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Multiple Organ Dysfunction in Children Mechanically Ventilated for Acute Respiratory Failure

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Abstract

Objective—The impact of extrapulmonary organ dysfunction, independent from sepsis and lung injury severity, on outcomes in pediatric acute respiratory failure is unclear. We sought to determine the frequency, timing, and risk factors for extrapulmonary organ dysfunction and independent association of multiple organ dysfunction syndrome (MODS) with outcomes in pediatric acute respiratory failure.

Design—Secondary observational analysis of the *RESTORE* cluster-randomized prospective clinical trial conducted between 2009 and 2013.

Setting—Thirty-one acacemic pediatric intensive care units in the U.S.

Patients—2,449 children mechanically ventilated for acute respiratory failure enrolled in *RESTORE*.

Measurements and Main Results—Organ dysfunction was defined using criteria published for pediatric sepsis. MODS was defined as respiratory dysfunction plus ≥1 extrapulmonary organ dysfunction. We used multivariable logistic regression to identify risk factors for MODS, and logistic or proportional hazards regression to compare clinical outcomes. All analyses accounted for PICU as a cluster variable. Overall, 73% exhibited extrapulmonary organ dysfunction, including 1547 (63%) with concurrent MODS defined by onset on day 0/1 and 244 (10%) with new MODS with onset on day 2 or later. Most patients (93%) with indirect lung injury from sepsis presented with concurrent MODS, whereas patients with direct lung injury had both concurrent (56%) and new (12%) MODS. Risk factors for concurrent MODS included older age, illness severity, sepsis, cancer, and moderate/severe lung injury. Risk factors for new MODS were moderate/severe lung injury and neuromuscular blockade. Both concurrent and new MODS were associated with 90-day in-hospital mortality (concurrent: adjusted odds ratio [aOR] 6.54, 95% CI 3.00–14.25; new: aOR 3.21, 95% CI 1.48–6.93) after adjusting for sepsis, moderate/severe lung injury, and other baseline characteristics.

Conclusions—Extrapulmonary organ dysfunction was common, generally occurred concurrent with respiratory dysfunction (especially in sepsis), and was a major risk factor for mortality in pediatric acute respiratory failure.

Keywords

multiple organ failure; respiratory distress syndrome; mortality; pediatrics

INTRODUCTION

Acute respiratory failure requiring invasive mechanical ventilation is a common reason for admission to the pediatric intensive care unit (PICU) (1, 2). Prior studies have reported mortality rates between 11–34% for children with moderate to severe pediatric acute respiratory distress syndrome (PARDS) (3–10). Previously reported risk factors for death include high ventilatory requirements, severe hypoxemia, immune deficiency, fluid overload,

indirect lung injury (most commonly sepsis), and extrapulmonary organ dysfunction (3–5, 7, 9, 11, 12).

As in other critical illnesses, multiple organ dysfunction syndrome (MODS) is often present at death in mechanically ventilated children (3–5, 7, 9, 10, 13). However, the timing and impact of extrapulmonary organ dysfunction and MODS on the outcomes of children with acute respiratory failure is not clear. An important challenge has been to separate the independent role of MODS on outcome from the impact of either sepsis or PARDS severity, since extrapulmonary organ dysfunction is more likely to be present in these two scenarios than in other cases of acute respiratory failure (7). Prior studies of extrapulmonary organ dysfunction in children with acute respiratory failure have been limited by small sample size (<350 patients) and have predominantly focused on PARDS (3–5, 7, 9, 10, 13). In addition, most prior pediatric studies have relied on the 1994 American European Consensus Conference adult definitions of ARDS, whereas the Pediatric Acute Lung Injury Consensus Conference (PALICC) published updated criteria for PARDS in 2015 (14, 15).

The Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) cluster-randomized trial compared a sedation protocol to usual care in 2,449 children mechanically ventilated for acute respiratory failure (ClinicalTrials.gov NCT00814099) (16). *RESTORE* provides a large, contemporary, prospectively collected dataset with extensive quality oversight that included daily review of extrapulmonary organ dysfunction. Through a secondary analysis of the *RESTORE* dataset, our objectives were to determine 1) the frequency, timing, and risk factors for extrapulmonary organ dysfunction and 2) the impact of MODS, independent from sepsis etiology and moderate/severe PARDS, on clinical outcomes for a broad spectrum of children with respiratory failure requiring invasive mechanical ventilation.

METHODS

Study Design

RESTORE was a prospective, cluster-randomized clinical trial conducted between 2009 and 2013 in 31 U.S. PICUs (16). The aim of *RESTORE* was to test whether a nurse-implemented, goal-directed sedation protocol could reduce the duration of invasive mechanical ventilation for children with acute respiratory failure compared to usual care. All care, other than the sedation protocol at intervention PICUs, was at the discretion of the clinical team. Details of the *RESTORE* methodology and primary results have been published (16).

Population

We included all patients enrolled in the *RESTORE* trial. Patients were 2 weeks to 17 years-old with new invasive mechanical ventilation for acute airways and/or parenchymal lung disease. Excluded were patients expected to be extubated within 24 hours, transferred from an outside PICU with sedative exposure >24 hours, or with unrepaired cyanotic heart disease, primary pulmonary hypertension, chronic ventilator-dependence, and

neuromuscular respiratory failure. Written informed consent was obtained from the legal guardian of each patient.

