Published in final edited form as:
Pediatr Crit Care Med. 2009 September ; 10(5): 562–570. doi:10.1097/PCC.0b013e3181a64be1.

Day One MODS is Associated with Poor Functional Outcome and Mortality in the Pediatric Intensive Care Unit

Katri V. Typpo, MD, MPH[1,2,*], **Nancy J. Petersen, PhD**[2], **D. Michael Hallman, PhD**[3], **Barry P. Markovitz, MD, MPH**[4], and **M. Michele Mariscalco, MD**[1]

[1]Baylor College of Medicine, Department of Pediatrics, Section of Critical Care Medicine, Houston, TX

[2]Houston Center for Quality of Care and Utilization Studies, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

[3]Division of Epidemiology and Disease Control and Human Genetics Center, University of Texas School of Public Health, Houston, TX

[4]Anesthesiology Critical Care Medicine, Childrens Hospital Los Angeles, USC Keck School of Medicine, Los Angeles, CA

Abstract

Objective—The epidemiology and outcomes of Multiple Organ Dysfunction Syndrome (MODS) are incompletely characterized in the pediatric population due to small sample size and conflicting diagnoses of organ failure. We sought to describe the epidemiology and outcomes of early MODS in a large clinical database of PICU patients based on consensus definitions of organ failure.

Design—Retrospective analysis of a contemporaneously collected clinical PICU database.

Setting—VPICU Performance System (VPS) database patient admissions from 1/2004-12/2005 for 35 US children's hospitals.

Patients—We evaluated 63,285 consecutive PICU admissions from 1/2004-12/2005 in the VPS database. We excluded patients <1 month or >18 years of age, and hospitals with >10% missing values for MODS variables. We identified day 1 MODS by International Pediatric Sepsis Consensus Conference (IPSCC) criteria with day 1 laboratory and vital sign values. We evaluated functional status using Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores from PICU admission and discharge.

Interventions—Analysis: Student's t-test, X^2, Mann-Whitney rank sum, Kruskal-Wallis, linear and logistic regression.

Measurements and Main Results—We analyzed 44,693 admissions from 28 hospitals meeting inclusion criteria. Overall PICU mortality was 2.8%. We identified day 1 MODS in 18.6% of admissions. Patients with day 1 MODS had higher mortality (10.0% v. 1.2%, p<0.001), longer PICU length of stay (3.6 v. 1.3 days, p<0.001) and larger change from baseline POPC and PCPC scores at

Corresponding Author: M. Michele Mariscalco, M.D., 6621 Fannin St. WT6-006, Houston, TX 77030, Phone: 832-826-6230, Fax: 832-825-6229, marym@bcm.tmc.edu.
*Fellow, Pediatric Critical Care Medicine, Baylor College of Medicine, Houston, TX
Address for reprints: M. Michele Mariscalco, M.D., 6621 Fannin St. WT6-006, Houston, TX 77030, No reprints will be ordered.

Work performed at: Baylor College of Medicine, Houston, TX , Texas Children's Hospital, Houston, TX, and Houston Center for Quality of Care and Utilization Studies, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

The authors have no potential conflicts of interest to disclose.

time of PICU discharge (p<0.001). Infants had the highest incidence of day 1 MODS (25.2% vs. 16.5%, p<0.001) compared to other age groups.

Conclusions—Using the largest clinical dataset to date and consensus definitions for organ failure, we found that children with MODS present on day one of ICU admission have worse functional outcomes, higher mortality, and longer PICU length of stay than children who do not have MODS on day one. Infants are disproportionally affected by MODS.

Six key words

Multiple organ failure; Pediatric; Intensive care; Critical Care; Outcomes Research; Epidemiology

Introduction

Organ dysfunction in the critically ill is assuming an increasing level of importance, both as a primary outcome marker in clinical trials and as a quality indicator for patients in the intensive care unit (ICU)([1–3]). Compared to adult ICUs, where overall mortality is 13.9%–29.1%([2–4]), mortality in the pediatric intensive care unit (PICU) is significantly lower, 3.5%–8.6%([5–8]). Thus the use of primary outcome measures other than mortality, such as organ failure, assume an even greater role in both the design of clinical trials and in measuring quality of care in PICUs.

We currently have an incomplete understanding of pediatric Multiple Organ Dysfunction Syndrome (MODS) epidemiology and outcomes in the U.S. Unlike our counterparts in adult medicine, we have had no large prospective clinical datasets to examine MODS across multiple institutions([9–12]). Thus reported incidence of MODS in children admitted to PICUs varies from 11%–56%([13;14]) and reported mortality from MODS varies from 11%–57%([15;16]). While length of stay appears to be longer for children with organ dysfunction, we have no information regarding functional outcome([17]). Unlike adults with MODS, it appears that maximal organ dysfunction is present within 24 hours of admission in 75–86% of all children who develop MODS in the ICU.([5;13])

There are several organ dysfunction scoring systems available to predict risk of mortality based upon admission organ dysfunction. The Pediatric Logistic Organ Dysfunction Score (PELOD), developed for use in children, has been validated in 1806 patients from 7 institutions in Canada, France, and Switzerland, but there have been concerns regarding its use([15;18;19]). It has not been validated in any large study to date in the US. There is no organ dysfunction scoring systems validated for use in the US pediatric critical care population. Recognizing the critical need for a uniform definition of organ failure, the International Pediatric Sepsis Consensus Conference (IPSCC) conference was convened in 2002, and a summary of their recommendations was published in 2005 ([20]). Organ dysfunction criteria were chosen on the basis of the specificity, sensitivity, availability of laboratory tests, and are age adjusted.

In the last several years, there has been the development of the Virtual Pediatric Intensive Care Unit Performance System (VPS, LLC). This a global, online network formed by NACHRI (National Association of Children's Hospitals and Related Institutions), Children's Hospital Los Angeles and Children's Hospital of Wisconsin to develop standardized clinical data collection and analysis. This system was primarily developed to measure and improve quality in PICUs. However as data is collected contemporaneously within the first day of PICU admission, it can also serve as a clinical database to examine critical questions.

