Myocardial Dysfunction Is Independently Associated With Mortality in Pediatric Septic Shock

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Objectives: Circulatory dysfunction has been associated with mortality in children with septic shock. However, the mortality risk attributable to myocardial dysfunction per se has not been established, and the association between myocardial dysfunction and mortality is confounded by illness severity. The objective was to determine if sepsis-associated myocardial dysfunction defined by low left ventricular ejection fraction or global longitudinal strain is associated with mortality in pediatric septic shock after adjusting for baseline mortality probability.

Design: Retrospective, observational study.

Setting: Single-center, quaternary-care PICU.

Patients: Children less than 18 years old admitted to the PICU from 2003 to 2018 who had an echocardiogram performed within 48 hours of septic shock identification and Pediatric Sepsis Biomarker Risk Model II data available.

Interventions: None.

Measurements and Main Results: All echocardiograms were reread by a cardiologist blinded to patient data for left ventricular ejection fraction and global longitudinal strain. Low left ventricular ejection fraction was defined as less than 45%, and low global longitudinal strain was defined as greater than z score of −2 for body surface area. Multivariable logistic regression separately analyzed the associations of low left ventricular ejection fraction and low global longitudinal strain with mortality, adjusting for Pediatric Sepsis Biomarker Risk Model II mortality risk. A post hoc logistic regression analyzed the association of left ventricular ejection fraction as a continuous variable with mortality, where linearity was maintained for left ventricular ejection fraction less than 65%. Eighteen percent of 181 children had low left ventricular ejection fraction. After adjusting for baseline mortality risk, low left ventricular ejection fraction remained independently associated with mortality (odds ratio, 4.4 [1.0–19.8]; $p = 0.0497$). Likewise, left ventricular ejection fraction was associated with mortality (odds ratio, 0.96 [0.93–0.99]; $p = 0.037$) on multivariable analysis for left ventricular ejection fraction less than 65%. Thirty-six percent of 169 children had low global longitudinal strain, and low global longitudinal strain was also independently associated with mortality (odds ratio, 4.6 [1.2–18.0]; $p = 0.027$).

Conclusions: Sepsis-associated myocardial dysfunction, whether defined by low left ventricular ejection fraction or low global longitudinal strain, is an independent risk factor for mortality in pediatric septic shock after accounting for the confounding effects of septic shock severity.

Key Words: mortality; myocardial dysfunction; pediatrics; septic shock

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Despite decades of research in the field of pediatric sepsis, mortality remains at approximately 25% for children with septic shock (1, 2). This mortality rate is largely driven by organ dysfunction (1, 3–5). Cardiovascular system dysfunction, characterized clinically by hypotension or the need for vasoactive agents, is one of the defining features of pediatric septic shock (6, 7) and has been associated with mortality in children with septic shock (3, 5, 8). However, the mortality risk attributable to myocardial dysfunction per se, separate from endothelial injury, and changes in vascular tone is largely unknown in the pediatric population.

It has also been difficult to disentangle any confounding by illness severity in associating myocardial dysfunction with mortality, because progression to septic shock in pediatric sepsis is in part defined by cardiovascular system failure. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) is validated as a biomarker-based prognostic enrichment tool to estimate baseline risk of mortality in pediatric septic shock (9, 10). PERSEVERE II is a

calibration of PERSEVERE with the addition of admission platelet count as a predictor variable and outperforms PERSEVERE in prospective mortality estimation (9, 11). Adjusting for baseline mortality probability with PERSEVERE II risk affords an opportunity to minimize confounding by illness severity.

Sepsis-associated myocardial dysfunction (SAMD) is heterogeneously defined in the literature. Conventional echocardiographic measurements have focused on changes in left ventricular ejection fraction (LVEF) to define systolic dysfunction (12–14). More recently, myocardial strain indices have been examined in septic shock (13, 15). Global longitudinal strain (GLS), representing the maximal change in myocardial longitudinal length during systole, has been associated with mortality in adults with septic shock (14, 16). No such association has been identified in children, though abnormal longitudinal strain has been correlated with illness severity in pediatric septic shock (17, 18).