Data Collection

Patient characteristics included demographic data, baseline Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) (17), Pediatric Risk of Mortality (PRISM) III-12 score (18), primary etiology of lung disease, and comorbid conditions. Acute respiratory failure due to sepsis was defined as a non-pulmonary systemic infection. Although pneumonia is often included as sepsis, for the purposes of differentiating direct from indirect etiologies of lung disease in this study, pneumonia and extrapulmonary sepsis were considered separately. PARDS severity on day 0/1 was defined using the 2015 PALICC criteria (15).[1] Study day 0/1 referred to the first two calendar days (up to 48 hours) of mechanical ventilation (16).

Respiratory dysfunction was defined as receipt of invasive mechanical ventilation. Extrapulmonary organ dysfunction was defined using modified criteria set by the International Pediatric Sepsis Consensus Conference (eTable 1) (19). Patients were assessed daily for organ dysfunction while in the PICU. Since all patients had respiratory dysfunction as part of the *RESTORE* inclusion criteria, MODS was defined as at least one additional extrapulmonary organ dysfunction. We defined “concurrent MODS” as extrapulmonary organ dysfunction present on study day 0/1 (i.e., concurrent with onset of respiratory failure) and “new MODS” as extrapulmonary organ dysfunction that developed on study day 2 or later (20).

Outcomes

The primary outcome for this study was development of MODS, trichotomized as respiratory dysfunction only, concurrent MODS, or new MODS. Clinical outcomes compared between MODS groups were duration of mechanical ventilation, PICU and hospital length of stay (LOS) in survivors (censored at study day 90), in-hospital mortality at 28 and 90 days, and proportion of patients not discharged home alive by day 90. For duration of mechanical ventilation, patients were assigned 28 days if they remained intubated, were transferred, or died prior to day 28 without being extubated for more than 24 hours. Therefore, this outcome is equivalent to ventilator-free days (21). Notably, there was no evidence in the *RESTORE* primary analysis that the sedation protocol intervention had a significant impact on duration of mechanical ventilation, LOS, or mortality (16).

Analysis

We used logistic regression to assess the effects of patient characteristics to predict 1) concurrent MODS versus all other patients and 2) new MODS versus respiratory dysfunction only. We graphically represented time to onset of first extrapulmonary organ dysfunction, assigning >28 days to patients with respiratory dysfunction only, and compared

[1]The 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) defined PARDS severity as 1) at-risk (oxygenation index [OI] <4.0 or oxygenation saturation index [OSI] <5.0), 2) mild (OI 4.0 to <8.0 or OSI 5.0 to <7.5), 3) moderate (OI 8.0 to <16.0 or OSI 7.5 to <12.3), or 4) severe (OI ≥16.0 or OSI ≥12.3).

between etiologies using the log-rank test. Maximum number of organ dysfunctions was compared between those with concurrent and new MODS using cumulative logit regression. The time course of respiratory and extrapulmonary organ dysfunction was analyzed graphically by plotting the proportion of patients with organ dysfunction amongst all patients remaining in the PICU on each study day and by calculating Spearman correlations between this proportion and study day.

We used stepwise multivariable logistic regression to identify independent risk factors for concurrent or new MODS from the patient characteristics listed in Table 1, using $p<0.05$ for a covariate to enter and stay in each model. For risk of concurrent or new MODS, we also *a priori* planned to adjust for age group, baseline functional impairment, and PRISM III-12 scores, even if these covariates would have otherwise been excluded through stepwise modeling. Next, clinical outcomes were compared between MODS groups using logistic or proportional hazards regression as appropriate. We then used multivariable modeling to further evaluate the independent effect of MODS on outcomes after controlling for the following covariates associated with outcome: age group, baseline functional impairment, PRISM III-12 score, sepsis etiology, and moderate/severe PARDS on day 0/1. Potential interactions between MODS and sepsis or PARDS were investigated as defined *a priori*. All regression analyses accounted for PICU as a cluster variable using generalized estimating equations. Analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC). Statistical significance was $p<0.05$.

RESULTS

Frequency and Timing of MODS

Of the 2,449 patients in the *RESTORE* trial, 1791 (73%) developed MODS with at least one extrapulmonary organ dysfunction, including 1547 (63%) who presented with concurrent MODS on day 0/1 of respiratory failure and 244 (10%) with new MODS initially developing between day 2 through 28. Characteristics for patients with respiratory dysfunction only, concurrent MODS, and new MODS are presented in Table 1. Patients with concurrent MODS were older and more likely to have cancer and have sepsis as the etiology for respiratory failure, with higher PRISM III-12 scores and more severe initial lung disease. Patients with new MODS had similar initial illness severity and distribution of etiologies for respiratory failure as patients with respiratory dysfunction only. However, patients with new MODS exhibited a higher rate of moderate/severe PARDS compared to patients with respiratory dysfunction only.

