

TOOLS FOR PREDICTING RISK OF MORTALITY IN THE ICU SETTING: DO WE NEED A CRYSTAL BALL OR ROSE COLORED GLASSES?

Vinay Nadkarni and Michael Trigg

Pediatric Intensive Care Unit, Department of Anesthesia and Critical Care, Alfred I. duPont Hospital for Children, 1600, Rockland Road, P.O. Box 269, Wilmington, DE 19899

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1. ABSTRACT

Hematopoietic stem cell transplantation (HSCT) applied to children is associated with high risk for organ failure, ICU admission, morbidity and mortality. "Respiratory failure" after HSCT carries a historically grave prognosis. Factors associated with high risk for critical care complications in HSCT patients have been identified, but are dependent on timing and intensity of interventions. Several ICU severity of illness scoring systems predict prognosis on the basis of physiologic stability, organ system involvement, and intensity of supportive measures; but these tend to underestimate post-transplantation mortality risk. Adjustment of scoring systems and logistic regression factor analysis are promising adjuncts, but have not been adequately validated. Specific endpoints such as death, length of ICU or hospital stay, and neurologic function are relatively easy to quantify; but, quality of life is difficult to assess and report. What constitutes "heroic therapy" in one institution may qualify as "routine" care in another. Therefore, tools to predict mortality in the pediatric HSCT recipient requiring intensive care are difficult to apply to the individual patient, and remain more an art than science. This manuscript attempts to briefly define and review the pertinent types of PICU severity of illness and mortality prognosis scoring systems, and their application to pediatric HSCT patients. Pitfalls in application of physiology, organ system failure, therapeutic intensity, disease specific, and history-based scoring systems are discussed. Prospective validation studies for severity of illness systems and the evolution to concurrent registry-style data collection and analysis are necessary for the HSCT patient requiring ICU care.

2. INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) applied to children with diverse underlying disease, immune suppressive conditioning regimens, therapies and complications is associated with high risk for acute or chronic organ failure, morbidity and mortality. Approximately 25% of HSCT patients will require "intensive care" admission and support during their hospitalization (1). Critical care supportive management is similar to that for all children who present with immune compromise and high dose chemotherapy, with additional attention focused toward potential contributions from graft rejection, Graft vs Host Disease (GVHD), and toxicity of total body irradiation. In adults, ICU admission for HSCT patients with the combination of respiratory failure and either hepato-renal or circulatory failure (refractory hypotension) appears fatal (2, 3). "Respiratory failure" after HSCT carries a grave prognosis, with a reported 6-month survival of only 2.5-9% (4). The outcome following acute hypoxemic respiratory failure in children following early studies of bone marrow transplantation was reported as similarly dismal (5-8). However, improving critical care supportive and treatment measures have suggested a more optimistic outlook (9-12). Inconsistent definitions of "respiratory failure" and "organ system failure", individual biases for timing of specific interventions and invasive supports, and disease specific markers of mortality risk make survival and outcome prognosis prediction difficult (13-15). Factors associated with high risk for critical care complications in HSCT patients can be identified, but are often dependent on timing and intensity of intervention and parameter assessment. Identical therapies (mechanical

Table 1. Categories of ICU Scoring Systems

Types of ICU Scoring System	Example	Example	Example	Example
Physiologic stability	PRISM (Pediatric Risk of Mortality) 1 st 24 hours	PIM (Paediatric Index of Mortality) 1 st 1 hour	SAPS (Simplified Acute Physiology Score)	O-PRISM (Oncologic -pediatric risk of mortality)
Anatomic Injury severity	ISS (Injury Severity Scale)	AIS (Abbreviated Injury Scale)	ASCOT (A Severity Characteristic of Trauma)	
Therapeutic interventions	TISS (therapeutic intervention severity score)	P-TISS (Prehospital -therapeutic intervention severity score)		
Disease Specific	Meningo-cocccemia	PTS (Pediatric Trauma Score)	AIDS	O-PRISM (Oncologic-PRISM)
Disease and organ failure markers	Lactate for shock severity	CRP for HSCT patients		
Subjective	Individual experience	Institutional experience	GCS (Glasgow coma score)	

ventilation, renal replacement therapies) instituted early vs late may not carry the same mortality risk. What constitutes "heroic therapy" in one institution may qualify as "routine" intensive care or even "routine" HCST unit care in another.

