OBSERVATIONAL STUDY

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Revisiting Post-ICU Admission Fluid Balance Across Pediatric Sepsis Mortality Risk Strata: A Secondary Analysis of a Prospective Observational Cohort Study

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OBJECTIVES: Post-ICU admission cumulative positive fluid balance (PFB) is associated with increased mortality among critically ill patients. We sought to test whether this risk varied across biomarker-based risk strata upon adjusting for illness severity, presence of severe acute kidney injury (acute kidney injury), and use of continuous renal replacement therapy (CRRT) in pediatric septic shock.

DESIGN: Ongoing multicenter prospective observational cohort.

SETTING: Thirteen PICUs in the United States (2003–2023).

PATIENTS: Six hundred and eighty-one children with septic shock.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Cumulative percent PFB between days 1 and 7 (days 1–7 %PFB) was determined. Primary outcome of interest was complicated course defined as death or persistence of greater than or equal to two organ dysfunctions by day 7. Pediatric Sepsis Biomarker Risk Model (PERSEVERE)-II biomarkers were used to assign mortality probability and categorize patients into high mortality ($n = 91$), intermediate mortality ($n = 134$), and low mortality ($n = 456$) risk strata. Cox proportional hazard regression models with adjustment for PERSEVERE-II mortality probability, presence of sepsis-associated acute kidney injury on day 3, and use of CRRT, demonstrated that time-dependent variable days 1–7%PFB was independently associated with an increased hazard of complicated course. Risk-stratified analyses revealed that each 10% increase in days 1–7 %PFB was associated with increased hazard of complicated course only among patients with high mortality risk strata (adjusted hazard ratio 1.24 (95% CI, 1.08–1.43), $p = 0.003$). However, this association was not causally mediated by PERSEVERE-II biomarkers.

CONCLUSIONS: Our data demonstrate the influence of cumulative %PFB on the risk of complicated course in pediatric septic shock. Contrary to our previous report, this risk was largely driven by patients categorized as having a high mortality risk based on PERSEVERE-II biomarkers. Incorporation of such prognostic enrichment tools in randomized trials of restrictive fluid management or early initiation of de-escalation strategies may inform targeted application of such interventions among at-risk patients.

KEYWORDS: acute kidney injury; biomarkers; critical illness; fluid overload; positive fluid balance; post-ICU admission fluid balance; sepsis; septic shock

Sepsis is associated with high morbidity and mortality among children and adults (1). Driven primarily by a dysregulated host immune response and consequent endothelial activation, sepsis is characterized by microvascular capillary leak (2). Further, a large increase in systemic vascular

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KEY POINTS

Question: Does the association between cumulative positive fluid balance (PFB) and complicated PICU course vary across biomarker-based risk strata among patients with pediatric septic shock?

Finding: After adjusting for several confounders, cumulative PFB after PICU admission was independently associated with increased hazard of complicated course. This association was attributed primarily to patients categorized as having a high mortality risk based on Pediatric Sepsis Biomarker Risk Model II biomarkers.

Meaning: Utilization of prognostic enrichment tools, including biomarker-based risk stratification, in randomized trials of restrictive fluid management or early de-escalation strategies holds potential to inform targeted application of such interventions.

capacitance necessitates fluid resuscitation to ensure adequate preload and systemic oxygen delivery in the initial phase of illness. However, fluid shifts over the course of disease result in extravascular fluid accumulation, consequent hypoxemia, and propagation of organ dysfunction(s) (3).

Persistence of a positive fluid balance (PFB) has been independently associated with poor clinical outcomes among patients with sepsis (4–10). Complicating matters further, patients may develop oliguria and sepsis-associated acute kidney injury (SA-AKI). A subset of patients will require continuous renal replacement therapy (CRRT). Both the presence of SA-AKI and CRRT use may serve to confound the association between cumulative PFB and clinical outcomes. Recent research has emphasized conservative fluid management, de-escalation, and deresuscitation where appropriate to negate the detrimental effects of PFB among critically ill patients (11). It is suggested that such approaches may improve liberation of patients from the intensive care unit (ICU). A key limitation is that few studies have explicitly considered biological heterogeneity among critically ill patients. It is thus likely that subsets of patients may benefit from tailored fluid management approaches (12–14).

Our group has previously used the Pediatric Sepsis Biomarker Risk Model (PERSEVERE)—a prospectively validated prognostic enrichment tool (15) reflective of the host inflammatory response—to test the association between post-ICU admission cumulative PFB across mortality risk strata in pediatric septic shock patients (16). Our group previously reported that only among patients with low mortality risk was cumulative PFB associated with increased odds of complicated course. Limitations of our prior study included: 1) reporting of univariate analyses that did not account for confounders, 2) the relatively small number of patients belonged to high- and intermediate-PERSEVERE mortality risk strata, and 3) the lack of consideration of the competing influence of early deaths on ICU length of stay, and consequently on the cumulative PFB among the most critically ill patients.

