Trajectories and Risk Factors for Altered Physical and Psychosocial Health-Related Quality of Life After Pediatric Community-Acquired Septic Shock*

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Objectives: To evaluate the physical and psychosocial domains of health-related quality of life among children during the first year following community-acquired septic shock, and explore factors associated with poor physical and psychosocial health-related quality of life outcomes.

Design: Secondary analysis of the Life After Pediatric Sepsis Evaluation.

Setting: Twelve academic PICUs in the United States.

Patients: Children greater than or equal to 1 month and less than 18 years old who were perceived to be without severe developmental disability by their family caregiver at baseline and who survived hospitalization for community-acquired septic shock.

Interventions: Family caregivers completed the Pediatric Quality of Life Inventory for children 2–18 years old or the Pediatric Quality of Life Inventory Infant Scales for children less than 2 years old at baseline (reflecting preadmission status), day 7, and months 1, 3, 6, and 12 following PICU admission. Higher Pediatric Quality of Life Inventory Physical and Psychosocial Health Summary Scores indicate better health-related quality of life.

Measurements and Main Results: Of 204 children, 58 (28.2%) had a complex chronic comorbid condition. Children with complex chronic comorbid conditions had lower baseline physical health-related quality of life (62.7 ± 22.6 vs 84.1 ± 19.7; $p < 0.001$) and psychosocial health-related quality of life (68.4 ± 14.1 vs 81.2 ± 15.3; $p < 0.001$) than reference norms, whereas children without such conditions had baseline scores similar to reference norms. Children with complex chronic comorbid conditions recovered to their baseline health-related quality of life, whereas children without such conditions did not (physical health-related quality of life 75.3 ± 23.7 vs 83.2 ± 20.1; $p = 0.008$ and psychosocial health-related quality of life 74.5 ± 18.7 vs 80.5 ± 17.9; $p = 0.006$). Age less than 2 years was independently associated with higher month 12 physical health-related quality of life, and abnormal neurologic examination and neurologic injury suspected by a healthcare provider during the PICU course were independently

*See also p. 899.

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associated with lower month 12 physical health-related quality of life. Treatment of increased intracranial pressure and medical device use at month 1 were independently associated with lower month 12 psychosocial health-related quality of life.

Conclusions: Physical and psychosocial health-related quality of life were reduced among children during the first year following community-acquired septic shock compared with reference norms, although many recovered to baseline. Risk factors for poor health-related quality of life included neurologic complications during the hospitalization and dependence on a medical device 1 month postadmission. (*Pediatr Crit Care Med* 2020; 21:869–878)

Key Words: child; chronic comorbid conditions; health-related quality of life; pediatric; sepsis; septic shock

Sepsis is a major cause of death in PICUs (1, 2). Sepsis-induced organ failures and functional disabilities may lead to impaired health-related quality of life (HRQL) among survivors. HRQL is a multidimensional construct that includes physical, mental, emotional, and social domains that focus on the impact of health status on quality of life (3, 4). Studies of adults with severe sepsis report a rapid decline in HRQL during the ICU course, partial recovery prior to hospital discharge, and gradual progression toward baseline over the next year (5–7). Sepsis in adults may not affect all dimensions of HRQL to the same degree; deficits in physical functioning appear most prolonged.

Studies in children suggest many have reduced HRQL after PICU admission (8–13), particularly after severe sepsis (14–16). However, most studies of HRQL in critically ill children lack baseline assessments with which to compare changes over time (17). Children admitted to PICUs often have chronic comorbid conditions and potential for altered baseline HRQL. Comparison to population norms rather than baseline may under- or over-estimate the change in HRQL attributable to critical illness. Studies also suggest that preexisting comorbidities are risk factors for reduced HRQL after PICU admission (8, 11, 13); however, how preexisting comorbidities impact the trajectory of change in HRQL has not been well investigated. Understanding dimensional and temporal changes in HRQL among children with severe sepsis would allow clinicians to tailor rehabilitation and follow-up care to the needs of survivors.

Life After Pediatric Sepsis Evaluation (LAPSE) was a multicenter, prospective, observational cohort study that longitudinally evaluated HRQL among children surviving community-acquired septic shock (18, 19). For children perceived to be without severe developmental disability by their family caregiver prior to the sepsis event, HRQL was assessed using the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL) (20–23) or PedsQL Infant Scales (23, 24) at baseline (reflecting preadmission status) and over the course of the ensuing year. About one-third of these children had a preexisting complex chronic comorbid condition (18, 19). Mortality was 9.7% during the hospitalization and 2.2% during follow-up. At 1 year, about one-third of survivors had not regained their premorbid global HRQL. Our objective is to evaluate the physical and psychosocial domains of HRQL among children during the first year following community-acquired septic shock and explore factors associated with poor physical and psychosocial HRQL outcomes. We hypothesize that the trajectories of physical and psychosocial HRQL will differ between children with and without preexisting complex chronic comorbid conditions.

