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Functional Outcomes in Pediatric Severe Sepsis; Further Analysis of the RESOLVE Trial

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Abstract

Objective—Evaluate risk factors for poor functional outcome in 28 day survivors after an episode of severe sepsis.

Design—Retrospective cohort study examining data from the RESOLVE (*RE*searching severe Sepsis and *Organ* dysfunction in children: a *g*lobal *p*erspecti*VE*, *F*IK-MC-EVBP) trial.

Setting—104 pediatric centers in 18 countries.

Subjects—Children with severe sepsis who required both vasoactive-inotropic infusions and mechanical ventilation and who survived to 28 days (n=384).

Interventions—None.

Measurements and Main Results—Poor functional outcome was defined as a Pediatric Overall Performance Category (POPC) score ≥ 3 and an increase from baseline when measured 28 days after trial enrollment. Median(IQR) POPC at enrollment was 1 (1–2). Median(IQR) POPC at 28 days was 2 (1–4).

34% of survivors had decline in their functional status at 28 days, and 18% were determined to have a “poor” functional outcome. Hispanic ethnicity was associated with poor functional outcome compared to the white referent group [RR= 1.9 (95% CI 1.0, 3.0)]. Clinical factors associated with increased risk of poor outcome included: central nervous system and intra-abdominal infection sources compared to the lung infection referent category [RR= 3.3 (95% CI 1.4, 5.6) and 2.4 (95% CI 1.0, 4.5) respectively]; a history of recent trauma [RR=3.9 (95% CI 1.4, 5.4)]; receipt of cardiopulmonary resuscitation prior to enrollment [RR=5.1 (95% CI 2.9, 5.7)]; and baseline Pediatric Risk of Mortality III (PRISM) score of 20 – 29 [RR=2.8 (95% CI 1.2, 5.2)] and PRISM ≥ 30 [RR=4.5 (95% CI 1.6, 8.0)] compared to the referent group with PRISM scores of 0 – 9.

Conclusions—In this sample of 28 day survivors of pediatric severe sepsis diminished functional status was common. This analysis provides evidence that particular patient characteristics and aspects of an individual's clinical course are associated with poor functional outcome 28 days after onset of severe sepsis. These characteristics may provide opportunity for intervention in order to improve functional outcome in pediatric patients with severe sepsis. Decline in functional status 28 days after onset of severe sepsis is a frequent and potentially clinically meaningful event. Further consideration should be given to functional status as the primary outcome that future trials of novel or unproven therapies are designed to affect.

Keywords

sepsis; septic shock; severe sepsis; outcome assessment; mechanical ventilation; multiple organ failure; functional status; Pediatric Overall Performance Category

INTRODUCTION

Sepsis is an infection-initiated clinical syndrome that can progress to shock, multiple organ dysfunction syndrome, and death (1). In 1995, the age and sex-adjusted incidence of severe sepsis in the United States was estimated at 0.6 per 1000 in individuals age 19 or less (2,3). Case fatality among children with sepsis ranges from 7.8–20%, depending on age, the presence of chronic comorbid conditions and the source of infection (3).

Even among survivors of sepsis, impairment in physical and mental function may be common. Gross cognitive and physical functioning have been measured in critically ill pediatric patients with two scoring tools. The Pediatric Cerebral Performance Category (PCPC) is a measure of a child's cognitive function. The Pediatric Overall Performance Category (POPC) is a measure that combines the PCPC with an assessment of developmentally appropriate physical abilities to provide an 'overall' measure of a child's cognitive and physical function (4–6). Each of these scores represents a composite measure on a scale of 1–6, with a score of 1 representing no impairment with full, typical function, a score of 2 representing mild dysfunction, a score of 3 denoting moderate impairment, a score of 4 indicating severe dysfunction, 5 representing an individual in a persistent vegetative state, and a score of 6 equivalent to death/brain death. Although a rough measure of overall function, POPC scoring has been validated against and shown to be associated with measures obtained using the Bayley Psychomotor Developmental Index and the Vineland Adaptive Behavior Scales scores (6).