In this study, we sought to test the independent influence of post-ICU admission PFB on the risk of complicated course in a large pediatric cohort of septic shock. We further conducted multivariate risk-stratified analyses to test differences in this association across PERSEVERE-II mortality risk strata and whether biomarker-based mortality probability causally mediated the primary association of interest.

MATERIALS AND METHODS

Study Design and Patient Selection

The study protocol was approved by institutional review boards (IRBs) of participating institutions (Cincinnati Children's Hospital IR, Study Title: "Genomic Analysis of Pediatric Systemic Inflammatory Syndrome," IRB ID: 2008-0558, Initial Approval May 9, 2002, Most Recent Approval: June 22, 2023) as well as all participating institutions. Informed consent was obtained from parents or guardians of patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRBs of participating institutions and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Our ongoing multi-institutional prospective observational cohort study of pediatric septic shock has been extensively detailed previously (15, 17, 18). Inclusion criteria for study enrollment were within 24 hours of meeting pediatric-specific consensus criteria for septic shock (19). Those with (A) missing admission height to estimate baseline serum creatinine (SCr) or weight to estimate percent PFB per kilogram body weight, (B) those with missing fluid balance details on day 1, and

those without PERSEVERE-II biomarker data, which includes platelet count on day 1, were excluded. All patients who were included in our previous study (16) were excluded.

Only nonresuscitative fluids received after ICU admission were documented in our cohort. The percent PFB was measured by dividing the net fluid balance (intake minus output) measured in liters on any given day by the admission weight in kilograms and multiplying it by a factor of 100. The primary exposure variable of interest was the cumulative percent PFB between days 1 and 7 (days 1–7 %PFB). The primary outcome of interest was complicated course defined as death within 7 days or the presence of two or more organ dysfunctions on day 7 of septic shock (18). Baseline illness severity was based on pediatric risk of mortality III score (PRISM-III) (20). Severe SA-AKI was defined as per Kidney Disease Improving Global Outcomes stage 2 AKI or higher, which corresponds to a two-fold or greater increase in SCr relative to baseline (21). Baseline SCr values were unknown for all patients in the cohort, and thus were imputed using their calculated body surface area (m^2) and an estimated glomerular filtration rate of 120 mL/min per 1.73 m^2, as validated in the literature (22, 23). Presence of persistent SA-AKI on day 3 (D3 SA-AKI) and the use of any CRRT between days 1 and 7 were considered as potential confounders and included in models. CRRT prescription parameters were not available and therefore could not be included.

PERSEVERE-II-Based Risk Stratification

PERSEVERE-II mortality probability and risk strata were determined, according to published methods (15, 24). Briefly, interleukin-8 (IL-8), heat shock protein 70 kDa, C–C chemokine ligand 3, C–C chemokine ligand 4, granzyme B, IL-1α, and matrix metallopeptidase 8 were previously measured in day 1 septic shock serum. Classification and regression tree (CART) analyses were used to derive a mortality probability risk score (0.000–0.999) using R (GNU Project, Boston, MA, USA) . Patients were classified as low-risk (mortality probability score ≤ 0.019), intermediate-risk (mortality probability score > 0.019 to ≤ 0.300) or high-risk (mortality probability score > 0.300).

Statistical Analyses

Statistically analyses were conducted using R software. Demographic and clinical data were summarized with numbers with percentages or median with interquartile range. Differences between groups were determined by χ^2 test for categorical variables and by the Kruskal-Wallis test for continuous variables with post hoc Dunn's test for multiple comparison testing between risk strata. Univariate and multivariable Cox proportional regression were used to estimate hazard of complicated course in the cohort and across PERSEVERE-II risk strata. To account for the possibility of changes in clinical practice patterns over time influencing the association of interest, we considered decade of sampling (2003–2013 vs. 2014–2023) as a potential confounder. This variable was coerced into the multivariable models despite not reaching significance on univariate analyses to ensure our data reflected contemporary practice. Models were adjusted for D3 SA-AKI, use of CRRT, with days 1–7 %PFB being considered a time-dependent variable. Day of study enrollment was considered as the starting time (time 0). Survivors who were transferred out of the ICU before day 7 and those who remained in the ICU on day 7 were right censored. A p value of 0.05 was used to test statistical significance throughout the study. Additional post hoc analyses are detailed in **Supplementary Methods** (http://links.lww.com/CCX/B296).