MATERIALS AND METHODS

Design and Setting

This study is a secondary analysis of the LAPSE investigation (18, 19). Twelve academic PICUs in the United States recruited children between January 1, 2014, and June 30, 2017. Details of LAPSE were previously published (18, 19). The study was approved by the institutional review boards at all study sites and the data coordinating center. Parental permission was obtained for all participants.

Participants

Children eligible for LAPSE were greater than or equal to 1 month and less than 18 years old and had documented or suspected community-acquired infection or sepsis. Eligible children also had body fluid cultures and/or polymerase chain reaction (PCR) testing, displayed greater than or equal to 2 systemic inflammatory response syndrome criteria including abnormal leukocyte count/differential and/or abnormal body temperature and were treated with antimicrobials, vasoactive inotropes, and invasive or noninvasive mechanical ventilation (18, 19). Exclusion criteria included inability to be enrolled within 48 hours of PICU admission; additional exclusion criteria have been published (18, 19). LAPSE enrolled 392 children. Family caregivers were asked to select the HRQL instrument they believed would be most meaningful for their child based on whether they subjectively perceived their child to have a severe physical or mental developmental delay or disability at preadmission baseline. Family caregivers of 226 subjectively perceived their child to be without severe developmental disability at preadmission baseline and completed PedsQL or PedsQL Infant Scales. Caregivers who perceived their children to have severe disabilities at baseline completed the Stein-Jessop Functional Status Scale (25) and were excluded from this report. Death occurred prior to hospital discharge for 22 children without severe baseline disability, leaving 204 available for follow-up.

Independent Variables

At study enrollment, data collected included child demographics, illness severity, organ dysfunction, presence of chronic comorbid conditions, immune deficiency, and documented versus suspected infection. Illness severity was assessed using Pediatric Risk of Mortality (PRISM) scores (26) and organ dysfunction using Pediatric Logistic Organ Dysfunction (PELOD)–2 scores (27). Chronic comorbid conditions were

determined using data from the Pediatric Health Information System (28) and the Pediatric Medical Complexity Algorithm (29) and categorized as none/noncomplex versus complex chronic comorbid condition. Documented infection was culture or PCR positive.

Data collected during the PICU course (truncated at day 28) included Vasoactive-Inotropic Scores (VISs) (30) and use of mechanical ventilation assessed at 08:00 and 20:00 daily. Additional daily data included the presence of abnormal neurologic findings on physical examination (i.e., anisocoria or absence of pupillary response, pathologic breathing pattern, stereotypic or flaccid posture, and autonomic storming), seizure activity and/or abnormal electroencephalogram, new anoxic-ischemic injury on brain imaging, treatment for increased intracranial pressure, neurologic injury suspected by a healthcare provider, PELOD-2 scores, cardiac arrest, and treatment with red cell transfusion, Extracorporeal Life Support (ECLS), or renal replacement therapy (RRT). Medical device use at month 1 (26–42 d following PICU admission) and length of stay in PICU and hospital were recorded.

Outcomes

Family caregivers completed the parent-proxy form of the PedsQL (20–23) for children 2–18 years old or the PedsQL Infant Scales (23, 24) for children less than 2 years old at study entry (reflecting preadmission status), and 6–14 (day 7), 26–42 (month 1), 83–120 (month 3), 176–213 (month 6), and 358–395 (month 12) calendar days following PICU admission. The parent-proxy form of the PedsQL is a 23-item measure that encompasses four domains of HRQL including physical, emotional, social, and school functioning. The PedsQL Infant Scales include a 36-item version for 1–12 month old infants and a 45-item version for 13–24 month old infants. Both infant versions cover the domains of physical symptoms and physical, emotional, social, and cognitive functioning. Physical Health Summary Scores (referred to hereafter as physical HRQL) and Psychosocial Health Summary Scores (referred to hereafter as psychosocial HRQL) are determined for both the PedsQL and the PedsQL Infant Scales. All scores are linearly transformed to a 0–100 scale with higher scores indicating better HRQL. Reference norms are available (21). Using parent proxy-report for the PedsQL, the minimal clinically important difference (MCID) between scores has been determined to be 4.50 for the total score, 6.92 for physical HRQL, and 5.49 for psychosocial HRQL (21). The MCID is the smallest difference in score that individuals perceive to be beneficial and that would mandate, in the absence of adverse side effects or excessive costs, a change in management. HRQL assessments were facilitated by researchers at the study sites during the hospitalization and by the Seattle Children's Research Institute after the child's discharge.

