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Association of New and/or Progressive Multiple Organ Dysfunction Syndrome With Mortality and New Morbidity Among Children Encountering Septic Shock

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Abstract

Despite reductions in sepsis mortality, there remains a substantial morbidity burden among children who survive sepsis. Furthermore, the majority develop multiple organ ‘group has historically been analyzed as a single cohort. Using the Life After Pediatric Sepsis Evaluation (LAPSE) investigation database, we studied the association of new and progressive multiple organ dysfunction syndrome (NPMODS) with morbidity and mortality among children with septic shock. We hypothesized that NPMODS represents a distinct phenotype based on evolving organ dysfunction. There was evidence of an association but it did not reach the 0.05 level of significance. We also hypothesized and confirmed that children with acute neurological dysfunction have greater functional deterioration and mortality compared to other organ dysfunctions. In addition, an expanded definition of acute neurological dysfunction identified a larger cohort of patients with similar functional deteriorations that are both clinically and statistically significant.

Introduction

Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" and results in the impaired function of various organ systems (Singer et al., 2016). Over the last few decades there have been significant reductions in sepsis mortality (Hartman et al., 2013; Watson et al., 2017). However, recent findings suggest a substantial morbidity burden among pediatric sepsis survivors (Balamuth et al., 2014; Weiss et al., 2015; Zimmerman et al., 2020). There are increasing numbers of sepsis survivors as prevalence of sepsis has increased 78% between 1995 and 2005 with a constant mortality rate (Hartman et al., 2013). Morbidity has rapidly become a more important primary outcome for patients with sepsis given the relatively low mortality rate. Measurement of functional impairment in the survivors of critical illness is a way of understanding how medical morbidity impacts lives. Impacted activities include how well children are able to return to school and perform age-appropriate tasks akin to feeding, clothing themselves, and interacting with friends and family. Costs for care of pediatric sepsis have risen nearly 25% between 2005 and 2016 in inflation adjusted price with a median cost of $26,592 per hospitalization and the total estimated national costs of pediatric hospitalizations for severe sepsis was $7.3 billion USD (Carlton et al., 2019).

In a meta-analysis, sepsis appears to be the leading cause of pediatric multiple organ dysfunction syndrome (MODS) with 17–73% of children with sepsis also developing MODS; This wide range reflects varying definitions of sepsis and organ dysfunctions (Goldstein et al., 2005; Watson et al., 2017). The number and type of organ system dysfunction appear to be important for mortality in patients with sepsis. For every additional dysfunctional organ system, the odds of death increased by 2.25 times (Odetola et al., 2007). The risk of death is two times higher with a neurological dysfunction than a respiratory dysfunction (Leteurtre et al., 2003).

There are two aims that this study would like to address. Aim #1: Among children with septic shock, examine the mortality and morbidity of patients exhibiting MODS. Report and investigate the functional outcomes of patients with new and progressive multiple organ dysfunction (NPMODS), a subgroup of MODS. Aim #2: Among children with septic shock, examine the association of neurologic dysfunction with mortality and morbidity using a traditional definition (Proulx et al., 1994), and an expanded definition based on available clinical data (Zimmerman et al., 2020).

Background

Sepsis and Multiple Organ Dysfunction

Definitions of sepsis have been continuously updated. The most recent and widely used definitions were created in 2005 by the International pediatric sepsis consensus conference and subsequently in 2016 by The Society of Critical Care Medicine (Goldstein et al., 2005; Singer et al., 2016). It has been established that the severity of clinical sepsis has been variable (Randolph & Mcculloh, 2014). However, the development of MODS has been consistently associated with higher mortality in pediatric patients (Goh et al., 1999; Lin et al., 2017). Proulx et al. (Proulx et al., 1994) defined MODS as the simultaneous dysfunction of at least two organ systems. An estimated 20% of pediatric intensive care unit (PICU) patients are admitted with MODS with another 13% developing an additional organ dysfunction during their hospital course (Tamburro & Jenkins, 2017). MODS is a syndrome and not an illness. It is a collection of frequently occurring symptoms. Currently, there is an incomplete understanding of what facilitates its pathobiology and its varied causes. This lack of understanding makes diagnosis and treating patients a complex dance. Identifying, treating, and hastening the resolution of organ dysfunction summarizes the work of critical care practitioners.

New and Progressive Multiple Organ Dysfunction

New and progressive multiple organ dysfunction syndrome (NPMODS) is a term meant to characterize patients who have evolving organ dysfunction during admission for sepsis, or other critical illness. Patients with NPMODS have generally been analyzed as a single group in previous studies (Goldstein et al., 2005; Proulx et al., 1994; Villeneuve et al., 2016). We hypothesize that NPMODS encapsulates patients with differing phenotypes and thus should be examined as separate groups. Differences in the morbidity and mortality of these two groups of children with sepsis (new versus progressive MODS) when examined separately is unknown and represents one of the focuses of this study. Furthermore, the degree of functional impairment present among critically ill children encountering sepsis with NPMODS has not been established. New and progressive MODS has been proposed as a better and more appropriate outcome measure (Watson et al., 2017). Our overall hypothesis is that NPMODS among children with septic shock is associated with both higher mortality and worse functional morbidity.

Neurological Dysfunction

Data for adults surviving sepsis have shown acute neurological, respiratory, and cardiac dysfunction as the three organ dysfunctions most strongly associated with short-term hospital mortality. Furthermore, acute neurological dysfunction was associated with an increase in long-term mortality (Schuler et al., 2018). Proulx et al. (Proulx et al., 1994) also remarked that neurological failure was the only prognostic variable in their bivariate analysis. Neurological dysfunction has been shown to account for 46% of pediatric logistic organ dysfunction (PELOD) score (Leteurtre et al., 2003). We also hypothesize that acute neurological dysfunction during pediatric sepsis leads to more severe functional impairment compared to those who do not experience this organ failure.

Data and Methods

Life After Pediatric Sepsis Evaluation Investigation

The Life After Pediatric Sepsis Evaluation (LAPSE) investigation was a prospective, descriptive cohort investigation involving 12 tertiary pediatric hospitals that clinically characterized critically ill children (n=389) with contemporary, community-acquired septic shock and described the trajectory of mortality and long-term health-related quality of life (HRQL) morbidity among survivors (Zimmerman et al., 2020). Most often by parent proxy-report, LAPSE assessed HRQL up to 12 months post PICU admission. HRQL measured how well the children were physically, emotionally, socially, and their school functioning. A majority of subjects in this study demonstrated complex, comorbid conditions at baseline. Hospital and one-year mortality were 9% and 13%, respectively. One year following hospitalization for septic shock, 35% of the cohort had still not regained their baseline HRQL. Regression analysis demonstrated intensity and duration of individual and composite organ dysfunction as predictors of poor outcomes, either death or persistent, severe deterioration of HRQL. The study collected information on both daily organ function as well as functional status as measured by commonly used tools. LAPSE also ascertained significant deterioration in functional status compared to baseline of the whole cohort at the time of hospital discharge or study day 28.

Inclusion and Exclusion Criteria

The inclusion criteria required: children between the ages of 44 weeks gestation and < 18 years, suspected of sepsis or infection, at least two of four criteria of systemic inflammatory response syndrome, diagnosis within 48 hours of community acquired infection or sepsis, cardiovascular organ dysfunction, and pulmonary organ dysfunction. Exclusion criteria included: primary reason for admission was thermal or electrical burn, lack of commitment to aggressive

intensive care, parents unable to speak English or Spanish, patient was a ward of the state, patient was unable to participate in long term follow up, patient was not enrolled within 48 hours of PICU admission.

Morbidity Measures

Patients were serially assessed by research staff for functional status utilizing Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) and the Functional Status Scale (FSS) at study entry (reflecting baseline pre-sepsis status during the month prior to PICU admission), study day 7, and study day 28 or hospital discharge, whichever occurred first (day 28*). **Table 1** summarizes the breakdown of all three morbidity measures used. PCPC and POPC is a six-point scale used to reflect gross functional status (Fiser et al., 2000). As opposed to POPC/PCPC, FSS is a more granular instrument for assessing functional status. It scores on a five-point scale across six different categories: mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status (Pollack et al., 2009). A minimum score of 6 represents normal functioning and a maximum score of 30 reflects severe dysfunction.

Pediatric Cerebral Performance Category (PCPC) Scale	**Score**	**Pediatric Overall Performance Category (POPC) Scale**
Normal	1	Good overall performance
Mild disability	2	Mild overall disability
Moderate disability	3	Moderate overall disability
Severe disability	4	Severe overall disability
Coma or vegetative state	5	Coma or vegetative state
Brain death	6	Brain death

Functional Status Scale (FSS)

	Score	**Categories**
Normal	1	Mental status
Mild dysfunction	2	Sensory functioning

Moderate dysfunction	3	Communication
Severe dysfunction	4	Motor functioning
Very severe dysfunction	5	Feeding
		Respiratory status

Table 1. *Three different morbidity measures used in this study. Pediatric Cerebral Performance Category (PCPC) Scale, Pediatric Overall Performance Category (POPC) Scale, and Functional Status Scale (FSS).*

All patients scores were normalized against their own baseline. Baseline scores were deducted from day 7 or day 28*. This normative score reflects an individual's progress in positive and negative numbers during their stay. Clinically significant deterioration of a patient's functional status for PCPC/POPC is either a score of 3 or higher or a change of 1 or greater, and for FSS a change of 3 or greater.

