Title

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Journal

Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 20(4)

ISSN

1529-7535

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Publication Date

2019-04-01

DOI

10.1097/pcc.0000000000001845

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Crit Care Med. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Pediatr Crit Care Med. 2019 April ; 20(4): 323–331. doi:10.1097/PCC.0000000000001845.

Positive Cumulative Fluid Balance is Associated with Mortality in Pediatric ARDS in the Setting of Acute Kidney Injury

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Abstract

Objective: As acute kidney injury (AKI) and elevated cumulative fluid balance (CFB) commonly co-occur in pediatric ARDS, we aimed to identify risk-factors for their development and evaluate their independent relationships with mortality. We hypothesized that AKI and elevated CFB would

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Conflicts of Interest: None

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Copyright form disclosure: Drs. Zinter, Spicer, Liu, Calfee, Matthay, and Sapru received support for article research from the National Institutes of Health (NIH). Dr. Zinter's institution received funding from the NIH (K12 training grant). Dr. Spicer's institution received funding from NIH (T32 training grant), and he received funding from American Academy of Pediatrics (best abstract award). Dr. Liu received funding from Potrero Medical, Quark, Theravance, National Policy Forum on Critical Care and Acute Renal Failure (funding for travel), National Kidney Foundation (ACKD Associate Editor), American Society of Nephrology (funding for travel), Abbott (gift of reagents), CMIC (gift of reagents), Amgen (stockholder), ZS Pharma (Advisory Board participant), and Durect, (consultant). She received other funding from Astute (adjudicated outcomes for clinical trials), Achaogen (consultant), and the NIH/National Heart, Lung and Blood Institute (NHLBI) (Grant Awardee). Dr. Calfee's institution received funding from GlaxoSmithKline and Bayer, and she received funding from GlaxoSmithKline, Bayer (consulting), and Boehringer Ingelheim (consulting). Dr. Matthay's institution received funding from the NHLBI, Amgen, GlaxoSmithKline, and Bayer Pharmaceuticals (ARDS observational study), and he received other funding from the Department of Defense for supporting a clinical trial of ARDS and Roche-Genentec (Chair of DSMB for asthma trials). Dr. Sapru's institution received funding from the NIH, National Institute for Child Health and Human Development, and the NHLBI. The remaining authors have disclosed that they do not have any potential conflicts of interest.

be associated with markers of inflammation, and that children with elevated CFB and concomitant AKI would have worse outcomes than other children.

Design: Prospective observational study using the pRIFLE AKI classification.

Setting: 5 academic pediatric intensive care units.

Patients: 260 patients ages 1 month to 18 years meeting the Berlin definition of ARDS between 2008–2014.

Interventions: None.

Results: PICU mortality was 13% (34/260). Relative to survivors, non-survivors had greater CFB on day 3 of ARDS (+90.1 mL/kg, IQR 26.6–161.7 versus +44.9 mL/kg, IQR 10.0–111.3, p=0.008) and also had higher incidence of AKI on day 3 of ARDS (50% versus 23%, p=0.001). On stratified analysis, greater CFB on day 3 of ARDS was associated with mortality among patients with concomitant AKI (+111.5 mL/kg for nonsurvivors, IQR 82.6–236.8 versus +58.5 mL/kg for survivors, IQR 0.9–176.2, p=0.041) but not among patients without AKI (p=0.308). The presence of AKI on ARDS day 3 was associated with mortality among patients with positive CFB (29.1% versus 10.4% mortality, p=0.001) but not among patients with even or negative CFB (p=0.430). Day 1 plasma IL-6 levels were associated with the development of day 3 positive CFB, day 3 AKI, and PICU mortality, and the association between elevated day 1 IL-6 and PICU mortality was partially mediated by the interval development of day 3 positive CFB and day 3 AKI (p<0.001).

Conclusions: In pediatric ARDS, elevated CFB on day 3 of ARDS is associated with mortality specifically in patients with concomitant AKI. Plasma IL-6 levels are associated with the development of positive CFB and AKI, suggesting a potential mechanism by which inflammation might predispose to mortality.

Take-home Message:

In a prospective pediatric ARDS cohort, increasing day 3 cumulative fluid balance was associated with mortality among patients who also had acute kidney injury (AKI). Elevated day 1 IL-6 levels predicted the development of day 3 fluid overload and AKI, which partially mediated the association between IL-6 and mortality.

Tweet:

In pediatric ARDS, elevations in day 3 cumulative fluid balance are associated with mortality among patients with acute kidney injury.