Statistical Analyses

Clinical characteristics were summarized using counts and percentages for categorical variables and medians and quartiles for interval variables. Longitudinal measures of PedsQL and the PedsQL Infant Scales were combined and summarized utilizing mean and SD by complex chronic comorbid condition status. The relationships between individual time points and baseline values were assessed with paired *t* tests, and relationships with reference values were assessed with one-sample *t* tests. To account for potential bias due to significant loss to follow-up, multiple imputation was used to impute missing data. PedsQL scores were imputed for 2% of children at baseline, 17% at day 7, 32% at month 1, 39% at month 3, 48% at month 6, and 47% at month 12. Details regarding the imputation methods were previously published (18, 19, 31). Briefly, a sequence of regression models was used to generate 10 imputed datasets. Each imputed dataset contained the observed data along with data drawn from a posterior predictive distribution replacing missing values. Each imputed dataset was analyzed separately and results were combined using the MIANALYSE procedure (a procedure used for analyzing multiply imputed data) in SAS software (Version 9.4; SAS Institute, Cary, NC).

The distributions of potential predictors were examined prior to modeling PedsQL physical HRQL and psychosocial HRQL summary scores. Univariable linear regression models for each of the candidate predictor variables were built to determine which were associated with each summary score at two time points, month 3 and month 12. Baseline summary scores were controlled for in all models. This step was taken to account for the difference in baseline summary scores between subjects and isolate the effect of covariates of subjects with similar baseline characteristics. All variables were considered for inclusion in the multivariable models. The final multivariable models were selected using bi-directional stepwise regression methods with a conservative criterion of *p* value of less than 0.2 to enter the model and *p* value of less than 0.1 to stay in the final model. Both baseline summary scores for the individual domains and complex chronic comorbid condition status were forced predictors. *p* values for both the univariable and multivariable analyses were based on a likelihood ratio test with a two-sided alternative, with values less than 0.05 considered significant. CIs were based on the profile likelihood method, with equal tails. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 204 children, 114 (55.9%) were male, 69 (33.8%) were less than 2 years old, 129 (63.0%) were white, and 48 (23.7%) Hispanic (**Table 1**). Fifty-eight children (28.2%) had a complex chronic comorbid condition. Infection at the time of study eligibility was documented for 87 (42.6%) and suspected for 117 (57.4%). A new abnormal neurologic examination finding during the PICU course occurred in 52 (25.5%) and seizures or abnormal electroencephalogram in 31 (15.2%); most of these occurred within the first week of the PICU stay (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B318; **legend**, Supplemental Digital Content 5, http://links.lww.com/PCC/B322). Thirty-nine (19.1%) had at least one medical device in use at month 1; of these, all had at least one chronic device (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/PCC/B319).

TABLE 1. Clinical Characteristics of Children with Community-Acquired Septic Shock at Baseline and On-Study

Characteristic	*n* = 204
Baseline	
Male	114 (55.9%)
Age	
0–12 mo	44 (21.6%)
13–24 mo	25 (12.3%)
2–4 yr	32 (15.7%)
5–7 yr	22 (10.8%)
8–12 yr	34 (16.7%)
13–17 yr	47 (23.0%)
Race	
White	129 (63.0%)
Black or African American	48 (23.5%)
Other	28 (13.5%)
Ethnicity	
Hispanic	48 (23.7%)
Chronic comorbid conditions[a]	
None/noncomplex	147 (71.8%)
Complex	58 (28.2%)
Immunocompromised	34 (16.7%)
Nature of infection at time of eligibility	
Documented	87 (42.6%)
Suspected	117 (57.4%)
Pediatric Risk of Mortality[b]	10.0 (5.0–16.5)
On-study	
Red cell transfusion administered	101 (49.5%)
Sum of Pediatric Logistic Organ Dysfunction-2 in PICU[c]	48.5 (29.5–80.5)
Maximum Vasoactive-Inotrope Score in PICU[d]	
Low	150 (73.5%)
High	54 (26.5%)
Abnormal neurologic examination finding[e]	52 (25.5%)
Seizure activity and/or abnormal electroencephalogram	31 (15.2%)
New anoxic-ischemic brain injury on CT/MRI	7 (3.4%)
Treatment for increased intracranial pressure	8 (3.9%)
Neurologic injury suspected by care provider	26 (12.7%)
Extracorporeal Life Support in PICU	12 (5.9%)
Renal replacement therapy during PICU stay	15 (7.4%)
Cardiopulmonary arrest or chest compressions	11 (5.4%)
Medical device use at month 1	39 (19.1%)
Number of mechanical ventilator days	7.0 (4.0–11.0)
PICU length of stay, d	8.2 (5.1–13.9)
Hospital length of stay, d	15.4 (9.3–25.3)

[a]Assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission.

[b]Pediatric Risk of Mortality data were collected during a modified period of 2 hr prior PICU admission through 4 hr post PICU admission.

[c]Sum of Pediatric Logistic Organ Dysfunction-2 refers to the summation of daily scores while in the ICU (truncated at 28 calendar days following ICU admission).