Causal Mediation Analyses

We used "CMAverse" package in R to conduct mediation analyses using a regression-based approach (25). Time to complicated course as an outcome was examined in relation to cumulative PFB and PERSEVERE-II mortality probability risk using a Weibull distribution. For the mediator model, we examined PERSEVERE-II mortality probability risk in relation to cumulative PFB through a linear model adjusted for day 3 SA-AKI and use of CRRT as covariates. The results were reported as proportion mediated by PERSEVERE-II mortality probability risk for the relationship between cumulative fluid balance and time to complicated course. In addition, the mean survival ratio for direct effect, indirect effect, and total effect were quantified.

RESULTS

A total of 681 children were included in the current study. **Figure 1** shows flow diagram detailing patients who were included in the study, 13 children with missing

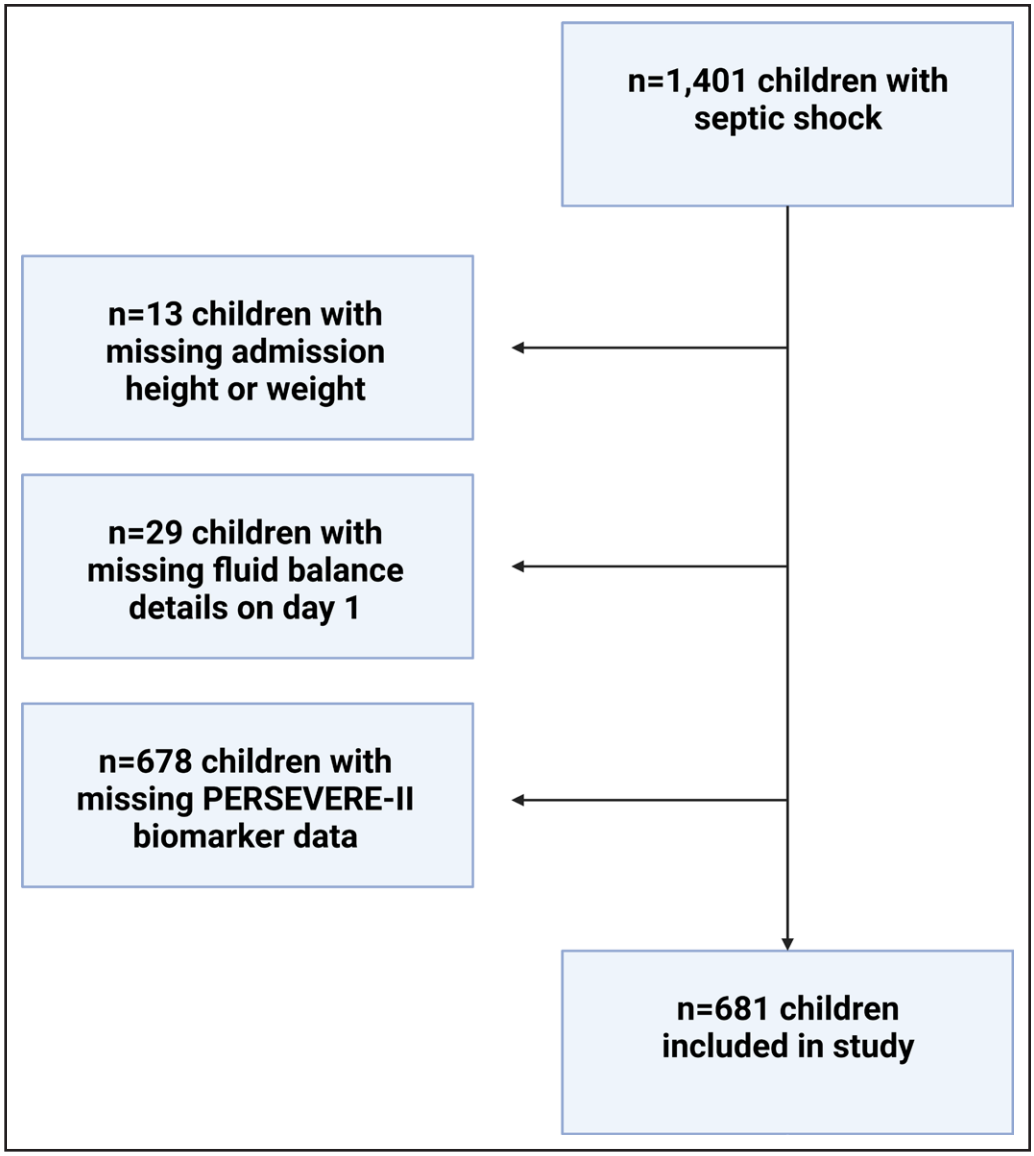

Figure 1. Flow diagram showing patients included in the study. PERSEVERE-II = Pediatric Sepsis Biomarker Risk Model II.

