Critical Illness Factors Associated With Long-Term Mortality and Health-Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock*

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Objectives: A companion article reports the trajectory of long-term mortality and significant health-related quality of life disability among children encountering septic shock. In this article, the investigators examine critical illness factors associated with these adverse outcomes.

Design: Prospective, cohort-outcome study, conducted 2013–2017.

Setting: Twelve United States academic PICUs.

Patients: Critically ill children, 1 month to 18 years, with community-acquired septic shock requiring vasoactive-inotropic support.

Interventions: Illness severity, organ dysfunction, and resource utilization data were collected during PICU admission. Change from baseline health-related quality of life at the month 3 follow-up was assessed by parent proxy-report employing the Pediatric Quality of Life Inventory or the Stein-Jessop Functional Status Scale.

Measurements and Main Results: In univariable modeling, critical illness variables associated with death and/or persistent, serious health-related quality of life deterioration were candidates for multivariable modeling using Bayesian information criterion. The most clinically relevant multivariable models were selected among models with near-optimal statistical fit. Three months following septic shock, 346 of 389 subjects (88.9%) were alive and 43 of 389 had died (11.1%); 203 of 389 (52.2%) had completed paired health-related quality of life surveys. Pediatric Risk of Mortality, cumulative Pediatric Logistic Organ Dysfunction scores, PICU and hospital durations of stay, maximum and cumulative vasoactive-inotropic scores, duration of mechanical ventilation, need for renal replacement therapy, extracorporeal life support or cardiopulmonary resuscitation, and appearance of pathologic neurologic signs were associated with adverse outcomes in univariable models. In multivariable regression analysis (odds ratio [95% CI]), summation of daily Pediatric Logistic Organ Dysfunction scores, 1.01/per point (1.01–1.02), $p < 0.001$; highest vasoactive-inotropic score, 1.02/per point (1.00–1.04), $p = 0.003$; and any acute pathologic neurologic sign/event, 5.04 (2.15–12.01), $p < 0.001$ were independently associated with death or persistent, serious deterioration of health-related quality of life at month 3.

Conclusions and Relevance: Biologically plausible factors related to sepsis-associated critical illness organ dysfunction and its treatment were associated with poor outcomes at month 3 follow-up among children encountering septic shock. (*Crit Care Med* 2020; 48:319–328)

Key Words: children; critical illness variables; health-related quality of life morbidity; mortality; organ dysfunction; septic shock

In resource-rich settings, in-hospital mortality associated with pediatric sepsis is less than 10% (1–3). However, a companion article reports that children surviving sepsis remain at significant, enduring risk for mortality as well as significant health-related quality of life (HRQL) morbidity at least 1 year following hospitalization for septic shock (4). Accordingly, mortality alone no longer adequately describes the overall impact of sepsis on children (5). Contemporary sepsis definitions stress the importance of life-threatening organ dysfunction (6). Furthermore, critical care provided for children with septic shock typically focuses on avoiding, treating, and hastening resolution of organ dysfunction. In a recent survey investigation, both families of critically ill children and critical care providers chose, after survival, HRQL/functional status, and duration of organ dysfunction, as the most personally important outcome measures for a hypothetical interventional trial enrolling critically ill children (7). Multiple publications have reported the relationship between individual and composite organ dysfunctions and risk for mortality among critically ill children including those with sepsis (8–17).

Recently the Surviving Sepsis Campaign identified, "What are the predictors of sepsis long-term morbidity and mortality?", as one of the top six clinical sepsis research priorities (18). Accordingly, to maintain consistency with the companion manuscript of the Life After Pediatric Sepsis Evaluation (LAPSE) prospective, cohort-outcome investigation (R01HD073362) was conducted to determine the association between risk of long-term mortality and persistent, serious HRQL disability with critical illness variables related to treatment of septic shock. LAPSE investigators hypothesized that intensity and duration of critical care for septic shock organ dysfunction would be associated with risk of death or persistent, serious HRQL morbidity 3 months following hospitalization for sepsis.

MATERIALS AND METHODS

Performance Sites and Study Participants

Details of LAPSE performance sites, study participants including study inclusion and exclusion criteria, and serial assessment of patient functional status and HRQL are provided in the LAPSE companion article (4).