Keywords

Acute Respiratory Distress Syndrome; Acute Lung Injury; Acute Kidney Injury; Pediatric Intensive Care Unit; Interleukin-6

INTRODUCTION

Pediatric Acute Respiratory Distress Syndrome (ARDS) has been associated with mortality in 15–20% of children (1). The hallmark of ARDS is non-cardiogenic pulmonary edema

accompanied by inflammation and increased circulating levels of cytokines such as interleukin-6 (IL-6) (2, 3). The severity of pulmonary edema, as quantified by chest radiography, chest ultrasonography, or transpulmonary thermodilution, is strongly associated with poor pulmonary compliance, oxygenation defects, duration of mechanical ventilation, and mortality (4–7). In ARDS, elevated cumulative fluid balance (CFB) has been associated with severity of ARDS, presumably by worsening pulmonary edema, and has also been associated with duration of mechanical ventilation and mortality (8–13). Efforts to minimize pulmonary edema through conservative fluid management have been associated with decreased duration of mechanical ventilation and ICU length of stay in both children and adults, and have therefore gained acceptance as an important therapeutic strategy in ARDS (14, 15).

The associations between ARDS mortality and excess CFB may be complicated by acute kidney injury (AKI). AKI frequently co-exists with ARDS and is itself associated with elevated mortality, though the mechanisms of this relationship are unclear. Decreased urine output in AKI may contribute to increasing mortality by increasing CFB and thus increasing pulmonary edema (8, 16). However, AKI occurs in the setting of increased vascular permeability, likely caused by elevated levels of inflammatory mediators such as IL-6 (17–20). AKI may therefore be an independent marker of increased vascular permeability, which in itself is associated with both elevated CFB and mortality in ARDS (21–23).

We therefore hypothesized that in a large cohort of children with ARDS, elevated CFB and AKI would each be associated with mortality and that patients with both elevated CFB *and* AKI might have particularly poor outcomes. We further hypothesized that elevations in IL-6 on day 1 of ARDS would be associated with the development of positive CFB and AKI on day 3 of ARDS, thus providing a potential mechanism by which early elevations in IL-6 might influence ARDS mortality.

MATERIALS AND METHODS

Setting and Patients:

As previously described (24), subjects were prospectively enrolled in a longitudinal study to evaluate ARDS clinical risk-factors and biomarkers between September 2008 and September 2014 in five academic pediatric intensive care units: UCSF Benioff Children’s Hospitals in San Francisco and Oakland; Children’s Hospital Los Angeles; Children’s Hospital Central California; and American Family Children’s Hospital. Children were screened for eligibility if they were receiving any noninvasive or invasive positive pressure support and were eligible if they met the Berlin criteria for ARDS (25), with chest radiograph interpretation performed by site investigators (this study predated the development of PALICC ARDS definitions). Patients were excluded from the cohort if they were <1 month of age, <36 weeks corrected gestational age, >18 years of age, had a documented Do Not Resuscitate or Do Not Intubate order at the time of screening, or had been enrolled in the cohort previously. Data were recorded daily at 8:00AM until the subject left intensive care. Cohort subjects were included in this study if height, weight, and fluid balance data were recorded. Management strategies, including ventilator management, fluid management, and other management, were not standardized across centers.

Design and Data Collection:

The primary outcome was PICU mortality, defined as death prior to discharge from the PICU. The primary predictors were CFB and AKI. ***CFB:*** CFB was defined as any fluid output (including but not limited to urine, chest tube, peritoneal tube, and gastrointestinal losses) subtracted from net fluid intake (including intravascular and enteral), calculated from the time ARDS criteria were met through the first, second, and third day after ARDS onset. CFB accumulated prior to the diagnosis of ARDS was not recorded. CFB was normalized to weight at ARDS onset (mL/kg) and a sensitivity analysis was performed with CFB normalized to body surface area (mL/m^2) in order to account for possible pre-existing fluid retention at the time of ARDS diagnosis. CFB was examined as a continuous variable and then patients with CFB of <0 mL/kg, 0 to +100mL/kg, +100 to +200 mL/kg, and greater than +200mL/kg were categorized as having negative fluid balance, and 0–10%, 10–20%, or >20% fluid overload (FO), respectively. ***AKI:*** AKI was defined according to the pediatric Risk, Injury, Failure, Loss, End-Stage (pRIFLE) criteria, which incorporate estimated creatinine clearance (eCCl) derived from the Schwartz equation (26), oliguria calculated from average urine output (UOP) over 24 hours, and use of renal replacement therapy (RRT), including intermittent or continuous venous or peritoneal dialysis, filtration, or diafiltration (27). Kidney injury according to pRIFLE was classified as ***None*** (eCCl >75% of baseline, UOP >0.5mL/kg/hr, and no use of RRT), ***Risk*** (eCCL within 50–75% of baseline, UOP > 0.5mL/kg/hr, and no use of RRT), ***Injury*** (eCCL within 35–50% of baseline or UOP <0.5mL/kg/hr but did not use RRT), or ***Failure*** (eCCL <35% of baseline or UOP < 0.3 mL/kg/hr or used RRT). Patient with pRIFLE classification of Injury or Failure were considered to have AKI. As baseline serum creatinine was not available, we assumed a baseline eCCl of 120 $mL/min/1.73m^2$ and performed a sensitivity analysis using an alternate baseline eCCL of 100 $mL/min/1.73m^2$ (28). To account for a potential underestimation of AKI due to a dilution of plasma creatinine by intravascular hypervolemia, we performed an additional sensitivity analysis using creatinine values adjusted for positive fluid balance (29, 30).