Data Collection, Organization, and Analysis

Clinical data related to PICU admission were entered into an electronic data capture system provided by the data coordinating center at the University of Utah (OpenClinica, LLC, Waltham, MA). Data managers monitored data quality throughout the study. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). P-values are based on a two-sided alternative with p-values of less than 0.05 considered significant. The following are a list of standard statistical tests used to assess significance. Kaplan Meier Estimate with Log Rank Test and Restricted Mean Survival Time (RMST) were used to compare mortality between groups. Due to violations of proportional hazard assumptions the RMST method was used as a non-parametric comparison (Uno et al., 2014). A Tukey-Kramer Post-Hoc adjustment was used to adjust for multiple comparisons. The Shapiro Wilks test was used to assess normality. The majority of all variables were not normally distributed and therefore the following non-parametric tests were used. Wilcoxon Rank-Sum Test were used for comparing categorical variables between two groups. Kruskal Wallis Test with Dwass-Steel-Critchlow-Fligner post hoc

adjustment were used for multiple group comparisons. A Cochran-Armitage or Cochran-Mantel-Haenszel Test was used to determine linear association between two ordinal variables. Subsequently, a generalized linear model was used to investigate a model and predict magnitude of associations between two variables.

Organ Dysfunction Definitions

The first set of diagnostic criteria for MODS was proposed by Wilkinson et al. in 1986 which was subsequently updated in 1994 by Proulx et al. Despite newer criteria, Proulx's definitions are still commonly used today. We used the organ dysfunctions criteria for cardiovascular, respiratory, renal, hematologic, and neurologic systems outlined by Proulx et al. (Proulx et al., 1994). **Appendix A** contains criteria used for classifying dysfunction for each organ system. These criteria generally require severe impairment to be present for patients to qualify for each of the organ system dysfunctions.

Expanded Neurological Dysfunction

The expanded definition of neurological dysfunction included clinical data captured in the LAPSE dataset. Patients were considered to have neurological dysfunction with a Glascow Coma Score of 11, rather than 5 used by Proulx et al., and included the presence of intracranial hypertension, new seizure activity, new ischemic injury, or autonomic storming.

Multiple Organ Dysfunction Definitions

Patients were defined as "No Multiple Organ Dysfunction Syndrome" (No MODS) if they had only one organ dysfunction at a time. In contrast, patients with MODS exhibited two or more concurrent organ dysfunctions during the same day. For MODS' subgroups, New MODS were patients that entered PICU without MODS and later developed MODS during their PICU stay. Patients with Progressive MODS entered the PICU with MODS and later during their PICU

stay developed one or more additional organ dysfunction(s). Finally, patients with Static MODS exhibited a consistent number of organ dysfunctions throughout their PICU stay.

Results

From January 1, 2014 to June 30, 2017, of the 632 patients eligible, 392 patients were enrolled, and 389 provided baseline clinical data. **Table 2** summarizes patient characteristics for the study cohort and by breakdown of MODS subgroups. The median age of the study cohort was 6.4 years and 46% female. Most patients were white, 64%, and not of Hispanic or Latino origin, 77%. The median hospital length of stay was 16 days and PICU stay was 9.3 days. Of the cohort, 23% had a hospital stay over 28 days. The overall crude mortality was 9%.

	Overall Study Cohort n = 389	**No MODS n = 22**	**Static MODS n = 209**	**New MODS n = 94**	**Progressive MODS n = 64**
Age - n (%)					
44 weeks to 1 year	67 (17)	1 (4.6)	30 (14)	20 (21)	16 (25)
1.1 - 3 years	57 (15)	1 (4.6)	37 (18)	13 (14)	6 (9.4)
3.1 – 6 years	66 (17)	8 (36)	34 (16)	14 (15)	10 (16)
6.1 – 10 years	60 (15)	2 (9.1)	29 (14)	12 (13)	17 (27)
10.1 – 14 years	60 (15)	2 (9.1)	31 (15)	20 (21)	7 (11)
14.1 - 18 years	79 (20)	8 (36)	48 (23)	15 (16)	8 (13)
Gender (Female) - n (%)	178 (46)	10 (45)	92 (44)	47 (50)	29 (45.31)
Hispanic or Latino	88 (23)	7 (32)	41 (20)	20 (21)	20 (31)
Race - n (%)					
American Indian or Alaska Native	12 (3.1)	0 (0)	9 (4.3)	3 (3.2)	0 (0)
Asian	22 (5.7)	1 (4.6)	8 (3.8)	8 (8.5)	5 (7.8)
Black or African American	86 (22)	4 (18)	47 (22)	19 (20)	16 (25)
Native Hawaiian or Other Pacific Islander	5 (1.3)	0 (0)	5 (2.4)	0 (0)	0 (0)
White	247 (64)	17 (77)	132 (63)	57 (61)	41 (64)
Unknown or Not Reported	31 (8.0)	0 (0)	17 (8)	9 (9.6)	9 (9.6)
Immunocompromised	68 (17)	5 (23)	34 (16)	16 (17)	13 (20)
Hospital LOS[A] median (IQR)	16 (9.3,26)	11 (6.5, 22)	15 (9.0, 24)	16 (8.6, 26)	21 (15, 40)
PICU LOS [A] median (IQR)	9.3 (5.6,15)	4.0 (2.2, 6.8)	9.1 (5.7, 15)	8.9 (5.7, 16)	13 (7.7, 23)
PRISM III [B] Score Baseline mean (SD)	19 (7.3)	18 (7.6)	19.26 (6.87)	19 (7.0)	22 (8.6)

PELOD 2 [c] Score Baseline mean (SD)	7.4 (3.9)	4.3 (2.8)	8.7 (3.5)	4.2 (2.7)	8.8 (3.8)
Crude Mortality n (%)	35 (9)	0 (0)	15 (7.2)	8(8.5)	12 (19)

Table 2*. Study Cohort Demographics of the overall group and the MODS subgroups.* ***A****.) Length of stay (LOS) was counted in days.* ***B****.) Pediatric Risk of Mortality, version III.* ***C****.) Pediatric Logistic Organ Dysfunction score, version 2, on day of admission.*

Aim #1

Mortality Assessment of MODS Subgroups

There were 22 patients identified with No MODS with the remaining cohort of 367 with MODS. Among patients in the No MODS group, none died, while in the MODS group 9.5%

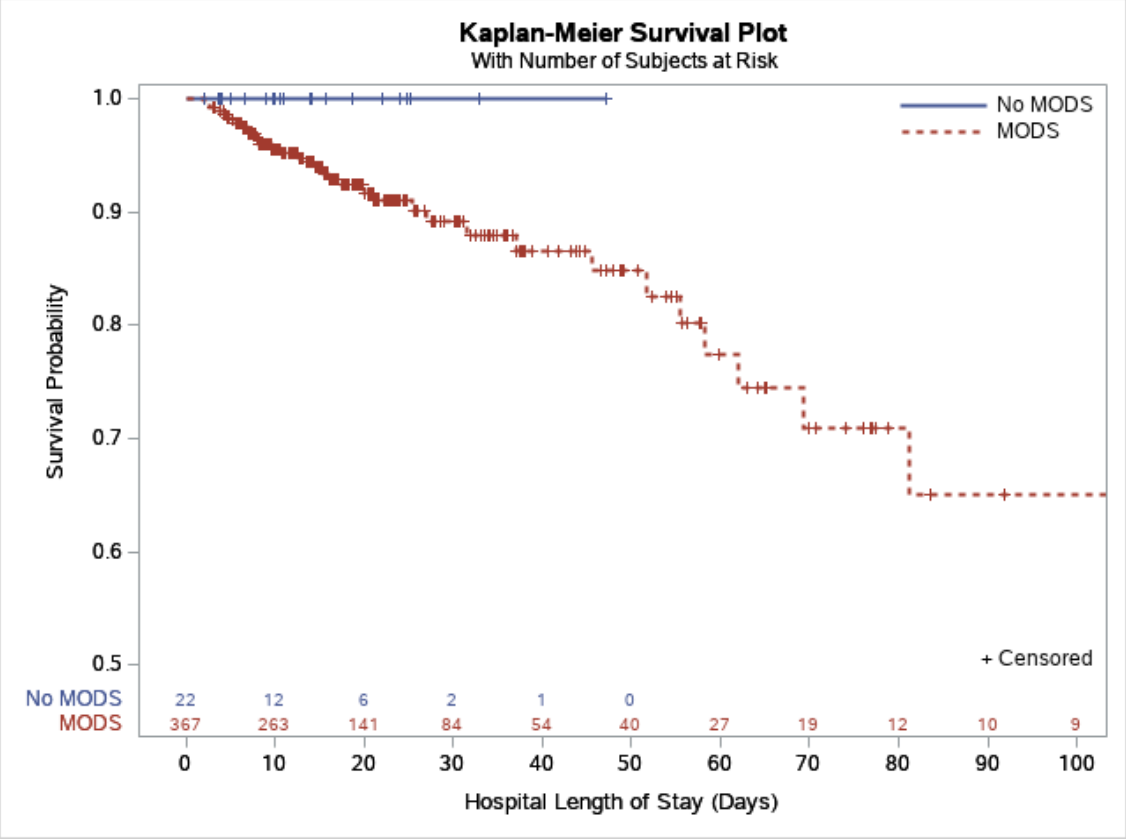


Figure 1*. Kaplan Meier survival plot for No MODS versus the collective MODS group.*

died, see **Figure 1** for a graphic representation. There was not a significant difference in mortality between these two groups by Kaplan Meier estimates. It was noted during analysis that the proportional hazard assumption was violated and had uneven sample sizes. Instead, the

RMST analysis was used to compensate for non-proportional hazards. When RMST was used, there was a significant difference between the two groups, $p<0.0001$.