admission height or weight, 29 children with missing fluid balance on day 1, and 678 children with missing PERSEVERE-II biomarker or day 1 platelet data were excluded from analyses. Most patients (566/681, 83.2%) were enrolled within 24 hours and 67 of 681 patients (9.8%) were enrolled within 48 hours of ICU admission. The remaining patients represented those admitted to the ICU for other indications and subsequently met criteria for septic shock. Demographic and clinical variables based on the presence of complicated course are presented in **Supplementary Table 1** (http://links.lww.com/CCX/B296). Patients with a complicated course had higher 28-day mortality, hospital length of stay, presence of D3 SA-AKI, and use of any CRRT. Percent PFB was higher between days 1 and 4 among those with a complicated course. Net daily even or negative fluid balance was achieved later among patients with a complicated course than those without. Finally, among patients who received CRRT, duration of CRRT use was longer among those with a complicated course than those without.

Differences in demographic and clinical characteristics according to PERSEVERE-II risk strata are shown in **Table 1** and the respective CART is shown in **Supplementary Figure 1** (http://links.lww.com/CCX/B296). A total of 91 patients were deemed high risk, 134 patients had intermediate risk, and 456 patients had low mortality risk. Patients categorized as high- and intermediate-risk categories had higher illness severity based on both PRISM-III score and PERSEVERE-II mortality probability. These patients also had worse clinical outcomes including the presence of D3 SA-AKI and use of CRRT with graded responses across risk strata. Relative to those classified as low mortality risk, fluid balance between days 1 and 3 and cumulatively over the first 7 days were more positive among patients with high- and intermediate-risk groups, with no differences between the latter groups noted.

Table 2 shows the results of univariate and multivariate Cox proportional hazard regression for complicated course in the entire cohort. After adjusting for PERSEVERE-II mortality probability, D3 SA-AKI, and use of CRRT, every 10% percent increase in days 1–7 %PFB was associated with an

TABLE 1.
Demographics and Clinical Outcomes of Cohort by Pediatric Sepsis Biomarker Risk Model II Risk Strata

Variables	High Risk (*n* = 91)	Intermediate Risk (*n* = 134)	Low Risk (*n* = 456)	*p*
Age (yr)	4.4 (1.5, 8.2)	5.4 (1.5, 9.6)	5.6 (1.6, 10.8)	0.204
Weight	17.1 (10.5, 24.8)	18.3 (10.3, 33.0)	20.0 (11.3, 35.7)	0.414
Sex, female (%)	48 (52.7%)	59 (44.1%)	223 (48.9%)	0.415
Race (self-identified)				
White/Caucasian	69 (75.8%)	100 (74.6%)	336 (73.7%)	0.866
Black/African American	8 (8.8%)	13 (9.7%)	55 (12.1%)	
Other	14 (15.4%)	21 (15.7%)	65 (14.3%)	
Ethnicity				
Hispanic or Latino	8 (8.8%)	18 (13.4%)	65 (14.3%)	0.715
Pediatric Risk of Mortality III Score	16 (9, 26)[a]	13 (8,18)[b]	9 (5,13)	< 0.001
Pediatric Sepsis Biomarker Risk Model II mortality probability	0.407 (0.07)[a]	0.186 (0.01)[b]	0.02 (0.07)	< 0.001
Day 1 Vasoactive Inotropic Score	20 (4, 55)[b]	23 (10, 54)[b]	10 (3, 30)	< 0.001
Complicated course	51 (56.1%)[b]	58 (43.2%)[b]	107 (23.5%)	< 0.001
7-d mortality	21 (23.1%)[b]	18 (13.4%)[b]	9 (1.9%)	< 0.001
28-d mortality	30 (32.9%)	23 (17.2%)	21 (4.6%)	< 0.001
PICU-free days	23 (16, 26)	21 (13, 25)	23 (16, 26)	0.308
Hospital length of stay	13 (5, 27)	16 (8, 27)	13 (7, 25)	0.476
Preexisting kidney disease	3 (3.3%)	8 (6.0%)	20 (4.4%)	0.613
Day 1 oliguria	24 (26.4%)	23 (17.2%)	64 (14.1%)	0.014
D3 sepsis-associated acute kidney injury	46 (50.5%)[a]	53 (39.6%)[b]	123 (26.8%)	< 0.001
Any CRRT	19 (20.8%)[a]	21(15.7%)[b]	32 (7.0%)	< 0.001
Day 1 %FB	6.3 (1.8, 10.2)	5.2 (2.1, 8.9)	3.4 (0.5, 6.5)	< 0.001
Day 2 %FB	3.2 (0.0, 8.2)	3.4 (1.3, 6.9)	1.4 (-0.7, 3.8)	< 0.001
Day 3 %FB	0.3 (−1.2, 3.4)	0.3 (−2.2, 3.3)	−0.1 (−1.9, 2.2)	0.184
Day 4 %FB	−0.8 (−3.6, 1.8)	−1.3 (−4.2, 1.5)	0.2 (−2.3, 1.9)	0.066
Day 5 %FB	0.1 (−4.1, 2.4)	−0.1 (−2.9, 1.8)	−0.3 (−2.4, 1.5)	0.887
Day 6 %FB	−0.4 (−2.7, 1.8)	−0.2 (−2.8, 2.3)	−0.1 (−2.4, 1.8)	0.773
Day 7 %FB	0.1 (−1.4, 3.2)	−0.1 (−1.4, 3.0)	0.2 (−1.8, 2.1)	0.476
Days 1–7 percent positive fluid balance	8.2 (1.8, 15.4)	6.8 (1.5, 15.3)	3.6 (−0.8, 9.3)	< 0.001
Days to achieve daily even or negative fluid balance	3 (2, 3)[b]	3 (2, 3)[b]	2 (1, 2)	< 0.001
Duration of CRRT (hr)	29 (21–37)[b]	16 (10–23)	8 (5–12)	< 0.001