Critical Illness Factors Potentially Associated With Poor Outcomes

Critical illness exposures examined for their association with long-term mortality and HRQL morbidity following pediatric

septic shock included: chronic comorbid condition classification (Pediatric Medical Complexity Algorithm) (19), immunodeficiency status, initial illness severity per Pediatric Risk of Mortality (PRISM), version IV (20), composite organ dysfunction per the Pediatric Logistic Organ Dysfunction (PELOD) score, version 2 (21), mechanical ventilation (MV) duration (invasive or noninvasive positive pressure support, excluding high flow nasal cannula oxygen) (22), vasoactive-inotropic support per vasoactive-inotropic score (VIS) (23), receipt of packed erythrocyte transfusion (24), renal replacement therapy (RRT), extracorporeal life support (ECLS), cardiopulmonary resuscitation (CPR), magnitude of acute deterioration of Pediatric Cerebral Performance Category (25), Pediatric Overall Performance Category (POPC) (25), and Functional Status Scale (FSS) (26) comparing baseline and day 7, PICU and hospital durations of stay, and any acute, pathologic neurologic sign or event (anisocoria, pathologic breathing pattern, stereotypic or flaccid posture, new seizure activity documented clinically or by electroencephalography, new anoxic-ischemic-reperfusion injury noted on brain imaging, treatment for increased intracranial pressure, and autonomic storming).

Primary Outcome Measure

A secondary aim of the LAPSE investigation was to ascertain the feasibility of a novel primary outcome measure for future pediatric sepsis interventional trials. LAPSE investigators focused on the patient-centered, clinically meaningful, composite outcome of death or persistent, serious deterioration of HRQL as compared to baseline (PSD-HRQL) (27). A priori, PSD-HRQL, was defined as HRQL persisting greater than 25% below baseline HRQL (before the sepsis event) as assessed 3 months following PICU admission for treatment of septic shock. Percent deterioration, instead of absolute change (number of points) from baseline HRQL was chosen because children encountering sepsis exhibit a spectrum of baseline HRQL (4).

Participating families completed serial parent-proxy assessments of their child's HRQL utilizing the Pediatric Quality of Life Inventory (PedsQL) (28, 29) or the Stein-Jessop Functional Status Scale (FSII-R) (30), as some families of children with severe developmental disabilities reported that the FSII-R instrument better quantified their child's status. These tools have been compared side-by-side (31). Both are reliable, valid instruments with internal consistency. PedsQL addresses the dimensions of physical, emotional, social and school functioning, while FSII-R addresses eating, sleeping, play behavior, and emotional. Scores from either instrument correlate highly with concurrently measured POPC scores (32, 33). Although the name, FSII-R, suggests this instrument is primarily a functional status measure, in fact, it is generally regarded as a validated measure of general health status for children of all ages (15). Both instruments employ a 0–100 point scale.

Persistent 25% deterioration below baseline can be envisioned for the PedsQL instrument with an established minimal clinically important difference (MCID) of 4.5 points (34): For generally healthy children (about 50% of LAPSE patients) with normative PedsQL scores of 82.5 ± 14.9 (mean ± SD), a 25% decrease from baseline would be 20.6 points or 1.4 SD or 4.6 MCID. For children with chronic comorbid conditions (about 50% of LAPSE patients) with normative PedsQL scores of 71.8 ± 18.4, a 25% decrease from baseline would be 18.0 points or 1.0 SD or 4.0 MCID. For the FSII-R instrument, MCID has not been reported. However, for generally healthy children with normative FSII-R scores of 96.1 ± 8.2, a 25% decrease from baseline would be 24.0 points or 2.9 SD. For children with chronic comorbid conditions and normative FSII-R scores of 86.8 ± 15.7, a 25% decrease from baseline would be 21.7 points or 1.4 SD. For each scenario, a persistent 25% deterioration below baseline HRQL would be significant and serious.

Again with reference to potential future sepsis interventional trials, this report focuses on month 3 but also provides information related to month 1 follow-up. Although the latter has been a traditional time point for (mortality) outcome assessment in clinical trials, the former represents a more realistic time for long-term assessment of the effect of a septic shock insult, without undue influence of postdischarge external factors that might also impact long-term mortality or HRQL disability. This report provides associations of critical illness variables with the outcomes of mortality, PSD-HRQL and the composite of these two measures as assessed at month 3.

Data Analysis and Reporting

Descriptive statistics are presented using counts and percentages for categorical variables, and the median and interquartile range for continuous variables. Differences in long-term outcomes were measured using standard statistical tests such as the Wilcoxon rank-sum test, Fisher exact test, the Cochran-Armitage test for trend, and the Spearman correlation coefficient with 95% CIs.

Univariable and multivariable logistic regression modeling were used to examine associations with clinical risk factors and adverse long-term outcomes. Variables assessed in greater than 90% of the cohort and at least marginally associated with outcome ($p < 0.20$) were chosen as candidate predictors in multivariable modeling (eTables 4–6, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). Multivariable models using every possible combination of candidate predictors were systematically constructed for each of the three outcomes as assessed at month 3. The Bayesian information criteria was used for model comparisons. Multivariable models of near-optimal statistical fit were presented to LAPSE investigators (eTables 7–9, Supplemental Digital Content 1, http://links.lww.com/CCM/F146), from which one model for each outcome was chosen based on clinical relevance for emphasis in text discussions (Table 3). All analyses were performed using SAS 9.4 (SAS Institute; Cary, NC). *p* values are based on a two-sided alternative with values of less than 0.05 considered significant. Results are reported according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Guidelines for cohort studies (35).