Next, we separated the collective MODS group into Static (n=209), New (n=94), and Progressive MODS (n=64) subgroups. From within this group, crude mortality was 7.18% for Static MODS, 8.51% for New MODS, and 18.75% for Progressive MODS, see **Figure 3**. There

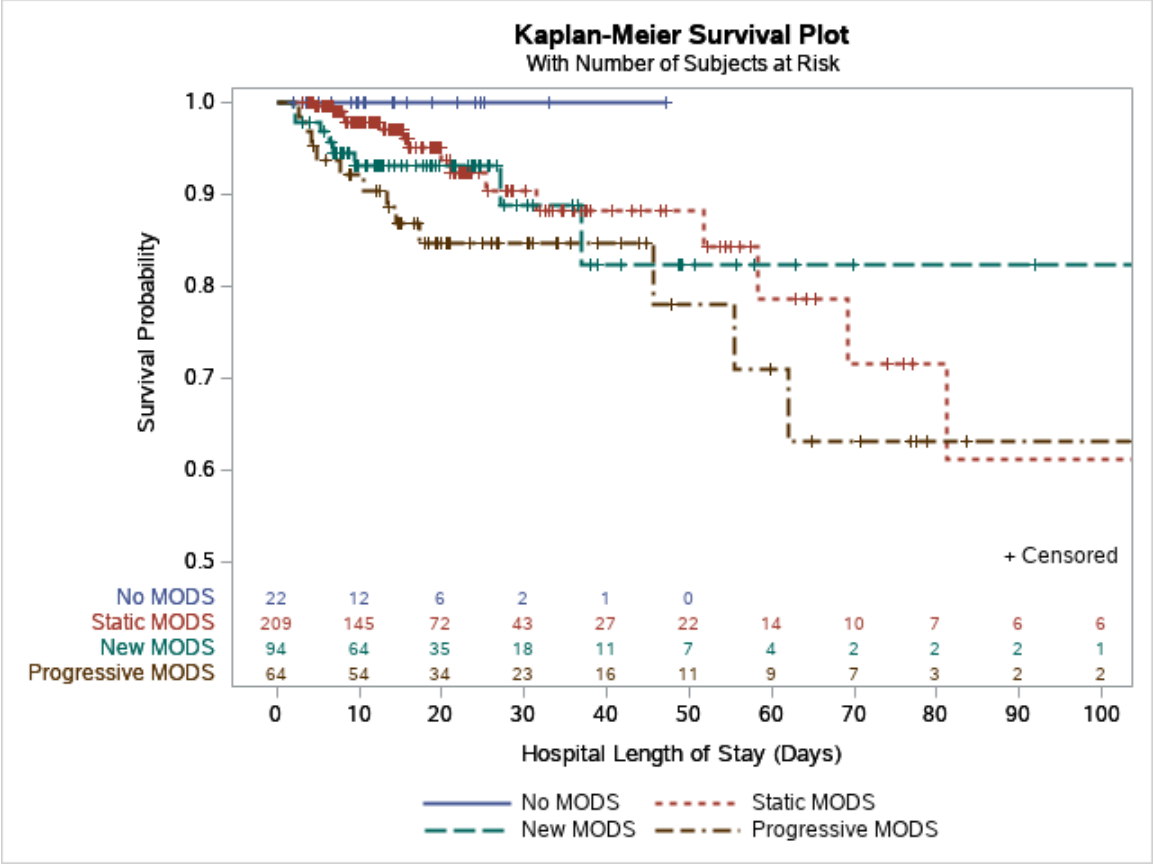


Figure 2. *Kaplan Meier survival plot for No MODS, Static MODS, New MODS, and Progressive MODS.*

was no significant difference in mortality between No MODS, Static MODS, New MODS, and Progressive MODS by Kaplan Meier estimates. As with the No MODS vs MODS analysis, the proportional hazard assumption was in violation with uneven sample sizes. When analyzed using RMST, there was a significant difference between the four groups, $p<0.0001$. Specifically, risk of mortality in all three MODS groups compared to patients with No MODS was significant:

Static MODS, p=0.0019; New MODS, p=0.0099; and Progressive MODS, p=0.0028. Other comparisons: Static MODS vs New MODS, Static MODS vs Progressive MODS, and New MODS vs Progressive MODS were not significant.

Assessment of Change in PCPC Scores

Refer to **Appendix B** for additional details on PCPC and POPC scores. Patients with No MODS had mean normative change in PCPC (ΔPCPC) on day 7 of -0.31 ± 0.6 and -0.18 ± 0.5 on day 28*. In contrast, patients who presented with MODS had a greater decline from baseline with a mean ΔPCPC day 7 and day 28 of -1.1 ± 1.3 and -0.55 ± 1.3. See **Figure 3** for histograms of both PCPC and POPC scores. ΔPCPC scores for day 7 were significant between the No MODS and MODS patient groups, p=0.020, but was not significant for ΔPCPC day 28*, p=0.31.

The mean ΔPCPC day 7 scores were -1.0 ± 1.3 for Static MODS patients, -0.9 ± 1.2 for New MODS, and -1.5 ± 1.5 for Progressive MODS. For day 28*, their mean ΔPCPC scores were Static MODS -0.48 ± 1.2, New MODS -0.52 ± 1.2, and Progressive MODS -0.84 ± 1.6. Between all four groups, ΔPCPC day 7 had significance, p=0.0062, although pairwise comparisons show significance only between the No MODS vs Progressive MODS set, p=0.012. The remaining pairwise comparisons were not significant, but New MODS vs Progressive MODS is marginally significant, p=0.061. For ΔPCPC day 28* there was no significance difference between the four groups, p=0.37. When ordered in increasing severity of MODS: No MODS, Static MODS, New MODS, and with Progressive MODS being the worst. There was a linear association between type of MODS and ΔPCPC scores for both day 7 and day 28*, p=0.0036 and p=0.028, respectively.

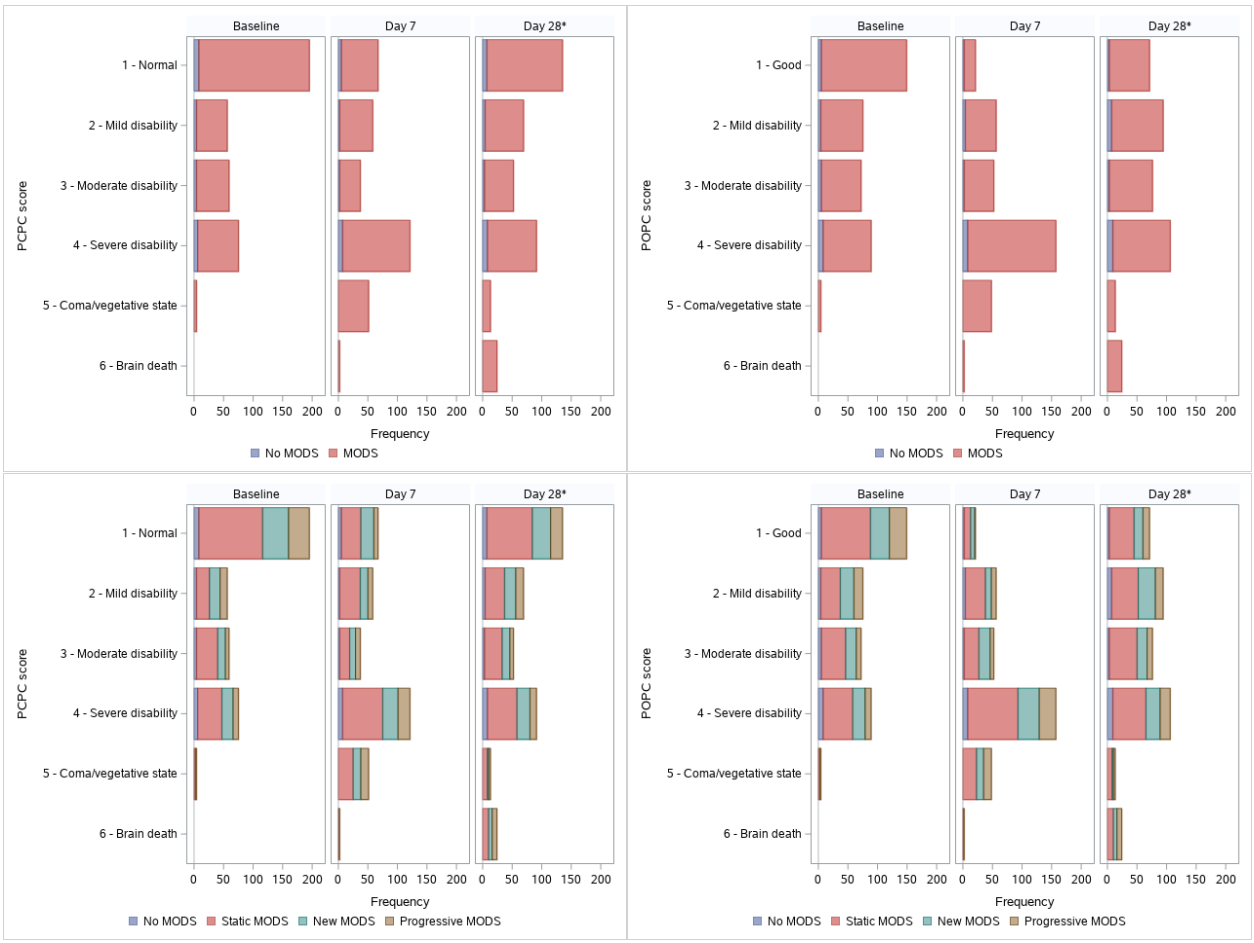


Figure 3*. Histograms of PCPC and POPC scores for MODS and subgroups. Timepoints are baseline taken during admittance to the PICU, day 7, and day 28 or hospital discharge, whichever occurred first.*

Assessment of Change in POPC Scores

Patients in the No MODS group had a mean change in POPC (ΔPOPC) on day 7 and day 28* of -0.25 ± 0.68 and -0.09 ± 0.43 respectively. Patients presenting with MODS had again a higher mean ΔPOPC on day 7 and day 28 were -1.2 ± 1.3 and -0.65 ± 1.2 respectively. ΔPOPC scores for day 7 and day 28* were significant comparing No MODS and MODS patient groups, p=0.002 and p=0.0361, respectively.