Criteria for initiation versus withholding emerging ICU technologies is not currently well developed or agreed upon by consensus. Several ICU severity of illness scoring systems attempt to predict prognosis on the basis of physiologic stability, organ system involvement, and intensity of supportive measures (16-23). These ICU prognostic scores are limited in application to the post-transplantation setting and often underestimate mortality risk (24-27). Adjustment of scoring systems to account for risk and support factors common in HSCT has been attempted, but has not been validated in large, multi-institutional populations of HCST patients (28). Evolving logistic regression models using sophisticated markers for prognostic assessment show promise, (29, 30) but are not well enough established to rely upon in the ICU setting. All prognostic scoring systems are population based and population predictors, and therefore are not designed or effective when applied to any single individual patient. Specific endpoints such as death, length of ICU or hospital stay, and neurologic function are relatively easy to quantify; but, quality of life is difficult to assess and report, and overshadows all other endpoints. Referral patterns and management styles can influence the use or disuse of aggressive support measures. Therefore, tools to predict mortality in the pediatric HSCT recipient requiring intensive care are difficult to apply to the individual patient, and remain more an art than science.

This manuscript attempts to briefly define and review the pertinent types of PICU severity of illness and mortality prognosis scoring systems, and their application to pediatric HSCT patients. Pitfalls in application of physiology, organ system failure, therapeutic intensity, disease specific, and history-based scoring systems are discussed. Prospective validation studies for severity of illness scoring systems applied to HSCT patients and the evolution to concurrent registry-style data collection and analysis are necessary.

2.1. What are the available tools for prediction of mortality risk in the PICU setting?

Survival from life threatening complications of HSCT depend on a multitude of interdependent factors. Prognostic scoring systems in the ICU are generally based upon physiologic stability measurements (PRISM= Pediatric Risk of Mortality, PIM= Paediatric Index of Mortality, Simplified Acute Physiology Score), Anatomic injury site (ISS=Injury Severity Score), intensity of therapeutic interventions (TISS=Therapeutic Intervention Severity Score, Prehospital-TISS), disease specific scoring, markers of shock or organ dysfunction (Lactate, CRP= C-reactive protein) or subjective measures (GCS=Glasgow Coma Score, historical perspective).

2.1.1. Physiologic stability assessment

Physiology based assessments of ICU mortality risk are increasingly available, accurate and easy to use (18-20, 30, 32). The PRISM score is most commonly applied in the PICU setting and is based on the most abnormal recorded values for 14 central physiologic parameters during the first 24 hours of ICU admission. The score is independent of the level of technologic support required to achieve those parameters. The score has been prospectively validated across general PICU populations (18), and has been modified to attempt to adapt it to HSCT recipients (28). The PIM (21) provides a much simpler method of assessing severity of illness based upon the first hour of contact with pediatric intensive care. Physiology based severity of illness scoring systems were originally designed as research tools to control for confounding factors of severity of illness and to allow comparison of quality measures and resource allocation between hospitals. Some authors have demonstrated the use of prediction models to provide individual patient risk assessment (33-35). However, when applied to PICU populations as large as 10,000 patients, survival predictors for patients with very high physiologic instability (PRISM) scores were rare, and mortality risk prediction unreliable for individuals (20).

The main pitfalls in application of physiology based mortality risk predictors include:

- Scoring systems were devised to quantify severity of illness, but were not designed for individual prognosis
- Scoring systems appear to predict mortality risk for populations, not individuals

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- Concern that reporting "most unstable" stability may not be the best estimate of overall mortality risk
- Although ICU mortality risk is more consistently related to organ and physiologic stability, than to underlying disease, no score prediction is validated to predict mortality 100% of the time
- Timing and quality of data entry influence outcome prediction greatly
- Most assessments are labor intensive and only include the initial 1 to 24 hours of patient data
- Scoring systems predict mortality, but do not factor in quality of life