We evaluated the following *a priori* selected variables for a potential confounding association with PICU mortality: age, sex, race, ethnicity, route of nutrition (none vs. parenteral vs. enteral), lung injury etiology, pre-existing medical conditions including cancer and/or hematopoietic cell transplant (HCT), the Pediatric Risk of Mortality (PRISM) 3 raw score (31), the worst PaO_2/FiO_2 (P/F) ratio on day 1, and the day 1 plasma IL-6 level. As previously reported, plasma IL-6 levels were measured with a Luminex multiplex ELISA immunoassay (Myriad RBM, Austin, TX, USA) (3).

Statistical Analysis:

We evaluated the association between CFB and mortality with the non-parametric Mann Whitney test and logistic regression, and evaluated the association between AKI and mortality with the Chi squared test and logistic regression. We evaluated for significant interactions between AKI and CFB quartile with respect to their associations with mortality using a threshold p-value of 0.1. We tested whether AKI and CFB mediated the association between day 1 IL-6 and mortality using a binary mediation analysis of direct and indirect effects, with 95% confidence interval estimated using 500 bootstrapped calculations (32).

IL-6 levels were $\log_{10}$-transformed to achieve normal distribution prior to conducting any parametric tests. All analyses were performed using STATA, version 13.1 (StataCorp, College Station, Texas).

RESULTS

Total pediatric enrollment during the study period was 305 subjects; after exclusion of 45 subjects due to missing height, weight or daily fluid balance, the final cohort included 260 children. There were no statistically significant differences in age, sex, P/F ratio, PRISM-3 score, and mortality between included and excluded subjects. Clinical characteristics of included patients are shown in Table 1. Thirty-four children (13.4%) died in the PICU, with deaths occurring between 3 and 109 days after ARDS onset. Nutrition practices are described in Figure E1 and were not associated with mortality (Table E1).

Elevated Cumulative Fluid Balance is Associated with PICU Mortality:

The median CFB at the end of ARDS days 1, 2, and 3 were +26.8 mL/kg (IQR 4.0–58.7), +47.7 mL/kg (IQR 4.1–101.7), and +48.6 mL/kg (IQR 11.3–116.3). Relative to survivors, non-survivors had similar CFB at the end of ARDS day 1, trended towards greater CFB at the end of ARDS day 2, and had significantly greater CFB at the end of ARDS day 3 (Table 2). These results were similar when calculating CFB using mL/m^2 rather than mL/kg. There was a significant linear association between greater CFB on ARDS day 3 and PICU death (odds ratio 1.10 for each additional +20 mL/kg, 95% CI 1.04–1.16, p=0.001, Figure E2**).** This association was robust to adjustment for day 1 P/F ratio and cancer/HCT status and clustering patients according to PICU site (adjusted OR 1.09, 95% CI 1.02–1.16, p=0.012). Interestingly, there was only a weak association between day 3 CFB and day 3 P/F ratio (Spearman $\rho=-0.168$, p=0.011). Increasing fluid overload as determined by *a priori* selected categories was also associated with PICU mortality (Figure 1). Younger age and greater day 1 plasma IL-6 level were each associated with greater day 3 CFB (Spearman $\rho=-0.37$, $p<0.001$ and Spearman $\rho=0.23$, $p<0.001$, respectively).