CRRT = continuous renal replacement therapy, %FB = percent fluid balance.

[a]$p < 0.05$ comparing high- and intermediate-mortality risk groups.

[b]$p < 0.05$ only with relative to low- mortality risk group.

increase in hazard of complicated course (adjusted hazard ratio [HR] 1.090 [95% CI, 1.013–1.172], $p = 0.021$). Importantly, PERSEVERE-II mortality probability and presence of D3 SA-AKI, but not use of CRRT, were independently associated with an increased hazard of complicated course.

TABLE 2.
Cox Proportional Hazard Model for Complicated Course for the Entire Cohort

Variables	Hazard Ratio (95% CI)	*p*
Univariate models		
Decade of enrollment[a]	0.806 (0.484–1.341)	0.406
Age	0.995 (0.975–1.016)	0.660
PERSEVERE-II mortality probability[b]	1.264 (1.169–1.367)	< 0.001
CRRT	1.822 (1.336–2.485)	< 0.001
D3 SA-AKI	2.677 (2.025–3.538)	< 0.001
Days 1–7 %PFB[b]	1.109 (1.040–1.183)	0.002
Multivariable model		
Decade of enrollment[a]	0.706 (0.402–1.239)	0.225
PERSEVERE-II mortality probability	1.145 (1.047–1.253)	0.003
CRRT	1.001 (0.694–1.443)	0.997
D3 SA-AKI	2.272 (1.670–3.092)	< 0.001
Day 1–7 %PFB[b]	1.090 (1.013–1.172)	0.021

CRRT = continuous renal replacement therapy, %PFB = percent positive fluid balance, PERSEVERE-II = Pediatric Sepsis Biomarker Risk Model II, SA-AKI = sepsis-associated acute kidney injury.
[a]Decade of enrollment: 2003–2013 vs. 2014–2023.
[b]Days 1–7 %PFB was multiplied by a factor of 10 for models.

RISK-STRATIFIED ANALYSES

Figure 2 shows days 1–7 %PFB according to occurrence of complicated course and PERSEVERE-II mortality risk strata. Only patients belonging to the high-mortality risk group with a complicated course had higher days 1–7 %PFB. Additional details of percent cumulative fluid balance according to the terminal nodes of the CART are shown in **Supplementary Figure 2** (http://links.lww.com/CCX/B296) and detailed in **Supplementary Table 2** (http://links.lww.com/CCX/B296). The interaction between percent cumulative fluid balance and risk strata on complicated courses across the cohort is detailed in **Supplementary Table 3** (http://links.lww.com/CCX/B296). **Table 3** shows the results of univariate and multivariate Cox proportional hazard for complicated course for each of the three risk strata. After adjusting for the potentially confounding influence of D3 SA-AKI and use of CRRT, every 10% increase in days 1–7 %PFB was associated with an increased hazard (adjusted HR 1.24 [95% CI, 1.08–1.43], $p = 0.003$) of complicated course among patients belonging to high PERSEVERE-II mortality risk, but not among those categorized as intermediate mortality risk ($p = 0.700$) or low mortality risk ($p = 0.339$). This association was not influenced by the decade of enrollment. The presence of D3 SA-AKI was independently associated with increased hazard of complicated course among patients with high mortality and low mortality risk but not among patients with intermediate mortality risk. Use of CRRT did not influence risk of complicated course in any of the mortality risk groups. For comparison, subgroup analyses based on arbitrary cutoffs of PRISM-III, rather than biomarker-risk strata, are shown in **Supplementary Table 4** (http://links.lww.com/CCX/B296).