The aim of this project is to examine day one MODS across pediatric intensive care units in the United States. Here we use for the first time organ failure criteria promulgated by the

IPSCC, and the VPS clinical dataset to examine functional outcomes as well as describe the epidemiology of day one MODS.

Materials and Methods

Data Source

The VPICU Performance System (VPS) database is a prospective observational cohort of consecutive PICU admissions from a diverse set of 35 pediatric hospitals in the United States (Table 1). Data is collected and entered by trained individuals at the bedside in near-real time. Prior to data collection at each institution, data collectors undergo training by VPS at the data collection site. They must complete an annual certification exam which tests application of data definitions. VPS performs initial and quarterly inter-rater reliability testing. The data entry system has automated data entry checks as well as automated and manual data cleaning queries. There is extensive quality control checking performed by VPS staff prior to release of the data for analysis, and thus the data has high fidelity. All institutions are required to include patient demographics, primary and secondary PICU diagnoses, PICU length of stay and mortality, and components of the Pediatric Index of Mortality (PIM2)([21]) score at PICU admission. Hospitals may also choose to collect Pediatric Overall Performance Category (POPC)([22;23]), Pediatric Cerebral Performance Category (PCPC)([22;23]), and Pediatric Risk of Mortality (PRISMII and PRISMIII)([24;25]) raw data and scores from the day of admission. At the time of this data collection, there was no collection of a Sequential Organ Failure Assessment (SOFA) or other organ failure score.

Using IPSCC criteria we evaluated PICU admission vital sign and laboratory information available from PIM2, PRISMII and PRISMIII raw variables (Table 2) to assign organ dysfunction. Missing data from PRISMII and PRISMIII were assumed to be normal. This is consistent with data collection instructions for these scores. PIM2 or PRISMII variables allowed for the diagnosis of cardiac and respiratory organ dysfunction, while PRISMIII data were necessary to define neurologic, hematologic, renal, and hepatic dysfunction. The data collected in VPS thus permitted us to fulfill at least one organ failure criteria listed by the IPSCC. MODS was defined as two or more dysfunctional organ systems out of six (Table 2).

POPC and PCPC scores—The global function score, the POPC, and the cognitive function score, the PCPC, have been validated for use at time of PICU admission and discharge in the United States ([22;23]). Though the scores depend on caregiver recall, they have been shown to correlate well with results from more intensive neurocognitive tests in children([22;23]). Both are graded on a 6-point scale with 1 indicating normal functional status and 6 indicating brain death. A score of two indicates mild dysfunction, three indicates moderate dysfunction with impairment in competitive function at school, while a score of four indicates severe functional impairment. A score of five indicates a persistent vegetative or comatose state. The POPC score correlates well with the Bayley Psychomotor Developmental Index and Vineland Adaptive Behavior Score. The PCPC score correlates with the Stanford-Binet IQ test and Bayley Mental Developmental Index.([22;23])

Patient Selection

We obtained data for all consecutive admissions in the VPS database occurring from January 1, 2004 to December 31, 2005. Hospitals were excluded from analysis if they had more than 10% missing data for systolic blood pressure measurements for PRISMII or PRISMIII components. Patients were excluded from analysis if they were neonates (< 1 month old), were over 18 years of age, or if they did not have any PRISMII or PRISMIII variables recorded (Figure 1). It was assumed that every patient who was admitted to the PICU would have at least one systolic blood pressure (SBP) measurement obtained on the first day of admission.

Therefore, this variable was used as a marker for reliable data collection as it did not depend on physician practice. Cut-off values for SBP as a measure of cardiovascular dysfunction were obtained from pediatric advanced life support (PALS)([26]) guidelines with a maximum SBP of 90mmHg defining 5th percentile in children. The upper limit for normal creatinine values was obtained from the Harriet Lane handbook([27]).

As this study involved the analysis of de-identified patient information, it was exempted from Institutional Review Board (IRB) review by the University of Texas Health Science Center at Houston and Baylor College of Medicine.

Statistical Analysis

We used PIM2 data to compare risk-adjusted mortality in patients either included or excluded from analysis, controlling for patient age, race, and sex. We reported mean values for variables with a normal distribution and median (25th, 75th percentile) values for variables with skewed distributions. We assessed group differences in categorical and non-normal continuous variables using χ^2 and Mann-Whitney rank sum tests, respectively. We assessed group differences in ordinal variables using χ^2 and Mann-Whitney rank sum tests. We assessed the effect of different dysfunctional organ systems on mortality and log-transformed length of stay using χ^2 and Student's t-tests, respectively.

We used logistic and linear regression to assess the independent effect of each dysfunctional organ system and the number of dysfunctional organ systems on PICU mortality and length of stay, respectively. We used linear regression to assess the independent effect of each dysfunctional organ system on the change from baseline of POPC and PCPC. For both logistic and linear regression models, we controlled for patient age, race, sex, and hospital of origin. Statistical analysis was accomplished using Statistical Analysis Systems, version 9.1.3 and STATA 9/SE software.

Results

Of the 63,285 patient admissions in the VPS dataset, there were 44,693 admissions from 28 pediatric hospitals meeting inclusion criteria (Figure 1). Four hospitals were excluded as they did not collect PRISM II or III data. Three hospitals were excluded because they had more than 10% missing data for PRISMII and/or III SBP. Of the remaining 28 hospitals, 4.1% of patients had no PRISM II and/or III data and were therefore excluded from our analysis dataset. Patients excluded from analysis due to missing PRISMII and/or III data had similar risk adjusted mortality as those patients who were included. There was a higher proportion of Caucasians (55.0% vs. 45.0%) and a smaller proportion of missing race values in the analysis group (15.7% vs. 25.5%) than in the excluded group. There were no sex or age differences between the two groups.