Mean ΔPOPC day 7 scores for Static MODS -1.1 ± 1.2, New MODS -1.2 ± 1.2, and Progressive MODS -1.8 ± 1.5. Mean ΔPOPC day 28 scores for Static MODS -0.56 ± 1.2, New MODS -0.56 ± 1.2, and Progressive MODS -1.1 ± 1.5. MODS subgroup analysis showed that

ΔPOPC day 7 was significant, p=0.0003, with the following pairs as significant: No MODS vs Static MODS p=0.031, No MODS vs New MODS p=0.015, No MODS vs Progressive MODS p=0.0010, and Static MODS vs Progressive MODS p=0.013. New MODS vs Progressive MODS patients were not significant, p=0.12. Lastly, ΔPOPC day 28* had overall significance, p=0.0044, for the two pairs: No MODS vs Progressive MODS patients, p=0.0099, and Static MODS vs Progressive MODS patients, p=0.022. New MODS vs Progressive MODS patients were again not significant, p=0.096. We also found there was a linear association between type of MODS and ΔPOPC scores for both day 7 and day 28*, p<0.0001 and p=0.0013, respectively.

Assessment of Change in FSS

The mean normative change in FSS (ΔFSS) on day 7 for the No MODS group was -1.5 ± 2.8 (mean ± SD) while those presenting with MODS had a much larger decrease from baseline, -6.8 ± 6.8. These differences were reduced when looking at ΔFSS day 28* for No MODS was -0.18 ± 0.85 while the MODS group was -1.89 ± 4.32. There was a significant difference between the No MODS and MODS group for both ΔFSS day 7 and day 28*, p=0.0005 and p=0.012 respectively.

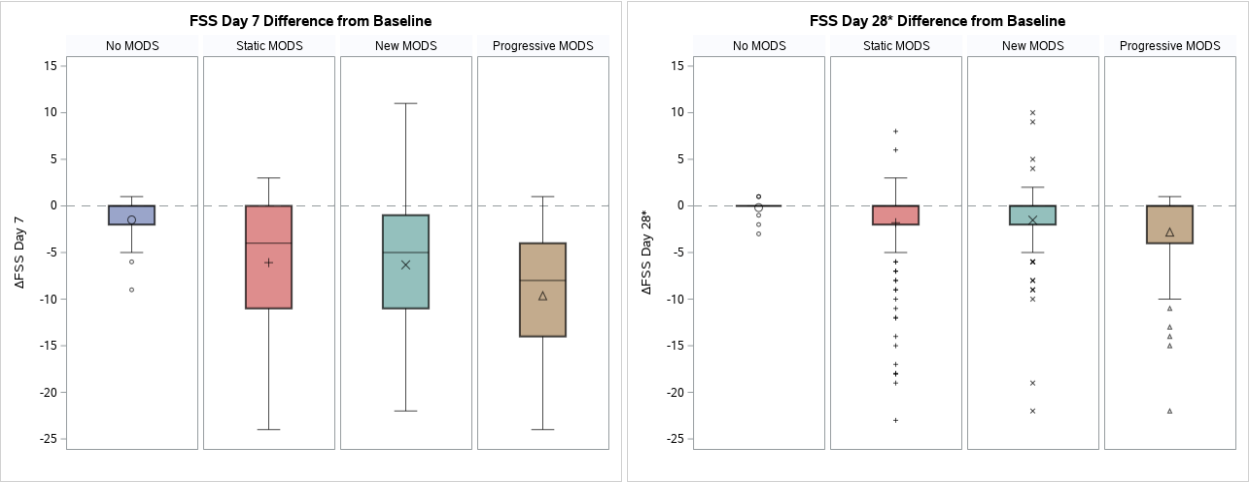


Figure 4*. The change in FSS from baseline score for MODS subgroups. Timepoints are day 7 and day 28 or hospital discharge, whichever occurred first.*

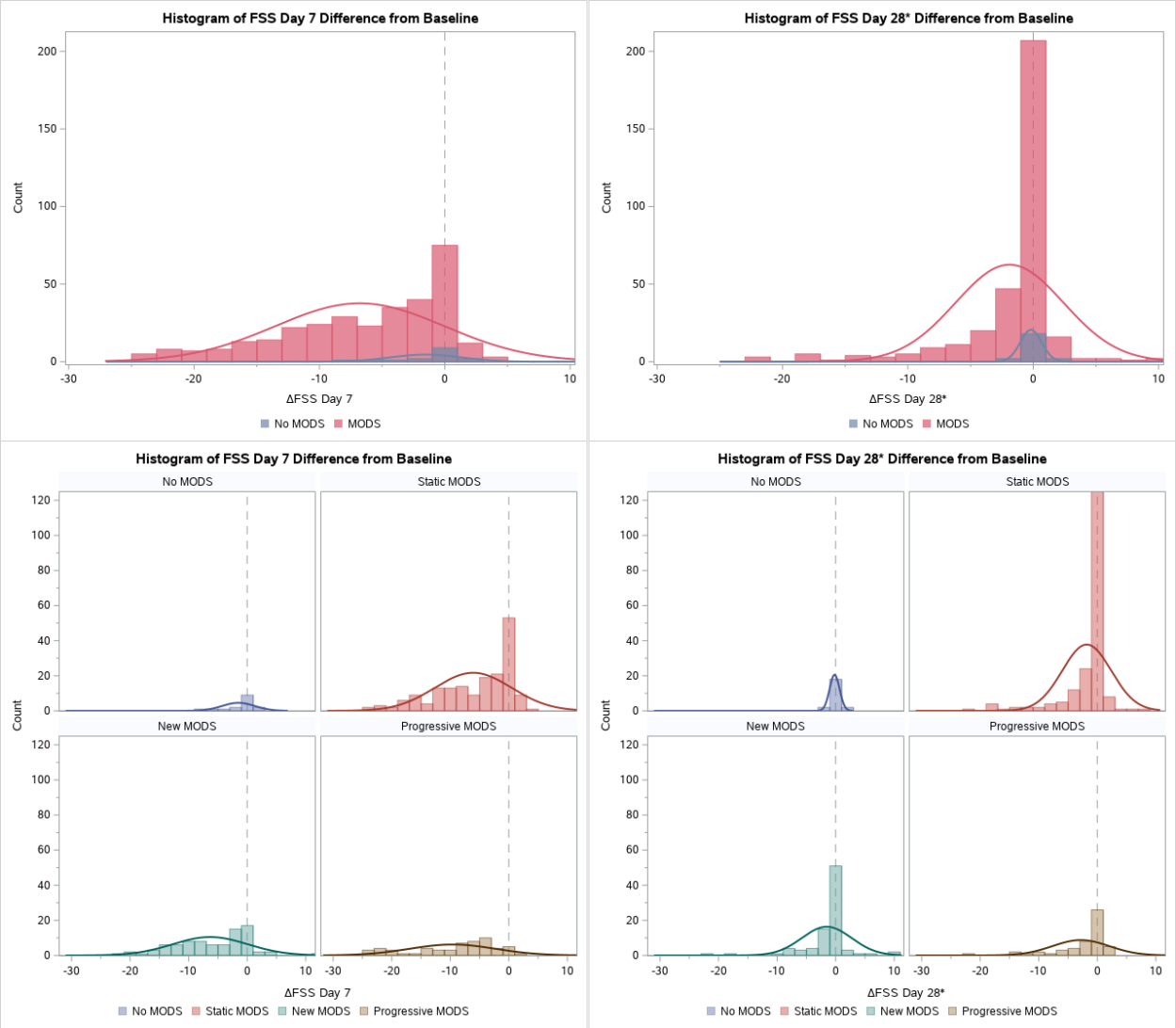


Figure 5. *Histograms of FSS for MODS and subgroups. Timepoints are day 7 and day 28 or hospital discharge, whichever occurred first.*

The mean normative ΔFSS day 7 for Static MODS -6.1 ± 6.6, New MODS -6.3 ± 6.4, and Progressive MODS -9.6 ± 7.4. The mean ΔFSS for day 28* for Static MODS -1.8 ± 4.2, New MODS -1.5 ± 4.3, and Progressive MODS -2.8 ± 4.8. Again, ΔFSS day 7 showed significance between all four groups, $p<0.0001$, with similar findings to the ΔPOPC scores and the same pairwise comparisons as significant: No MODS vs Static MODS, $p=0.015$; No MODS vs New MODS, $p=0.0042$; No MODS vs Progressive MODS, $p<0.0001$; and Static MODS vs Progressive MODS, $p=0.0028$. New MODS vs Progressive MODS patients were again not

significant, p=0.061. Finally, among the four groups ΔFSS day 28* was borderline but not significant, p=0.0518, see **Figure 4**. There was a linear association between MODS type and ΔFSS score but only for day 7, p<0.0001. For every increasing MODS type there was a decrease of 0.028 in ΔFSS. Day 28* ΔFSS was not significant for linear association, p=0.062.