AKI is Associated with PICU Mortality:

Rates of AKI on ARDS days 1, 2, and 3 were 25.1%, 27.8%, and 26.2%. On ARDS Day 3, the majority of patients qualified for a diagnosis of AKI based on decreased eCCl alone (39/68), while an additional 29/68 patients had oliguria or used of RRT (Figure 2). Relative to survivors, non-survivors had similar rates of AKI on ARDS day 1 but significantly greater rates on ARDS days 2 and 3 (Table 2). Increasing pRIFLE severity was associated with increasing mortality with the notable exception that on ARDS day 1, patients with pRIFLE Risk demonstrated higher mortality than those with already existing Injury or Failure (Figure 3). The incidence of AKI was slightly less if a baseline eCCl of 100 mL/min/1.73m^2 rather than 120 mL/min/1.73m^2 was assumed, and the incidence of AKI was slightly greater if the creatinine values were adjusted based on the assumption of plasma dilution in patients with fluid overload (Table E2). However, the associations between AKI and mortality remained significant, suggesting validity of the original classification approach. AKI on Day 3 was strongly associated with PICU mortality (OR 3.4, 95% CI 1.6–7.2, p=0.001), and this finding was independent of the day 1 P/F ratio, cancer/HCT status, and clustering by site

(adjusted OR 3.8, 95% CI 1.6–9.2, p=0.003). History of cancer/HCT and IL-6 level on Day 1 were both associated with the development of AKI on ARDS day 3 (OR 3.4, 95% CI 1.7–6.8, p<0.001 if cancer/HCT present and OR 2.1, 95% CI 1.4–3.1, p<0.001 per $\log_{10}$IL-6, respectively).

Stratified Analyses:

A logistic regression model demonstrated that both day 3 AKI and day 3 CFB were independently associated with PICU mortality with adjustment for cancer/HCT, day 1 P/F ratio, and clustering by site (AKI OR 2.1, 95% CI 1.3–3.3, p=0.002 and CFB OR 1.06 per each +20mL/kg, 95% CI 1.02–1.09, p=0.001). To test for an association between day 3 CFB and day 3 AKI, we noted that day 3 CFB was significantly higher in the presence of AKI (+82.3 mL/kg, IQR 11.2–182.5 versus +44.9 mL/kg, IQR 11.6–100.3, p=0.013). Relative to patients without AKI on day 3, patients with AKI on day 3 had greater net fluid intake (+109.9 mL/kg, IQR 770.3–16.2 versus +93.7 mL/kg, IQR 61.0–118.7, p=0.010) but similar net fluid output (−80.7 mL/kg, IQR 39.9–134.5 versus −80.9 mL/kg, IQR 55.9–117.4, p=0.972). Given the strong associations between CFB and mortality as well as between AKI and mortality, we tested for an interaction between CFB and AKI with respect to their associations with mortality. There was a strong statistical interaction between day 3 CFB and day 3 AKI with respect to mortality in a logistic model (p=0.001), and therefore, we stratified further analyses based on presence or absence of AKI. Among patients with day 3 AKI (n=68), day 3 CFB was significantly greater for non-survivors than survivors (+111.5 mL/kg, IQR 82.6–236.8 versus +58.5 mL/kg, IQR 0.9–176.2, p=0.041, Figure 4). The presence of any positive day 3 CFB was associated with mortality (29.1% mortality if positive CFB versus 10.4% if even or negative CFB, p=0.001), and each additional +20mL/kg of CFB was associated with an 8% increase in the odds of mortality (OR 1.08, 95% CI 1.01–1.17, p=0.032). In contrast, among patients without day 3 AKI (n=192), day 3 CFB was similar among non-survivors and survivors (+60.1 mL/kg, IQR 18.4–134.4 versus +43.0 mL/kg, IQR 11.6–96.1, p=0.308). The presence of positive day 3 CFB was not associated with mortality (7.7% mortality if positive CFB versus 2.7% if even or negative CFB, p=0.430), and there was no linear relationship between mortality and each additional +20mL/kg of CFB (p=0.252).

Day 1 IL-6 Levels are associated with CFB, AKI, and Mortality:

IL-6 levels were measured on day 1 in 186 patients (n=74 patients had insufficient study plasma for IL-6 measurement). There were no statistically significant differences in age, gender, day 1 P/F ratio, PRISM 3 score, and mortality between subjects with and without measured IL-6; however, Caucasian race was overrepresented in the group with IL-6 levels. Day 1 IL-6 was strongly associated with PICU mortality (OR 2.2 per $\log_{10}$ increase in IL-6, 95% CI 1.3–3.5, p=0.002). On univariate regression, elevated plasma IL-6 on ARDS day 1 was associated with the development of AKI on ARDS day 3 (OR 2.1 per $\log_{10}$ increase in IL-6, 95% CI 1.4–4.1, p<0.001) and was also associated with greater positive CFB on ARDS day 3 (+37 mL/kg per $\log_{10}$ increase in IL-6, 95% CI 20–54, p<0.001, R^2=). On mediation analysis, 33.1% of the association between day 1 IL-6 and ICU mortality was mediated by the combination of day 3 AKI and day 3 positive CFB (95% CI 14.8–51.5%, p<0.001 Figure 5).