Epidemiology

Overall unadjusted mortality for the VPS dataset for the study time period was 3.1%. For patients included in analysis, overall PICU mortality was 2.8%. Of patient admissions, 10.6% were admitted for trauma, 41.9% of patients were operative, and 58.1% of patients were medical. The most common reasons for PICU admission were: respiratory distress/failure (31.2%), neurologic compromise (23.8%), and shock (18.7%). On hospital day one, 18.6% of patients had MODS. Day one MODS had a complex association with age (Table 3). Day one MODS was disproportionately present in the youngest patients. While 24.1% of all patients were infants (between one and 12 months of age), 32.8% of all patients with day one MODS were in this age group. The incidence of day one MODS was highest in infants (25.2% vs. 16.5%) compared to other age groups (Table 3). In multivariable logistic regression models

with day one MODS as the outcome variable, and using infants as the reference group, all other age groups had less MODS at PICU admission (Odds ratio (OR) < 1.0, p<0.001).

There was an association between race and day one MODS in univariate analysis (Table 3). However, in logistic regression analysis controlling for patient age and hospital of origin, all race groups had similar risk of day one MODS. There was no association between sex and day one MODS. Operative patients had a significantly higher incidence of MODS (20.4%) than medical patients (17.0%), but medical patients had higher mortality rates (4.2% vs 1.3%), p<0.0001. Patients admitted for shock had the highest incidence of MODS (33.3%, p<0.0001) and the highest mortality rates compared to patients with other reasons for admission (4.5%, p<0.0001)

Overall PICU mortality was significantly higher (10.0% versus 1.2%, p<0.0001) for patients with MODS at admission (Table 3). Of 1259 patients who died, 66% had MODS at time of PICU admission. In multivariable logistic regression models including age, race, sex, and hospital of origin as covariates, day one MODS significantly increased the risk of death (OR = 11.1 [95% Confidence Interval (CI) 9.8–12.6]).

There was differential PICU mortality based on age. Infants had the highest overall PICU mortality (3.6% vs. 2.6%) compared to other age groups in both univariate analysis (p<0.001) and multivariable analysis (p<0.04 comparing infants to1–2 year age group and p<0.008 comparing infants to all other age groups). However, when controlling for the presence of day one MODS, infants no longer had increased mortality compared to other age groups. The higher overall mortality rate for infants can be explained by their increased incidence of MODS present at PICU admission.

The type and number of dysfunctional organ systems present at PICU admission were associated with PICU mortality. Respiratory dysfunction was most common, occurring in 34.0% of patients admitted. This was followed by cardiovascular (20.9%) and neurologic dysfunction (10.6%) (Table 4). Dysfunction of each individual organ system on day one was associated with mortality in both univariate and multivariable analysis. In univariate analysis, hepatic, hematologic, and renal dysfunction resulted in the highest mortality (16.5%, 14.4%, and 14.2%, respectively). However, in logistic regression analysis controlling for the presence of all other dysfunctional organ systems, respiratory dysfunction conferred the greatest independent risk of mortality, with an OR of 5.5 (95% CI 4.7–6.5) (Table 4). Hepatic, hematologic, and renal dysfunction were associated with greater numbers of dysfunctional organ systems when they were present. Mortality for failure of two, three, and four or more organ systems at PICU admission was 6.8%, 16.2%, and 43.5%, respectively (Table 5).

Length of Stay

PICU length of stay was significantly longer (median of 3.6 vs. 1.3 days, p<0.0001) for patients with day one MODS. Compared to other age groups, infants had longer length of stay whether or not MODS was present at PICU admission. In linear regression analysis controlling for every other organ system, each organ system was independently associated with increased length of stay (p<0.0001). When controlling for all other dysfunctional organ systems, day one respiratory failure made the greatest contribution to length of stay (beta coefficient 0.73, p<0.001) (Table 4). The number of dysfunctional organ systems present at PICU admission was also associated with increased length of stay. Length of stay increased for each additional organ system affected (p=0.0001) (Table 5).

Functional Outcomes

In a subset of patients from the database who had POPC and PCPC scores recorded at PICU admission and discharge, we analyzed the impact of day one MODS on functional outcomes scores after PICU hospitalization. Forty-eight percent of patients included in analysis had both POPC and PCPC scores recorded at PICU admission and discharge. There was no difference in risk-adjusted mortality between patients who did and did not have these scores recorded. Patients with POPC and PCPC scores recorded were older (median of 62 vs. 46 months) than patients without them. The incidence of MODS in patients with POPC and PCPC scores recorded was 19.5%, compared to 17.7% in patients without them.

Day one MODS survivors had significant morbidity after their PICU hospitalization. Day one MODS was associated with higher baseline and discharge POPC and PCPC scores ($p<0.0001$) as well as a greater (worse) change in POPC and PCPC from PICU admission to discharge ($p<0.0001$). Patients with MODS at PICU admission were more likely to have a discharge POPC score greater than three (36.3% vs. 17.4%, $p<0.0001$) as well as a discharge PCPC score greater than three (29.3% vs. 12.2%, $p<0.0001$), indicating at least moderate impairment in their projected global and cognitive functional status at time of PICU discharge. Of patients discharged from the PICU in a vegetative or comatose state, 64.0% had MODS at admission to the PICU.

The type and number of dysfunctional organ systems present at PICU admission were also associated with a rise in POPC and PCPC as measured at PICU discharge (Table 6). Each dysfunctional organ system was independently associated with a change from baseline POPC and PCPC in multivariable linear regression analysis; hematologic, neurologic, and hepatic dysfunction conferred the largest change in POPC and PCPC ($p<0.0001$). Higher numbers of dysfunctional organ systems on day one were associated with a larger change from baseline in POPC and PCPC scores (Table 6).