The FIK-MC-EVBP, RESOLVE (*RE*searching severe Sepsis and *OR*gan dysfunction in children: a *g*lobal perspeCtiVE) trial (NCT00049764), evaluating the efficacy and safety of activated protein C (Xigris; Eli Lilly and Company, Indianapolis, IN), was the largest international randomized trial of a pharmacologic therapy targeted at improving outcomes in severe pediatric sepsis (7). The investigators used a composite organ failure resolution score as their primary outcome. Paired POPC scores were collected as well.

It is the intent of this study to report the 28-day functional outcomes of a large cohort of pediatric subjects who survived an episode of severe sepsis and to examine the risk factors for "poor" functional outcome in them.

METHODS

Data Source

The RESOLVE trial was conducted from November 2002 through April 2005. Subjects were enrolled at 104 study sites in 18 countries and were eligible if they were between the ages of 38 weeks corrected gestation and 17 years. Inclusion criteria included a suspected or proven infection and systemic inflammation, as well as the presence of sepsis-induced cardiovascular dysfunction (despite adequate fluid resuscitation) and respiratory dysfunction within the 12 hours preceding enrollment. Subjects could meet criteria for study enrollment at any point in their hospitalization. Additionally, it was not a requirement for enrollment that severe sepsis was present on admission. Subjects were excluded if they were judged to have a high risk of intracranial bleeding, or if they were expected to die before the end of the 28 day study from pre-existing conditions, end-stage renal or end-stage liver failure. Subjects were randomized to an infusion of placebo (0.9% NaCl) or activated protein C for 96 hours. Clinical management was otherwise at the discretion of the primary physician and not per a study protocol (7). Baseline (pre-illness) POPC score was evaluated by trained study personnel both at the time of enrollment via caregiver history, for all 477 enrolled subjects, and for 466 subjects (98% follow-up) 28 days later at the conclusion of the trial. These assessments were performed either by direct evaluation if the subject remained hospitalized or via caregiver history if discharged. The 82 subjects (17% of full cohort) who did not survive to 28 days were not considered in this study, leaving 384 subjects available for univariate analysis. Another 21 subjects were eliminated from the multivariate analysis due to missing data or characteristics perfectly predictive of the outcome of interest, thus providing 363 subjects for inclusion in the model (Figure 1).

Statistical Methods

We dichotomized functional outcome for the purpose of analysis, with “poor” functional outcome defined as a 28 day POPC score from 3 – 5 AND an increase in score of 1 or more. This definition takes into account the relatively short follow-up period as well as the fact that a certain proportion of subjects were moderately to severely impaired at baseline. Although a multitude of variables were available for analysis, we selected a limited range from the data set for univariate analysis based upon completeness of data, clinical relevance and likely association with functional outcome assessed at 28 days from enrollment in the trial. We assessed univariate differences in functional outcome using χ^2 and Fischer’s exact tests.

In order to explore the multivariate relationships, we further limited the variables of interest based on the presence of an association represented by the statistical threshold of a p-value <0.25 in the univariate analysis. The multivariate analysis was performed using backward stepwise logistic regression with likelihood ratio tests. Variables were assessed for collinearity prior to inclusion in the stepwise analysis and no missing data were imputed. Demographic characteristics (gender, age and ethnicity) were forced into the model, as were all levels of a categorical variable if any one level met inclusion criteria. The 9 Asian subjects who had complete data for inclusion in the multivariate model all had good functional outcomes, and thus these observations were dropped from this aspect of the

analysis. Due to the frequency of the primary outcome, odds ratios obtained from logistic regression were corrected to provide more accurate estimates of relative risk (8,9). Subject randomization status in the RESOLVE trial was excluded from the stepwise model, although frequency of exposure to activated protein C is provided in the results for descriptive purposes.