2.1.2. Anatomic injury severity scoring

Anatomic injury based assessments of mortality risk are widely used in the outside of ICU, predominately in assessing trauma morbidity and mortality risk (36). The Injury severity scale (ISS) defines injury severity for comparative purposes, and was not intended as a triage or prognostic tool. Evaluation of outcomes is facilitated by application of a combination of anatomic and severity parameters, with simple data entry. The Abbreviated Injury Scale (AIS) further was developed as an automotive safety industry tool to quantify injury severity by anatomic location. To some degree, the Pediatric Trauma Score similarly combines anatomic and physiologic parameter assessment to a specific disease entity to predict injury severity. Reliable identification of increased risk of mortality in the field has permitted effective triage and retrospective aggregate outcome evaluation, (37, 38) but has not resulted in individual prognostic decision making. Further attempts to combine statistical predictive ability require additional complexity in data collection, as seen with the ASCOT (A Severity Characteristic of Trauma), (39) but may only apply to specific injury or illness subsets of patients.

The main pitfalls in application of anatomy based mortality risk predictors include:

- Scoring systems appear were devised to quantify severity of illness, assist in triage and compare outcomes across systems, but not to predict ICU mortality
- Most scoring systems are labor intensive and applied outside the ICU, and in trauma patients
- Single anatomic or organ system involvement rarely accurately predicts mortality

2.1.3. Therapeutic intervention intensity assessment

Therapeutic intervention intensity based assessments of mortality risk are widely used to assess intensity of support provided, evaluate resource utilization and cost efficiency. Intensity of interventions are assumed to be surrogate assessments for severity of illness and risk of mortality. The Prehospital TISS scores (22) includes 73 items and describes intensity of treatment before referral to ICU. The TISS (23) quantifies intensity of treatment within the ICU. Use of cumulative therapeutic intensity assessment can improve the prognostic utility of the scores. However, the actual severity of illness and mortality risk can be greatly influenced by the medical approach to organ failures (e.g. oliguric renal failure can be managed with

diuretics and fluid restriction or by continuous renal replacement [dialytic] therapies).

The main pitfalls in application of therapeutic intervention based mortality risk predictors include:

- Character and aggressiveness of interventions influence scoring greatly
- Timing and quality of data entry influence outcome prediction
- Most assessments are labor intensive include cumulative patient data
- Scoring systems may predict mortality, but do not factor in quality of life

2.1.4. Disease specific scoring systems

Disease specific scoring systems have evolved to address specific pediatric prognostic morbidity and mortality risk assessments for infectious diseases such as meningococcemia and acquired immune deficiency syndrome. One study comparing 8 meningococcemia severity scoring systems (40) found that all were reasonable predictors of morbidity and mortality of the aggregate, but none correctly identified all survivors. A comparison of standard ICU physiologic instability predictors (PRISM) and meningococcemia specific severity indices suggest their utility in dividing patients into "risk categories", but do not allow for individual prognostication, or for significantly improved identification of those at risk for death (15).

The most pertinent disease specific adjustment to ICU severity of illness assessment was the development of the O-PRISM (Oncologic-PRISM) score, which added risk factors specific to pediatric HSCT patients that were derived from retrospective review of 28 patients from a single institution (28). Of importance, selection of the prognostic endpoint determined the important components to add to the score for these patients. Death in the ICU was associated with circulatory shock on admission, CRP level > 10 mg/dl and evidence of macroscopic bleeding. However, long term survival to hospital discharge was better correlated with HSCT related parameters such as severity of GVHD, CRP level > 10 mg/dl, and the presence of macroscopic bleeding. However, this scoring system has not been prospectively validated in a larger, multi-institutional population.

The main pitfalls in application of disease specific mortality risk predictors include:

- ICU mortality risk is more consistently related to organ and physiologic stability, than to underlying disease diagnosis and no score is able to predict mortality 100% of the time
- Timing and quality of data entry influence outcome prediction greatly
- Assessments are disease based, and as supportive management improves over time the outcome correlation needs to be continuously updated and validated
- Scoring systems predict mortality, but do not factor in quality of life

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2.1.5. Disease and organ failure markers