DISCUSSION

In this study, we found that both CFB and AKI are associated with mortality in children with ARDS. There is a statistically significant interaction between elevated CFB and AKI with respect to their association with mortality, such that positive CFB is *most harmful* amongst children with AKI and appears less harmful in the absence of AKI. Further, day 1 plasma IL-6 levels are associated with the development of day 3 AKI, day 3 positive CFB, and PICU mortality, and the association between day 1 plasma IL-6 and PICU mortality appears to be partially mediated by the development of day 3 AKI and positive CFB.

Our finding that elevated CFB is associated with PICU mortality adds to the growing body of work associating fluid overload with poor clinical outcomes in pediatric acute lung injury, sepsis, and renal failure (9–11, 13, 33, 34). We confirmed work associating severe fluid overload (>20%) with mortality and also demonstrated a near-linear relationship between incremental increases in positive CFB and mortality even among patients with <10% FO. Although the direct mechanisms by which excess CFB might increase mortality risk are unknown, we speculate that due to increase pulmonary capillary permeability, ARDS patients are likely to be sensitive to CFB-induced changes in hydrostatic pressure, resulting in worsened pulmonary edema, escalating mechanical ventilation needs, and subsequent atelectotrauma, barotrauma, and volutrauma (23, 35). Others have proposed that FO may increase atrial natriuretic peptide secretion, impair the endothelial glycocalyx, and worsen microvascular perfusion (36–40).

Our finding that excess CFB is associated with PICU mortality specifically among patients with AKI is novel as it suggests that appropriate renal clearance might mitigate the deleterious state of fluid overload even prior to re-establishing a euvolemic state. We speculate this may be due to improved solute clearance and improved homeostasis of renal hormone signaling, although we were not able to test these hypotheses in this study (41). As 50% of non-survivors had AKI by ARDS day 3, this study adds to a growing list of investigations demonstrating an association between AKI and PICU mortality (27, 42–44). In 2008, *Zappitelli et al* demonstrated that the incidence of and mortality rates associated with AKI vary according to underlying assumptions about baseline renal function (28). In our study, AKI was less prevalent when assuming a baseline eCCL of 100 mL/min/1.73m^2 rather than 120 mL/min/1.73m^2 and was more prevalent when adjusting serum creatinine levels for hemodilution due to FO; however, associations between AKI and mortality remained significant despite varying definitions.

While this study strongly implicates excess CFB and AKI with mortality, it does not provide evidence that minimizing excess CFB through either conservative fluid administration, increased diuresis, or diafiltration can improve clinical outcomes. However, a recent report by *Diaz et al* demonstrated that a bundle to reduce exogenous fluid administration was associated with decreased length of mechanical ventilation and a shorter PICU length of stay (15). Similarly, in adults, the Fluid and Catheter Treatment Trial (FACTT) and other studies have demonstrated that a conservative fluid administration strategy is associated with decreased length of mechanical ventilation (14, 45). Although no interventional studies of conservative versus liberal fluid administration or removal in pediatric patients have been

performed, data do support that greater FO at the onset of RRT therapy is associated with mortality (8, 46–48). Interestingly, we found that on day 3 of ARDS, patients with AKI had significantly greater net fluid intake but similar net fluid output. Ultimately, a prospective randomized controlled trial is required to assess whether modulation of CFB in ARDS patients with AKI might be associated with improved survival.

Given our previous work associating elevated day 1 IL-6 with PICU mortality in ARDS (3), and the established literature associating elevated IL-6 with the development of AKI (17–20), a primary aim of this study was to establish whether elevated day 1 IL-6 could be associated with AKI and positive CFB in ARDS. In this cohort, elevated day 1 IL-6 was associated both with the development of day 3 AKI and with the development of day 3 positive CFB, and the development of these interim complications appeared to mediate a portion of the association between day 1 IL-6 and PICU mortality. Recently, *Famous et al* demonstrated that adult ARDS patients with a hyper-inflamed endotype characterized by elevated IL-6 displayed significant markers of renal injury and showed more favorable response to fluid-conservative therapy (49, 50). Together, these data suggest that children with ARDS and early elevations in IL-6 are at increased risk for renal injury and might be an ideal subpopulation for a future interventional trial aimed at reducing fluid overload in ARDS.