All statistical analyses were performed using STATA 10.1 SE (StataCorp, College Station, TX). In accordance with the Common Rule (10) and the policies of Seattle Children's Hospital Institutional Review Board, our research, using a de-identified data set, was considered exempt human subjects research.

RESULTS

The majority (77%) of subjects had a POPC score of 1 prior to their illness, indicative of a child performing at a level considered typical for age (Table 1). Poor functional outcome, as defined in this study, was observed in 315 (18%) subjects who survived for 28 days (Table 2). The variables that did not meet our statistical threshold for inclusion in the multivariate model or were excluded due to perceived collinearity are presented in Table 2 but lack odds ratios and 95% confidence intervals.

The POPC score remained unchanged for 249 subjects (65%) and was noted to deteriorate at least one point from pre-illness in 132 subjects (34%). In 3 subjects (0.7%) the POPC score improved 1 point over the 28 days of observation (Figure 2). The majority of subjects (71%) with good functional outcomes were home at the time of outcome assessment at 28 days. An additional 85 subjects (27%), with good functional outcomes, remained hospitalized at 28 days. In contrast, the majority of the subjects with poor functional outcomes (83%) remained hospitalized at 28 days (Table 3). 49 subjects remained in the ICU at the 28-day outcome assessment, 19 (39%) with good functional outcomes and 30 (61%) with poor functional outcomes. A number of subjects continued to receive support for dysfunctional organ systems at the time of the 28 day assessment. Four subjects remained on renal replacement therapy, none were considered to have a good functional outcome. Eight subjects continued to receive vasoactive infusions at 28 days, 3 (38%) of whom were considered to have a good functional outcome. A total of 22 subjects were receiving mechanical ventilator support at 28 days, 5 (23%) were considered to have a good functional outcome. It is not clear how many of these subjects were receiving their ventilatory support via tracheostomy at the time of their 28 day evaluation. The changes observed differed somewhat between subjects felt to have impairments at baseline (POPC >1) and those felt to have good overall function (POPC=1). Of the 296 28-day survivors considered to have good overall function at baseline, 115 (39%) had deterioration in their functional status at the end of the observation period, whereas, of the 88 subjects with a baseline POPC score of 2 or more, 17 (19%) had a worsening.

In general, few differences were noted when comparing the proportion of subjects with a poor functional outcome among categories of gender and age. A somewhat lower proportion of infants <1 month old had a poor functional outcome compared to the 1 – 5 year old referent group. However, there were only 2 subjects in this age category with a poor

outcome. No substantial differences in outcome according to age were noted in the multivariate analysis (Table 2).

Hispanic subjects were more likely to have a poor functional outcome compared to the overall cohort, whereas Asian subjects were more likely to have a good functional outcome compared to the cohort as a whole. These differences persisted in the multivariate model. Hispanic ethnicity was associated with an 86% increased risk of poor functional outcome compared to the White referent group [RR=1.9 (95%CI 1.0, 3.0)]. Most of the Asian subjects (91%) for whom a POPC score was available at 28 days had a good functional outcome. All of the Asian subjects (n=9) for whom complete data was available for inclusion in the multivariate model had good functional outcomes.

Individuals with a history of malignancy (n=16) as well as those considered immune compromised (n=34) had increased frequency of “poor” functional outcome. However, because almost all of the subjects with a history of malignancy were considered immune compromised at the time of their infection (n=14), a history of malignancy was not included in the multivariate model. Immune compromised status was associated with an almost 2 fold increased risk of “poor” functional outcome [RR=1.9 (95% CI 0.94, 3.3)].

Children with intra-abdominal and central nervous system (CNS) infections had an increased frequency of “poor” functional outcome (30.3% and 26.7% respectively) compared to the children whose infections originated elsewhere in the body [multivariate RR=2.4 (95%CI 0.98, 4.5) and RR=3.3 (95%CI 1.4, 5.6), respectively]. Subtle, but not statistically significant, differences in outcome at 28 days were observed based on the type of organism identified as causing the episode of sepsis. The relatively few subjects identified with viral infections (n=15) more frequently had good functional outcomes.