Cardiovascular (38%) and neurologic (37%) dysfunction were the most common extrapulmonary organ dysfunctions on day 0/1, followed by hematologic (15%), hepatic (14%), and renal (5%). All extrapulmonary organ dysfunctions were more common in sepsis than other etiologies of respiratory failure (eTable 2). However, the types of extrapulmonary organ dysfunction were similar across etiologies with the exception that patients with sepsis and pneumonia had a higher proportion of hematologic dysfunction compared to those with bronchiolitis, asthma, or aspiration. Forty-three percent with MODS had a maximum of two organ dysfunctions (including respiratory) and 27% had three organ dysfunctions. Patients

with concurrent MODS had a higher maximum number of organ dysfunctions compared to patients with new MODS (median 3 [interquartile range 2–4] vs 2 [2–3], $p<0.001$).

Overall, 86% of patients with MODS exhibited their first day of extrapulmonary organ dysfunction on day 0/1 and 58% presented with their maximum number of organ dysfunctions on day 0/1. However, the timing of first extrapulmonary organ dysfunction differed by etiology of respiratory failure (log-rank $p<0.001$; Figure 1) with shortest onset in sepsis and longest in bronchiolitis. Patients with *indirect* lung injury from sepsis were most likely to present with concurrent MODS, with 332 of 357 (93%) exhibiting MODS by day 0/1 of respiratory failure and only 8 (2%) developing new MODS. In contrast, 1023 (56%) of 1839 patients with *direct* lung injury from pneumonia, bronchiolitis, asthma, and aspiration presented with concurrent MODS and 221 (12%) developed new MODS (Table 1).

Extrapulmonary organ dysfunction decreased over the first seven days to a plateau of 37%, then increased slightly for patients who remained in the PICU (Figure 2A). Most cardiovascular and neurologic dysfunction was present on day 0/1, hematologic and hepatic dysfunction increased over time (hematologic: Spearman r=0.48, $p=0.01$; hepatic: r=0.78, $p<0.001$), and renal dysfunction remained relatively constant (r=0.24, $p=0.21$; Figure 2B).

Risk Factors for MODS

Independent risk factors for concurrent MODS included older age, higher baseline illness severity, sepsis etiology, cancer comorbidity, and moderate/severe PARDS on day 0/1 (Table 2). Baseline functional impairment and pre-existing seizure disorder were independently associated with a decreased risk for concurrent MODS. The only independent risk factors for new MODS were moderate/severe PARDS on day 0/1 and use of neuromuscular blockade for entire duration of days 0 to 2 (Table 2). Notably, intervention group was not associated with either concurrent or new MODS in the multivariable models.

Impact of MODS on Clinical Outcomes

Of the 110 non-survivors by day 28, 103 (94%) exhibited concurrent MODS and two (2%) exhibited new MODS. Table 3 compares clinical outcomes between patients with respiratory dysfunction only, concurrent MODS, and new MODS. Patients with concurrent MODS had the highest 28- and 90-day in-hospital mortality and the highest proportion of patients not discharged home alive by day 90. Patients with new MODS had the longest duration of mechanical ventilation and PICU and hospital LOS, though mortality was similar to patients with respiratory dysfunction only.

Both moderate/severe PARDS on day 0/1 and MODS were independently associated with 90-day in-hospital mortality and discharge to home alive by day 90 (Table 4). Concurrent MODS was associated with both early (28-day; adjusted odds ratio [aOR] 4.36, 95% CI 1.97–9.66) and late (90-day; aOR 6.54, 95% CI 3.00–14.25) mortality, whereas new MODS was only significantly associated with 90-day mortality (aOR 3.21, 95% CI 1.48–6.93) after adjusting for age group, baseline functional impairment, PRISM III-12 score, sepsis etiology, and moderate/severe PARDS. In multivariable analyses of duration of mechanical ventilation and LOS, there was a significant interaction between MODS and moderate/

severe PARDS on day 0/1. Concurrent MODS was associated with worse outcomes irrespective of PARDS severity, whereas new MODS was only associated with duration of mechanical ventilation and LOS in patients with at-risk/mild PARDS (eTable 3).

DISCUSSION

MODS occurred frequently in pediatric patients with a broad spectrum of acute respiratory failure requiring invasive mechanical ventilation, with nearly three-quarters exhibiting at least one extrapulmonary organ dysfunction. The majority of organ dysfunctions were present concurrent with the onset of respiratory failure, especially in patients with sepsis-induced *indirect* lung injury. In patients with *direct* lung injury, however, many also developed new MODS on day 2 or later. Moderate/severe PARDS was an independent risk factor for both concurrent and new MODS while sepsis was a risk factor only for concurrent MODS. Nearly all deaths occurred in patients with concurrent MODS though new MODS was associated with worse outcomes in the subset with less severe lung injury (i.e., at-risk and mild PARDS).