Organ dysfunction syndromes are a progressive concurrent failure of two or more organ systems. This failure is frequently a non-specific expression of critical illness. However, multiple organ system dysfunction is a leading cause of death in the ICU, and may represent a non-specific inflammatory response to a variety of insults. For instance, risk of mortality for ARDS patients in the ICU have been correlated to inflammatory markers of leukotrienes and interleukins on day 1 of ICU hospitalization (29). Non-specific markers of organ shock, such as amount or duration of lactate for circulatory failure (41) or C-reactive protein > 10 mg/dl for HSCT patients (28) have been suggestive of mortality risk. Specific criteria have been developed to identify failure criteria for the major organ systems (17,42). Mortality for PICU patients has consistently been associated with multiple organ system failure (42), even in HSCT patients, (28) but is not sufficiently discriminating to determine continuation or withdrawal of ICU support. These markers of organ dysfunction can be highly influenced by the timing and circumstances of assessment.

The main pitfalls in application of disease and organ failure marker mortality risk predictors include:

- Although ICU mortality risk is more consistently related to organ and physiologic stability, than to underlying disease diagnosis, no score is able to predict mortality 100% of the time
- Timing, organ failure criteria and amount of support affect quality of data entry and influence outcome prediction greatly
- Assessments are disease based, and as supportive management improves over time the outcome correlation needs to be continuously updated and validated
- Markers of organ dysfunction are greatly influenced by the timing and aggressiveness of supportive care

2.1.6. Subjective assessments

Subjective reliance on personal and institutional experience is commonly necessary. Lack of a single validated and evidence-based tool that allows prediction of individual mortality risk forces subjective interpretation of the population data to the individual. Consideration of the appropriate action requires consideration of the following questions:

- Is the physiologic stability or instability due to patient factors or iatrogenic treatments?
- What is the endpoint for reversible or recoverable disease: survival vs. quality of life?
- What does the family and caregiver consider "good outcome" and adequate "quality of life"?

2.1.7 What specific risk factors have been identified for HSCT patients in the ICU?

Literature review suggests that HSCT patients referred for ICU support have an overall ICU survival rate between 12 and 46% (3, 6, 9, 24, 44, 46). Survival to

hospital discharge when invasive mechanical ventilation is provided is reported as lower: 4-36%, (3, 6, 8, 10, 24, 45, 47, 48) with additional risk of mortality suggested if respiratory failure precipitated endotracheal intubation, pulmonary infection was present, or more than one organ system was failing (48). Referral practices and underlying conditions may account for widely variable outcomes between centers. Most risk factors for acute ICU death follow parameters that characterize multiple acute organ system failure such as circulatory collapse, infection and coagulopathy rather than parameters related to HSCT (e.g. type of transplant, conditioning therapy) (28). However, several studies report risk adjustment for critical care complications such as allograft match, (10) presence of GVHD, (28) high doses of specific cytotoxic therapy (e.g. Ara-C), (49) cyclophosphamide, Busulfan, (Carmustine), diagnosis of lymphoma, and pre-existing lung disease with an oxygen requirement (2). At PICU admission, one recent study reports high risk for fatal outcome in HSCT patients associated with the combination of cardiovascular collapse, high CRP levels, and presence of macroscopic bleeding (e.g. evidence of multiple organ failure) (28). Long term survival after discharge from intensive care was more correlated to type of transplant and severity of GVHD (28).

Pre-admission pulmonary function test results are not consistently predictive of risk or severity of respiratory complications in pediatric HSCT (51). "Idiopathic pneumonia syndrome (IPS)" characterized by negative BAL cultures, diffuse infiltrates on chest radiographs, and severe clinical pneumonitis occurs in approximately 8% of HSCT patients at a median of 12 days post-transplant with rapid progression and reported 70% fatality (51). Several recent reports suggest early identification of pulmonary pathogens including unusual or resistant organisms and early application of aggressive supportive care for respiratory failure (e.g. non-invasive mechanical ventilation, hemofiltration of mediators, high frequency ventilation) may impact HSCT patient's outcome (9, 10, 50).

2.1.8 What can we extrapolate from adult experience?

Adult HSCT patients admitted to a Medical ICU but not requiring mechanical ventilation are reported to have excellent survival > 85%. In the same MICU, HSCT patients requiring mechanical ventilation had only < 4% survival (3-4). Most studies in adults report survival rates of 2.5 to 9% for HSCT ICU patients with respiratory failure requiring invasive mechanical ventilation and <1% survival if other organ system failures accompany respiratory failure (2). However, recent use of non-invasive mechanical support of impending respiratory failure has dramatically impacted the concept and outcome of respiratory support in solid organ transplant recipients (53, 4).