The percentage of patients with a discharge POPC and PCPC greater than three, indicating at least moderate impairment of projected functional status at time of PICU discharge, rose with increased number of day one dysfunctional organ systems ($p<0.0001$, Table 6). The percentage of patients with a POPC greater than three for those with two or more organ dysfunction on day one was 36.3%, while only 17.4% of patients with zero or one dysfunctional organ system had a POPC greater than three at PICU discharge. The percentage of patients with a PCPC greater than three for those with two or more organ dysfunction on day one was 29.3%. Of patients with one or fewer dysfunctional organ systems at PICU admission, only 12.2% had a PCPC greater than three at PICU discharge.

Higher baseline POPC and PCPC scores were also associated with day one MODS. Patients with higher baseline POPC and PCPC scores were more likely to have day one MODS ($p<0.0001$) and were more likely to have greater numbers of dysfunctional organ systems when MODS was present at PICU admission ($p<0.0001$). Patients with higher baseline POPC and PCPC scores also had higher overall PICU mortality.

Discussion

This current investigation represents the largest PICU-specific study of early pediatric MODS epidemiology to date. We demonstrate that that the overall ICU mortality, 2.8%, and as critically the MODS mortality of 10%, has decreased substantially from the first reports 20 years ago (Table 7). This overall PICU mortality is low, but is consistent with recent published reports of US PICU mortality rates.([6]) Here we also identify for the first time that the presence of multiple organ dysfunction on day one of PICU admission is associated with poor functional outcome.

This is the first study to evaluate functional outcomes from MODS in the PICU. We demonstrated that survivors of MODS present at PICU admission bear considerable morbidity, and were more likely to have a POPC or PCPC score indicating at least moderate impairment in functional status at time of PICU discharge. Worsening of POPC and PCPC scores from PICU admission to discharge was associated with the number of dysfunctional organ systems present at admission. Patients who had 3 or more dysfunctional organ systems had the worst functional outcomes. In a cohort of children admitted to the PICU in the United Kingdom, 27.3% of patients studied had impairments in their functional status 6 months after admission ([28]). Our findings indicate that organ dysfunction may contribute to this long term functional impairment. We have also found that approximately 10% of children with no organ failure and 20% of those with single organ failure have significant morbidity at PICU discharge ,i.e. POPC score of ≥ 3 (Table 6). The mean change in functional outcome score in these groups overall is quite low, implying that many children present with significant baseline morbidities. The effect of co-morbid disease in the ICU population overall, and the effect on organ dysfunction and mortality are complex. This will require within patient analysis and classification of co-morbid illnesses by type, number, and severity. This is currently an area of our investigation.

We found that infants represented a particularly vulnerable age group compared to other age groups, as they had an overall higher PICU mortality rate and higher incidence of MODS. However, when we controlled for organ dysfunction, infants no longer had an increased mortality rate. This suggests that their increased mortality may be a direct result of their increased incidence of MODS. In addition to a higher incidence of MODS and higher overall PICU mortality, infants also had longer PICU length of stay compared to other age groups, regardless of MODS diagnosis. An increased incidence of MODS in the youngest children has been seen in other studies([13]). Infants have also been shown to have a higher incidence of organ dysfunction in the setting of severe sepsis([29]).

Worldwide MODS incidence and mortality rates vary considerably with geographic location and decade (Table 7). In 2003, Tantalean reported a population of patients with a MODS incidence of 56.5%, MODS mortality of 42%, and overall PICU mortality of 25.7%.([14]) These differences in MODS incidence and mortality are attributed to differences in patient case-mix, access to tertiary care, and the presence of significant comorbidities at PICU admission.([14]) In the Tantalean study, a significant proportion of patients presented to the PICU with co-morbid malnutrition.

The large number of participating institutions and large number of PICU patient admissions with clinically relevant data is one of the particular strengths of this analysis. The VPS database has rigorous quality control with frequent review to ensure ongoing high fidelity data entry. It currently is the only large dataset of PICU patients. The only other study that examined a population of children comparable in size to ours used the 1997 Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) ([17]). In that study, Johnston *et. al.* examined all children admitted to the hospital, and not those just to the PICU([17]). Of the 1.1 million patients in the KID database, 0.5–2.6% had MODS, depending on the definition used. In the study organ dysfunction was classified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) codes. In our study consensus definitions of organ failure were used based on age-dependent physiologic/laboratory parameters. Thus we believe that we capture a clinically relevant diagnosis of organ failure.

An additional strength of the current study is the use of consensus definitions of organ dysfunction. The reported incidence of MODS has ranged from 10.9 to 56.5% in different studies, and reported MODS mortality rates have ranged from 11–19% (Table 7). Mortality from MODS in this study was lower that previously reported, but consistent with the overall improvement in PICU mortality over the last two decades([6;15;30]). Previous data from US and

French/Swiss/Canadian groups demonstrate MODS-related mortality between 11–19% in PICUs with 6.4–8.6% overall mortality ([5;15;17]). We believe differences in incidence may be due to differences in PICU patient case-mix (which is abrogated with a large database across institutions, such as this one), and differences in the definition of MODS.

Limitations and Future Directions

A limitation of our study is that MODS is identified on day one of PICU admission. We may therefore underestimate the incidence of MODS present at PICU admission and throughout the PICU stay. Previously published studies identified MODS occurring at any time point during the hospital admission (Table 7). As the VPS database collects vital sign and laboratory information at admission, we may misclassify patients as not having MODS if they developed organ dysfunction later in their PICU stay. Thus we may underestimate the incidence of MODS. However, in the only pediatric prospective study to specifically evaluate the timing of MODS, 86% of patients who were eventually identified as having MODS met MODS criteria on the day one of admission and most were admitted with their maximal number of organ failure ([13]). Recent work from our institution specifically examining renal injury, demonstrated that the majority of renal injury is identified on the first day of admission to the PICU([31]). We also assume that missing PRISMII and III datapoints represent normal values when assigning day 1 organ dysfunction in an individual patient. This may further underestimate the incidence of MODS. Here we report an incidence of day one MODS of 18.6%, thus we estimate that MODS incidence overall may be up to 19% based on Proulx' work([13]). This is consistent with many single center studies of MODS epidemiology of 11–20% (Table 7). Furthermore, the death rate of MODS in our present study is remarkably similar to that reported in other studies during this decade (Table 7).