Our findings are consistent with smaller studies that have demonstrated an association of extrapulmonary organ dysfunction with increased risk of death in pediatric acute respiratory failure (3–5, 9). Our data add to this body of literature by 1) confirming the common occurrence of extrapulmonary organ dysfunction in a larger and broader cohort of pediatric patients with acute respiratory failure, 2) bolstering the association of extrapulmonary organ dysfunction with outcomes beyond PICU mortality to include 90-day in-hospital mortality, mechanical ventilation duration, and LOS, and 3) differentiating between extrapulmonary organ dysfunction existing concurrent with or developing subsequent to the onset of respiratory failure. Concurrent MODS present within 48 hours of initiation of invasive mechanical ventilation for acute respiratory failure was substantially more common than new MODS developing on day 2 or later. Patients with concurrent MODS also exhibited a greater overall number of extrapulmonary organ dysfunctions and had higher mortality than patients with new MODS.

Several independent risk factors were noted for concurrent MODS, most notably cancer and sepsis. Prior studies have consistently shown that extrapulmonary sepsis is the second or third most common cause of PARDS (3–5, 7, 9, 13, 22). Sepsis is also responsible for a disproportionate number of deaths compared to causes of direct lung injury (3–5, 7). It is likely that sepsis-induced respiratory failure shares pathobiologic mechanisms of extrapulmonary organ dysfunction in severe infection, such as microvascular thromboses and malperfusion. In contrast, new MODS was more common with direct lung injury, suggesting that primary hypoxemia and pulmonary biotrauma may precede—and perhaps even contribute to—later onset of extrapulmonary organ dysfunction in patients without sepsis, as suggested by Traschel et al. (7). The association of moderate/severe PARDS, defined as a more severe oxygenation defect at higher ventilatory pressures, with development of new MODS supports such a link between severity of lung injury and progression of extrapulmonary organ dysfunction. The association of early neuromuscular blockade, most commonly used with severe, refractory hypoxemia, with new MODS further suggests that early oxygenation defects could be linked to evolving extrapulmonary organ

dysfunction; however, we cannot differentiate this explanation from an alternative connection between pharmacologic neuromuscular blockade and new MODS.

In contrast to smaller studies, we were also able to separate the independent impact of MODS on outcome from the effect of either sepsis or PARDS severity. The presence of extrapulmonary organ dysfunction was a strong independent risk factor for adverse outcomes after controlling for both sepsis and moderate/severe PARDS. This finding is consistent with reports that MODS is a more common cause of death than refractory hypoxemia in PARDS (3, 5, 7, 9, 10, 13). The predominant early onset of MODS in our study further supports that, in most cases, MODS is not merely a reflection of the immediate process of dying. A similar pattern of early extrapulmonary organ dysfunction was reported in a large prospective study of adult ARDS (22). Together, these data suggest interventions beyond lung-based therapies that reverse hypoxemia as a solitary therapeutic strategy may be necessary to improve outcomes in PARDS. Reversing hypoxia and improving lung disease could prove inadequate to rescue patients from death if extrapulmonary organ dysfunction cannot be simultaneously managed. Indeed, numerous attempts to reverse hypoxemia have not consistently translated into beneficial patient outcomes (8, 23–26). In children, where extrapulmonary organ dysfunction is largely present at onset of acute respiratory failure, improved oxygenation should be tested alongside novel therapies that also target extrapulmonary organ injury.

Our findings also support including extrapulmonary organ dysfunction in the risk-stratification scheme for PARDS. Existing criteria and most ARDS research focus on severity of hypoxemia in conjunction with ventilatory parameters (5, 9, 13, 27–29). However, data in this study and prior investigations demonstrate that extrapulmonary organ dysfunction is a strong risk factor for death independent from severity of hypoxemia or other respiratory criteria (3–5). However, neither PALICC nor the Berlin conference included extrapulmonary organ dysfunction in their risk-stratification schemes (15, 30). In pediatrics, this was despite the finding by a PALICC sub-committee that MODS “is the single most important independent clinical risk factor for mortality at the onset of ARDS” (31).

There are several limitations to this study. First, only patients with informed consent for the parent trial were included. Fortunately, *RESTORE* achieved a 78.4% consent rate (16), and the large sample size distributed across 31 sites likely mitigated selection bias in comparison to prior smaller studies. Second, patients with unrepaired cyanotic heart disease were excluded from *RESTORE*, though these patients are included in the updated PARDS definition. Third, we did not retain group assignment from the parent trial in our multivariable models to evaluate the impact of MODS on outcomes. However, the sedation protocol did not affect clinical outcomes (16) and was unlikely to differentially impact organ injury than sedation practices used at usual care sites. Fourth, published criteria were used to define organ dysfunction (19) but several modifications were employed in the parent study. For example, patients with chronically abnormal organ dysfunction-defining laboratory variables (e.g., platelet count, creatinine) were not evaluated differently from patients with normal baseline values. However, any potential misclassification bias would have been towards the null by attributing chronic organ dysfunction to an acute process in some patients. The need to address inconsistent definitions for organ dysfunction in PARDS has

been acknowledged (31). Moreover, while the optimal timing of OI/OSI to define PARDS is controversial (e.g., initial versus worst OI/OSI in the first 24 hours), (15) because the RESTORE dataset only included the worst OI/OSI on day 0/1 we could only evaluate this parameter as a risk factor for MODS and clinical outcomes. Fifth, we cannot determine if one contributing factor to the association of new MODS with longer LOS and duration of mechanical ventilation was that patients with prolonged respiratory failure had more time to develop extrapulmonary organ dysfunction. Finally, data indicating whether extrapulmonary organ dysfunction preceded study day 0/1 were not available. It is likely that some patients with concurrent MODS actually had acute organ dysfunction preceeding respiratory failure. Moreover, because testing for organ dysfunction was at the discretion of the clinician, some cases of mild organ dysfunction may have been missed.