Aim 2

Table 3 summarizes patient characteristics for the study cohort divided between the two neurologic definitions used. The median age of patients with neurological dysfunction are younger than those without. Females comprise anywhere from 37-47% of their group. Patients that do not have neurological dysfunction based on Proulx et al. definition were 74% Hispanic or Latino origin while other groups were 20-23%. Both median hospital length of stay and PICU length of stay were increased for those with neurological dysfunction. The crude mortality was higher for those with neurological dysfunctions.

		Proulx		Expanded	
	Overall Study Cohort n = 389	**No Neurological Dysfunction n = 188**	**Neurological Dysfunction n = 201**	**No Neurological Dysfunction n = 65**	**Neurological Dysfunction n = 324**
Age - n (%)					
44 weeks to 1 year	67 (17)	28 (15)	39 (19)	15 (23)	52 (16)
1.1 - 3 years	57 (15)	19 (10)	38 (19)	3 (4.6)	54 (17)
3.1 - 6 years	66 (17)	35 (19)	31 (15)	8 (12)	58 (18)
6.1 - 10 years	60 (15)	28 (15)	32 (16)	8 (12)	52 (16)
10.1 - 14 years	60 (15)	32 (17)	28 (14)	11 (17)	49 (15)
14.1 - 18 years	79 (20)	46 (24)	33 (16)	20 (31)	59 (18)
Gender (Female) - n (%)	178 (46)	87 (46)	91 (45)	25 (38)	153 (47)
Hispanic or Latino	88 (23)	47 (74)	41 (20)	19 (29)	69 (21)
Race - n (%)					
American Indian or Alaska Native	12 (3.1)	7 (3.7)	5 (2.5)	4 (6.2)	8 (2.5)
Asian	22 (5.7)	10 (5.3)	12 (6.0)	2 (3.1)	20 (6.2)
Black or African American	86 (22)	34 (18)	52 (26)	11 (17)	75 (23)
Native Hawaiian or Other Pacific Islander	5 (1.3)	2 (1.1)	3 (1.5)	1 (1.5)	4 (1.2)
White	247 (64)	126 (67)	121 (60)	47 (72)	200 (62)

Unknown or Not Reported	31 (8.0)	16 (8.5)	15 (7.5)	5 (7.7)	26 (8.0)
Immunocompromised	68 (17)	36 (19)	32 (16)	20 (31)	48 (15)
Hospital LOS[A] median (IQR)	16 (9.3,26)	13 (7.9,21)	19 (11,35)	12 (6.9,20)	17 (9.7,28)
PICU LOS [A] median (IQR)	9.3 (5.6,15)	6.9 (4.4,11)	12 (7.5,22)	5.8 (3.4,10)	10 (6.0,17)
PRISM III [B] Score Baseline mean (SD)	19 (7.3)	19 (6.9)	20 (7.5)	20 (6.8)	19 (7.4)
PELOD 2 [c] Score Baseline mean (SD)	7.4 (3.9)	5.4 (2.9)	9.2 (3.9)	4.3 (2.7)	8.0 (3.9)
Crude Mortality n (%)	35 (9)	3 (1.6)	32 (16)	1 (1.5)	34 (10)

Table 3*. Study cohort demographics of the overall group and two different neurological dysfunction definitions. A.) Length of stay (LOS) was counted in days. B.) Pediatric Risk of Mortality, version III. C.) Pediatric Logistic Organ Dysfunction score, version 2, on day of admission.*

Mortality Comparison Between Proulx and the Expanded Neurological Dysfunction Definition

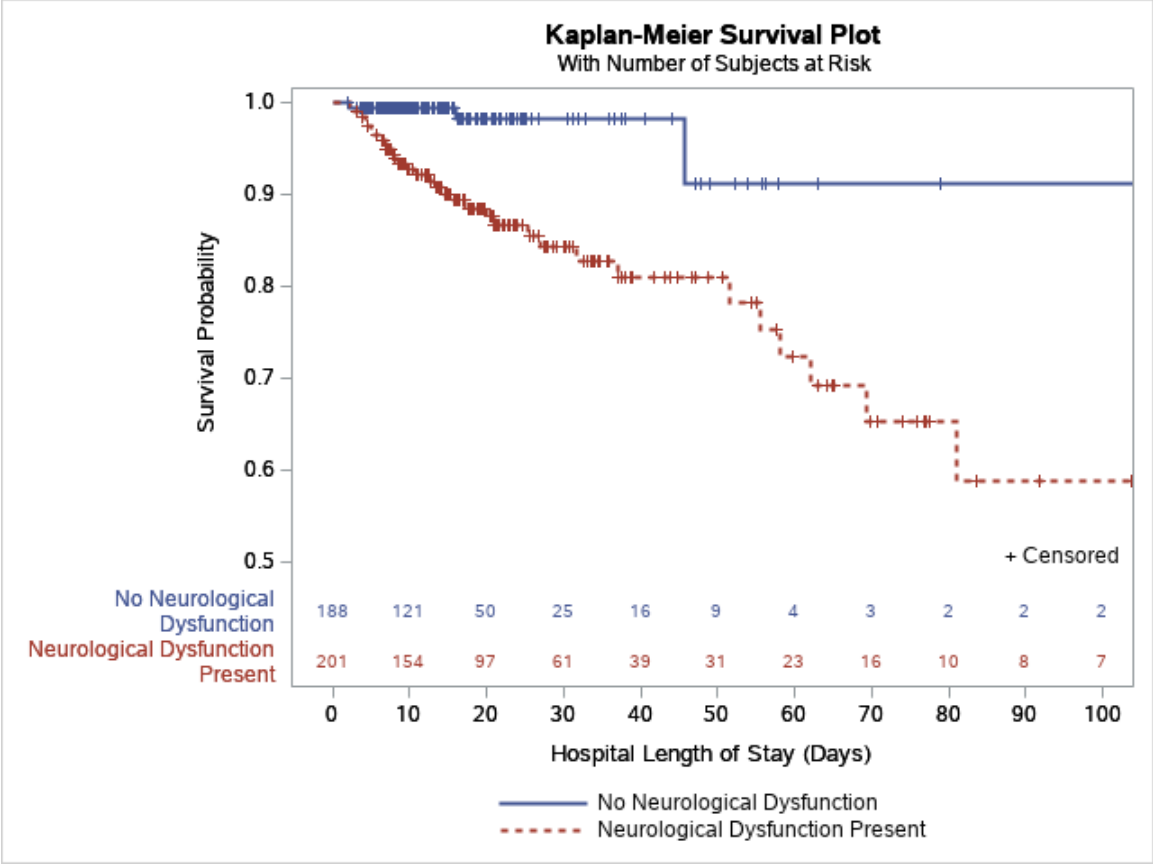


Figure 4*. Kaplan Meier survival plot under Proulx definition of neurological dysfunction.*

There were 188 patients with no neurological dysfunction during their PICU stay with the remaining 201 demonstrating neurological dysfunction. Patients without neurological dysfunction had a crude mortality rate of 1.6% while those with neurological dysfunction had 16%. There was a significant difference in mortality between the patients with no neurological dysfunction and those with neurological dysfunction present using both Kaplan Meier estimate and RMST, p=0.0004 and p=0.0016.

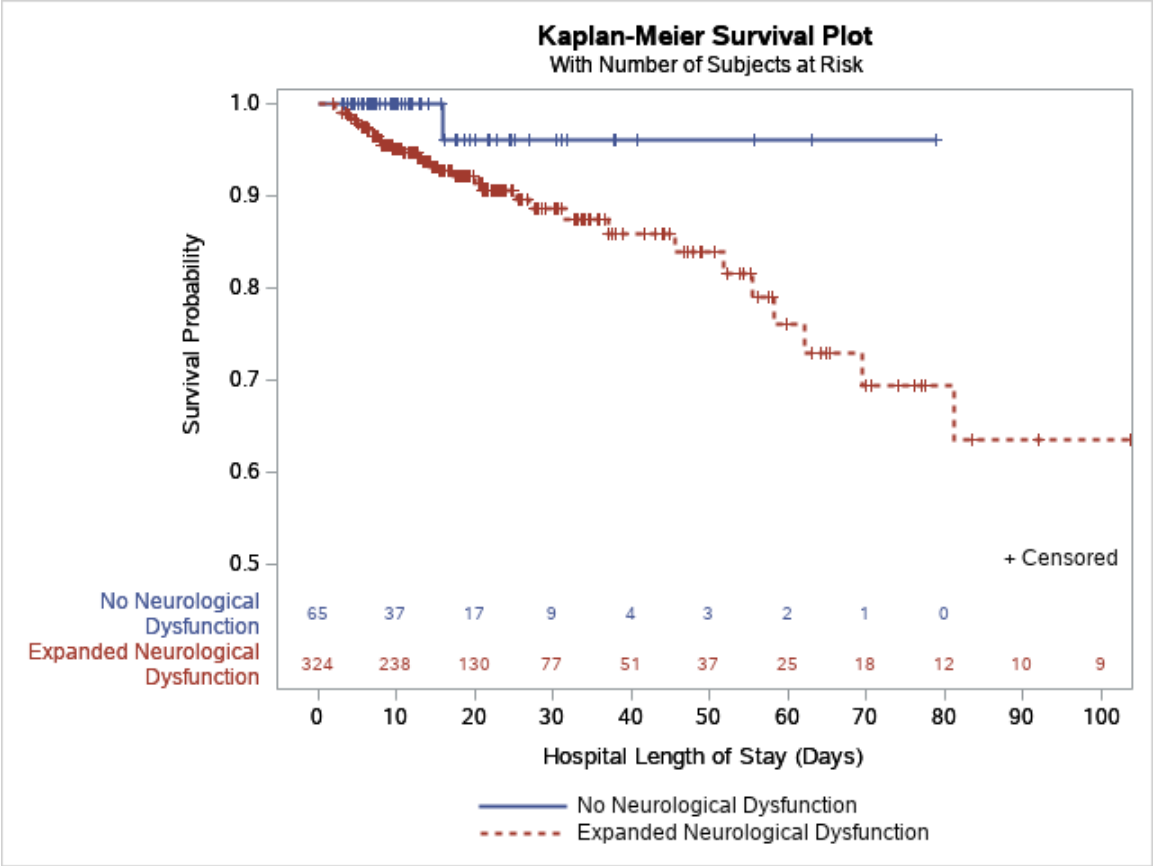


Figure 5. *Kaplan Meier survival plot using the expanded definition of neurological dysfunction.*

Using the expanded definition of neurological dysfunction, only 65 patients exhibited no neurological dysfunction, while those with neurological dysfunction present increased to 324 patients. Crude mortality rate in these groups were 1.5% and 10.5% respectively. By Kaplan Meier estimates, there was no significant difference between the two groups. However, it was

again noted that the proportional hazard assumption was in possible violation with uneven sample sizes. Accordingly, with RMST analysis there is a significant difference, p=0.0021.