Finally, as shown in **Table 4**, PERSEVERE-II mortality risk-probability did not causally mediate the association between cumulative percent PFB and time to complicated course, with an estimate of overall proportion mediated of 0.156, 95% CI of –17.11 to 0.20, and $p = 0.6$.

DISCUSSION

We provide evidence that cumulative PFB is independently associated with increased hazard of death and multiple organ dysfunctions among pediatric septic shock patients. Further, risk-stratified analyses based on PERSEVERE-II biomarkers demonstrated that

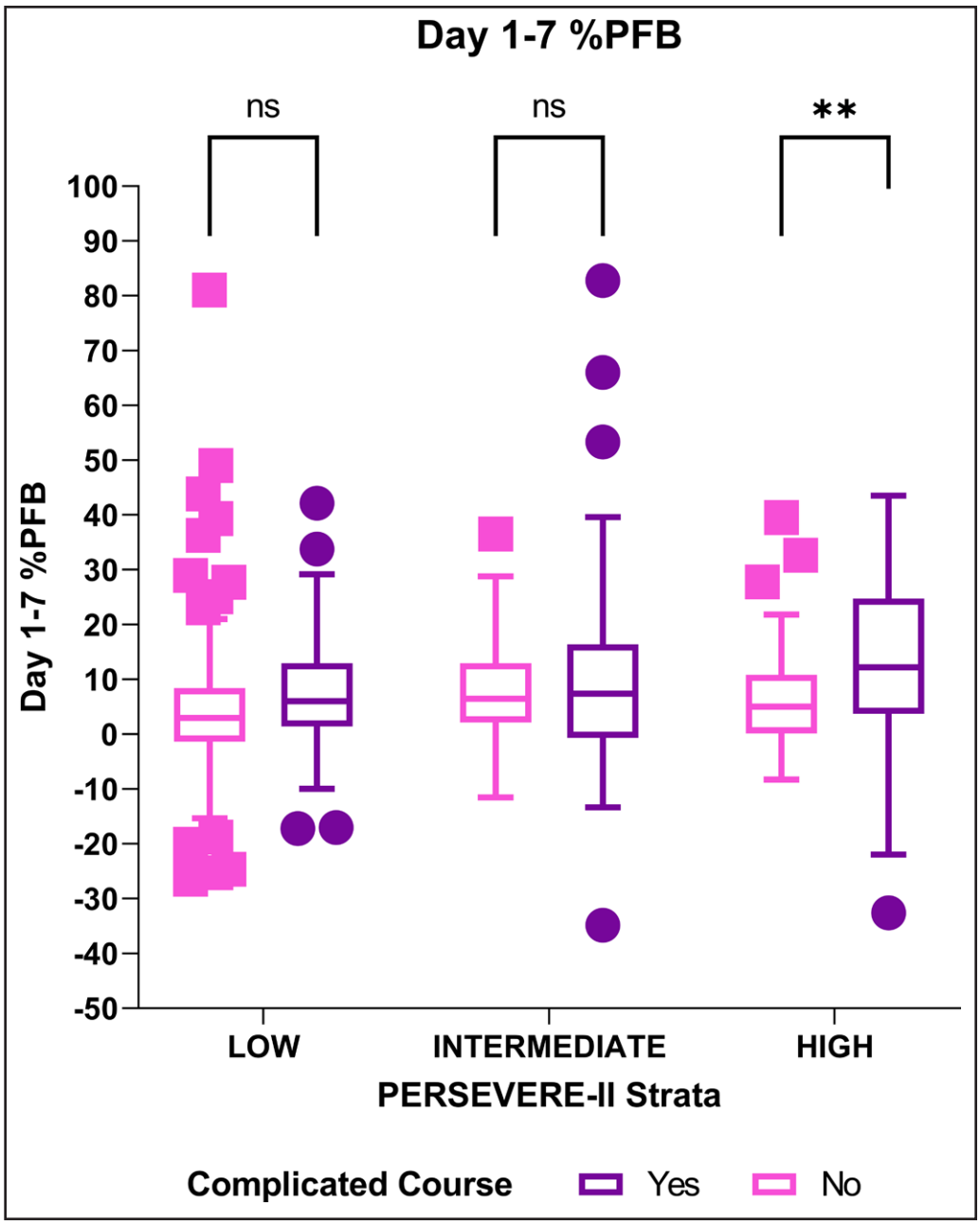

Figure 2. Days 1–7 cumulative percent fluid overload by presence of complicated course across Pediatric Sepsis Biomarker Risk Model (PERSEVERE)-II risk strata. Patients with a complicated course had higher days 1–7 percent positive fluid balance (%PFB) than those without, only among patients categorized as high PERSEVERE-II mortality risk.

this increased risk is attributable primarily to patients categorized as having a high mortality risk. Lastly, although PERSEVERE-II mortality risk strata served as an effect modifier, our data do not indicate that these biomarkers causally mediated the primary association of interest.