Adult experience with modification of APACHE (Acute Physiologic and Chronic Health Evaluation) severity of scoring systems to specific disease entities have improved calibration and discrimination in solid organ transplant (55) and maternal eclampsia (56) models. However, no currently available adult scoring systems predict mortality extremely well in all multidisciplinary ICUs (57) or when applied specifically to adult HSCT patients.

2.1.9 Under what circumstances is ICU care futile? When is the appropriate time to consider withdrawal of support?

Survival prediction tools in the ICU setting are usually based on severity of illness assessment, physiologic abnormalities (18, 18, 31), intensity of supportive ICU interventions required to maintain physiologic stability (P-TISS, TISS scores), organ system dysfunction indices (42-59), or markers of organ failure (e.g. elevated lactate) (60). Population mortality prediction tools may not be directly applicable to individual patients. Predictions for an individual patient's risk of death are statistically imprecise because of small numbers of cohorts in these groups and resultant wide confidence intervals (20). Even serial assessment of mortality risk combined with logistic regression analysis has not resulted in perfect predictive models (14, 19, 30).

The results of a study to understand prognoses and preferences for outcomes and risks of treatment (SUPPORT) indicated that physicians may not be willing to use objective risk assessment in clinical decision making (61). For example, Paz *et al* (3-4) studied factors associated with dismal outcome in HSCT patients admitted to the ICU over a 5-year period. Adult HSCT patients without associated respiratory failure admitted to the MICU had an 87% survival; those requiring mechanical ventilation 4% survival. Referring oncologists were informed and educated about the lack of survival benefit for ICU admission of HSCT with respiratory failure, but saw no change in ICU referral practice patterns. There was a slight shift to earlier consultation with families on desire for aggressive ICU support and DNAR issues. Specific search for prognostic factors (ICU admission, respiratory failure leading to mechanical ventilation, multiple organ failure involvement) suggesting non-survival in the specific ICU setting combined with patient and disease specific information (primary disease, type of graft, GVHD presence, macroscopic bleeding) should precede end-of-life discussion (62, 63). Special considerations for patient age, prospect for eventual disease free survival, and personal quality of life issues will always need to be factored in.

2.1.10. Time for evolution to prospective/concurrent registry style data collection and analysis

Predictors of severity of illness, ICU morbidity or mortality based upon physiologic, anatomic or intervention intensity data are only as good as the data entered. Predictors based on local populations and practice cannot be expected to compare to regional or national benchmarks. Several large, multi-institutional and multi-national organizations have created registry style databases that have served to facilitate outcome prediction in complex disease processes, including resuscitation (64), acute myocardial infarction management, (65) and pediatric oncology (66-68). This has resulted in major advance in the understanding and treatment of these disease processes. The time has come to combine the knowledge of ICU severity of illness prediction with the pediatric approach to clinical outcome research often taken by pediatric cancer groups.

3. SUMMARY

This manuscript briefly defined and reviewed the pertinent categories PICU severity of illness and mortality prognosis scoring systems, and their application to pediatric HSCT patients. Pitfalls in application of physiology, anatomy, organ system failure, therapeutic intensity, disease specific, and history-based scoring systems are discussed. Failure to respond too early, aggressive support of acute respiratory failure and multiple organ failure remain poor prognostic signs. The inability to appropriately translate population based data to individual prognostic prediction limits utility of current mortality predictors for limitation or discontinuation of aggressive supportive care. Evolution of disease processes and treatments, improving technological support measures and earlier timing of ICU interventions preclude decision-making based on historic controls. Prospective validation studies for severity of illness systems and the evolution to concurrent registry-style data collection and analysis are necessary for the HSCT patient requiring ICU care.

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Send correspondence to: Vinay Nadkarni, M.D., Director, Pediatric Intensive Care Unit, Department of Anesthesia and Critical Care, Alfred I. duPont Hospital for Children, 1600 Rockland Road, P.O. Box 269, Wilmington, DE 19899, Tel: 302-6515159, Fax: 302-651-6410, E-mail: vnadkar@nemours.org