[d]Maximum Vasoactive-Inotrope Score (VIS) is defined as being high if the VIS was > 20 at some point during the child's PICU stay (truncated at 28 calendar days following ICU admission).

[e]Abnormal neurologic examination findings include anisocoria or absence of pupillary response, pathologic breathing pattern, stereotypic posturing, flaccid posture, and autonomic storming.

Data are summarized as *n* (%) and median (interquartile range).

For children without a complex chronic comorbid condition, baseline physical and psychosocial HRQL were similar to reference norms (**Table 2**). Summary scores significantly declined from baseline by day 7 following PICU admission. This decline was followed by a gradual increase in scores with most improvement occurring by month 3 and lesser degree of improvement between month 3 and month 12. Physical and psychosocial HRQL were significantly less than baseline at all subsequent time points.

For children with complex chronic comorbid conditions, baseline physical and psychosocial HRQL were significantly less than reference norms (**Table 3**). Physical and psychosocial HRQL significantly declined from baseline by day 7, followed by a gradual increase and return to baseline by month 3 and month 1, respectively. **Figure 1** displays physical and psychosocial HRQL at baseline and month 12 by chronic comorbid condition versus reference norms.

Univariable associations between child characteristics and physical HRQL at months 3 and 12 are shown in **Supplemental Table 2** (Supplemental Digital Content 3, http://links.lww.com/PCC/B320). Higher PRISM score, higher sum of PELOD-2 scores in PICU, longer duration of mechanical ventilation, longer PICU and hospital stays, and medical device use at month 1 were associated with lower month 3 physical HRQL scores, and age less than 2 years was associated with higher month 3 physical HRQL scores. Abnormal neurologic examination findings, neurologic injury suspected by provider, and medical device use at month 1 were associated with lower month 12 physical HRQL scores.

Univariable associations between child characteristics and psychosocial HRQL at months 3 and 12 are shown in **Supplemental Table 3** (Supplemental Digital Content 4, http://links.lww.com/PCC/B321). Age less than 2 years was associated with higher month 3 psychosocial HRQL scores. Treatment for increased intracranial pressure, neurologic injury suspected by provider, and medical device use at month 1 were associated with lower month 12 psychosocial HRQL scores.