We sought to identify the extent to which SAMD, characterized by systolic dysfunction as defined by both LVEF and GLS, is associated with mortality in pediatric septic shock after adjusting for baseline mortality probability. We hypothesized that in a large cohort of children with septic shock, in whom we could assign a reliable baseline risk of mortality, low LVEF would be independently associated with mortality. Secondarily, we hypothesized that worse GLS would be independently associated with mortality.

MATERIALS AND METHODS

Patient Selection and Study Design
We conducted a single-center, retrospective observational study of all patients less than 18 years old admitted to the PICU at the Cincinnati Children's Hospital Medical Center (CCHMC) from 2003 to 2018 who had: 1) an echocardiogram performed within 48 hours of the identification of septic shock and 2) PERSEVERE II biomarker data available for analysis. The study protocol was approved by the CCHMC Institutional Review Board. These patients had been prospectively identified as meeting pediatric consensus criteria for septic shock (6) as part of an observational cohort study and had blood samples obtained for measurement of PERSEVERE II biomarkers (9, 11). The institution's echocardiogram database was cross-referenced to identify patients who had an echocardiogram performed at clinician discretion within 48 hours of identification of septic shock, timed at PERSEVERE study enrollment. This timeframe was chosen to balance sensitivity and specificity and is in accordance with a large meta-analysis of myocardial dysfunction in adults with

septic shock (14). Exclusion criteria included age greater than or equal to 18 years, congenital heart disease including preexisting cardiomyopathy, cannulation to extracorporeal life support prior to echocardiography, poor image quality with inability to determine LVEF, and lack of PERSEVERE II biomarker data. For patients with multiple episodes of sepsis during the study time period, only data from the first sepsis episode associated with an echocardiogram within 48 hours were included (**Fig. 1**).

Clinical Characteristics
Baseline demographic and clinical characteristics were collected from the medical record. Pediatric Risk of Mortality (PRISM)-III scores were recorded as an estimate of baseline illness severity (19). Vasoactive-Inotrope Scores (VIS) were calculated at the time the echocardiogram was performed (20). Presence of comorbidities, duration of PICU admission, bacteremia, requirement for mechanical ventilation, and peak lactate were recorded. Clinical outcomes included 28-day mortality and the composite outcome complicated course, defined as the persistence of at least two organ failures at 7 days or mortality by 28 days.

