crit Care Med* 2000; 28(7):2616–20.
21. Fiser DH, Tilford JM, Roberson PK. Relationship of illness severity and length of stay to functional outcomes in the pediatric intensive care unit: a multi-institutional study. *Crit Care Med* 2000;28(4):1173–9.
22. Pollack MM, Holubkov R, Funai T, et al. Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales. *JAMA Pediatr* 2014;168(7):671–6.
23. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. *Lancet Neurol* 2013;12(6):546–53.
24. Larsen GY, Schober M, Fabio A, et al. Structure, process, and culture differences of pediatric trauma centers participating in an international comparative

- effectiveness study of children with severe traumatic brain injury. *Neurocrit Care* 2016;24(3):353–60.
25. Varni JW, Seid M, Knight TS, et al. The PedsQL 4.0 generic core scales: sensitivity, responsiveness, and impact on clinical decision-making. *J Behav Med* 2002;25(2):175–93.
 26. Varni JW, Limbers CA, Neighbors K, et al. The PedsQLTM infant scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. *Qual Life Res* 2011;20(1):45–55.
 27. Drotar D, Schwartz L, Palermo TM, et al. Factor structure of the child health questionnaire-parent form in pediatric populations. *J Pediatr Psychol* 2006;31(2):127–38.
 28. Raat H, Bonsel GJ, Essink-Bot ML, et al. Reliability and validity of comprehensive health status measures in children: the child health questionnaire in relation to the health utilities index. *J Clin Epidemiol* 2002;55(1):67–76.
 29. Jardine J, Glinianaia SV, McConachie H, et al. Self-reported quality of life of young children with conditions from early infancy: a systematic review. *Pediatrics* 2014;134(4):e1129–48.
 30. Aspesberro F, Mangione-Smith R, Zimmerman JJ. Health-related quality of life following pediatric critical illness. *Intensive Care Med* 2015;41(7):1235–46.
 31. Sparrow S, Cicchetti D, Balla D. Vineland-II. Vineland adaptive behavior scales - survey forms manual. 2nd edition. Circle Pines, MN: AGS Publishing; 2005.
 32. Harrison PL, Oakland T. ABAS II. Adaptive behavior assessment system. 2nd edition. San Antonio, TX: PsychCorp; 2003.
 33. Raggio DJ, Massingale TW. Comparison of the vineland social maturity scale, the vineland adaptive behavior scales–survey form, and the bayley scales of infant development with infants evaluated for developmental delay. *Percept Mot Skills* 1993;77(3 Pt 1):931–7.
 34. Raggio DJ, Massingale TW, Bass JD. Comparison of vineland adaptive behavior scales-survey form age equivalent and standard score with the bayley mental development index. *Percept Mot Skills* 1994;79(1 Pt 1):203–6.
 35. Bennett TD, Dixon RR, Kartchner C, et al. Functional status scale in children with traumatic brain injury: a prospective cohort study. *Pediatr Crit Care Med* 2016;17(12):1147–56.
 36. Namachivayam P, Shann F, Shekerdemian L, et al. Three decades of pediatric intensive care: who was admitted, what happened in intensive care, and what happened afterward. *Pediatr Crit Care Med* 2010;11(5):549–55.
 37. Bone MF, Feinglass JM, Goodman DM. Risk factors for acquiring functional and cognitive disabilities during admission to a PICU*. *Pediatr Crit Care Med* 2014;15(7):640–8.
 38. Ebrahim S, Singh S, Hutchison JS, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. *Pediatr Crit Care Med* 2013;14(1):10–8.
 39. Als LC, Nadel S, Cooper M, et al. Neuropsychologic function three to six months following admission to the PICU with meningoencephalitis, sepsis, and other disorders: a prospective study of school-aged children. *Crit Care Med* 2013;41(4):1094–103.
 40. Als LC, Tennant A, Nadel S, et al. Persistence of neuropsychological deficits following pediatric critical illness. *Crit Care Med* 2015;43(8):e312–5.
 41. Davydow DS, Richardson LP, Zatzick DF, et al. Psychiatric morbidity in pediatric critical illness survivors: a comprehensive review of the literature. *Arch Pediatr Adolesc Med* 2010;164(4):377–85.

42. Berger JT, Holubkov R, Reeder R, et al. Morbidity and mortality prediction in pediatric heart surgery: physiological profiles and surgical complexity. *J Thorac Cardiovasc Surg* 2017. [Epub ahead of print].
43. Committee on the future of emergency care. Future of emergency care: emergency care for children: growing pains. Washington, DC: The National Academies Press; 2006.
44. Amer Coll of Surgeon. ACS NTDB National trauma data standard: data dictionary. 2015. Available at: <https://www.facs.org/quality-programs/trauma/ntdb/ntds>. Accessed July 11, 2017.
45. Dumas HM, Haley SM, Carey TM, et al. The relationship between functional mobility and the intensity of physical therapy intervention in children with traumatic brain injury. *Pediatr Phys Ther* 2004;16(3):157–64.
46. Shakkai S, Peretz R, Spasser R, et al. Long-term functional outcome after moderate-to-severe paediatric traumatic brain injury. *Brain Inj* 2014;28(7):915–21.
47. Gabbe BJ, Simpson PM, Sutherland AM, et al. Functional and health-related quality of life outcomes after pediatric trauma. *J Trauma* 2011;70(6):1532–8.