TABLE 2. Pediatric Quality of Life Inventory Over Time for Children Without Complex Chronic Comorbid Conditions[a]

		Time Point					
Total or Domain	Reference[b]	Baseline ($n = 147$)	Day 7 ($n = 147$)	Month 1 ($n = 147$)	Month 3 ($n = 145$)	Month 6 ($n = 145$)	Month 12 ($n = 145$)
Total Pediatric Quality of Life Inventory score	82.3 ± 15.6	81.5 ± 16.0; $p = 0.562$[c]	48.9 ± 23.2; $p \leq 0.001$[c]; $p \leq 0.001$[d]	63.5 ± 19.5; $p \leq 0.001$[c]; $p \leq 0.001$[d]	71.4 ± 18.8; $p \leq 0.001$[c]; $p \leq 0.001$[d]	73.6 ± 19.2; $p \leq 0.001$[c]; $p \leq 0.001$[d]	74.9 ± 18.5; $p \leq 0.001$[c]; $p = 0.002$[d]
Physical Health Summary Score	84.1 ± 19.7	83.2 ± 20.1; $p = 0.580$[c]	49.1 ± 32.8; $p \leq 0.001$[c]; $p \leq 0.001$[d]	59.3 ± 30.0; $p \leq 0.001$[c]; $p \leq 0.001$[d]	69.0 ± 26.1; $p \leq 0.001$[c]; $p \leq 0.001$[d]	74.0 ± 26.6; $p \leq 0.001$[c]; $p = 0.005$[d]	75.3 ± 23.7; $p \leq 0.001$[c]; $p = 0.008$[d]
Physical function		84.6 ± 20.9	40.7 ± 35.5; $p \leq 0.001$[d]	58.4 ± 30.9; $p \leq 0.001$[d]	67.5 ± 27.8; $p \leq 0.001$[d]	73.7 ± 27.5; $p = 0.002$[d]	74.8 ± 25.9; $p = 0.006$[d]
Physical symptoms (< 2 yr old only)		82.1 ± 13.2	74.6 ± 16.0; $p = 0.004$[d]	80.8 ± 12.4; $p = 0.627$[d]	81.2 ± 19.9; $p = 0.774$[d]	80.2 ± 20.5; $p = 0.551$[d]	80.4 ± 19.2; $p = 0.652$[d]
Psychosocial Health Summary Score	81.2 ± 15.3	80.5 ± 17.9; $p = 0.623$[c]	49.2 ± 23.0; $p \leq 0.001$[c]; $p \leq 0.001$[d]	65.3 ± 18.0; $p \leq 0.001$[c]; $p \leq 0.001$[d]	72.6 ± 17.8; $p \leq 0.001$[c]; $p \leq 0.001$[d]	73.2 ± 19.0; $p \leq 0.001$[c]; $p \leq 0.001$[d]	74.5 ± 18.7; $p = 0.001$[c]; $p = 0.006$[d]
Emotional function	81.2 ± 16.4	78.7 ± 19.8; $p = 0.138$[c]	59.8 ± 26.9; $p \leq 0.001$[c]; $p \leq 0.001$[d]	65.6 ± 23.8; $p \leq 0.001$[c]; $p \leq 0.001$[d]	73.0 ± 20.9; $p = 0.002$[c]; $p = 0.028$[d]	72.5 ± 21.6; $p \leq 0.001$[c]; $p = 0.006$[d]	72.3 ± 24.1; $p = 0.001$[c]; $p = 0.032$[d]
Social function	83.1 ± 19.7	83.9 ± 20.8; $p = 0.618$[c]	62.2 ± 33.1; $p \leq 0.001$[c]; $p \leq 0.001$[d]	72.6 ± 25.3; $p \leq 0.001$[c]; $p \leq 0.001$[d]	78.8 ± 21.6; $p = 0.088$[c]; $p = 0.053$[d]	78.9 ± 23.8; $p = 0.059$[c]; $p = 0.035$[d]	79.8 ± 22.4; $p = 0.154$[c]; $p = 0.102$[d]
School function (≥ 2 yr old only)	78.3 ± 19.6	78.4 ± 22.5; $p = 0.960$[c]		53.2 ± 30.2; $p \leq 0.001$[c]; $p \leq 0.001$[d]	63.3 ± 24.3; $p \leq 0.001$[c]; $p \leq 0.001$[d]	65.8 ± 26.9; $p = 0.001$[c]; $p = 0.002$[d]	73.1 ± 22.6; $p = 0.237$[c]; $p = 0.188$[d]
Cognitive function (< 2 yr old only)		82.1 ± 24.66	54.9 ± 35.8; $p \leq 0.001$[d]	67.7 ± 30.4; $p = 0.022$[d]	71.1 ± 29.4; $p = 0.043$[d]	79.1 ± 24.7; $p = 0.544$[d]	74.4 ± 26.6; $p = 0.129$[d]