PERSEVERE II Biomarkers and Baseline Mortality Risk
The PERSEVERE biomarkers include interleukin 8, granzyme B, heat shock protein 70-kDa 1B, C-C chemokine ligand 3, and matrix metallopeptidase 8 and were measured from serum samples within 24 hours of septic shock diagnosis, as previously published (9, 11). PERSEVERE II mortality risk, ranging from 0.000 to 0.571, was assigned using biomarker concentrations and admission platelet count (9, 11). This PERSEVERE II mortality risk was
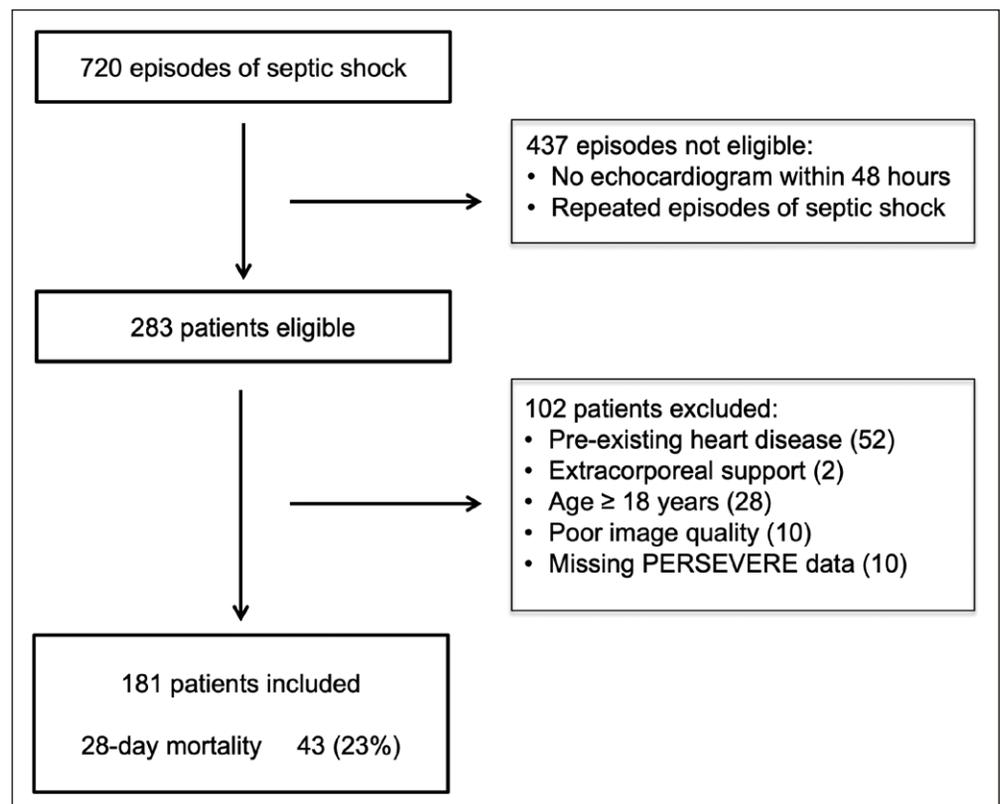

Figure 1. Flow diagram of patients included in analysis. PERSEVERE = Pediatric Sepsis Biomarker Risk Model.

used to account for underlying mortality probability in logistic regression modeling, as detailed below.

Echocardiographic Measurements

Instead of relying on historical documentation, all echocardiograms were reread by a single cardiologist blinded to PERSEVERE data and outcome for the determination of LVEF and GLS. If multiple echocardiograms were available within the study window, the study with the worst historically documented LVEF was selected for reread and analysis. LVEF was calculated using the 5/6 area length method. TOMTEC software (TOMTEC Corporation USA, Chicago, IL) was used for strain analyses. GLS was determined in the apical four-chamber view.

The overall goal was to evaluate whether children with at least moderate left ventricular (LV) systolic dysfunction had higher odds of mortality. We hypothesized that LVEF did not have a linear association with mortality, as LVEF approached physiologically normal values. As such, we chose to apply an a priori cutoff to classify a cohort of critically ill children with at least moderate LV systolic dysfunction. In an effort to avoid potential misclassification of children with minimal LV dysfunction due to inherent variability in LVEF measurement (21), SAMD was defined a priori as LVEF less than 45%. In contrast to LVEF, strain indices vary significantly by body surface area (BSA) and, thus, age (22, 23). Therefore, a published model for the determination of BSA-based GLS z scores was employed for each patient (22), and low GLS was defined as a GLS worse (less negative) than a BSA-based z score of –2. BSA was calculated using the Mosteller formula from patients' heights and weights and imputed from patients' weights when height data were missing (24), as was the case in 46 included children (25%).

Statistical Analyses

Statistical analyses were performed using Stata Version 16 (StataCorp, College Station, TX) and PRISM Version 8 (GraphPad, La Jolla, CA). Dichotomous variables were compared with Fisher exact test or chi-square test, as appropriate. Nonparametric continuous variables were described as medians with interquartile ranges (IQRs) and compared with the Wilcoxon rank-sum test or Kruskal-Wallis test. Multivariable logistic regression was employed to analyze separately the associations of low LVEF and low GLS with mortality. In addition to PERSEVERE II mortality risk, PRISM-III scores were also candidate variables to account for illness severity in regression modeling. Variables were only included in final multivariable logistic regression models if the prespecified statistical threshold $p < 0.10$ was achieved on univariable analysis. Interaction terms were included in multivariable logistic regression models to account explicitly for associations of low LVEF and low GLS with baseline mortality probability, in an effort to isolate the specific impact of low LVEF and low GLS on mortality. Statistical significance was defined as $p < 0.05$.