A further limitation of our study is that we do not know the duration of illness prior to PICU admission in our patients. There may exist differences in PICU admission criteria between institutions resulting in more or less progression of MODS at time of PICU admission, and patients may transfer from other institutions with greater illness severity at time of transfer. The large number of participating institutions is an asset in this regard. We anticipate that differences in admitting practices and patient populations will be normally distributed and limit skew of our results as might occur with single institution differences in practice.

In data bases such as these, we are dependant on scores such as the POPC and PCPC scores which are proxy determinations of functional outcomes. These scores have been developed and validated in the US PICU population and correlated well with more intensive neurocognitive tests([22;23]). However there have been concerns regarding the robustness of proxy scores to evaluate functional status.([32;33])

A final limitation of our study is that the VPS database does not include a specific MODS score and we were unable to identify every component of the IPSCC definitions for organ failure. The Pediatric Multiple Organ Dysfunction Score (P-MODS) or the PELOD score were not reported in VPS during this period. We were not able to adhere strictly to all the IPSCC definitions of MODS-related organ dysfunction, although we were able to identify components of the definition for each organ system. We may have identified additional patients as having MODS present at PICU admission if we were able to adhere strictly to IPSCC criteria for each category of organ dysfunction. Each of these factors may result in an underestimate of MODS incidence and an over or under-estimate of overall MODS mortality.

Conclusions

We found that admission organ dysfunction impacts functional outcome after critical illness. Our findings support previous reports that children with MODS present at PICU admission

have higher PICU mortality and longer PICU length of stay. Understanding the effect of organ dysfunction on functional outcome may allow us to examine the impact of care quality on discharge functional status in the future. We found that IPSCC criteria, intended to define sepsis related organ dysfunction, are clinically useful to identify MODS in a general PICU population.

Acknowledgments

We would like to thank Dr. Mona McPherson, Dr. Irena Cech, and Dr. Stuart Goldstein for their advice and assistance during this project. VPICU Performance System (VPS) data was provided from the VPS, LLC. No endorsement or editorial restriction of the interpretation of these data or opinions of the authors has been implied or stated. Work was performed at the Houston Center for Quality of Care and Utilization Studies, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX.

Financial Support for this work: NIH T32HL007939 (KVT) and American Thoracic Society Fellow's Career Development Award ATS F-07-014 (KVT).

References List

1. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006 June 15;354(24):2564–2575. [PubMed: 16714767]
2. Peres BD, Melot C, Lopes FF, Nguyen BV, Vincent JL. The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. Intensive Care Med 2002 November;28(11):1619–1624. [PubMed: 12415450]
3. Rivera-Fernandez R, Nap R, Vazquez-Mata G, Reis MD. Analysis of physiologic alterations in intensive care unit patients and their relationship with mortality. J Crit Care 2007 June;22(2):120–128. [PubMed: 17548023]
4. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE. Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest 2005 November;128(5): 3109–3116. [PubMed: 16304250]
5. Leclerc F, Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Martinot A, Gauvin F, Hubert P, Lacroix J. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. Am J Respir Crit Care Med 2005 February 15;171(4):348–353. [PubMed: 15516535]
6. Han YY, Carcillo JA, Venkataraman ST, Clark RS, Watson RS, Nguyen TC, Bayir H, Orr RA. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics 2005 December;116(6):1506–1512. [PubMed: 16322178]
7. Del Beccaro MA, Jeffries HE, Eisenberg MA, Harry ED. Computerized provider order entry implementation: no association with increased mortality rates in an intensive care unit. Pediatrics 2006 July;118(1):290–295. [PubMed: 16818577]
8. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics 2006 July;118(1):173–179. [PubMed: 16818563]
9. Zimmerman JE, Knaus WA, Wagner DP, Sun X, Hakim RB, Nystrom PO. A comparison of risks and outcomes for patients with organ system failure: 1982–1990. Crit Care Med 1996 October;24(10): 1633–1641. [PubMed: 8874298]
10. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998 November;26(11):1793–1800. [PubMed: 9824069]
11. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002 January 16;287(3):345–355. [PubMed: 11790214]
12. Sashegyi A, Trzaskoma BL, Nelson DR, Williams MD, Macias W. International INtegrated Database for the Evaluation of severe sePsis and drotrecogin alfa (activated) THerapy: component trials and

statistical methods for INDEPTH. Curr Med Res Opin 2006 May;22(5):1001–1012. [PubMed: 16709322]