CONCLUSIONS

Extrapulmonary organ dysfunction was common, generally occurred concurrent with respiratory failure (especially in sepsis), and was the largest independent risk factor for death and longer duration of mechanical ventilation and LOS in pediatric patients mechanically ventilated for acute respiratory failure. Future studies should consider extrapulmonary organ dysfunction as both a risk-stratification variable and a target for therapeutic intervention along with lung-supportive strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

MAQ Curley and D Wypij full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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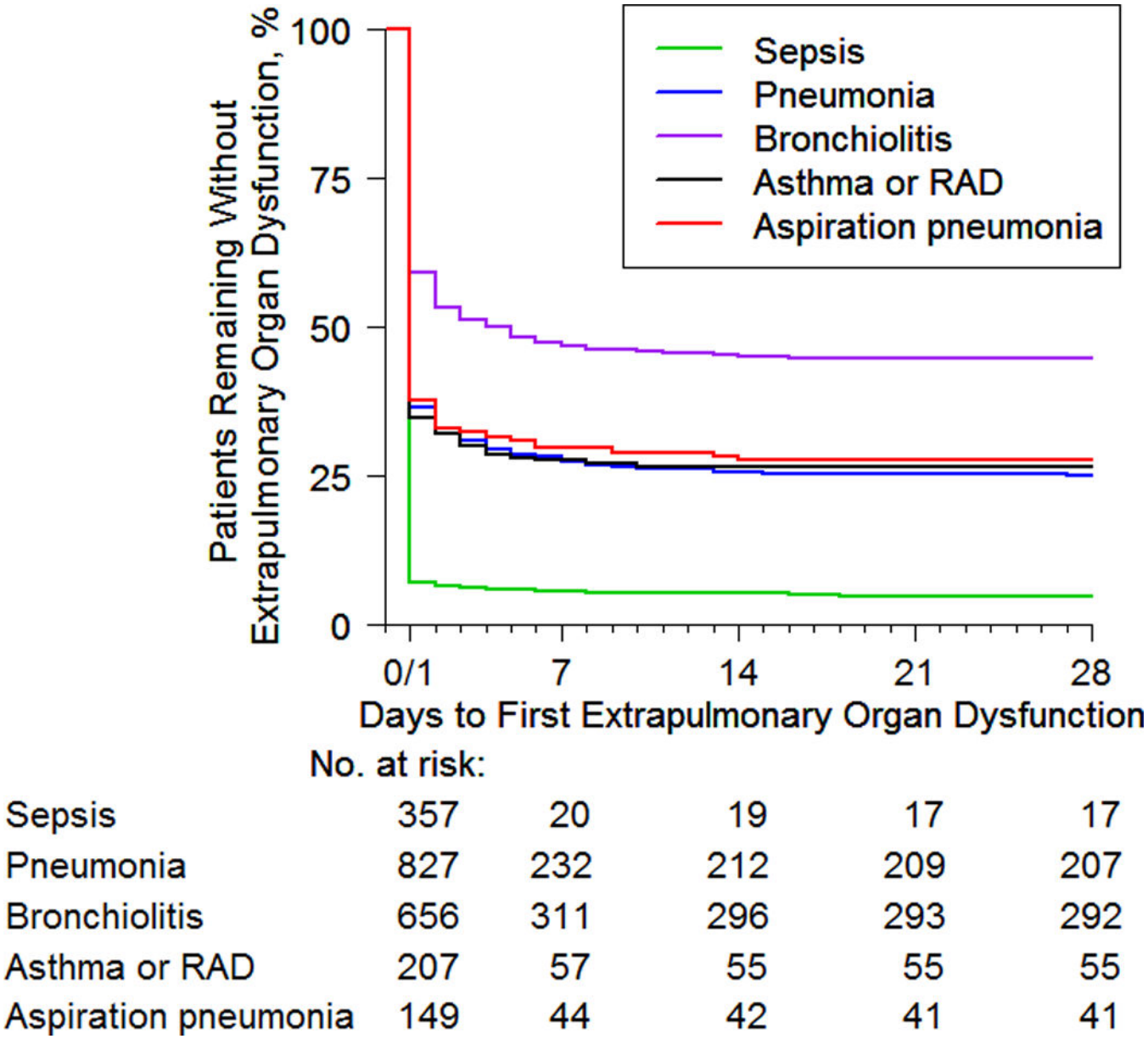

Figure 1. Time to first extrapulmonary organ dysfunction by etiology of respiratory failure

Time to onset of first extrapulmonary organ dysfunction differed according to etiology of acute respiratory failure (log-rank $p<0.001$). Patients were removed from the number at risk after the first day of meeting criteria for at least one extrapulmonary organ dysfunction. Patients who never developed extrapulmonary organ dysfunction were included through day 28, including those patients who left the hospital for whom it was presumed that no further organ dysfunction occurred beyond discharge. *RAD* reactive airways disease, *PICU* pediatric intensive care unit