The hypothesized nonlinear relationship between LVEF and mortality was modeled via continuous restricted cubic spline of mean LVEF with predicted mortality. Internal knots for the spline were placed at default percentiles for five knots (5th, 27.5th, 50th, 72.5th, and 95th percentiles) (25). The fitted spline is a smoothed curve of predicted mortality as a continuous function of LVEF,
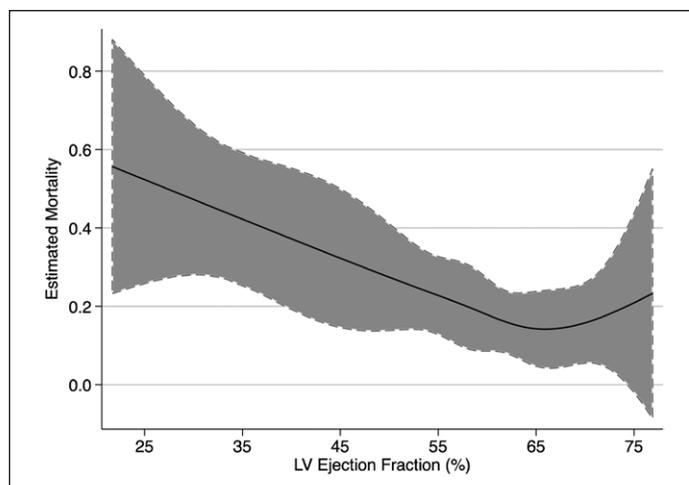

Figure 2. Continuous restricted cubic spline curve showing association of mean left ventricular (LV) ejection fraction (LVEF) with estimated 28-d mortality. *Dashed lower and upper lines* represent the 5% and 95% CIs. Curve was generated for mean LVEF with five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

plotted with 95% CIs (**Fig. 2**). The restricted cubic spline was graphed using the "postrcspline" package in Stata. Based on the observed linear relationship with LVEF less than 65%, a post hoc logistic regression model examined the association with LVEF as a continuous variable with mortality for children with LVEF less than 65%, adjusted for PERSEVERE II mortality probability.

RESULTS

There were 181 children with septic shock without preexisting heart disease who had echocardiograms performed within 48 hours of identification of septic shock. Seventy-four percent ($n = 134$) of the echocardiograms were performed at clinician discretion within the first 24 hours of sepsis identification. Overall 28-day mortality was 23% for the cohort (Fig. 1).

Thirty-two children (18%) had SAMD defined by low LVEF. Median age did not differ among those with and without low LVEF (7.0 yr [IQR, 1.6–14.0 yr] vs 3.5 yr [1.2–11.6 yr]; $p = 0.26$). Common comorbidities did not differ in those with and without low LVEF, but 28-day mortality was higher among children with low LVEF (47% vs 18%; $p < 0.001$). Median VIS was higher in children with low LVEF (49 [11–82] vs 15 [0–40]; $p = 0.001$). Demographic and clinical characteristics of patients with and without low LVEF are delineated in **Table 1**.

By univariable logistic regression, PRISM-III scores were not associated with 28-day mortality (odds ratio [OR], 1.0 [95% CI, 1.0–1.1]; $p = 0.127$) and did not meet the prespecified univariable threshold of $p < 0.10$ for inclusion in the multivariable model. In contrast, both low LVEF (OR, 4.0 [1.8–9.0]; $p = 0.001$) and PERSEVERE II risk (OR, 1.9 [1.5–2.3]; $p < 0.001$) were associated with 28-day mortality. After adjustment for PERSEVERE II risk and the explicit association between PERSEVERE II risk and low LVEF, SAMD defined by low LVEF remained independently associated with mortality (OR, 4.4 [1.0–19.8]; $p = 0.0497$) (**Table 2**).