PCPC/POPC Comparison Between Proulx and Expanded Definition of Neurological Dysfunction

When Proulx et al.'s definition of neurological dysfunction was used, the mean normative ΔPCPC on day 7 and day 28* for patients with no neurological dysfunction was -0.68 ± 1.0 and -0.15 ± 0.58, respectively. Those exhibiting neurological dysfunction had a mean score for ΔPCPC on day 7 and day 28* were -1.4 ± 1.4 and -0.89 ± 1.6, respectively. The mean ΔPOPC day 7 and day 28* for patients without neurological dysfunction were -0.82 ± 1.05 and -0.23 ±

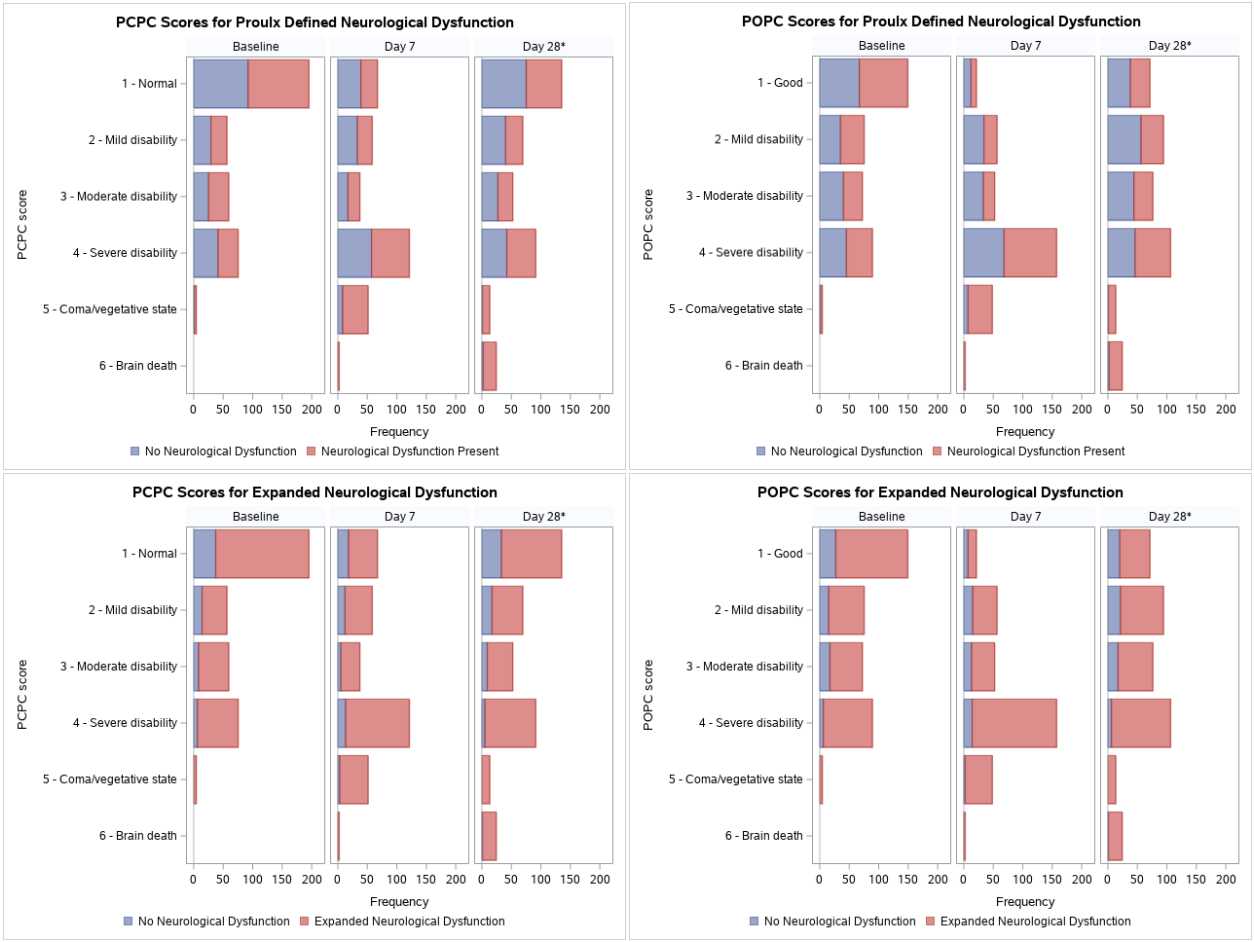


Figure 6*. Histograms of PCPC and POPC scores for Proulx defined and expanded neurological dysfunction. Timepoints are baseline taken during admittance to the PICU, day 7, and day 28 or hospital discharge, whichever was first.*

0.68, respectively. Their counterparts had a mean ΔPOPC for day 7 and day 28* was -1.5 ± 1.4 and -1.0 ± 1.5. All ΔPCPC and ΔPOPC scores for day 7 and day 28* had a strong significant difference between the no neurological dysfunction and neurological dysfunction groups, $p<0.0001$.

Next, we applied the expanded definition of neurological dysfunction. The mean normative ΔPCPC day 7 and day 28* for those without neurological dysfunction were -0.75 ± 1.3 and -0.11 ± 0.59, respectively. The expanded neurological dysfunction group had a greater decrease from baseline with a mean ΔPCPC score on day 7 and day 28* of -1.1 ± 1.3 and -0.61 ± 1.32, respectively. Mean ΔPCPC scores for day 7 and day 28* were significantly different between these two groups, $p=0.036$ and $p=0.0027$. The ΔPOPC scores followed the same patterns. Patients without neurological dysfunction had a mean ΔPOPC score for day 7 and day 28* of -0.78 ± 1.2 and -0.17 ± 0.72, respectively. While their counterparts, the expanded neurologic dysfunction group, had a mean ΔPOPC day 7 and day 28* of -1.3 ± 1.3 and -0.71 ± 1.3. There was a significant difference between these two groups as well on both day 7, $p=0.025$, and day 28*, $p=0.0036$.

FSS Comparison Between Proulx and Expanded Defined Neurological Dysfunction

Using Proulx's definition resulted in a normative mean ΔFSS on day 7 for patients without neurological dysfunction was -3.9 ± 4.9 (mean ± SD), while those with neurological dysfunction had a much greater decrease at -8.8 ± 7.2. Similar in the previous No MODS vs MODS comparison, the differences are reduced when looking at day 28*. The mean ΔFSS on day 28* for the no neurological dysfunction group was -0.48 ± 2.3 while the neurological dysfunction group was -3.2 ± 5.2. There were strong significant differences between the no neurological dysfunction and the neurological dysfunction groups on both day 7 and day 28*,

p<0.0001. There was also a strong significance for trend with ΔFSS on both day 7 and day 28*, p<0.0001. For every decrease of 1 in ΔFSS on day 7, increases the probability of having neurological dysfunction by 0.013. For day 28*, for every decrease of 1 in ΔFSS, increases the probability of having neurological dysfunction by 0.24.