Our study has several strengths. Specifically, this is a novel analysis with biological plausibility undertaken in a large, multi-center, prospectively enrolled cohort with broad inclusion criteria. Second, the inclusion of children with a history of cancer/HCT in our cohort enabled study of the population at highest risk of ARDS mortality (51, 52). Prior work in this population has demonstrated the increased mortality risk with fluid overload in the setting of AKI, and although these prior analyses did not specifically evaluate ARDS patients, they indirectly support our hypothesis that early fluid conservative management may be most effective in children with AKI (53). Third, we addressed the classification of CFB and AKI using several sensitivity analyses to confirm internal validity of our results.

Our study does have limitations. First, as we did not have access to baseline renal function data, we may have misclassified some patients with non-dialysis-dependent chronic kidney disease as having AKI. However, chronic kidney disease is rare in children, with a prevalence of 75 or fewer cases per million age-related population (54), and whether acute versus chronic renal injury differentially affect pediatric ARDS pathobiology and outcomes is currently unknown. Second, actual AKI likely predates the date of assignment in our study, as rises in serum creatinine are known to lag behind actual injury. Third, CFB was not assessed prior to the onset of ARDS, and therefore this study could not assess whether elevated CFB can prognosticate the development of ARDS in high-risk cohorts, or whether elevated CFB prior to ARDS onset might be associated with downstream clinical outcomes such as mortality and ventilator-free days. As our study remains observational in nature, a prospective trial of a conservative versus liberal fluid management in pediatric ARDS patients with or at high risk for AKI, perhaps including measurement of IL-6, could determine the safety and potential therapeutic value of reducing CFB.

Conclusions

In summary, the combination of elevated CFB and AKI on the third day after ARDS onset was associated with higher mortality in a cohort of 260 children with ARDS. Elevated CFB and AKI were each associated with mortality, and patients with both elevated CFB and AKI were most at-risk. Day 1 IL-6 levels are associated with the development of elevated CFB and AKI on day 3. These findings suggest that patients with both ARDS and AKI are most at risk from deleterious effects of fluid overload, and may benefit more than other ARDS patients from careful fluid management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank our patients and their families for participating in this research. We also would like to thank Heidi Flori, MD; Robinder Khemani, MD; Ana Graciano, MD; and Juan Boriosi, MD for their assistance recruiting patients for this study.

NIH Funding: NICHD K12HD000850 (MSZ), NICHD T32HD049303 (ACS), NIDDK R01DK098233 and R01DK101507 (KDL), NHLBI R01HL110969 (CSC), NHLBI R37HL051856 and U01HL108713 (MAM), NHLBI K23 HL085526 and R01HL114484 (AS)

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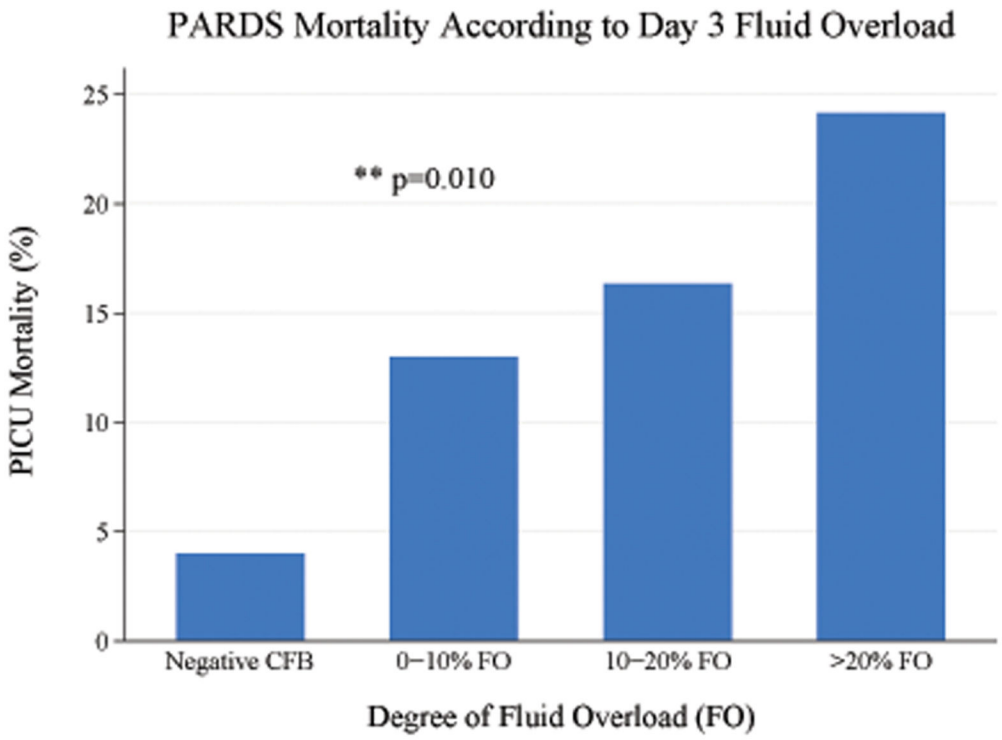