RESULTS

A detailed flow diagram for the LAPSE cohort is presented in **Figure 1**. At month 1 following PICU admission for the septic

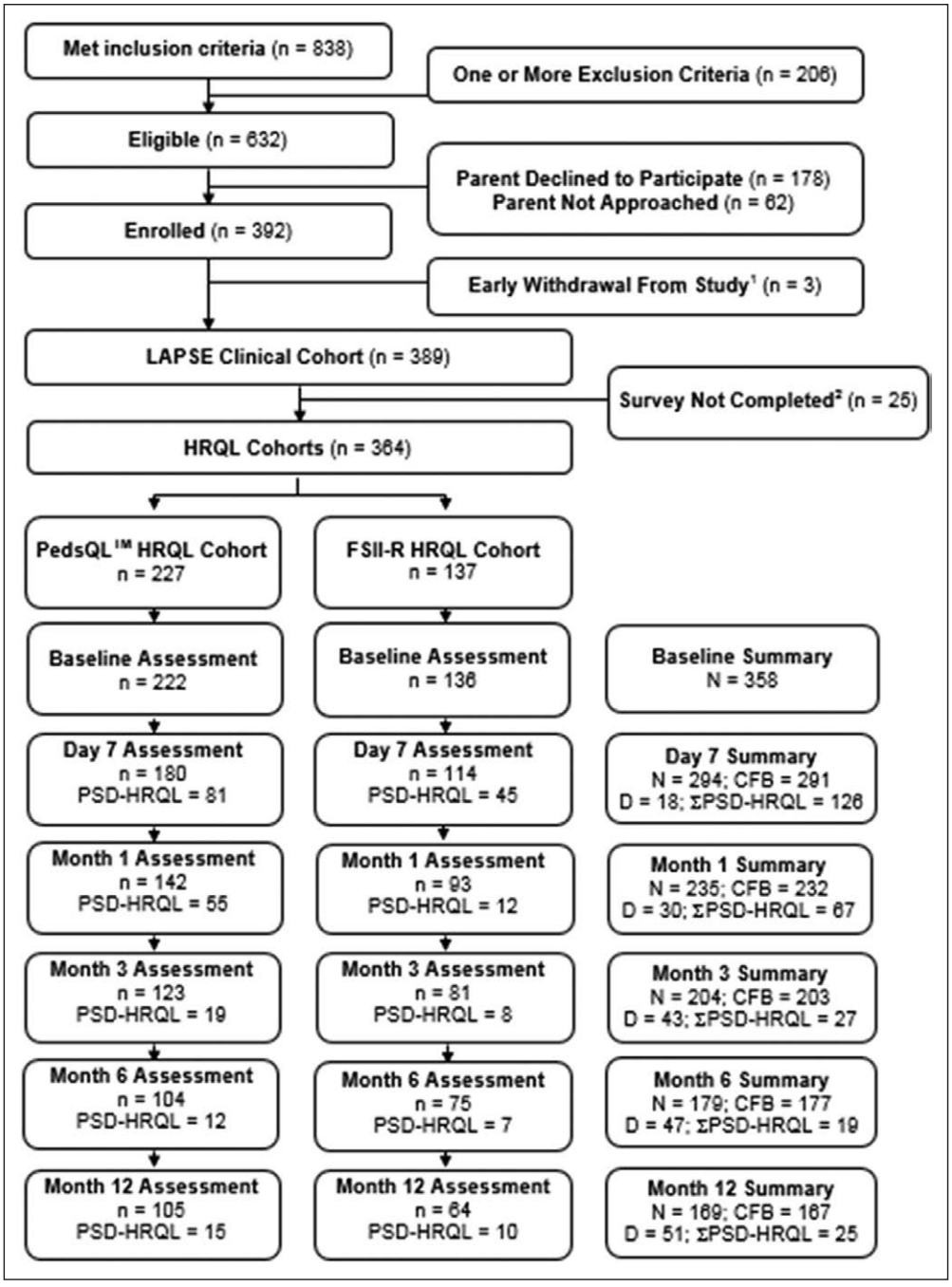

Figure 1. Detailed flow diagram for the cohort. Seven of the 35 patients who died in the hospital did so after the day 28 study time point. Two subjects were discharged from the hospital alive before day 28, but died later during the day 28 time point interval; ΣPSD-HRQL, total patients with persistent, severe deterioration of HRQL below baseline from PedsQL or FSII-R cohorts. [1]No clinical data was available due to early family-initiated withdrawal from the study or refusal to complete HRQL surveys. [2]Families never initiated a survey, even the baseline survey, or surveys were inadequately completed and could not be used for analysis. CFB = change from baseline, D = cumulative deaths among the entire LAPSE clinical cohort (*n* = 389), FSII-R = Stein-Jessop Functional Status Scale, HRQL = health-related quality of life, LAPSE = Life After Pediatric Sepsis Evaluation, *n* = total number of patients with available, adequate, change from baseline survey data at a particular time point, PedsQL = Pediatric Quality of Life Inventory, PSD-HRQL = persistent, severe deterioration of HRQL below baseline, specifically, HRQL scores (PedsQL or FSII-R) persisting greater than 25% below the baseline HRQL assessment at follow-up.

shock event, 262 of 389 (67%) of the LAPSE participants could be assessed for outcomes. Among these, 30 of 389 had died (8%), 232 were alive with complete change-from-baseline HRQL information, and 67 of 232 had PSD-HRQL (29%); accordingly death or PSD-HRQL