[a]Chronic comorbid condition assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission.

[b]Reference group obtained in Varni et al (21).

[c]One-sample *t* test comparing time point to reference value.

[d]Paired *t* test comparing time point to baseline value.

Data are summarized as mean ± SD.

TABLE 3. Pediatric Quality of Life Inventory Over Time for Children With Complex Chronic Comorbid Conditions[a]

Total or Domain	Reference[b]	Time Point					
		Baseline (*n* = 58)	Day 7 (*n* = 58)	Month 1 (*n* = 58)	Month 3 (*n* = 57)	Month 6 (*n* = 56)	Month 12 (*n* = 55)
Total Pediatric Quality of Life Inventory score	82.3 ± 15.6	66.3 ± 14.7; $p \leq 0.001$[c]	49.8 ± 18.4; $p \leq 0.001$[c]; $p \leq 0.001$[d]	61.0 ± 20.0; $p \leq 0.001$[c]; $p = 0.076$[d]	67.7 ± 16.3; $p \leq 0.001$[c]; $p = 0.517$[d]	69.4 ± 16.3; $p \leq 0.001$[c]; $p = 0.253$[d]	70.6 ± 20.0; $p \leq 0.001$[c]; $p = 0.139$[d]
Physical Health Summary Score	84.1 ± 19.7	62.7 ± 22.6; $p \leq 0.001$[c]	51.9 ± 26.9; $p \leq 0.001$[c]; $p = 0.019$[d]	51.0 ± 32.8; $p \leq 0.001$[c]; $p = 0.010$[d]	61.1 ± 25.6; $p \leq 0.001$[c]; $p = 0.719$[d]	64.9 ± 27.3; $p \leq 0.001$[c]; $p = 0.644$[d]	68.2 ± 28.7; $p = 0.001$[c]; $p = 0.249$[d]
Physical function		62.8 ± 23.0	47.6 ± 29.5; $p = 0.004$[d]	49.1 ± 33.9; $p = 0.004$[d]	61.6 ± 25.7; $p = 0.780$[d]	64.8 ± 27.9; $p = 0.671$[d]	67.8 ± 29.2; $p = 0.297$[d]
Physical symptoms (< 2 yr old only)		71.6 ± 12.2	74.2 ± 10.3; $p = 0.439$[d]	79.3 ± 16.7; $p = 0.091$[d]	76.4 ± 25.0; $p = 0.427$[d]	83.4 ± 11.4; $p = 0.016$[d]	84.2 ± 17.8; $p = 0.090$[d]
Psychosocial Health Summary Score	81.2 ± 15.3	68.4 ± 14.1; $p \leq 0.001$[c]	48.7 ± 19.8; $p \leq 0.001$[c]; $p \leq 0.001$[d]	66.4 ± 17.6; $p \leq 0.001$[c]; $p = 0.466$[d]	71.4 ± 14.9; $p \leq 0.001$[c]; $p = 0.148$[d]	71.8 ± 16.4; $p \leq 0.001$[c]; $p = 0.229$[d]	71.8 ± 18.1; $p \leq 0.001$[c]; $p = 0.205$[d]
Emotional function	81.2 ± 16.4	70.2 ± 18.8; $p \leq 0.001$[c]	61.2 ± 23.7; $p \leq 0.001$[c]; $p = 0.018$[d]	67.5 ± 23.1; $p \leq 0.001$[c]; $p = 0.360$[d]	74.4 ± 17.5; $p = 0.010$[c]; $p = 0.163$[d]	72.5 ± 21.1; $p = 0.006$[c]; $p = 0.573$[d]	73.9 ± 20.6; $p = 0.032$[c]; $p = 0.313$[d]
Social function	83.1 ± 19.7	71.0 ± 21.7; $p \leq 0.001$[c]	65.3 ± 26.8; $p \leq 0.001$[c]; $p = 0.179$[d]	71.4 ± 24.5; $p \leq 0.001$[c]; $p = 0.910$[d]	76.2 ± 21.0; $p = 0.030$[c]; $p = 0.109$[d]	75.9 ± 21.4; $p = 0.034$[c]; $p = 0.200$[d]	77.3 ± 23.8; $p = 0.128$[c]; $p = 0.125$[d]
School function (≥ 2 yr old only)	78.3 ± 19.6	59.4 ± 19.8; $p \leq 0.001$[c]		58.4 ± 26.9; $p = 0.002$[c]; $p = 0.886$[d]	59.3 ± 22.2; $p \leq 0.001$[c]; $p = 0.983$[d]	64.5 ± 23.1; $p = 0.005$[c]; $p = 0.448$[d]	64.2 ± 23.8; $p = 0.001$[c]; $p = 0.275$[d]
Cognitive function (< 2 yr old only)		76.7 ± 20.5	57.8 ± 34.5; $p = 0.085$[d]	64.7 ± 29.7; $p = 0.120$[d]	74.1 ± 26.2; $p = 0.775$[d]	77.8 ± 24.3; $p = 0.863$[d]	69.7 ± 25.4; $p = 0.305$[d]

[a]Chronic comorbid condition assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission.

[b]Reference group obtained in Varni et al (21).

[c]One-sample *t* test comparing time point to reference value.

[d]Paired *t* test comparing time point to baseline value.

Data are summarized as mean ± SD.

Multivariable models of physical HRQL at months 3 and 12 are shown in **Table 4**. Longer hospital stay was independently associated with lower month 3 physical HRQL score. Higher baseline physical HRQL and age less than 2 years were independently associated with higher month 3 physical HRQL score. Abnormal neurologic examination findings and neurologic injury suspected by provider were independently associated with lower month 12 physical HRQL score. Higher baseline physical HRQL and age less than 2 years were independently associated with higher month 12 physical HRQL score.

Multivariable models of psychosocial HRQL at months 3 and 12 are shown in **Table 5**. Longer hospital stay was independently associated with lower month 3 psychosocial HRQL score. Higher baseline psychosocial HRQL and age less than 2 years were independently associated with higher month 3 psychosocial HRQL score. Treatment for increased intracranial pressure and medical device use at month 1 were independently associated with lower month 12 psychosocial HRQL score. Higher baseline psychosocial HRQL was independently associated with higher month 12 psychosocial HRQL score.

DISCUSSION

HRQL is a multidimensional construct that reflects a person's subjective evaluation of their physical, mental, emotional, and social well-being (3, 4). In the case of young children or the critically ill, HRQL is often assessed by proxy-report from a family caregiver. Parents and health professionals have identified HRQL as the most important outcome for PICU survivors (32). Our findings demonstrate that the physical and psychosocial domains of HRQL are substantially reduced among children surviving community-acquired septic shock during the first year following their hospitalization compared with reference norms. By month 12 following their hospitalization, children in our study were on average 1–3 times the MCID lower than reference norms for physical and psychosocial HRQL.