The relationship between LVEF as a continuous variable and mortality was modeled via continuous restricted cubic spline and is depicted in Figure 2. There is a linear relationship between LVEF

TABLE 1. Demographic and Clinical Characteristics by Low Ejection Fraction

Variable	Normal EF (n = 149)	Low EF (n = 32)	p
Age, yr	3.5 (1.2–11.6)	7.0 (1.6–14.0)	0.26
Female	71 (48%)	15 (47%)	0.94
Race			
Caucasian	101 (68%)	25 (78%)	0.61
African American	21 (14%)	5 (16%)	
Other	27 (18%)	2 (6%)	
Comorbidities			
None	47 (31%)	10 (31%)	0.97
Active or past malignancy	26 (17%)	7 (22%)	0.56
Bone marrow transplant	23 (15%)	5 (16%)	0.98
Solid organ transplant	6 (4%)	0 (0%)	0.59
Trach/vent	6 (4%)	2 (6%)	0.63
Genetic syndrome	27 (18%)	5 (16%)	0.74
Duration PICU admission, d	9 (4–15)	7 (2–15)	0.10
Bacteremia	43 (29%)	11 (34%)	0.54
Mechanical ventilation	126 (85%)	31 (97%)	0.06
Vasoactive-Inotrope Score[a]	15 (0–40)	49 (11–82)	0.001
Peak lactate, mmol/L[b]	2.6 (1.4–5.5)	3.7 (2.7–8.2)	0.04
Pediatric Risk of Mortality-III score	13 (7–18)	19 (11–28)	0.004
Pediatric Sepsis Biomarker Risk Model II risk	0.019 (0.007–0.189)	0.300 (0.019–0.388)	< 0.001
Complicated course	59 (40%)	18 (56%)	0.08
Mortality	27 (18%)	15 (47%)	< 0.001

EF = ejection fraction.
[a]Vasoactive-Inotrope Score available for n = 151 patients.
[b]Peak lactate available for n = 117 patients.
Data are presented as median (IQR) or n (%).

TABLE 2. Univariable and Multivariable Analyses of Candidate Variables Associated With Mortality

Variable	n	Univariable Analysis			Multivariable Analysis		
		OR	(95% CI)	p	OR	(95% CI)	p
PERSEVERE II risk[a]	181	1.9	1.5–2.3	< 0.001	1.9	1.5–2.5	< 0.001
Pediatric Risk of Mortality-III scores[b]		1.0	1.0–1.1	0.127	—	—	—
Low LVEF		4.0	1.8–9.0	0.001	4.4	1.0–19.8	0.0497
Interaction variable (low LVEF × PERSEVERE II)		—	—	—	0.8	0.5–1.3	0.292

LVEF = left ventricular ejection fraction, OR = odds ratio, PERSEVERE = Pediatric Sepsis Biomarker Risk Model.
[a]The raw PERSEVERE mortality probability was transformed by a factor of 10 for the logistic regression analyses.
[b]Pediatric Risk of Mortality-III was excluded from the multivariable analysis, since it did not reach the prespecified threshold p value of < 0.10 on univariable analysis.

and mortality when LVEF is less than 65%, after which the association becomes nonlinear. One-hundred thirty-five (75%) children had an LVEF less than 65%. LVEF as a continuous variable is significantly associated with mortality in children with LVEF less than 65% by univariable logistic regression (OR, 0.95 [0.92–0.98]; p = 0.001) and after adjustment by PERSEVERE II mortality probability (OR, 0.96 [0.93–0.99]; p = 0.037) (Supplemental Table 1, http://links.lww.com/CCX/A369).