occurred in 97 of 262 (37%) evaluable patients at month 1. At month 3, 246 of 389 (63%) of the LAPSE participants could be assessed for outcomes. Among these, 43 of 389 had died (11%), 203 were alive with complete change-from-baseline HRQL information, and 27 of 203 had PSD-HRQL (13%); accordingly death or PSD-HRQL occurred in 70 of 246 (28%) evaluable patients at month 3. In the interval between month 1 and month 3, 13 additional children died, but among evaluable patients, the absolute percent with PSD-HRQL decreased by 16%.

eTables 1–3 (Supplemental Digital Content 1, http://links.lww.com/CCM/F146) summarize month 3 participant demographics at PICU admission by HRQL survey status (completed or not completed) and vital status; hospital variables reflecting illness severity, organ dysfunction and resource utilization by HRQL survey completion status and vital status; and PICU admission demographics by outcomes respectively. Families of previously healthy children (without chronic conditions) were less likely to have completed the month 3 survey (eTable 1, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). Although PRISM was not different between patients with and without a complete month 3 survey, higher summation of PELOD and VIS, greater duration of MV, increased need for RRT, ECLS, and CPR, and more frequent occurrence of pathologic neurologic signs/events, suggested greater illness severity among patients without a month 3 survey (eTable 2, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). Surviving subjects with PSD-HRQL tended to be older and previously healthy (eTable 3, Supplemental Digital Content 1, http://links.lww.com/CCM/F146).