The small number of individuals with a history of trauma (n=7) within the 30 days prior to study enrollment were more likely to have a poor functional outcome than those without such a history [RR=3.9 (95%CI 1.4, 5.4)]. Those who received cardiopulmonary resuscitation (CPR) (n=6) prior to enrollment were 5 times more likely to have a poor functional outcome 28 days after the onset of sepsis [RR=5.1 (95%CI 2.9, 5.7)].

A high degree of illness severity at the time the subject met clinical criteria for enrollment in the study, as measured by Pediatric Risk of Mortality Score III, was associated with “poor” functional outcome. The relationship between frequency of poor functional outcome and PRISM III score demonstrated a positive association across categories of increasing PRISM III (Figure 3). This relationship persisted in the multivariate model. Those survivors with a PRISM score from 20 to 29 had a 2.8 fold increased risk of poor function at 28 days compared to the referent group with PRISM scores from 0 to 9, RR=2.8 (95%CI 1.2, 5.2). Individuals with a PRISM score ≥ 30 had even greater risk compared to the referent group, RR=4.5 (95%CI 1.6, 8.0).

No substantial difference was noted in the functional outcomes of the subjects that received activated protein C compared to those that received placebo.

DISCUSSION

Major Findings

This study represents the first description of short-term functional outcomes in a cohort of pediatric survivors of severe sepsis. The definition used here for poor functional outcome is a conservative one. In order to be categorized as having a poor functional outcome a subject with normal function (POPC=1) prior to their illness would have to have moderate dysfunction (POPC=3) at the 28 day evaluation. This represents a significant functional decline in a relatively short time period. In spite of this conservatism, poor functional outcome was observed in 18% of the cohort. A third of subjects (34%) had some degree of decline in functional status as represented by any increase in POPC from baseline to 28 days. Whether this decline in functional status persists over time in this cohort is unknown as this study is unable to evaluate longer-term functional outcomes. In addition, the specific reasons for functional decline in this cohort are not clear and could be related to any number of processes including: organ injury, deconditioning, persistent technology dependence, medications, limb loss, and many more. The reasoning for improvement in functional status over the course of the trial in a small number of subjects is not entirely clear. It is possible that what the subject or parent defined as their baseline functional status reflects the presence of a comorbid condition that improved by the 28 day assessment. An improved understanding of functional status outcomes and risk factors for functional decline in pediatric critical illness may allow providers to target and develop therapies to not only prevent mortality, but also minimize morbidity.

Many of the findings presented here are consistent with those obtained in studies of other groups of hospitalized, critically ill children. The functional outcomes of general pediatric ICU populations have been evaluated utilizing POPC as an assessment tool. Beyond the foundational work done by Fiser, the functional outcomes of pediatric patients after an ICU stay have been associated with baseline functional status as well as measures of illness severity at the time of ICU admission (4, 11–13). The association between organ dysfunction and alteration in functional status has been previously described, although at the time of discharge from the ICU rather than at a predetermined time point (14). In addition, although this study assessed an international cohort, the case fatality of 17% is within the ranges reported by Watson, et al. in their epidemiologic study of pediatric severe sepsis in the United States. Some of the risk factors for poor functional outcome identified here, including the presence of an immunologic or oncologic comorbidity and a CNS infection are consistent with characteristics placing individuals at higher risk of mortality in that nationally representative sample (2).

The findings related to categories of ethnicity are difficult to interpret. Ethnic category was assigned by study personnel based on a combination of racial category and ‘geographic origin’ and may or may not be consistent with how a subject or their family might categorize themselves. Exploratory review of the Hispanic and Asian subjects risk factors for poor functional outcome did not reveal any convincing trends. Hispanic subjects did have somewhat more frequent intra-abdominal infections although in general this group had somewhat lower severity of illness scores.