TABLE 3. Multivariable Analysis of Global Longitudinal Strain

Variable	n	OR (95% CI)	p
PERSEVERE II[a]	169	2.6 (1.8–4.0)	< 0.001
Low GLS		4.6 (1.2–18.0)	0.027
Interaction variable (low GLS × PERSEVERE II)		0.5 (0.3–0.9)	0.013

GLS = global longitudinal strain, OR = odds ratio, PERSEVERE = Pediatric Sepsis Biomarker Risk Model.
[a]The raw PERSEVERE mortality probability was transformed by a factor of 10 for the logistic regression analyses.

GLS was measurable in 169 children with septic shock. Sixty-one children (36%) had SAMD defined by low GLS, with GLS worse (less negative) than z score of –2 for BSA. As in SAMD defined by low LVEF, age was not different in patients with and without low GLS (5.5 yr [1.6–12.7 yr] vs 3.3 yr [1.2–11.9 yr]; $p = 0.26$). Similarly, comorbidities did not differ between children with and without SAMD defined by low GLS, but 28-day mortality was worse in those with low GLS (31% vs 18%; $p = 0.043$). Likewise, VIS was higher in children with low GLS (20 [4–55] vs 10 [0–35]; $p = 0.025$). Demographic and clinical characteristics in patients with low GLS and normal GLS are described in Supplemental Table 2 (http://links.lww.com/CCX/A370). By univariable logistic regression, low GLS was associated with 28-day mortality (OR, 2.12 [1.02–4.42]; $p = 0.045$). After adjustment for PERSEVERE II mortality risk and the association between low GLS and PERSEVERE II risk, SAMD defined by low GLS remained independently associated with 28-day mortality (OR, 4.6 [1.2–18.0]; $p = 0.027$) (**Table 3**).

There were 33 children classified as having normal LVEF (LVEF > 45%) who had low GLS. Demographic and clinical data of children stratified by both GLS and LVEF are described in **Table 4**.

TABLE 4. Demographic and Clinical Characteristics Stratified by Both Global Longitudinal Strain and Left Ventricular Ejection Fraction

Variable	Normal GLS and LVEF (n = 107)	Low GLS and Normal LVEF (n = 33)	Low GLS and LVEF (n = 28)	p
Age, yr	3.3 (1.2–12.0)	5.0 (1.5–9.7)	7.7 (1.7–14.2)	0.32
Female	49 (46%)	16 (48%)	14 (50%)	0.91
Race				
Caucasian	74 (69%)	19 (58%)	22 (79%)	0.61
African American	15 (14%)	6 (18%)	4 (14%)	
Other	18 (17%)	8 (24%)	2 (7%)	
Comorbidities				
None	33 (31%)	8 (24%)	9 (32%)	0.74
Active or past malignancy	19 (18%)	7 (21%)	7 (25%)	0.67
Bone marrow transplant	15 (14%)	8 (24%)	5 (18%)	0.38
Solid organ transplant	5 (5%)	1 (3%)	0 (0%)	0.83
Trach/vent	5 (5%)	1 (3%)	1 (4%)	1.00
Genetic syndrome	18 (17%)	8 (24%)	3 (11%)	0.39
Duration PICU admission, d	9 (4–15)	12 (4–16)	7 (2–15)	0.36
Bacteremia	32 (30%)	7 (21%)	9 (32%)	0.56
Mechanical ventilation	89 (83%)	28 (85%)	27 (96%)	0.19
Vasoactive-Inotrope Score[a]	10 (0–35)	15 (2–25)	42 (11–70)	0.002
Peak lactate, mmol/L[b]	2.7 (1.4–5.6)	2.6 (1.3–4.3)	3.5 (2.3–8.2)	0.20
Pediatric Risk of Mortality-III score	12 (7–16)	15 (9–19)	19 (11–26)	0.011
Pediatric Sepsis Biomarker Risk Model II risk	0.019 (0.007–0.189)	0.019 (0.007–0.333)	0.245 (0.019–0.333)	0.002
Complicated course	42 (39%)	13 (39%)	14 (50%)	0.58
Mortality	18 (17%)	8 (24%)	11 (39%)	0.036

GLS = global longitudinal strain, LVEF = left ventricular ejection fraction.
[a]Vasoactive-Inotrope Score available for $n = 139$ patients.
[b]Peak lactate available for $n = 112$ patients.
Data are presented as median (IQR) or n (%).