13. Proulx F, Gauthier M, Nadeau D, Lacroix J, Farrell CA. Timing and predictors of death in pediatric patients with multiple organ system failure. Crit Care Med 1994 June;22(6):1025–1031. [PubMed: 8205810]
14. Tantalean JA, Leon RJ, Santos AA, Sanchez E. Multiple organ dysfunction syndrome in children. Pediatr Crit Care Med 2003 April;4(2):181–185. [PubMed: 12749649]
15. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, Gottesman R, Joffe A, Pfenninger J, Hubert P, Lacroix J, Leclerc F. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 2003 July 19;362(9379):192–197. [PubMed: 12885479]
16. Goh A, Lum L. Sepsis, severe sepsis and septic shock in paediatric multiple organ dysfunction syndrome. J Paediatr Child Health 1999 October;35(5):488–492. [PubMed: 10571765]
17. Johnston JA, Yi MS, Britto MT, Mrus JM. Importance of organ dysfunction in determining hospital outcomes in children. J Pediatr 2004 May;144(5):595–601. [PubMed: 15126992]
18. Leteurtre S, Duhamel A, Grandbastien B, Lacroix J, Leclerc F. Paediatric logistic organ dysfunction (PELOD) score. Lancet 2006 March 18;367(9514):897–892. [PubMed: 16546531]
19. Garcia PC, Eulmesekian P, Sffogia A, Perez A, Branco RG, Piva JP, Tasker RC. Limitation in paediatric logistic organ dysfunction score. Lancet 2006 September 30;368(9542):1151–1152. [PubMed: 17011936]
20. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005 January;6(1):2–8. [PubMed: 15636651]
21. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003 February;29(2):278–285. [PubMed: 12541154]
22. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, Brodie-Fowler M. 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 July;28(7):2616–2620. [PubMed: 10921604]
23. 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 April; 28(4):1173–1179. [PubMed: 10809301]
24. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988 November;16(11):1110–1116. [PubMed: 3048900]
25. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996 May;24(5):743–752. [PubMed: 8706448]
26. Pediatric Advanced Life Support Provider Manual. Dallas, TX: American Heart Association; 2002.
27. Johns Hopkins: The Harriet Lane Handbook: A Manual for Pediatric House Officers. Vol. 15th Edition. Mosby: St. Louis, MO; 2002.
28. Jones S, Rantell K, Stevens K, Colwell B, Ratcliffe JR, Holland P, Rowan K, Parry GJ. Outcome at 6 months after admission for pediatric intensive care: a report of a national study of pediatric intensive care units in the United kingdom. Pediatrics 2006 November;118(5):2101–2108. [PubMed: 17079584]
29. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003 March 1;167(5): 695–701. [PubMed: 12433670]
30. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest 1996 April;109(4):1033–1037. [PubMed: 8635327]
31. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007 May;71(10):1028–1035. [PubMed: 17396113]
32. Yasuda N, Zimmerman S, Hawkes WG, Gruber-Baldini AL, Hebel JR, Magaziner J. Concordance of proxy-perceived change and measured change in multiple domains of function in older persons. J Am Geriatr Soc 2004 July;52(7):1157–1162. [PubMed: 15209655]

33. FDA. Guidance for industry: Patient-reported outcome measures: Use in medical product development to support labeling claims. Rockville, MD: Center for Drug Evaluation and Research, Food and Drug Administration; 2006. Ref Type: Generic

34. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988 November;16(11):1110–1116. [PubMed: 3048900]

35. Wilkinson JD, Pollack MM, Ruttimann UE, Glass NL, Yeh TS. Outcome of pediatric patients with multiple organ system failure. Crit Care Med 1986 April;14(4):271–274. [PubMed: 3956214]

36. Wilkinson JD, Pollack MM, Glass NL, Kanter RK, Katz RW, Steinhart CM. Mortality associated with multiple organ system failure and sepsis in pediatric intensive care unit. J Pediatr 1987 September;111(3):324–328. [PubMed: 3625400]

37. Khilnani P, Sarma D, Zimmerman J. Epidemiology and peculiarities of pediatric multiple organ dysfunction syndrome in New Delhi, India. Intensive Care Med 2006 November;32(11):1856–1862. [PubMed: 16977482]