TABLE 1. Critical Illness-Related Variables and Outcomes at Month 3

Patient Characteristic	PSD-HRQL			Mortality or PSD-HRQL		
	Yes (*n* = 27)	No (*n* = 176)	*p*	Yes (*n* = 70)	No (*n* = 176)	*p*
Admission data						
Pediatric Risk of Mortality, version IV[a]	11.0 (6.0–19.0)	11.0 (6.0–16.0)	0.648[b]	12.0 (7.0–21.0)	11.0 (6.0–16.0)	0.029[b]
PELOD, day 0	9.0 (7.0–14.0)	7.0 (5.0–10.0)	0.009[b]	9.0 (7.0–14.0)	7.0 (5.0–10.0)	< 0.001[b]
Immunocompromised	3 (11.1%)	29 (16.5%)	0.583[c]	13 (18.6%)	29 (16.5%)	0.709[c]
PELOD, first day[d]	9.0 (6.0–14.0)	8.0 (6.0–10.0)	0.104[b]	11.0 (7.0–14.0)	8.0 (6.0–10.0)	< 0.001[b]
Hospital summary						
Functional Status Scale CFB at day 7 (> 0 implies worsening)[e]	7.5 (4.0–14.0)	3.0 (0.0–8.0)	< 0.001[b]	10.5 (4.0–16.0)	3.0 (0.0–8.0)	< 0.001[b]
Pediatric Cerebral Performance Category CFB at day 7 (> 0 implies worsening)[e]	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.052[b]	2.0 (0.0–3.0)	0.0 (0.0–1.0)	< 0.001[b]
Pediatric Overall Performance Category CFB at day 7 (> 0 implies worsening)[e]	1.0 (0.0–3.0)	0.0 (0.0–1.0)	0.003[b]	2.0 (1.0–3.0)	0.0 (0.0–1.0)	< 0.001[b]
Sum of PELOD in PICU	72.0 (52.0–178.0)	45.5 (27.0–74.5)	< 0.001[b]	91.5 (57.0–178.0)	45.5 (27.0–74.5)	< 0.001[b]
Packed RBC first transfer (relative to day 0)	1.0 (0.0–5.0)	1.0 (0.0–2.5)	0.900[b]	1.0 (0.0–2.0)	1.0 (0.0–2.5)	0.260[b]
Hospital length of stay (d)	28.0 (19.8–57.9)	15.0 (9.2–23.8)	< 0.001[b]	21.3 (9.5–47.9)	15.0 (9.2–23.8)	0.015[b]
PICU length of stay (d)	14.5 (8.7–25.4)	8.1 (4.9–13.8)	< 0.001[b]	12.7 (7.9–24.2)	8.1 (4.9–13.8)	< 0.001[b]
Highest VIS in PICU	13.0 (8.0–25.0)	10.0 (5.0–20.0)	0.116[b]	18.8 (8.0–30.0)	10.0 (5.0–20.0)	< 0.001[b]
Highest VIS in PICU			0.194[f]			0.002[f]
< 5	2 (7.4%)	29 (16.5%)		4 (5.7%)	29 (16.5%)	
5–30	21 (77.8%)	129 (73.3%)		50 (71.4%)	129 (73.3%)	
> 30	4 (14.8%)	18 (10.2%)		16 (22.9%)	18 (10.2%)	
Sum of VIS in PICU	43.0 (27.0–130.0)	25.0 (8.0–57.0)	0.005[b]	85.5 (25.0–226.5)	25.0 (8.0–57.0)	< 0.001[b]
Mechanical ventilator days	10.0 (7.0–24.0)	7.0 (4.0–11.5)	0.005[b]	10.5 (6.0–21.0)	7.0 (4.0–11.5)	< 0.001[b]
Renal replacement therapy in PICU	4 (14.8%)	10 (5.7%)	0.097[c]	18 (25.7%)	10 (5.7%)	< 0.001[c]
Extracorporeal life support in PICU	2 (7.4%)	5 (2.8%)	0.235[c]	14 (20.0%)	5 (2.8%)	< 0.001[c]
Anisocoria or absence of pupillary response	5 (18.5%)	16 (9.1%)	0.168[c]	29 (41.4%)	16 (9.1%)	< 0.001[c]
Pathologic breathing pattern	3 (11.1%)	16 (9.1%)	0.724[c]	17 (24.3%)	16 (9.1%)	0.003[c]
Stereotypic posturing or flaccid posture	3 (11.1%)	17 (9.7%)	0.735[c]	15 (21.4%)	17 (9.7%)	0.020[c]

(*Continued*)

TABLE 1. (*Continued*). Critical Illness-Related Variables and Outcomes at Month 3

	PSD-HRQL			Mortality or PSD-HRQL		
Patient Characteristic	Yes ($n = 27$)	No ($n = 176$)	p	Yes ($n = 70$)	No ($n = 176$)	p
Seizure activity and or abnormal electroencephalogram	4 (14.8%)	37 (21.0%)	0.609[c]	23 (32.9%)	37 (21.0%)	0.070[c]
New anoxic-ischemic injury on CT/MRI imaging	3 (11.1%)	7 (4.0%)	0.133[c]	14 (20.0%)	7 (4.0%)	< 0.001[c]
Treatment for increased intracranial pressure	2 (7.4%)	2 (1.1%)	0.086[c]	7 (10.0%)	2 (1.1%)	0.003[c]
Neurologic injury suspected by care provider	6 (22.2%)	15 (8.5%)	0.041[c]	27 (38.6%)	15 (8.5%)	< 0.001[c]
Autonomic storming	2 (7.4%)	1 (0.6%)	0.047[c]	5 (7.1%)	1 (0.6%)	0.008[c]
Cardiopulmonary arrest or chest compressions	2 (7.4%)	9 (5.1%)	0.643[c]	21 (30.0%)	9 (5.1%)	< 0.001[c]
Neurologic insult(s)	13 (48.1%)	66 (37.5%)	0.298[c]	48 (68.6%)	66 (37.5%)	< 0.001[c]

CFB = change from baseline, PELOD-2 = Pediatric Logistic Organ Dysfunction score, version 2, PSD-HRQL = persistent, serious deterioration of health-related quality of life > 25% below baseline at month 3, VIS = vasoactive-inotropic score.

[a]Collected during a modified 6-hr period of 2 hr prior to PICU admission through 4 hr post PICU admission.

[b]Wilcoxon rank-sum test.

[c]Fisher exact test.

[d]First day is defined as day of admission if admission time is before 12:00 PM or following day if admission is after 12:00 PM.

[e]CFB at day 7 for Pediatric Cerebral Performance Category, Pediatric Overall Performance Category, and Functional Status Scale reflect days post ICU admission or hospital discharge whichever occured first.