Mortality was the lowest in children with normal GLS and LVEF (17%), was increased in children with low GLS but normal LVEF (24%), and was the highest in those with both low GLS and LVEF (39%; $p = 0.036$).

DISCUSSION

We found that SAMD, whether defined by low LVEF or low (worse) GLS, is independently associated with mortality in a large cohort of children with septic shock after adjusting for baseline mortality probability with PERSEVERE II risk. The association of LVEF with mortality was robust, as both LV systolic dysfunction defined by LVEF less than 45% and LVEF as a continuous variable (when the linearity requirement was met for LVEF less than 65%) were associated with increased 28-day mortality after adjustment with PERSEVERE II risk. The continuous restricted cubic spline curve of LVEF confirmed nonlinearity as LVEF approached physiologically normal values; at present, it is unclear the extent to which profoundly hyperdynamic high LVEF more clearly suggests changes in vascular tone than myocardial dysfunction. Similarly, low GLS, defined by GLS worse (less negative) than a z score of -2 for BSA, was associated with increased 28-day mortality after adjustment with PERSEVERE II mortality probability. Taken together, these data suggest that SAMD has an important association with mortality that is not simply a reflection of severity of illness or baseline mortality risk. Instead, SAMD merits consideration and investigation as a potentially modifiable risk factor for mortality in pediatric septic shock.

In addition to delineating the relationship between SAMD and mortality in children with septic shock, these data also provide insights into the epidemiology of SAMD in the PICU. Though this is a retrospective, single-center cohort spanning 15 years of children with septic shock in whom clinicians obtained echocardiograms, the overall 28-day mortality of 23% is remarkably similar to recently published mortality rates for septic shock in the PICU (1). SAMD as defined by low LVEF or low GLS is relatively common in children with septic shock for whom clinicians obtain echocardiograms, ranging from nearly one in five children by LVEF to more than one in three by GLS. SAMD occurs in children of all ages in the PICU, whether measured by low LVEF or low GLS, and did not occur more commonly in children with comorbidities, including chronic mechanical ventilation via tracheostomy, malignancy, bone marrow or solid organ transplant, or underlying genetic syndromes; importantly, though, children with congenital heart disease and with heart transplants were excluded from this study. It is perhaps not surprising that children with low LVEF or low GLS had higher VIS around the time of echocardiogram. In this retrospective study, higher vasoactive and inotrope use by bedside clinicians likely reflected increased severity of shock in children with higher PERSEVERE II risk and 28-day mortality. Since epinephrine and norepinephrine were the predominantly administered agents, the inotropic effects of these drugs would be expected to improve LVEF (26–28) and likely GLS. The net effect would be to potentially underestimate the degree of myocardial dysfunction in children with higher VIS.

Strain indices such as GLS have been proposed to identify children with subtle cardiac dysfunction not evident with conventional measurements, including LVEF (17, 29). In our cohort, 33 children were categorized as having normal LVEF but low GLS, and mortality for this group was intermediate between those with both low or both normal LVEF and GLS. Boissier et al (13) prospectively studied adults during the first 72 hours of septic shock and found that GLS was abnormal in patients with preserved LVEF in the first 24 hours who subsequently developed low LVEF. Additionally, data from children with progressive cardiac disease, such as Duchenne muscular dystrophy, suggest abnormal strain indices are apparent in children who still have preserved function by conventional measurements (30). Thus, these children with low GLS but preserved LVEF might have manifested low LVEF if imaged later in the course of illness, though our retrospective data cannot support definitive conclusions. Regardless of whether these children progress to low LVEF, though, low GLS represents a clinically important phenotype for children with septic shock, given the increased mortality relative to children with normal GLS. Clearly, prospective longitudinal research is needed to better understand the clinical course of low GLS but preserved LVEF in this population.