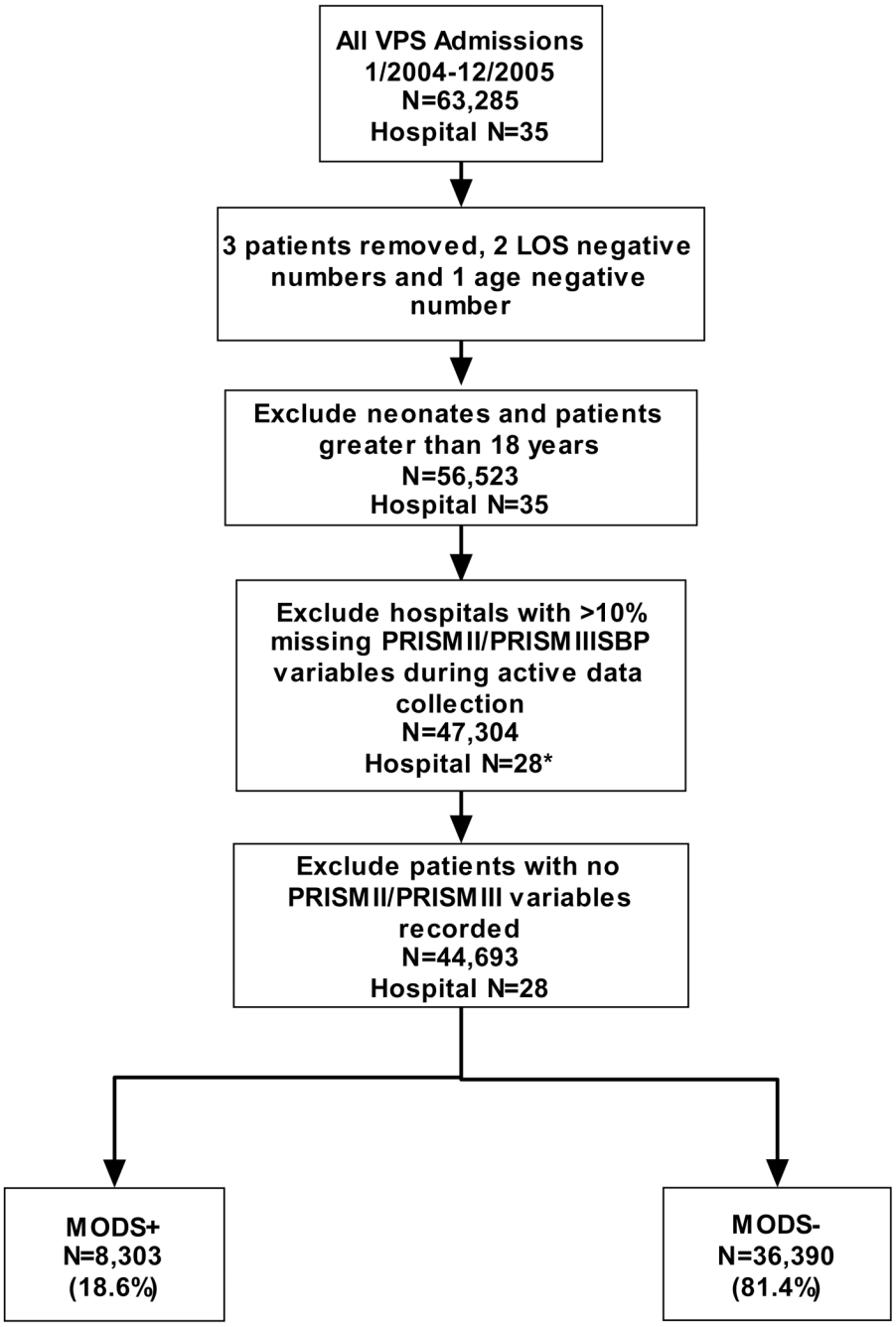

Figure 1. Flow Diagram for database management

VPS= VPICU Performance system database

LOS= Length of stay

PRISM=Pediatric risk of mortality score

SBP= Systolic blood pressure

MODS+= Multiple organ dysfunction syndrome present

MODS−= Multiple organ dysfunction syndrome absent

*Four hospitals did not choose to collect PRISM II and/or III data. Three additional hospitals demonstrated high missing data patterns of PRISMII and/or III data collection and were

excluded. The pattern was consistent with a trial period of data collection and then discontinuation of this element of data collection.

Table 1

VPICU Performance System Hospital Characteristics

VPS Hospital Characteristics	Database	Analysis dataset
Total N	35	28
Presence of a step down unit	11	9
Fellowship program	14	10
Accredited pediatric residency training program	15	11
Stand alone children's hospital	17	13
PICU admissions per year		
<900 admissions per year	14	11
900–1500 admissions per year	14	11
>1500 admissions per year	7	6
Data Collected		
PRISM II*	16	15
PRISMIII*	29	27
POPC and PCPC	23	22

VPS = VPICU Performance System

PICU=Pediatric Intensive Care Unit

PRISMII/PRISMIII= Pediatric Risk of Mortality

POPC= Pediatric Overall Performance Category Score

PCPC= Pediatric Cerebral Performance Category Score

* Some institutions collect both PRISMII and PRISMIII

Table 2

IPSCC organ dysfunction definition and mortality prediction scores

IPSCC Criteria for Organ Dysfunction([20])	PIM2([21])	PRISMII([34])	PRISMIII([25])
Cardiovascular			
Despite administration of isotonic intravenous fluid bolus ≥40cc/kg in 1 hour			
• **Decrease in BP <5th percentile for age of systolic BP <2 SD below normal for age**	+	+	+
OR			
• Need for vasoactive drug to maintain BP in normal range (dopamine >5mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)	–	–	–
OR			
• Two of the following Unexplained metabolic acidosis: base deficit >5 mEq/L Increased arterial lactate >2 times upper limit of normal Oliguria: urine output <0.5cc/kg/hour Prolonged capillary refill: >5 secs Core to peripheral temperature gap >3°C	–	–	–
Respiratory			
• **PaO_2/FiO_2 <300** in absence of cyanotic heart disease or preexisting lung disease	+	+	–
OR			
• **$PaCO_2$ >65 torr** or 20mm Hg over baseline $PaCO_2$	–	+	+
OR			
• Proven need or >50% FiO_2 to maintain saturation ≥92%	–	–	–
OR			
• **Need for nonelective invasive or noninvasive mechanical ventilation**	+	–	–
Neurologic			
• **Glasgow Coma Score ≤11**	–	+	+
OR			
• Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline	–	–	–
Hematologic			
• **Platelet count <80,000/mm^3** or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)	–	–	+
OR			
• International normalized ratio >2	–	–	–
Renal			
• **Serum creatinine ≥2 times upper limit of normal** for age or 2-fold increase in baseline creatinine	–	–	+
Hepatic			
• **Total bilirubin ≥4 mg/dl (not applicable for newborn)**	–	+	+
OR			
• ALT 2 times upper limit of normal for age	–	–	–

IPSCC= International Pediatric Sepsis Consensus Conference

PIM2= Pediatric Index of Mortality 2

PRISMII/PRISMIII= Pediatric Risk of Mortality

Items in bold typeface indicate variables that could be found in the VPICU Performance System (VPS) database. These were the variables used to indicate the presence of organ dysfunction and MODS.

Table 3

Descriptive statistics for patients with and without MODS

Total N=44,693	**MODS + (N) N=8,303**	**(%)**	**MODS- (N) N=36,390**	**(%)**	**P value**
Age	(18.6%)	100.0	(81.4%)	100.0	<0.0001
1 mos-<12mos (Infant)	2,722	32.8	8,071	22.2	
1–2 y	1,338	16.1	6,849	18.8	
3–6 y	1,204	14.5	6,683	18.4	
7–10 y	965	11.6	4,519	12.4	
11–14 y	1,188	14.3	5,803	15.9	
15–18 y	886	10.7	4,465	12.3	
Sex (11 missing)	8,301		36,381		0.5
Male	4,696	56.6	20,432	56.2	
Race/Ethnicity					<0.0001
Caucasian	4,898	59.0	19,666	54.0	
African American	1,282	15.4	6,315	17.4	
Hispanic	755	9.1	3,568	9.8	
Asian	229	2.8	939	2.6	
Other/Mixed/Missing	1,139	13.7	5,902	16.2	
Case-Mix					
Operative Patients	4,251	51.2	16,633	45.7	<0.0001
Trauma Patients	891	10.7	3834	10.5	0.6
Sepsis					<0.0001
Yes	1,185	14.3	2,068	5.7	
Outcome					<0.0001
Died	832	10.0	427	1.2	
LOS (days)					<0.0001
Median (25%,75%)	3.6 (1.8,7.9)		1.3 (0.9,2.8)		