[f]Cochran-Armitage test for trend.

Values are expressed as median (interquartile range) or *n* (%).

Table 1 summarizes critical illness-related variables reflecting illness severity, organ dysfunction, and resource utilization by outcomes at month 3. Magnitude of deterioration of functional status during the first 7 days of PICU admission, intensity and duration of individual and composite organ dysfunctions, durations of stay in the PICU and hospital, and pathologic neurologic signs/events were all associated with mortality or PSD-HRQL. **Table 2** summarizes Spearman correlations of change in HRQL from baseline to month 3, for both PedsQL and FSII-R HRQL measures, with various critical illness variables.

eTables 4–6 (Supplemental Digital Content 1, http://links.lww.com/CCM/F146) summarize univariable logistic regression modeling for death, PSD-HRQL, and death or PSD-HRQL as outcomes at month 3. Initial illness severity (PRISM), first day and cumulative PELOD scores, maximal and cumulative VIS, cumulative MV days, need for RRT, ECLS, and CPR, acute deterioration of functional status (comparing baseline and day 7), and new pathologic neurologic signs/events were most strongly associated with risk for mortality (eTable 4, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). First day and cumulative PELOD scores, maximal and cumulative VIS, cumulative MV days, and acute deterioration of functional status as well as patient age and duration of PICU and hospital stays were most strongly associated with PSD-HRQL at month 3 (eTable 5, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). Initial illness severity (PRISM), first day and cumulative PELOD scores, maximal and cumulative VIS, cumulative MV days, need for RRT, ECLS, and CPR, acute deterioration of functional status, new pathologic neurologic signs/events, and PICU duration of stay were most strongly associated with risk for mortality or PSD-HRQL at month 3 (eTable 6, Supplemental Digital Content 1, http://links.lww.com/CCM/F146). In general, illness severity measures were negatively correlated with the absolute measures of each individual HRQL assessment. Change in FSS or POPC from baseline to day 7 or to day 28 were negatively correlated with HRQL measures at month 3, and the day 28 correlations were slightly stronger.

Statistically equivalent multivariable models, with mortality, PSD-HRQL, and mortality or PSD-HRQL at month 3, as the outcome measure, are provided in **eTables 7–9** (Supplemental Digital Content 1, http://links.lww.com/CCM/F146). These models highlight the association of single and composite organ dysfunctions during septic shock critical illness with long-term adverse outcomes. **Table 3** summarizes clinically relevant multivariable models for mortality, PSD-HRQL, and mortality or PSD-HRQL at month 3 following PICU admission for septic shock. Risk of mortality at month 3 was independently associated with cumulative VIS scores and new pathologic pupillary activity. It is estimated that for every 1-point increase in the sum of VIS scores, the odds of mortality increases between 0 and 1 percent, and a new pathologic pupillary sign is associated with 5.3-fold increased risk of death. Among children surviving septic shock at month 3, sum of daily PICU PELOD scores and age were independently associated with increased odds of PSD-HRQL. It is estimated that for every 1-point increase in the sum of daily PICU PELOD scores, the odds of a PSD-HRQL outcome increases

TABLE 2. Spearman Correlations of Change in Health-Related Quality of Life With Critical Illness Variables

Severity of Illness Measures	No. of PedsQL	No. of FSII-R	Δ PedsQL Month 3 r_s (95% CI)	Δ FSII-R Month 3 r_s (95% CI)
Pediatric Risk of Mortality score, version IV	122	81	−0.110 (−0.282 to 0.069)	−0.013 (−0.231 to 0.205)
PELOD, day 0	122	81	−0.176 (−0.343 to 0.002)	0.012 (−0.207 to 0.23)
PELOD, first day	122	81	−0.142 (−0.312 to 0.037)	0.009 (−0.210 to 0.227)
Sum of PELOD-2 in PICU	122	81	−0.276 (−0.433 to −0.104)	−0.236 (−0.432 to −0.019)
Packed RBC first transfusion (relative to day 0)	63	32	0.071 (−0.180 to 0.313)	−0.43 (−0.677 to −0.096)
Highest VIS in PICU	122	81	−0.140 (−0.310 to 0.038)	0.013 (−0.206 to 0.231)
Sum of VIS in PICU	122	81	−0.187 (−0.353 to −0.009)	−0.142 (−0.350 to 0.079)
Mechanical ventilator days	122	81	−0.194 (−0.359 to −0.016)	−0.207 (−0.407 to 0.012)
PICU length of stay (d)	122	81	−0.235 (−0.396 to −0.060)	−0.260 (−0.452 to −0.044)
Hospital length of stay (d)	122	81	−0.254 (−0.413 to −0.080)	−0.227 (−0.424 to −0.009)
PCPC CFB at day 28 (> 0 is worsening)	122	81	−0.165 (−0.333 to 0.014)	0.010 (−0.209 to 0.228)
PCPC CFB at day 7 (> 0 is worsening)	122	81	−0.188 (−0.354 to −0.010)	−0.038 (−0.254 to 0.182)
POPC CFB at day 28 (> 0 is worsening)	122	81	−0.284 (−0.440 to −0.112)	−0.165 (−0.370 to 0.055)
POPC CFB at day 7 (> 0 is worsening)	122	81	−0.251 (−0.410 to −0.076)	−0.172 (−0.376 to 0.048)
FSS CFB at day 28 (> 0 is worsening)	122	81	−0.368 (−0.513 to −0.204)	−0.301 (−0.488 to −0.089)
FSS CFB at day 7 (> 0 is worsening)	121	80	−0.259 (−0.418 to −0.085)	−0.272 (−0.464 to −0.055)
PedsQL baseline	122		−0.531 (−0.647 to −0.390)	
PedsQL CFB at day 7	112		0.393 (0.223–0.539)	
PedsQL CFB at day 28	106		0.692 (0.577–0.780)	
FSII-R baseline		81		−0.532 (−0.672 to −0.355)
FSII-R CFB at day 7		69		0.365 (0.140–0.554)
FSII-R CFB at day 28		65		0.563 (0.370–0.709)