To our knowledge, this is the first study demonstrating the association of low LVEF with mortality in pediatric septic shock. Williams et al (31) retrospectively reported 78 patients with fluid- and catecholamine-refractory septic shock and found a similar prevalence of 19% with at least moderate LV systolic dysfunction by conventional echocardiography but did not find any association with mortality. Similarly, El-Zayat and Shalaby (32) prospectively examined 50 children with septic shock but did not find a difference in LVEF in survivors and nonsurvivors. The clear association with mortality in our study likely results from a larger sample size. These findings stand in contrast to the adult literature, which has not found an association of LVEF with mortality in adults with septic shock (12–14). This may reflect heterogeneity in inclusion of patients with preexisting heart disease (12, 13), age-based differences in SAMD pathophysiology or in preload and afterload conditions, or differences in comorbidities, including ischemic and valvular heart disease.

Prior studies have associated abnormal longitudinal strain with severity of illness in pediatric septic shock (17, 18). We extend this association of GLS to mortality for the first time with a larger sample size of pediatric patients. In contrast to LVEF, our GLS data align well with published associations of GLS with mortality in adults with septic shock (12–14). One possible unifying explanation for the disparity in LVEF findings but similarity in GLS data is a potential difference in preload and afterload conditions between children and adults with septic shock, since GLS may be less sensitive to alterations in loading conditions (13, 15), though our data are insufficient to specifically address this question.

We identified SAMD as an independent risk factor for mortality in children with septic shock. Prospective clinical research is needed to determine whether targeted clinical management with inotropes, modulation of vasopressors, and changes in fluid resuscitation alter mortality for children with SAMD. El-Nawawy et al (33) randomized 90 children with septic shock to echocardiography-guided therapy or standard therapy and found higher rates of shock reversal, reduced time to shock reversal, and lower mortality

from unresolved shock in patients treated with protocolized fluids and inotropes adjusted by echocardiography data. These findings need to be validated with larger, multicenter studies. Ultimately, early identification of SAMD is necessary for both potential treatment and prospective clinical research. Given recent calls for prognostic enrichment to improve sepsis trial designs (34, 35), models to identify which patients merit echocardiography to evaluate for SAMD may be particularly valuable.

Strengths of this study include independent analyses of echocardiograms by a cardiologist blinded to PERSEVERE data and clinical outcomes. Additionally, echocardiograms were performed proximate to the prospective identification of septic shock: nearly three-quarters occurred within 24 hours, and all occurred within a timeframe consistent with a large retrospective adult analysis (14). Our study has limitations. Myocardial function was only evaluated among patients who had echocardiograms performed at clinician discretion, raising the concern for selection bias. Thus, our study findings may be limited to children with septic shock for whom clinicians are considering echocardiography. Furthermore, fluid resuscitation and vasoactive administration were not standardized in this observational study, though any potential misclassification of patients imaged after initiation of inotropes would be expected to bias our results toward the null and diminish the mortality difference between the groups. Finally, height data were missing from 25% of patients, predominantly in the early years of the study period, affecting the calculation of BSA. Rather than ignoring missing data, height was imputed from weight, though this estimation may not have been accurate for very obese patients.

CONCLUSIONS

In summary, after accounting for the confounding effects of septic shock severity and baseline mortality probability, SAMD, whether defined by low LVEF or GLS, is independently associated with increased mortality among children with septic shock. These results highlight the important contribution of myocardial dysfunction to poor outcome from pediatric septic shock.

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