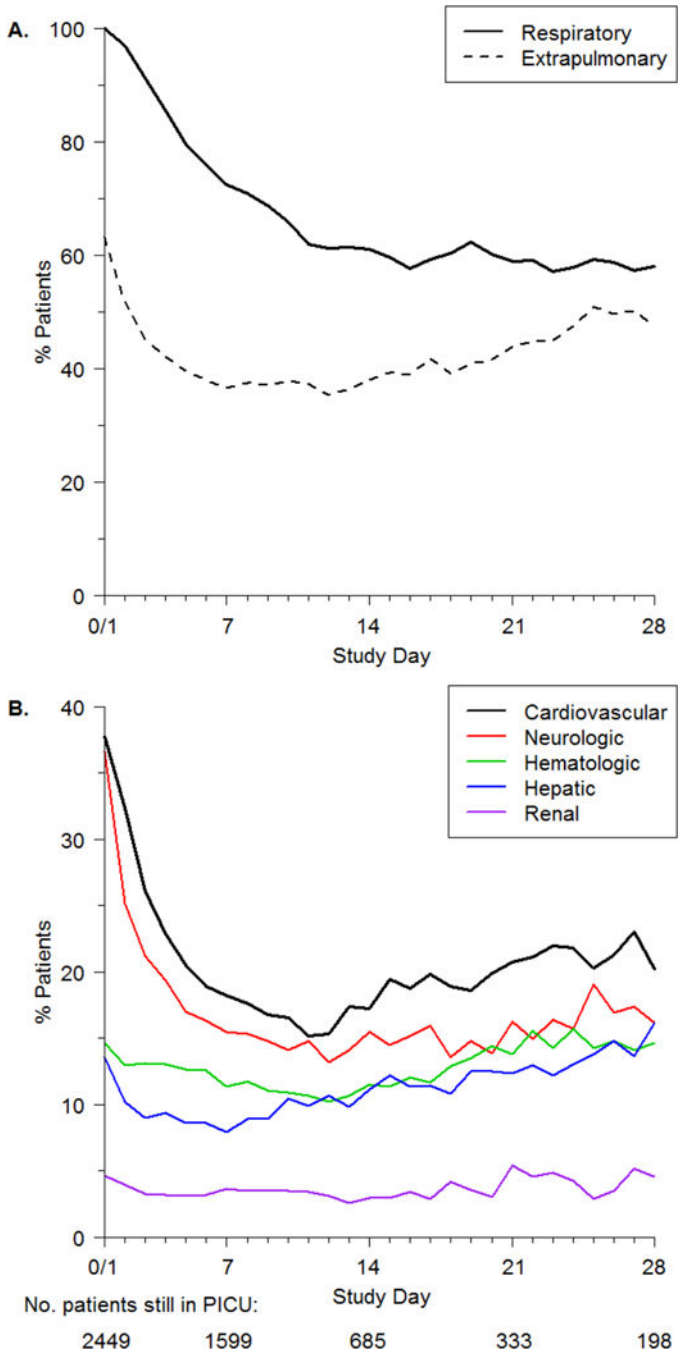

Figure 2. Time course of organ dysfunction

Time course of respiratory and extrapulmonary organ dysfunction (A) and individual extrapulmonary organ system dysfunctions (B). Data for each day were calculated as the proportion of patients with the specified organ dysfunction amongst all patients remaining in the PICU on that day. All patients who remained in the PICU with organ dysfunction were included in the numerator irrespective of whether organ dysfunction developed on that day or a prior day but were removed from the numerator if organ dysfunction resolved. Patients

were included in the denominator if they remained in the PICU on that day, irrespective of whether organ dysfunction continued or resolved. PICU pediatric intensive care unit