Some of the findings presented here likely reflect the performance of the POPC score itself. The increased frequency of functional status decline in subjects with a POPC=1 at baseline may represent the fact that the degree of dysfunction that results in an increase in score from 1 to 2 is likely different from that required to increase from 2 to 3 or 3 to 4. This finding is consistent with Fiser's original description and validation of the POPC score (4).

The clinical implications of the high frequency of impaired function in children treated in an ICU for severe sepsis may include a need for increased attention to the functional status of these patients throughout their clinical course. An improved understanding of specific risk factors for decline in functional status during a severe illness and ICU stay may help clinicians rationally alter the care provided in an effort to minimize functional decline. These interventions may include early provision of various therapeutic supports including physical and occupational services initiated early in the ICU course. These efforts have been studied in adult critical care settings and have demonstrated effectiveness (15).

Limitations

This study represents a secondary analysis of data obtained from 2002 to 2005. It is certainly possible that changes in therapy and practice over the last 10 years have altered the generalizability of these findings in the modern era. In addition, the reliability of our outcome depends on the accurate and precise application of the POPC scoring system. Although trained study personnel conducted the assessments, inter-rater reliability data is unavailable for the cohort presented here, limiting our ability to assess the possible impact of improper evaluations.

The initial, pre-illness assessment was obtained by parental history at the time of enrollment in the clinical trial. Parental assessment of the subject's pre-illness function may have been biased by recently acquired co-morbidities and possible decline in function prior to onset of their episode of severe sepsis. If this were true, one would expect a decreased ability to detect a change in status in these subjects at 28 days, resulting in bias toward an under-ascertainment of functional decline.

The pathophysiologic processes present in this cohort of subjects were widely varying. It is possible that the risk factors for "poor" functional outcome identified here apply broadly to a general population of patients with severe sepsis and may not apply to specific subgroups of patients with a particular type of severe sepsis, *e.g.* patients with meningococcemia and purpura fulminans.

Receipt of mechanical ventilation and a continuous infusion of a vasoactive or inotropic medication were both criteria for study enrollment. Although the duration that an individual subject required these therapies was dependent on severity of illness as well as local practice, the care that was necessary to provide these therapies to children could conceivably have had an impact on their functional status in the near term. For example, in order to safely and effectively provide mechanical ventilation to a developmentally appropriate two year old, sedative medications and neuromuscular blockade are often utilized. Requiring this type of support for a prolonged period may lead to a decline in functional status if the patient is assessed in the days to weeks following discontinuation of that support. Differentiating

the relative contributions of illness severity and the residual effects of critical care supportive therapies that may impact global function in the short-term was not possible in this study.

In addition, the 28 day time point at which these subjects were assessed represents a relatively short time frame of follow-up. It is likely that some proportion of the subjects who experienced significant functional declines will improve over time. This study does not address long-term functional status.

CONCLUSIONS

The primary outcome of poor functional outcome in 28 day survivors of pediatric severe sepsis was relatively frequent (18%). Specific subject characteristics and aspects of their clinical course were associated with poor functional outcome 28 days after onset of severe sepsis. These characteristics may represent opportunities for intervention in order to improve functional outcomes in pediatric patients with severe sepsis.

A composite outcome of mortality OR poor functional outcome was present in 151(32%) of the 466 total subjects for whom 28 day data were available. Almost half of the total cohort, 214(46%) subjects, had a measurable decline in functional status at 28 days. Comparing 28 day mortality to the composite outcome and to any decline in functional status at 28 days shows that adequately powered randomized trials designed to detect a 30% improvement are more logistically feasible with both the composite functional outcome as well as any change in functional status (Table 4). Further consideration should be given to utilizing functional outcome or a composite of mortality and functional outcome as the primary outcome in pediatric critical care trials going forward.