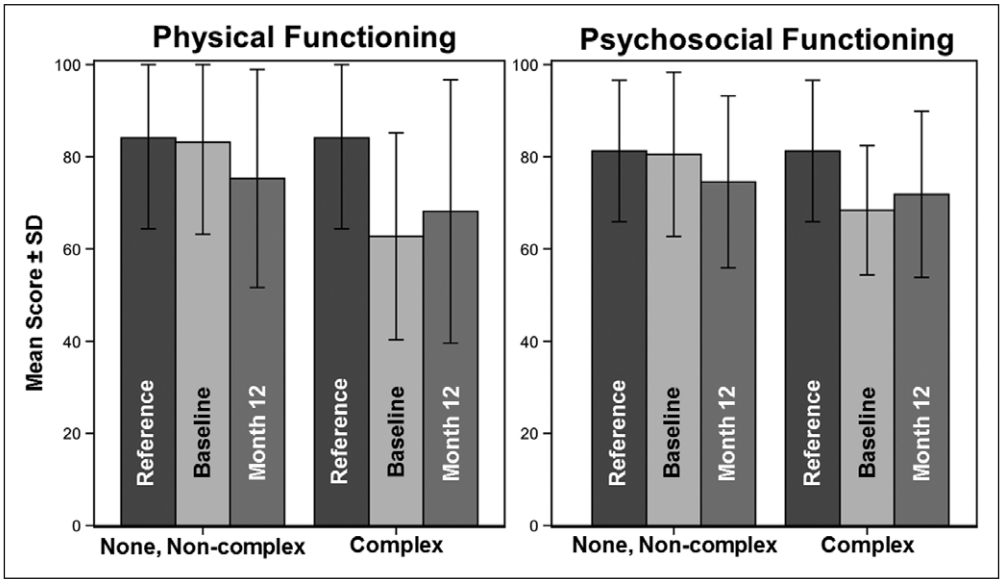

Figure 1. Pediatric Quality of Life Inventory Physical and Psychosocial Health Summary Scores at baseline and month 12 by chronic comorbid condition versus reference norms. Reference group obtained in Varni et al (21). Chronic comorbid condition assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission (30).

Our findings suggest that the trajectories of HRQL domains during the first year after community-acquired septic shock differ between children with and without complex chronic comorbid conditions. As expected, children without complex chronic comorbid conditions had physical and psychosocial HRQL scores at baseline that were similar to reference norms. Scores declined by day 7 and gradually improved thereafter with most improvement occurring by month 3. However, by month 12, physical and psychosocial HRQL scores were still below baseline suggesting that reduced HRQL was long-lasting for these children and related to the sepsis event. SDs of month 12 HRQL domain scores were wide suggesting that some children recovered to baseline, although many did not.

Children with complex chronic comorbid conditions had physical and psychosocial HRQL scores at baseline that were below reference norms. Scores declined further by day 7 and gradually recovered to baseline by month 1–3. Children with complex chronic comorbid conditions may have lower HRQL than reference norms at baseline because of their chronic illness and associated functional limitations, frequent hospitalizations, and school absences (21). Recovery to baseline may reflect improvement or stabilization of their underlying chronic condition in spite of the sepsis event, or response shift on the part of the caregiver providing the proxy report (5, 33). Response shift may occur if a caregiver's internal frame of reference for HRQL changes after confronting a life-threatening event such as septic shock in their child. It is also possible that measurement scales have reduced ability to detect differences in HRQL at the lower end of the HRQL spectrum. Similar to children without complex chronic comorbid conditions, SDs of month 12 HRQL domain scores were wide.

On multivariable analysis, age was independently associated with physical and psychosocial HRQL scores following septic shock. Children less than 2 years old had higher physical HRQL at months 3 and 12, and higher psychosocial HRQL at month 3 compared with older children. Caregivers may not recognize physical and cognitive deficits in young children that contribute to reduced HRQL until the children are older and fail to develop (34).

Longer hospital stay was independently associated with reduced physical HRQL scores at month 3 consistent with other reports (8, 35, 36). Abnormal neurologic examination findings and neurologic injury suspected by provider were independently associated with reduced physical HRQL at month 12. Prior research has shown that neurodevelopmental disabilities are an important predictor of poor HRQL following intensive care (37, 38). Reliance on a medical device at month 1 following PICU admission was independently associated with reduced psychosocial HRQL score at month 12. For children who were still hospitalized at month 1, use of a medical device (e.g., central venous catheter) may represent more prolonged and severe illness. For children who have been discharged, use of medical device at home (e.g., wheel chair) may interfere with family, school, or social activities. In either case, reliance on a medical device appears to contribute to lower psychosocial HRQL. Baseline HRQL was also an independent predictor of later HRQL.

Several clinical variables often associated with poor outcomes such as maximum VIS, seizures, new anoxic-ischemic brain injury on imaging, ECLS, RRT, and cardiac arrest were not associated with reduced physical of psychosocial HRQL in our study. This may be related to the association of these variables with mortality (18, 19). Only children who survived their PICU stay were included in this analysis, as only survivors had potential for follow-up HRQL assessments.