MODS+= Multiple organ dysfunction syndrome present

MODS−= Multiple organ dysfunction syndrome absent

Table 4

Each organ system and the association with mortality and length of stay

Dysfunctional Organ System	Hospitalizations N(%)	Mortality %*	Odds Ratio*	95% CI	Length of Stay Median (IQR)	Beta Coefficients†
Respiratory	15,186 (34.0%)	6.7	5.5	4.7–6.5	3.0 (1.6–7.0)	0.73
Cardiovascular	9,353 (20.9%)	6.9	2.8	2.5–3.2	2.2 (1.0–5.8)	0.21
Neurologic	4,753 (10.6)	8.8	3.2	2.7–3.8	2.8 (1.3–6.8)	0.19
Hematologic	1,678 (3.7%)	14.4	3.9	3.3–4.6	3.5 (1.7–8.0)	0.43
Renal	1,078 (2.4%)	14.2	3.4	2.8–4.3	3.0 (1.4–7.9)	0.41
Hepatic	411 (0.9%)	16.5	3.7	2.7–5.1	3.1 (1.5–8.6)	0.35

CI= Confidence Interval

IQR= Interquartile range

*Each organ system is associated with mortality in univariate analysis, p<0.0001. Each organ system is independently associated with mortality in multivariable logistic regression models controlling for age, race, sex, hospital of origin, and each other organ system dysfunction. Reference group are those patients with no organ dysfunction.

†Linear regression model evaluating log-transformed length of stay and controlling for age, race, sex, hospital of origin, and all other dysfunctional organ systems. All reported beta coefficients had p values <0.0001.

Table 5

Number of dysfunctional organ systems and the association with mortality and length of stay>

Number of dysfunctional organ systems	Hospitalizations N(%)	Mortality* %	Odds Ratio	95% CI	Length of Stay Median (IQR)	Beta Coefficients†
0	22,867(51.2)	0.5	--	--	1.1 (0.8–2.1)	--
1	13,523 (30.3)	2.4	5.2	4.2–6.5	2.0 (1.0–4.3)	0.5
2	6,333 (14.2)	6.8	19.6	15.7–24.4	3.2 (1.7–7.6)	1.0
3	1,664 (3.7)	16.2	61.7	48.2–78.8	4.4 (2.0–9.2)	1.2
4 or greater	306 (0.7)	43.5	267.4	195.2–366.2	4.9 (1.5–12.2)	1.2

CI= Confidence Interval

IQR= Interquartile range

*Mortality increased with increased number of dysfunctional organ systems, Mann-Whitney rank sum, $p<0.0001$. The odds of death increased with rising number of dysfunctional organ systems when controlling for age, race, sex and hospital of origin. Reference group consisted of those patients with no organ dysfunction.

†Linear regression model evaluating log-transformed length of stay and controlling for age, race, sex, and hospital of origin. All beta coefficients had p values <0.0001.

Table 6

Change from baseline POPC and PCPC with MODS

Number of dysfunctional organ systems	Hospitalizations N(%)*	Delta POPC† Mean, Median(IQR)	Delta PCPC† Mean, Median(IQR)	Discharge POPC≥3‡ %	Discharge PCPC≥3‡ %
0	11,207(52.2)	0.07,0(0,0)	0.03,0(0,0)	13.6	9.0
1	6,070(28.3)	0.17,0(0,0)	0.13,0(0,0)	24.4	18.2
2	3,139(14.6)	0.45,0(0,0)	0.41,0(0,0)	35.4	28.5
3	861(4.0)	0.91,0(0,1)	0.89,0(0,1)	38.4	31.7
4 or greater	188(0.9)	2.0,2(0,4)	2.1,1(0,5)	47.1	34.3

IQR= Interquartile range
POPC= Pediatric Overall Performance Category Score
PCPC= Pediatric Cerebral Performance Category Score
Delta POPC=(discharge POPC) - (baseline POPC)
Delta PCPC=(discharge PCPC) - (baseline PCPC)

*Only patient admissions with admission and discharge POPC and PCPC values are included in this table.

†Increased delta POPC and delta PCPC with increasing numbers of dysfunctional organ systems, Kruskal-Wallis, p=0.0001. Increased baseline POPC and baseline PCPC were associated with increased numbers of dysfunctional organ systems, Kruskal-Wallis, p=0.0001.

‡Increased numbers of dysfunctional organ systems were associated with greater percentage of patients with discharge POPC and PCPC greater than or equal to three, Mann-Whitney rank sum, p<0.001.

Table 7

Comparison of published pediatric MODS studies and this study

Author	Wilkinson 1986([35])	Wilkinson 1987([36])	Proulx 1994([13])	Proulx 1996([30])	Goh 1999([16])	Tantalean 2003([14])	Leteurtre 2003([15])	Johnston 2004([17])	Leclerc 2005([5])	Khilnani 2006([37])	Typpo 2007
Region	US	US	Canada	France/ Canada	Singapore	Peru	France/ Canada/ Switzerland	US	France/ Canada	India	US
Type of study	Cohort	Cohort	Chart Review	Cohort	Cohort	Cohort	Cohort	Database	Cohort	Cohort	Database
MODS definition	Wilkinson	Modified Wilkinson	Modified Wilkinson	Modified Wilkinson	Modified Wilkinson	Modified Wilkinson	PELOD	ICD-9	PELOD	OFI	IPSCC
Number of patients	831	726	777	869	495	269	1806	1.1 million	593	1722	44,693
Overall ICU Mortality (%)	7.5%	11%	----	6%	10%	25.7%	6.4%	--	8.6%	7.9%	2.8%
Incidence of MODS (%)	27%	24%	10.9%	18%	16.9%	56.5%	53.4%	0.5–2.6%	45%	17.3%	18.6%
Mortality for MODS (%)	54%	47%	50.6%	35%	57%	42%	11%	19%	19%	25.8%	10.0%

US=United States

Cohort= prospective cohort study

PELOD=Pediatric Logistic Organ Dysfunction score

ICD-9= International classification of diseases, 9threvision

OFI= Organ Failure Index

IPSCC=International Pediatric Sepsis Consensus Conference