In addition, the findings presented here suggest directions for future study. As mentioned, the duration of follow-up in this particular cohort was relatively short. Increased observation time points spread over a longer duration would provide an improved sense of the severity and duration of morbidity experienced by survivors of pediatric severe sepsis. Longer duration of follow-up would also provide an indication of the proportion of patients that return to their baseline functional status and how much time is required to achieve this.

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Figure 1.
Diagram of RESOLVE subjects analyzed in univariate and multivariate analysis

Figure 2. Change in Pediatric Overall Performance Category (POPC) Scores in pediatric sepsis survivors (N=384) from baseline to 28 days

Figure 3.

Frequency of survivor poor functional outcome by Pediatric Risk of Mortality III Score

Table 1

Distribution of Pediatric Overall Performance Category scores at baseline and at 28 days in pediatric survivors of severe sepsis (N=384)

	Baseline POPC median(IQR) or n (%)	28 Day POPC median(IQR) or n (%)
Median	1 (1–1)	2 (1–3)
1 - Good Overall Performance	296 (77.1)	183 (47.7)
2 - Mild Overall Disability	33 (8.6)	87 (22.7)
3 - Moderate Overall Disability	25 (6.5)	46 (12.0)
4 - Severe Overall Disability	30 (7.8)	63 (16.4)
5 - Coma or Vegetative State	0	5 (1.3)

Table 2

Characteristics of 28 day survivors at the time of enrollment in trial of activated protein C for pediatric severe sepsis, stratified by functional outcome

	Total n (%)	Children with Good Functional Outcome n (%)	Children with Poor Functional Outcome n (%)	Relative Risk ^a	95% Confidence Interval
Entire Cohort	384	315 (82.0)	69 (18.0)		
Gender					
Male	204	165 (80.9)	39 (19.1)		Referent
Female	180	150 (83.3)	30 (16.7)	0.67	0.38, 1.1
Age					
<1 month	24	22 (91.7)	2 (8.3)	0.44	0.06, 2.3
1 month - <1 year	92	73 (79.4)	19 (20.7)	1.5	0.77, 2.6
1 – < 5 years	125	104 (83.2)	21 (16.8)		Referent
5 – < 12 years	82	69 (84.2)	13 (15.9)	0.89	0.39, 1.8
12 – < 18 years	61	47 (77.1)	14 (23.0)	1.5	0.72, 2.7
Ethnicity					
White	259	215 (83.0)	44 (17.0)		Referent
Hispanic	71	52 (73.2)	19 (26.8)	1.9	1.0, 3.0
African Descent	21	17 (81.0)	4 (19.1)	0.99	0.32, 2.5
Other (Mixed Racial)	22	21 (95.5)	1 (4.6)	0.28	0.03, 1.8
Asian (Western & South East) ^b	11	10 (90.9)	1 (9.1)	0	
Immune Status					
Non-compromised	338	283 (83.7)	55 (16.3)		Referent
Compromised	34	23 (67.7)	11 (32.4)	1.9	0.94, 3.3
Source of Infection					
Lung	133	117 (88.0)	16 (12.0)		Referent
Blood	131	105 (80.2)	26 (19.9)	1.8	0.89, 3.2
Intra-Abdominal	33	23 (69.7)	10 (30.3)	2.4	0.98, 4.5
CNS	30	22 (73.3)	8 (26.7)	3.3	1.4, 5.6
Other ^c	57	48 (84.2)	9 (15.8)	1.1	0.43, 2.5