CFB = change from baseline, FSII-R = Stein-Jessop Functional Status Scale, FSS = Functional Status Scale, PCPC = Pediatric Cerebral Performance Category, PedsQL = Pediatric Quality of Life Inventory, PELOD-2 = Pediatric Logistic Organ Dysfunction score, version 2, POPC = Pediatric Overall Performance Category, r_s = Spearman correlation, VIS = vasoactive-inotropic score.

between 1 and 2 percent, while every additional year increases the risk by 4–23%. Sum of daily PELOD scores while in the PICU, maximum VIS, and new pathologic neurologic signs/events were independently associated with mortality or PSD-HRQL. It is estimated that for every 1-point increase in the sum of daily PICU PELOD scores, the odds of a poor outcome increases between 1 and 2%; that for every 1-point increase in the highest VIS score, the odds of a poor outcome increases between 0% and 4%; and that a new pathologic neurologic sign/event during critical care for septic shock increases the odds of poor outcome five-fold.

DISCUSSION

Univariable and multivariable analyses verify that magnitude and duration of organ dysfunction and need for organ failure rescue (RRT, ECLS, CPR) during treatment of pediatric septic shock highlight risk factors consistently associated with death and/or PSD-HRQL 3 months following admission to the PICU for a septic shock event. Magnitude of acute functional status deterioration during the first week of sepsis; duration of PICU stay, reflecting the interval of support for dysfunctional organs; and duration of hospitalization, reflecting ongoing acute convalescence following critical illness, were also associated with adverse outcomes. Among children surviving septic shock older age was also associated with risk for PSD-HRQL.

As previously noted, multiple investigations have ascertained a dose-response association of number of dysfunctional organs with risk for death among children with sepsis (8–17). Similarly, in an adult prospective, multicenter, observational, cohort study, a high Sequential Organ Failure Assessment score was significantly associated with increased risk of death 3 months following admission for septic shock (36). Dose-response hazard ratios for death from pediatric systemic

TABLE 3. Selected Multivariable Models for Mortality, PSD-HRQL, and Mortality or PSD-HRQL at Month 3

Variable	Mortality OR (95% CI) (*p*)	PSD-HRQL OR (95% CI) (*p*)	Mortality or PSD-HRQL OR (95% CI) (*p*)
	Δ BIC = 0.6	Δ BIC = 0.0	Δ BIC = 0.0
	Modeling based on 341 complete records	Modeling based on 201 complete records	Modeling based on 229 complete records
∑ Daily PICU Pediatric Logistic Organ Dysfunction, version 2 scores	–	1.01 (1.01–1.02) (< 0.001)	1.01 (1.01–1.02) (< 0.001)
Highest VIS in PICU	–	–	1.02 (1.00–1.04) (0.003)
Pathologic neurologic signs/events			
No	–	–	Reference
Yes	–	–	5.04 (2.15–12.01) (< 0.001)
Age (yr)	–	1.13 (1.04–1.23) (0.003)	–
Sum of VIS in PICU	1.01 (1.00–1.01) (< 0.001)	–	–
Anisocoria or absence of pupillary response			
No	Reference	–	–
Yes	5.26 (2.06–13.20) (< 0.001)	–	–