Figure 1). Pediatric ARDS Mortality According to Day 3 Fluid Overload

Mortality rates for pediatric ARDS patients according to day 3 Fluid Overload were 4% if negative CFB (n=2/50), 13.0% if 0–10% FO (n=17/131), 16.3% if 10–20% FO (n=8/49), and 24.4% if >20% FO (n=7/29). Non-parametric test of significance of ordered categories demonstrated an association between increasing category of FO and mortality (p=0.010).

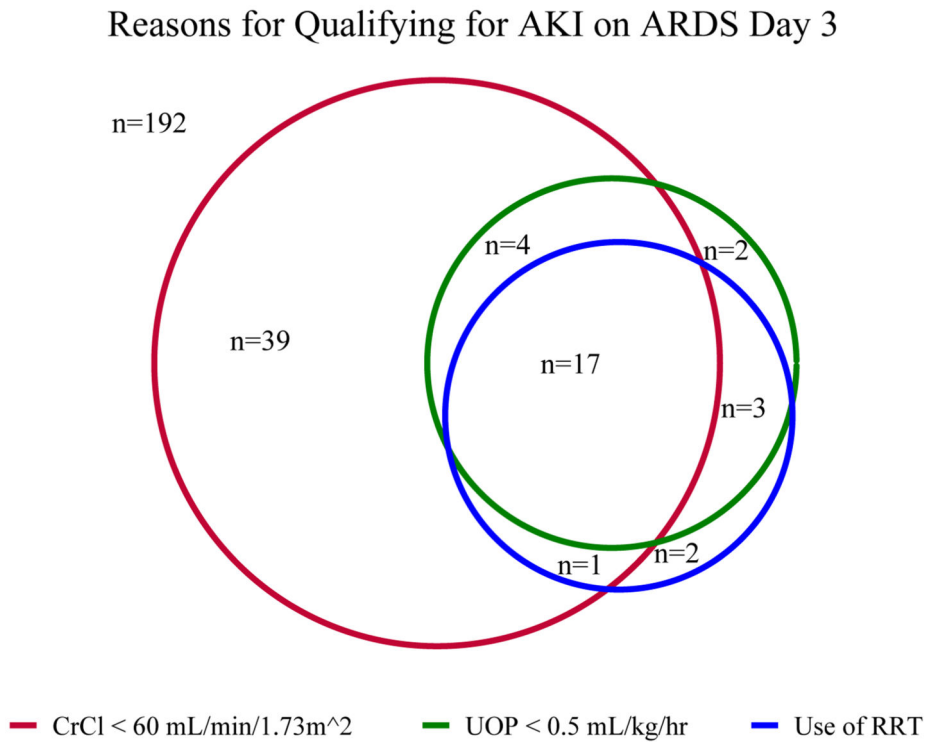

Figure 2). Reasons for Qualifying for AKI Diagnosis on ARDS Day 3

Patients qualified for a diagnosis of AKI according to pRIFLE criteria of Injury or Failure, as described in the Methods section of the text.