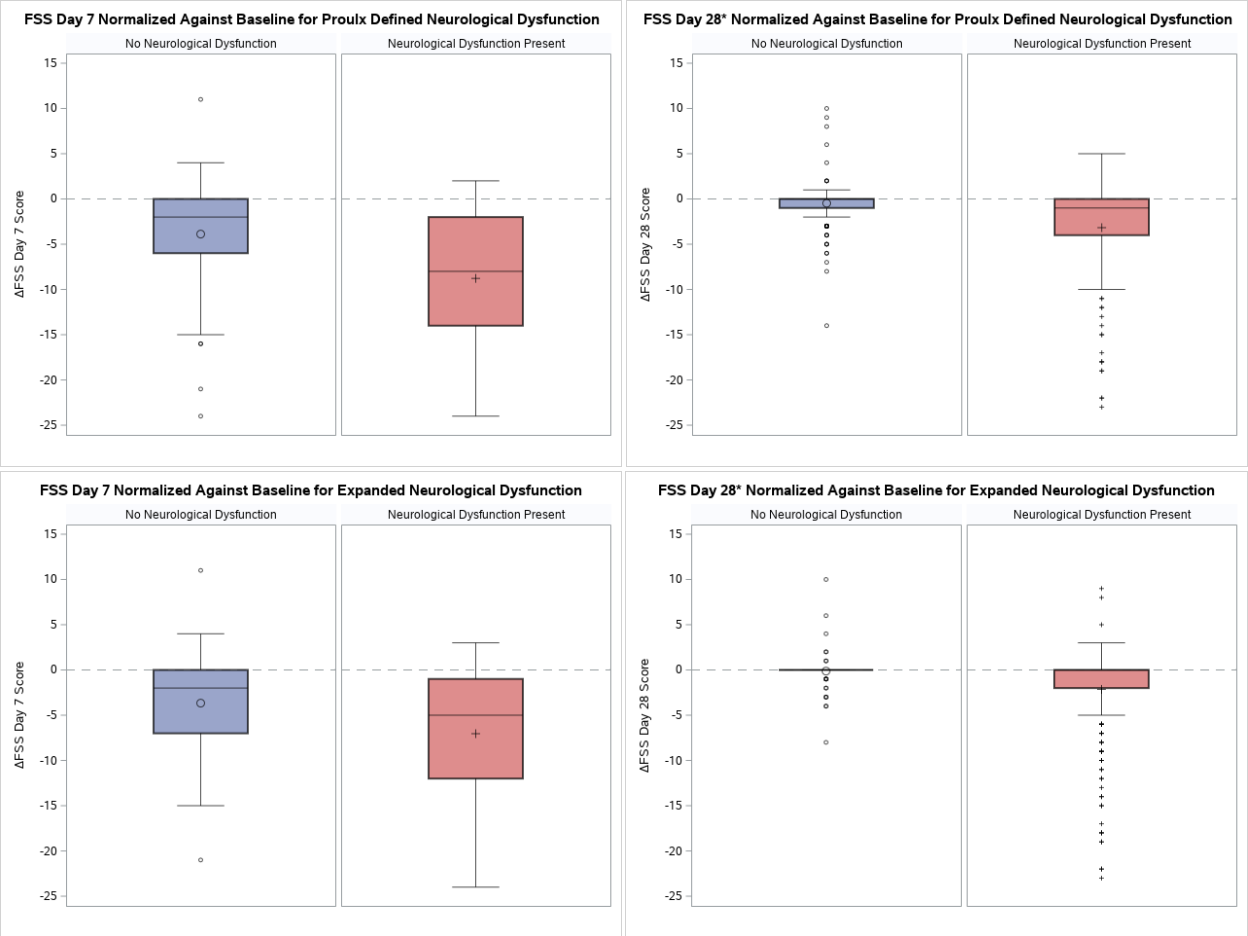


Figure 7. *The change in FSS from baseline score for Proulx and expanded definitions of neurological dysfunction. Timepoints are day 7 and day 28 or hospital discharge, whichever was first.*

Switching back to the expanded definition, the mean ΔFSS on day 7 for the no neurological dysfunction group was -3.7 ± 5.6 while the neurological dysfunction group was -7.0 ± 6.8. The mean ΔFSS on day 28* for the no neurological dysfunction group was -0.13 ± 2.2 while the neurological dysfunction group was -2.2 ± 4.5. There was a strong significant difference between the no neurological dysfunction and the neurological dysfunction groups on

both day 7 and day 28*, p=0.0012 and p<0.0001, respectively. Again, there was significance for trend with normative ΔFSS day 7 and day 28*, p=0.001 and p=0.0006, respectively. For every decrease of 1 in ΔFSS on day 7, the probability of having neurological dysfunction increases by 0.092. On day 28*, for every decrease of 1 in ΔFSS, the probability of having neurological dysfunction increases by 0.23.

Discussion

Aim 1

Our cohort exhibits a similar overall mortality rate of 9% and outcomes comparable to other studies of pediatric sepsis (Watson et al., 2017). The standard method of grouping and comparing No MODS vs MODS showed significant differences also consistent with previous literature. We believe that our findings of functional impairment are generalizable to pediatric patients with severe sepsis treated in industrialized countries. It is unsurprising that day 28* morbidity measures are not as severe and occasionally do not show significance. We see some level of reversal and children frequently return to their baseline scores by the time they are released from the hospital. Especially, compared to day 7, when they are still receiving critical care and are often in their worst condition.

During the NPMODS comparisons, we see that there is typically a difference between all three subgroups of MODS, Static MODS, New MODS, and Progressive MODS, versus the No MODS groups. This is consistent and follows our previous No MODS vs MODS analysis. Analysis of gross functional status by PCPC/POPC follows the same general trend as well. The pattern continues with FSS, which shows granular functional differences between the No MODS versus MODS subgroups. When examining mortality rates among subgroups of patients with MODS, we found that patients with progressive MODS had the highest rate of mortality of 19%,

compared to those with no MODS (no deaths), and new MODS (8%). Although, we did not see statistical significance between the New MODS versus Progressive MODS in this study we believe it warrants future analysis. Since this was a secondary analysis of the LAPSE dataset there was, unfortunately, not enough sample size/power to adequately determine differences between these two groups. Trend analysis showed that worse morbidity measures are associated with worse types of MODS. As a single group new MODS and progressive MODS have generally worse morbidity measures than Static MODS. But Progressive MODS had consistently worse mortality and morbidity measures than new MODS. Patients with new MODS may have evolving organ injury from their initial illness that becomes apparent during care in the PICU after physiologic stabilization. Patients with progressive MODS may have ongoing tissue damage on a microcirculation level that is difficult to measure at the bedside from ongoing disease processes despite critical care. This may reflect ongoing sepsis injury or, alternatively, injury related to the delivery of critical care.

Aim 2

The presence of neurological dysfunction is strongly associated with risk of mortality and morbidity. There was a strong statistical significance on all mortality and morbidity measures. This same conclusion has been mentioned in other studies of MODS (Pollack et al., 2014; Proulx et al., 1994; Schuler et al., 2018; Watson et al., 2017).

On all mortality and morbidity measures, with Proulx et al.'s definition, there was a strong statistically significant difference between those with and without neurological dysfunction. Despite the expanded definition occasionally having not as strong significance (e.g. Proulx ΔPCPC day 7, $p<0.0001$ versus Expanded ΔPCPC day 7, $p=0.0358$) it still had statistical significance that matches on all measures. This supports the additional criteria used to qualify a

larger subset of children who have not historically been considered to have neurological dysfunction. This expanded definition identifies a larger cohort of patients who have also experienced clinically significant functional impairment after survival of pediatric sepsis.

We did not look at the cross section between patients with and without neurological dysfunction against MODS subgroups. None of the No MODS patients presented neurological dysfunction by either definition. We can assume that neurological dysfunction is associated with MODS. Analyzing the correlation between neurological dysfunction within the MODS subgroups would be of future interest.

Limitations

Due to the inclusion criteria of the study, patients with cardiac and respiratory failure were the majority, 89.5%, of the cohort, n=348. This made analysis of which individual organ dysfunction may have had the strongest association with mortality or morbidity measures difficult and likely biased. It is of future interest to see the associations between specific organs and their impact on both mortality and morbidity measures. A larger cohort would greatly aide in determining the differences between different organ dysfunctions. We also did not have respiratory rate available to us and thus, we were limited in criteria used to determine respiratory dysfunction. This lack of data is unlikely to have a large effect on results since a majority of the study population already presented with respiratory dysfunction.

When performing survival analysis using Kaplan Meier estimates, there were violations in proportional hazard assumptions. This combined with the large number of censored events, particularly for patients with No MODS since they leave the hospital quickly, skews survival estimates towards these earlier time points. It is likely not the most appropriate test to use. Restricted mean survival times is a suggested non-parametric method of dealing with analysis

with not only violations in proportional hazards but as well as the uneven sample sizes (Uno et al., 2014). In this cohort of children with septic shock, mortality was a relatively rare event. When further divided into the three subgroups of MODS, this further amplifies the rarity and unevenness of group sizes. Future studies of NPMODS should take this into account and enroll a larger cohort.

We did not look at exact timing of when organ dysfunctions occurred during hospital stay. Moreover, we did not address if patients had changing types of organ dysfunctions throughout their stay. It is possible that patients with frequently changing types organ dysfunction, regardless of absolute number of concurrent organ dysfunction, have different outcomes. This could be an important insight for patients classified with Static MODS, as they represented nearly half of the MODS subgroup, 57%. This in conjunction with when a specific organ fails could hold valuable information in the variable severity and phenotypes patients can exhibit.

Conclusion

In conclusion, we saw the same mortality and acute morbidity burden in children with severe sepsis and NPMODS. Several studies have used NPMODS as their primary outcome measure (Demaret et al., 2015; Lacroix et al., 2007). These studies instead relegate mortality as a secondary outcome measure. Demaret et al. nearly doubled the number of outcome events used in their study with 13% and 11% of 842 admissions had new or progressive MODS, respectively. Using NPMODS as a primary outcome in future studies would boost practical analysis and help uncover subtler differences. Carcillo et al. saw in pediatric severe sepsis, children with multiple organ failure and one of the three different inflammation phenotypes had over two-fold higher mortality than those with multiple organ failure but did not have an inflammation phenotype

(Carcillo et al., 2019). Inflammatory phenotypes may reveal pathobiological reasons for NPMODS. While we were unable to detect statistical difference between new and progressive MODS, we do see associations and gross differences in mortality and morbidity. Moreover, patients with neurological dysfunction have strong significant association with mortality and morbidity which was maintained using an expanded definition.

Appendix A: Criteria for Organ Dysfunction

The following criteria was used to determine organ dysfunction (Proulx et al., 1994).