	Total n (%)	Children with Good Functional Outcome n (%)	Children with Poor Functional Outcome n (%)	Relative Risk ^a	95% Confidence Interval
Recent Trauma					
No	377	312 (82.8)	65 (17.2)		Referent
Yes	7	3 (42.9)	4 (57.1)	3.9	1.4, 5.4
CPR prior to Enrollment					
No	378	313 (82.8)	64 (17.2)		Referent
Yes	6	2 (33.3)	4 (66.7)	5.1	2.9, 5.7
PRISM III^d					
0 to 9	75	68 (90.7)	7 (9.3)		Referent
10 to 19	186	158 (85.0)	28 (15.1)	1.2	0.47, 2.8
20 to 29	103	76 (73.8)	27 (26.2)	2.8	1.2, 5.2
30	20	13 (65.0)	7 (35.0)	4.5	1.6, 8.0
Dysfunctional Organ Systems					
2	77	72 (93.5)	5 (6.5)		
3	108	86 (79.6)	22 (20.4)		
4	101	87 (86.1)	14 (13.9)		
5	98	70 (71.4)	28 (28.6)		
Chronic Disease^e					
None	227	187 (82.4)	40 (17.6)		
Cardiac	24	20 (83.3)	4 (16.7)		
Respiratory	24	22 (91.7)	2 (8.3)		
Malignancy	16	10 (62.5)	6 (37.5)		
Neurologic	45	38 (84.4)	7 (15.6)		
Diabetes	4	4 (100%)	0 (0%)		
Congenital Anomaly	43	37 (86.1)	6 (14.0)		
Infection Type					
No culture done or culture negative	124	108 (87.1)	16 (12.9)		
Viral	15	14 (93.3)	1 (6.7)		
Fungal	24	20 (83.3)	4 (16.7)		

	Total n (%)	Children with Good Functional Outcome n (%)	Children with Poor Functional Outcome n (%)	Relative Risk ^a	95% Confidence Interval
Bacterial					
pure gram positive	105	83 (79.1)	22 (21.0)		
pure gram negative	77	60 (77.9)	17 (22.1)		
mixed gram	39	30 (76.9)	9 (23.1)		
ARDS at Enrollment					
No	323	266 (82.4)	57 (17.7)		
Yes	37	27 (73.0)	10 (27.0)		
Recent Surgery					
No	343	280 (81.6)	63 (18.4)		
Yes	41	35 (85.4)	6 (14.6)		
Randomized to Receive Activated Protein C					
No	190	159 (83.7)	31 (16.3)		
Yes	194	156 (80.4)	38 (19.6)		
Baseline Steroids					
No	234	193 (82.5)	41 (17.5)		
Yes	150	122 (81.3)	28 (18.7)		
Prior ICU Admission					
No	379	312 (82.3)	67 (17.7)		
Yes	5	3 (60.0)	2 (40.0)		

^a Odds Ratio obtained from multivariate logistic regression model adjusted for frequent outcome

^b Asian patients with non-missing data all had 'good' functional outcome

^c Includes Cardiac, Gynecologic, Pleural, Urinary Tract, Vascular Catheter, Skin, Head/EENT & Bone/Joint

^d Pediatric Risk of Mortality Score III

^e Does not represent mutually exclusive categories

Table 3

Subject location at the time of 28 day functional status assessment

	Subjects with Good Functional Outcome n(%) N=315	Subjects with Poor Functional Outcome n(%) N=69
Home		
No support	164 (52.1)	3 (4.4)
Unpaid support	46 (14.6)	4 (5.8)
Paid support	14 (4.4)	4 (5.8)
Rehabilitation Center	0	1 (1.5)
Study Hospital	74 (23.5)	55 (79.7)
Other Hospital	11 (3.5)	2 (2.9)
Other	6 (1.9)	0

Table 4

Trial sample sizes required to demonstrate improvement in different outcomes

28 Day Outcome	POPC Scoring	Baseline Frequency	Treatment Effect (30% improvement)	Subjects Required ^a
All Cause Mortality	28 day score = 6	17%	11.9%	1568
At least Moderate Disability	3 AND increase from baseline	32%	22.4%	714
At Least Mild Disability	Any increase from baseline	46%	32.2%	420

^a $\alpha = 0.05$, and $1-\beta = 0.8$