Strengths of our study include the multicenter, prospective, longitudinal design, and use of the PedsQL Scales which are reliable and valid over a wide age range. Additional strengths include the assessment of chronic comorbid conditions and baseline HRQL which allowed us to better elucidate the contribution of septic shock to HRQL at later time points. Limitations include the use of proxy-report HRQL measurements (39). A caregiver's report of their child's HRQL may differ from the child's self-report; however, caregiver report was necessary to collect baseline data during the early phase of septic shock, and over time in young children. The large number of children lost to follow-up is a limitation. Children with missing HRQL data were less healthy than those whose caregivers participated in

TABLE 4. Multivariable Model for Month 3 and Month 12 Physical Health Summary Scores

	Month 3 Physical Domain		Month 12 Physical Domain	
Clinical Characteristic	**Effect (95% CI)**	***p***	**Effect (95% CI)**	***p***
Age		< 0.001		0.015
0–12 mo	11.37 (–0.48 to 23.21)		4.58 (–7.18 to 16.34)	
13–24 mo	19.59 (7.28–31.90)		21.07 (8.30–33.85)	
2–4 yr	–2.32 (–13.37 to 8.73)		–1.01 (–14.88 to 12.87)	
5–7 yr	7.21 (–5.35 to 19.78)		–6.75 (–21.70 to 8.20)	
8–12 yr	–14.15 (–27.47 to –0.84)		4.78 (–7.46 to 17.02)	
13–17 yr	Reference		Reference	
Chronic comorbid conditions[a,b]		0.971		0.967
Complex	0.16 (–8.12 to 8.43)		0.19 (–8.91 to 9.29)	
None/noncomplex	Reference		Reference	
Hospital length of stay, d	–0.27 (–0.38 to –0.16)	< 0.001		
Abnormal neurologic examination finding			–11.20 (–21.22 to –1.19)	0.029
Neurologic injury suspected by care provider			–12.70 (–24.87 to –0.53)	0.041
Physical Health Summary Score at baseline[b]	0.20 (0.02–0.38)	0.026	0.23 (0.01–0.44)	0.037

[a]Assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission.

[b]Chronic comorbid conditions and baseline Physical Summary Score and are forced predictors.

TABLE 5. Multivariable Model for Month 3 and Month 12 Psychosocial Health Summary Scores

	3 mo Psychosocial Domain		12 mo Psychosocial Domain	
Clinical Characteristic	**Effect (95% CI)**	***p***	**Effect (95% CI)**	***p***
Age		0.011		
0–12 mo	2.52 (–6.67 to 11.72)			
13–24 mo	5.85 (–3.80 to 15.51)			
2–4 yr	–7.68 (–16.90 to 1.54)			
5–7 yr	5.20 (–3.77 to 14.18)			
8–12 yr	–8.90 (–18.10 to 0.30)			
13–17 yr	Reference			
Chronic comorbid conditions[a,b]		0.245		0.722
Complex	3.68 (–2.51 to 9.86)		1.25 (–5.68 to 8.17)	
None/noncomplex	Reference		Reference	
Treatment for increased intracranial pressure			–14.28 (–28.05 to –0.52)	0.042
Hospital length of stay, d	–0.09 (–0.18 to –0.01)	0.038		
Medical device use at month 1			–7.76 (–14.26 to –1.26)	0.019
Psychosocial Health Summary Score at baseline[b]	0.23 (0.06–0.40)	0.009	0.29 (0.12–0.47)	0.001

[a]Assessed according to the Pediatric Medical Complexity Algorithm and determined using *International Classification of Diseases*, 9th and 10th Edition diagnosis codes up to 3 yr prior the ICU sepsis admission.

[b]Chronic comorbid conditions and baseline Psychosocial Summary Score and are forced predictors.

follow-up (18, 19); however, imputation was used to avoid potential bias from loss of less healthy children. Only 28% of children had complex chronic comorbid conditions which is likely due to the exclusion of children with severe developmental disability. Although abnormal neurologic examination findings during the PICU course were associated with reduced month 12 physical HRQL, the potential etiologies of the abnormal neurologic findings were not recorded and their specific timing was not considered in the analyses. Also, the specific factors that led clinicians to suspect neurologic injury in an individual child were not recorded. Because LAPSE was an observational study, not all children underwent diagnostic tests such as electroencephalogram or brain imaging potentially biasing our results. Many variables potentially affecting children's HRQL were not evaluated including social and environmental characteristics such as socioeconomics, parental education, family functioning, and access, utilization, and types of rehabilitation services. Our subset of LAPSE participants who were without severe developmental disability at baseline had a hospital mortality rate of 9.7% and estimated risk-adjusted hospital mortality rate of 12.5% (26, 40) and may not be generalizable to other sepsis cohorts.

CONCLUSIONS

Physical and psychosocial HRQL are reduced among children during the first year following community-acquired septic shock compared with reference norms. Children with complex chronic comorbid conditions appear to recover to their baseline HRQL during this timeframe, whereas children without such conditions may not. Most recovery occurs by month 3 suggesting interventions should occur early. Risk factors for poor HRQL included neurologic complications during the hospitalization, and dependence on a medical device 1 month postadmission.

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