Cardiovascular System

a.) Systolic blood pressure (SBP) < 40 mmHg for patients aged < 12 months, or < 50 mmHg for patients aged ≥ 12 months OR

b.) Heart rate < 50 bpm or > 220 bpm for patients aged < 12 months, or < 40 bpm or > 200 bpm for patients aged ≥ 12 months OR

c.) Cardiac arrest OR

d.) Serum pH of <7.2 with a normal $PaCO_2$ value OR

e.) Continuous intravenous infusions of inotropic agents to maintain blood pressure and/or cardiac output (use of dopamine ≤ 5 μg/kg/min was excluded)

Respiratory System

a.) Respiratory rate of > 90 breaths/min for patients aged < 12 months, or > 70 breaths/min for patients aged ≥ 12 months OR

b.) $PaCO_2$ > 65 torr (8.7 kPa) OR

c.) PaO_2 < 40 torr (5.3 kPa) in the absence of cyanotic heart disease OR

d.) Mechanical ventilation (for > 24 hours in a postoperative patient) OR

e.) PaO_2/FIO_2 < 200 in the absence of cyanotic heart disease

Neurologic System

a.) Glasgow Coma Score < 5 OR

b.) Fixed dilated pupils

Hematologic System

a.) Hemoglobin < 5 g/dL OR

b.) White blood cell count < 3 x $10^3/mm^3$ ($10^9/L$) OR

c.) Platelet < 20 x $10^3/mm^3$ ($10^9/L$)

Renal System

a.) Serum Urea Nitrogen ≥ 100 mg/dL (36 mmol/L) OR

b.) Serum creatinine ≥ 2.0 mg/dL in absence of preexisting renal disease OR

c.) Dialysis

Expanded Criteria for Neurological Dysfunction

The following criteria was used to determine neurological organ dysfunction based on LAPSE investigation.

a.) Glasgow Coma Score < 11 OR

b.) Fixed dilated pupils OR

c.) Presence of intracranial hypertension OR

d.) New seizure activity OR

e.) New ischemic injury OR

f.) Autonomic storming

Appendix B: Detail of PCPC and POPC Categories Over Time

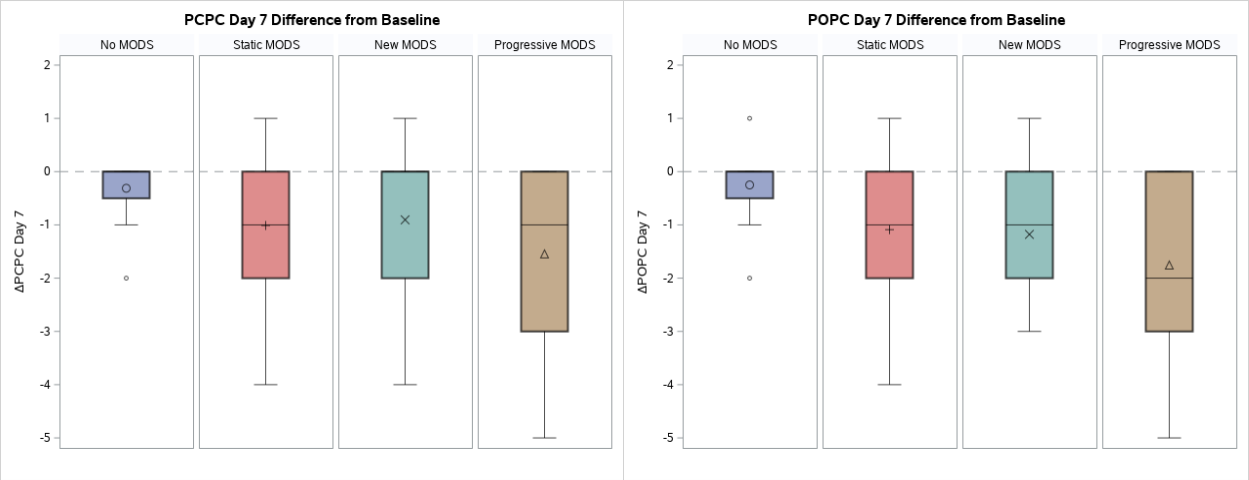
PCPC and POPC Scores with MODS Subgroups

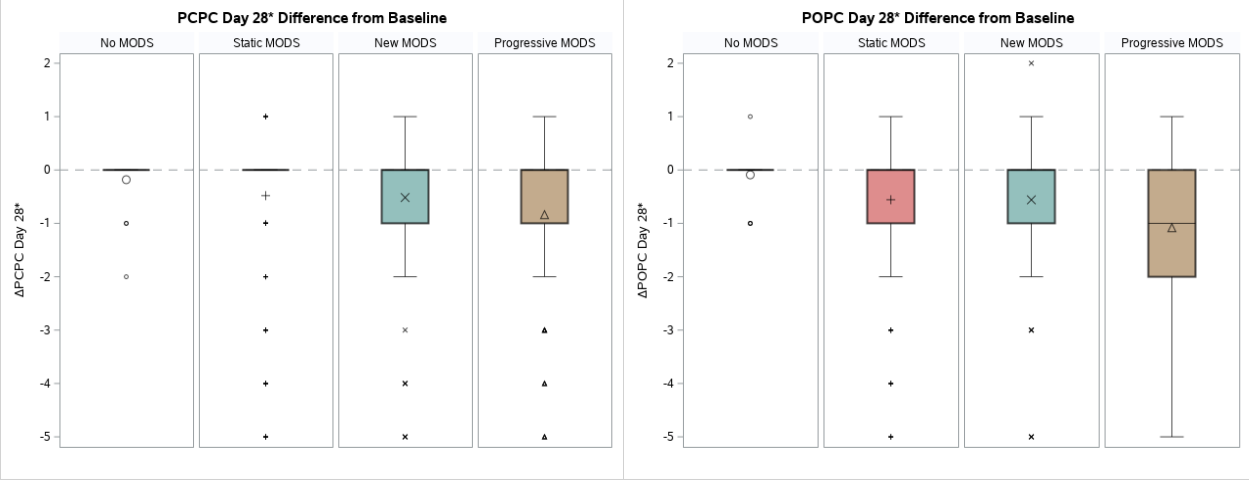
	Overall Study Cohort n = 389	No MODS n = 22	Static MODS n = 209	New MODS n = 94	Progressive MODS n = 64
PCPC Baseline mean (SD)	2.1 (1.2)	2.4 (1.3)	2.1 (1.3)	2.1 (1.2)	1.9 (1.2)
PCPC Day 7	3.1 (1.4)	2.7 (1.4)	3.1 (1.4)	2.9 (1.5)	3.5 (1.4)
PCPC Day 28/Hospital Discharge	2.6 (1.5)	2.6 (1.3)	2.6 (1.5)	2.6 (1.5)	2.8 (1.8)
ΔPCPC Day 7	-1.0 (1.3)	-0.31 (0.6)	-1.01 (1.28)	-0.9 (1.19)	-1.54 (1.51)
ΔPCPC Day 28/Hospital Discharge	-0.53 (1.2)	-0.18 (0.5)	-0.48 (1.18)	-0.52 (1.22)	-0.84 (1.56)
POPC Baseline	2.3 (1.2)	2.7 (1.2)	2.3 (1.2)	2.3 (1.2)	2.1 (1.2)
POPC Day 7	3.5 (1.1)	3.0 (1.2)	3.4 (1.1)	3.4 (1.1)	3.8 (1.1)
POPC Day 28/Hospital Discharge	2.9 (1.4)	2.8 (1.1)	2.9 (1.4)	2.9 (1.4)	3.2 (1.6)
ΔPOPC Day 7	-1.2 (1.3)	-0.25 (0.68)	-1.09 (1.24)	-1.18 (1.18)	-1.75 (1.47)
ΔPOPC Day 28/Hospital Discharge	-0.61 (1.2)	-0.09 (0.43)	-0.56 (1.17)	-0.56 (1.2)	-1.08 (1.48)

PCPC and POPC Scores with Neurological Dysfunction Definitions

		Proulx		Expanded	
	Overall Study Cohort n = 389	**No Neurological Dysfunction n = 188**	**Neurological Dysfunction n = 201**	**No Neurological Dysfunction n = 65**	**Neurological Dysfunction n = 324**
PCPC Baseline mean (SD)	2.1 (1.2)	2.1 (1.2)	2.0 (1.2)	1.7 (1.0)	2.1 (1.3)
PCPC Day 7	3.1 (1.4)	2.8 (1.3)	3.4 (1.4)	2.4 (1.4)	3.2 (1.4)
PCPC Day 28/Hospital Discharge	2.6 (1.5)	2.3 (1.3)	3.0 (1.7)	1.9 (1.1)	2.8 (1.6)
ΔPCPC Day 7	-1.0 (1.3)	-0.68 (1.0)	-1.4 (1.4)	-0.75 (1.3)	-1.1 (1.3)
ΔPCPC Day 28/Hospital Discharge	-0.5 (1.2)	-0.15 (0.58)	-0.89 (1.6)	-0.11 (0.59)	-0.61 (1.3)
POPC Baseline	2.3 (1.2)	2.4 (1.2)	2.2 (1.2)	2.0 (1.0)	2.3 (1.3)
POPC Day 7	3.5 (1.1)	3.2 (1.1)	3.8 (1.1)	2.8 (1.1)	3.6 (1.1)
POPC Day 28/Hospital Discharge	2.9 (1.4)	2.6 (1.1)	3.2 (1.5)	2.2 (1.1)	3.1 (1.4)
ΔPOPC Day 7	-1.2 (1.3)	-0.82 (1.1)	-1.5 (1.4)	-0.78 (1.2)	-1.3 (1.3)
ΔPOPC Day 28/Hospital Discharge	-0.61 (1.2)	-0.23 (0.68)	-0.99 (1.5)	-0.17 (0.72)	-0.71 (1.3)

PCPC and POPC Change from Baseline on Day 7 and Day 28* Box Plots





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