Table 1

Patient Characteristics According to MODS Group

Characteristics	Respiratory Dysfunction Only (*n* = 658)	Concurrent MODS (*n* = 1547)	New MODS (*n* = 244)	*P* Value to Predict Concurrent MODS vs All Other Patients[a]	*P* Value to Predict New MODS vs Respiratory Dysfunction Only[a]
Age at PICU admission					
Median (IQR), yr	0.8 (0.2–3.1)	3.4 (0.6–10.7)	1.1 (0.3–3.3)	<0.001	0.64
Number (%)				<0.001	0.93
2 weeks to <2 years	450 (68)	650 (42)	165 (68)		
2 years to <6 years	100 (15)	283 (18)	35 (14)		
6 years to <18 years	108 (16)	614 (40)	44 (18)		
Female, n (%)	272 (41)	720 (47)	109 (45)	0.13	0.39
Non-Hispanic white, n/total (%)	315/653 (48)	805/1528 (53)	113/244 (46)	0.11	0.87
Cognitive impairment (baseline PCPC score >1), n (%)	153 (23)	362 (23)	69 (28)	0.13	0.25
Functional impairment (baseline POPC score >1), n (%)	173 (26)	450 (29)	79 (32)	0.52	0.21
PRISM III-12 score, median (IQR)	4 (2–7)	10 (5–15)	5 (1–8)	<0.001	0.18
Risk of mortality based on PRISM III-12 score, median (IQR), %	1.3 (0.7–3.4)	6.4 (2.2–23.2)	1.7 (0.7–4.6)	<0.001	0.07
Primary diagnosis, n (%)				<0.001	0.48
Sepsis	17 (3)	332 (21)	8 (3)		
Pneumonia	207 (31)	527 (34)	93 (38)		
Bronchiolitis	292 (44)	268 (17)	96 (39)		
Asthma or reactive airway disease	55 (8)	135 (9)	17 (7)		
Aspiration pneumonia	41 (6)	93 (6)	15 (6)		
Other	46 (7)	192 (12)	15 (6)		
Past medical history, n (%)					
Prematurity (<36 wk postmenstrual age)	113 (17)	208 (13)	48 (20)	<0.001	0.64
Seizure disorder (prescribed anticonvulsants)	72 (11)	128 (8)	24 (10)	0.02	0.34
Cancer (current or previous diagnosis)	3 (<1)	190 (12)	4 (2)	<0.001	0.19
Known chromosomal abnormality	28 (4)	70 (5)	10 (4)	0.71	0.76
Pre-PICU CPR, n (%)	8 (1)	58 (4)	3 (1)	<0.001	0.85

Characteristics	Respiratory Dysfunction Only (*n* = 658)	Concurrent MODS (*n* = 1547)	New MODS (*n* = 244)	*P* Value to Predict Concurrent MODS vs All Other Patients[a]	*P* Value to Predict New MODS vs Respiratory Dysfunction Only[a]
Intervention group, n (%)	389 (59)	696 (45)	140 (57)	0.02	0.93
Worst OI on days 0–1, median (IQR)[b]	8.5 (4.9–13.8)	12.4 (7.0–22.9)	10.5 (6.0–16.1)	<0.001	0.006
Worst OSI on days 0–1, median (IQR)[b]	6.1 (3.6–10.1)	7.8 (4.3–14.5)	7.7 (4.4–13.8)	<0.001	<0.001
PARDS based on worst OI or OSI on days 0–1, n (%)[b]				<0.001	<0.001
At risk (OI <4.0 or OSI <5.0)	157 (24)	183 (12)	37 (15)		
Mild (OI 4.0–7.9 or OSI 5.0–7.4)	180 (27)	298 (19)	55 (23)		
Moderate (OI 8.0–15.9 or OSI 7.5–12.2)	205 (31)	419 (27)	72 (30)		
Severe (OI ≥16.0 or OSI ≥12.3)	116 (18)	647 (42)	80 (33)		
Moderate/severe PARDS based on worst OI or OSI on days 0/1, n (%)[b]	321 (49)	1066 (69)	152 (62)	<0.001	<0.001
Neuromuscular blockade for the entire duration of days 0 to 2, n (%)	12 (2)	145 (9)	17 (7)	<0.001	<0.001

MODS multiple organ dysfunction syndrome, *PICU* pediatric intensive care unit, *IQR* interquartile range, *PCPC* Pediatric Cerebral Performance Category, *POPC* Pediatric Overall Performance Category, *PRISM III-12* Pediatric Risk of Mortality score from first 12 hours in the PICU, *CPR* cardiopulmonary resuscitation, *OI* oxygenation index, *OSI* oxygen saturation index, *PARDS* pediatric acute respiratory distress syndrome

[a]To assess the effects of patient characteristics to predict 1) concurrent MODS vs all other patients and 2) new MODS vs respiratory dysfunction only (excluding concurrent MODS), *P* values were calculated using logistic regression accounting for PICU as a cluster variable using generalized estimating equations

[b]Oxygenation index was calculated as ([100 × FIO2 × mean airway pressure]/PaO2). When an arterial blood gas measurement was not available, SpO2 was used to estimate PaO2 to calculate OSI ([100 × FIO2 × mean airway pressure]/SpO2). Lower scores reflect better oxygenation. Worst OI on day 0/1 calculated for 278 respiratory dysfunction only, 1174 concurrent MODS, and 145 new MODS patients. Worst OSI on day 0/1 calculated for 518 respiratory dysfunction only, 714 concurrent MODS, and 154 new MODS patients