Numerous studies among adults have sought to address the link between PFB and clinical outcomes in the previous decade. Data from recent meta-analyses of 31 observational studies and 3 randomized trials showed an independent association between positive cumulative fluid balance and mortality (26). However, there was substantial variation in adjustment for confounding factors with most accounting for illness severity and some adjusting for use and timing of CRRT. Few studies have adjusted for the concomitant presence of AKI (27). Recent results from the assessment of worldwide acute kidney injury renal angina and epidemiology (AWARE) study from over 5,000 critically ill children demonstrate that mild-to-moderate fluid overload as early at the end of the ICU day 1 was associated with adverse outcomes including higher mortality and fewer ICU and ventilator-free days (10). Our current data from a prospective observational study from multiple-pediatric centers are corroborative.

Patients meeting syndromic criteria for septic shock have underlying clinical and biological heterogeneity. However, few studies have considered variable responses across critical illness subclasses or risk strata as they pertain to cumulative fluid balance and mortality outcomes. Through latent profile analyses of electronic health record data, Zhang et al (12) showed that sepsis "profile 3," characterized by shock and multiple organ dysfunctions, demonstrated a survival benefit with a higher

TABLE 3.

Cox Proportional Hazard Models for Complicated Course by Pediatric Sepsis Biomarker Risk Model II Mortality Risk Strata

Pediatric Sepsis Biomarker Risk Model II Risk Strata	High Risk		Intermediate Risk		Low Risk	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Univariate models						
Decade of enrollment[a]	0.79 (0.28–2.19)	0.651	0.92 (0.40–2.14)	0.846	0.66 (0.29–1.51)	0.323
Age	1.00 (0.96–1.03)	0.787	1.01 (0.97–1.05)	0.644	0.99 (0.96–1.02)	0.427
Any CRRT	1.04 (0.57–1.88)	0.898	1.65 (0.94–2.90)	0.084	2.00 (1.23–3.25)	0.005
D3 SA-AKI	2.18 (1.14–4.19)	0.019	1.84 (1.10–3.10)	0.021	2.94 (1.99–4.35)	< 0.001
Days 1–7 %PFB[b]	1.24 (1.08–1.42)	0.002	1.04 (0.94–1.16)	0.453	1.09 (0.94–1.26)	0.282
Multivariable model						
Decade of enrollment[a]	0.72 (0.22–2.42)	0.600	0.78 (0.30–2.06)	0.621	0.71 (0.31–1.62)	0.412
Any CRRT	0.62 (0.31–1.23)	0.170	1.57 (0.84–2.91)	0.155	1.27 (0.76–2.14)	0.363
D3 SA-AKI	2.28 (1.10–4.74)	0.027	1.48 (0.84–2.60)	0.177	2.67 (1.77–4.02)	< 0.001
Days 1–7 %PFB[b]	1.24 (1.08–1.43)	0.003	1.02 (0.91–1.15)	0.700	1.08 (0.92–1.27)	0.339

CRRT = continuous renal replacement therapy, HR = hazard ratio, %PFB = percent positive fluid balance, SA-AKI = sepsis-associated acute kidney injury.

[a]Decade of enrollment: 2003–2013 vs. 2014–2023.

[b]Days 1–7 %PFB was multiplied by a factor of 10 for models.

TABLE 4.

Causal Mediation Analyses Testing Whether Pediatric Sepsis Biomarker Risk Model II Mortality Risk Probability Mediated the Relationship Between Cumulative Fluid Overload and Risk of Complicated Course

Mean Survival Ratio	Estimate (SE)	95% CI	*p*
Controlled direct effect	1.033 (0.07)	0.98 to 1.20	0.2
Pure natural direct effect	1.033 (0.07)	0.98 to 1.20	0.2
Total natural direct effect	1.033 (0.07)	0.98 to 1.20	0.2
Pure natural indirect effect	1.006 (0.01)	0.99 to 1.03	0.4
Total natural indirect effect	1.006 (0.01)	0.99 to 1.03	0.4
Total effect	1.040 (0.08)	1.00 to 1.24	0.2
Overall proportion mediated	0.156 (7.01)	–17.11 to 0.20	0.6

Models were adjusted for D3 sepsis-associated acute kidney injury and renal replacement therapy use as covariates.

cumulative fluid balance in the first 48 hours. In contrast, "profile 4" demonstrated an increased odds of death with a more PFB. Wang et al (28) studied fluid balance trajectories among critically ill patients a significant proportion of whom had sepsis. They demonstrated that relative to patients with a low fluid balance, those with a high fluid balance demonstrated an increased odds of mortality. In contrast, patients with a "decreasing" fluid balance trajectory demonstrated a survival benefit.