BIC = Bayesian information criterion, OR = odds ratio, PSD-HRQL = persistent, severe health-related quality of life deterioration, defined as > 25% below baseline health-related quality of life, as assessed at month 3, VIS = vasoactive-inotropic score.
Dashes refer to the fact that a given variable was not utilized in modeling for a given outcome.

inflammatory response syndrome, sepsis, severe sepsis and septic shock in relation to severity of sepsis-associated organ dysfunction were validated utilizing the PELOD (organ dysfunction) score (15). Post hoc analysis of the RESTORE (REsearching severe Sepsis and Organ dysfunction in children: A gLobal perspective) (37) database revealed a strong association between both illness severity (PRISM) and number of organ dysfunctions with poor functional outcome (POPC) at 28 days (38). Similarly in a subinvestigation of the SPROUT (Sepsis Prevalence, Outcomes, and Therapy) international point prevalence study (39), children with a history of new or progressive multiple organ dysfunction syndrome, exhibited a higher mortality, and among survivors, increased frequency of moderate-to-severe disability at hospital discharge (17).

Supporting the association of the magnitude of vasoactive-inotropic support with adverse outcomes, VIS at 48 hours after PICU admission, was independently associated with short-term outcomes including duration of ventilation and PICU stay, as well as the composite outcome of cardiac arrest/need for ECLS/in-hospital mortality, among children with sepsis requiring vasoactive-inotropic support (23). Not surprisingly new pathologic neurologic signs/symptoms identified during critical illness for septic shock have previously been noted to be highly associated with poor outcomes (40). A large retrospective cohort of critically ill children, reported that greater illness severity, longer PICU duration of stay, as well as the rescue interventions of invasive MV, CPR, RRT, and ECLS were associated with acquired global dysfunction and cognitive disability (41).

Other investigations have demonstrated older age as a risk factor for poorer HRQL outcomes compared with population norms among children surviving critical illness, including sepsis (42, 43). This finding may indicate greater resilience among younger children, but might also reflect increasing ability of participant survivors to provide self-report input information to their parents conducting HRQL proxy-reporting. In addition, it is possible that rapidly developing infants and toddlers may demonstrate the impact of septic shock on subsequent HRQL by lack of developmentally expected improvement rather than actual decline (43).

Other investigators have emphasized the importance of chronic, comorbid conditions as a risk factor for impaired HRQL following pediatric critical illness (44–46). Similarly, children with chronic conditions surviving sepsis were reported to be at particularly increased risk for hospital readmission and late mortality (47). However, in the current investigation, utilizing univariable analyses, medical complexity algorithm category was not strongly associated with adverse outcomes. However, it should be stressed that the current investigation employed paired HRQL assessments in relation to baseline status that likely affected this lack of association.

LAPSE is the first investigation to identify specific variables encountered by critically ill children with septic shock treated in the PICU, and risk for 3-month mortality and/or PSD-HRQL. Clearly, a strength of the current study was quantifying participants' baseline HRQL and assessing change from baseline for subsequent measures. As detailed in the companion manuscript (4), the primary liability of this examination of critical care variables associated with adverse outcomes following pediatric septic shock, relates to significant, nonrandom loss of subjects for assessment of HRQL at month 3 follow-up. However, participants without completed surveys exhibited some measures of higher illness severity, and higher illness severity, associated with higher risk for adverse outcomes, was confirmed with imputation of missing data. The current analysis focused on critical illness variables; certainly, factors intrinsic to the individual and environment will also influence long-term risk for mortality and/or HRQL disability following septic shock and represent the subject of additional scrutiny of the data set (48). As presently defined, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (6). LAPSE did not primarily examine a "dysregulated host response," although a subanalysis of selected sepsis host response biomarkers in relation to risk of poor outcome is in progress (49).

Consistent with previous recommendations (27), data from this investigation establishes the biological plausibility and logistical feasibility of the patient-centered, clinically meaningful, composite outcome, death, or PSD-HRQL, at 1 or 3 months following PICU admission for pediatric septic shock. At these timepoints, this adverse outcome measure occurred in 37% and 28% of patients. To assess an intervention with a relative treatment effect of 25%, α 0.05 and power 0.9, would require 568 or 967 patients in each treatment arm, respectively.

CONCLUSIONS

This investigation suggests that the early morbidity of septic shock, reflected as organ dysfunction and the need for PICU supportive care, exemplifies biologically plausible antecedents associated with risk of death and/or PSD-HRQL 3 months following hospitalization for the septic shock event. Although a good save from septic shock requires that a child resolve sepsis-associated organ dysfunction (1), LAPSE establishes that this achievement alone no longer exemplifies complete sepsis treatment. Specifically, intensity and duration of sepsis-associated organ dysfunction portends ongoing risk for long-term mortality and HRQL disability after children are discharged from the PICU and hospital.

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