Table 2

Multivariable Models of Risk Factors to Predict Concurrent and New MODS

Variable	Odds Ratio (95% CI)[a]	*P* Value[b]
Concurrent MODS (1547 of 2449 patients)		
Age at PICU admission		<0.001
2 weeks to <2 years	1.0	
2 years to <6 years	1.55 (1.25–1.92)	
6 years to <18 years	2.31 (1.87–2.84)	
Functional impairment (baseline POPC score >1)	0.74 (0.59–0.92)	0.007
PRISM III-12 score (one-point increase)	1.14 (1.12–1.16)	<0.001
Primary diagnosis of sepsis	4.52 (2.95–6.95)	<0.001
Seizure disorder (prescribed anticonvulsants)	0.56 (0.36–0.87)	0.01
Cancer (current or previous diagnosis)	6.33 (2.72–14.72)	<0.001
Moderate/severe PARDS based on worst OI or OSI on days 0–1	1.54 (1.24–1.92)	<0.001
New MODS (244 of 902 patients)[c]		
Age at PICU admission		0.56
2 wk–1.99 yr	1.0	
2.00–5.99 yr	0.79 (0.48–1.29)	
6.00–17.99 yr	0.82 (0.52–1.28)	
Functional impairment (baseline POPC score >1)	1.26 (0.88–1.81)	0.21
PRISM III-12 score (one-point increase)	1.01 (0.98–1.05)	0.42
Moderate/severe PARDS based on worst OI or OSI on days 0–1	1.72 (1.32–2.23)	<0.001
Neuromuscular blockade for the entire duration of days 0 to 2	4.57 (2.84–7.35)	<0.001

MODS multiple organ dysfunction syndrome, *CI* confidence interval, *PICU* pediatric intensive care unit, *POPC* Pediatric Overall Performance Category, *PRISM III-12* Pediatric Risk of Mortality score from first 12 hours in the PICU, *PARDS* pediatric acute respiratory distress syndrome, *OI* oxygenation index, *OSI* oxygen saturation index

[a] Odds ratio >1 indicates higher risk of MODS

[b] *P* values were calculated using logistic regression accounting for PICU as a cluster variable using generalized estimating equations

[c] Patients with concurrent MODS (n = 1547) not included

Table 3

Outcomes According to MODS Group

Outcomes	Respiratory Dysfunction Only (*n* = 658)	Concurrent MODS (*n* = 1547)	New MODS (*n* = 244)	*P* Value[a]
Duration of mechanical ventilation, median (IQR), d[b]	4.7 (3.1–7.4)	7.3 (4.2–13.7)	9.1 (5.9–13.3)	<0.001
Length of stay, median (IQR), d[c]				
PICU	7.6 (4.9–10.9)	10.7 (6.3–17.8)	12.7 (8.1–19.6)	<0.001
Hospital	12 (8–17)	17 (10–30)	19 (12–30)	<0.001
In-hospital mortality, n (%)				
At 28 d	5 (<1)	103 (7)	2 (<1)	<0.001
At 90 d	5 (<1)	143 (9)	7 (3)	<0.001
Not discharged home by 90 d, n (%)[d]	26 (4)	317 (20)	33 (14)	<0.001

MODS multiple organ dysfunction syndrome, *IQR* interquartile range, *PICU* pediatric intensive care unit

[a] *P* values for the comparison between MODS groups were calculated using proportional hazards and logistic regression accounting for PICU as a cluster variable using generalized estimating equations for time-to-event and binary variables, respectively

[b] Patients were assigned 28 days if they remained intubated or were transferred or died prior to day 28 without remaining extubated for more than 24 hours, therefore making this outcome equivalent to ventilator-free days

[c] PICU and hospital length of stay exclude 155 nonsurvivors by day 90. For the length of stay variables, patients still in the PICU or hospital on day 90 were censored at day 90

[d] Not discharged home by day 90 comprises non-survivors and patients still in the hospital on day 90, transferred to another hospital, or discharged to a chronic care or rehabilitation facility

Table 4

Multivariable Models to Predict Binary Outcomes

Variable	In-hospital Mortality at 28 days	In-hospital Mortality at 90 days	Not Discharged Home by 90 days
Age at PICU admission			
2 weeks to <2 years	1.0	1.0	1.0
2 years to <6 years	1.48 (0.90–2.43)	1.32 (0.96–1.81)	1.38 (0.96–1.99)
6 years to <18 years	2.06 (1.18–3.58)	1.91 (1.26–2.90)	1.83 (1.28–2.61)
Functional impairment (baseline POPC score >1)	1.44 (0.97–2.15)	1.67 (1.22–2.29)	1.58 (1.17–2.14)
PRISM III-12 score (one-point increase)	1.06 (1.04–1.08)	1.05 (1.03–1.06)	1.04 (1.02–1.05)
Primary diagnosis of sepsis	1.14 (0.74–1.77)	1.36 (0.94–1.96)	1.37 (0.98–1.90)
Moderate/severe PARDS based on worst OI or OSI on days 0–1	1.77 (1.05–2.97)	2.29 (1.36–3.85)	1.82 (1.39–2.38)
MODS			
Respiratory dysfunction only	1.0	1.0	1.0
Concurrent MODS	4.36 (1.97–9.66)	6.54 (3.00–14.25)	3.13 (2.23–4.39)
New MODS	0.93 (0.28–3.07)	3.21 (1.48–6.93)	3.02 (1.83–4.96)

Results are presented as adjusted odds ratio (95% confidence interval) with all listed variables included as covariates. Odds ratio >1 indicates a higher risk of mortality or lower likelihood of discharge home *PICU* pediatric intensive care unit, *POPC* Pediatric Overall Performance Category, *PRISM III-12* Pediatric Risk of Mortality score from first 12 hours in the PICU, *PARDS* pediatric acute respiratory distress syndrome, *OI* oxygenation index, *OSI* oxygen saturation index, *MODS* multiple organ dysfunction syndrome