Our data contradict those previously published by our group, where we reported worse outcomes with high PFB among those categorized as having a low mortality risk strata based on PERSEVERE biomarkers, but not among those categorized as intermediate

or high-risk (16). There are several important contributors to the differences in direction of association. The use of multivariable models that account for D3 SA-AKI and CRRT in the current study is likely to have contributed to the lack of association previously reported among low-risk patients. Further, the larger sample size of high-risk patients allowed us to detect statistically significant differences among this subgroup of patients. Finally, the statistical approaches used as entirely different. The previous study used a denominator of 7 days irrespective of the number of actual days patients remained in the ICU, likely biasing cumulative PFB among high-risk patients, who had also had an increased risk of early death, toward the null. In contrast, in the current study, we used multivariate Cox proportional hazards model to account for the competing influence of early death on ICU length of stay and on the primary association of interest.

An advantage of our data is that biomarkers were collected on day 1 of illness with subsequent assessment of cumulative fluid balance. Our data show that patients with the highest burden of systemic inflammation as indicated by PERSEVERE-II biomarkers on day 1 of illness, were more likely to have had a PFB in the postresuscitative and stabilization phases of septic shock and the worst outcomes.

As such our data indicate that PERSEVERE-II mortality risk served as an effect modifier but did not causally mediate the primary association of interest. Recent work by our group indicates that patients deemed high-risk based on PERSEVERE-II biomarkers also had the greatest degree of endothelial dysfunction with significant elevations of serum angiopoietin-2/tie-2 ratio, which is known to mediate capillary leak (29). In future independent studies, we will seek to test whether endothelial biomarkers play a causal role between cumulative PFB and risk of complicated course.

A recent randomized trial of restrictive versus standard fluid management among adult patients with septic shock demonstrated no mortality benefit (30). Results of similar studies among pediatric septic shock patients randomized to fluid-sparing resuscitation strategy with early initiation of vasoactive support are eagerly awaited (31). Incorporation of prognostic enrichment strategies, including PERSEVERE-II biomarkers within the framework of randomized trials holds potential to show quantitative heterogeneity in treatment effect across risk strata. Pending such validation, it is plausible that PERSEVERE-II-based risk stratification may inform the targeted application of interventions such as restrictive fluid management with early initiation of vasoactive support, early de-escalation, and/or deresuscitation strategies among patients deemed high-risk.

Our study has several limitations: 1) data on resuscitative fluids received outside of the PICU were not available and thus not included. It is thus likely that cumulative percent PFB was significantly underestimated biasing the results toward the null. 2) fluid choice (crystalloid vs colloid, isotonic vs. nonisotonic) was not documented and could not be accounted for, 3) CRRT prescription data were not available, 4) given the relatively limited number of patients on CRRT, we did not adjust for duration and timing of CRRT in multivariate regression models. Each of these potentially confounding variables has been shown in other studies to potentially influence the association between post-ICU admission PFB and clinical outcomes (5). Finally, we imputed baseline SCr values in the cohort. However, only a small fraction of patients in the cohort had known preexisting kidney disease, and we therefore believe that this is less likely to have influenced the association of interest tested.

CONCLUSIONS

Cumulative PFB is independently associated with worse clinical outcomes among children with septic shock after adjusting for illness severity, presence of severe AKI, and use of CRRT. Risk-stratified analyses demonstrated that patients with a high mortality risk, based on PERSEVERE-II biomarkers, primarily contributed to this association. Incorporation of prognostic enrichment tools, including measurement of PERSEVERE-II biomarkers, in randomized trials of restrictive fluid management with early initiation of vasoactive or early de-escalation and deresuscitation strategies, may inform targeted application of such interventions among those at high risk.

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Dr. Atreya and Cincinnati Children's Hospital (CCHMC) hold a provisional patent for a unified biomarker model–PERSEVERENCE that incorporates Pediatric Sepsis Biomarker Risk Model (PERSEVERE) and endothelial dysfunction markers to predict the risk of multiple organ dysfunctions in sepsis. Dr. Atreya received funding through the Cincinnati Children's Research Foundation (CCRF) Procter-Scholar Award. Dr. Stanski and CCHMC hold a provisional patent for the use of PERSEVERE biomarkers in sepsis-associated acute kidney injury. Dr. Stanski is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) (KL2TR001426). Dr. Atreya, Dr. Stanski, and CCHMC hold a provisional patent for PERSEVERENCE sepsis-associated acute kidney injury model to identify high-risk patients for microvascular modulating therapies. Dr. Fitzgerald, Dr. Weiss, Dr. Haileselassie, Dr. Quasney, and Dr. Alder received funding from the NIH.

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