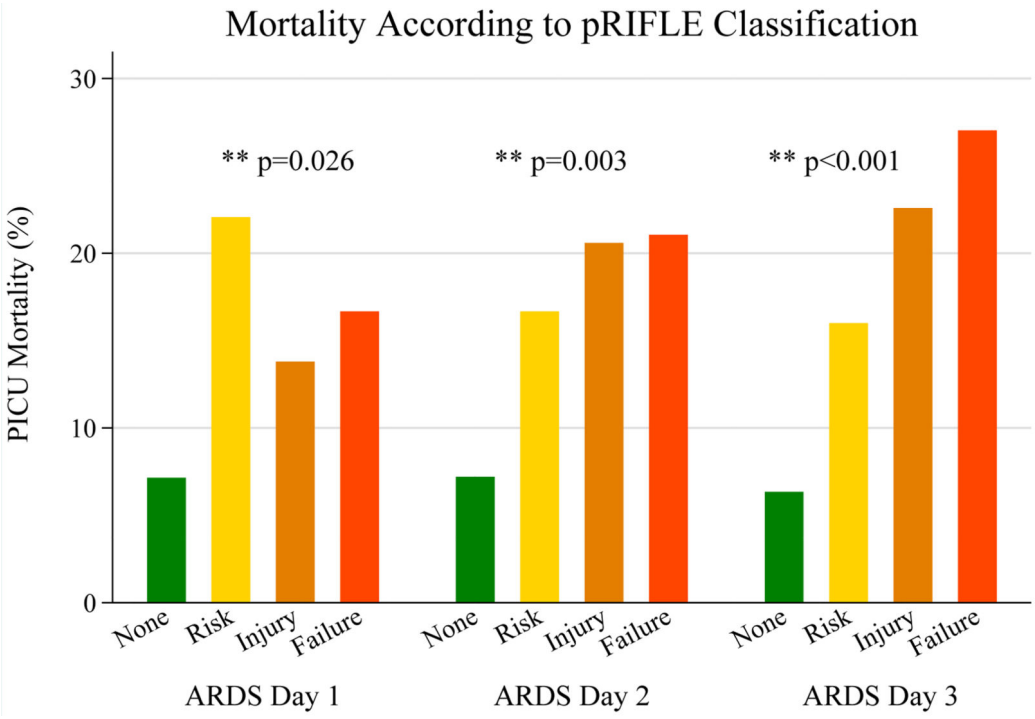

Figure 3). Mortality According to pRIFLE Classification

p-values refer to non-parametric test of significance of ordered categories demonstrating an association between increasing pRIFLE severity and mortality on each of ARDS days 1, 2, and 3.

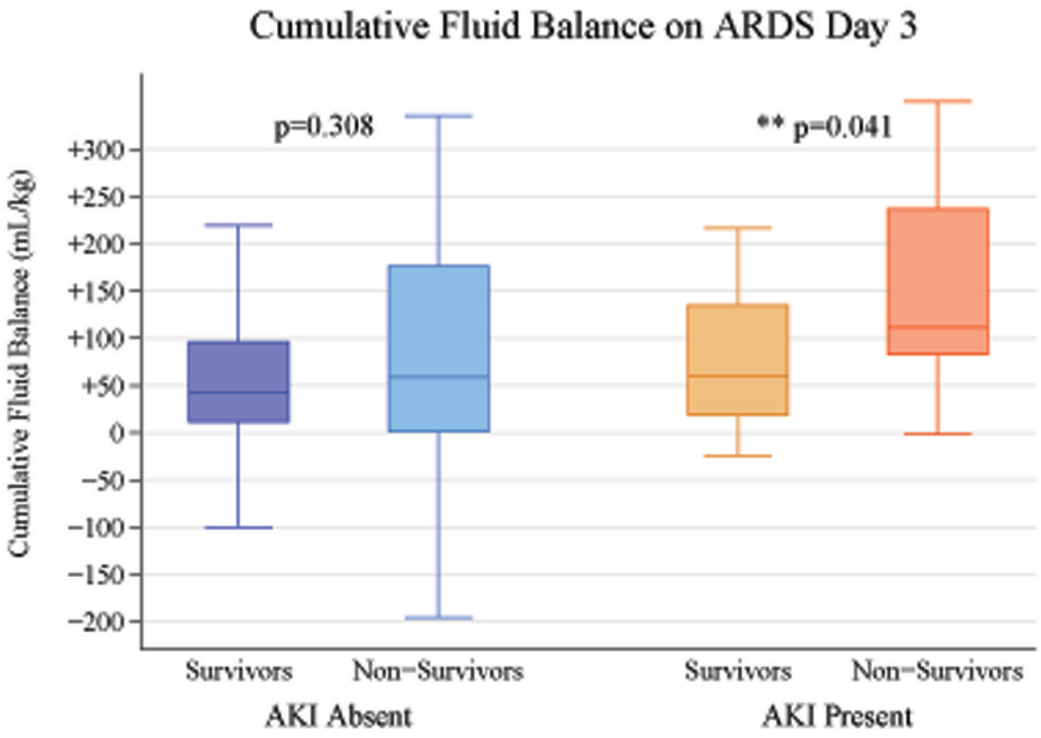

Figure 4). Cumulative Fluid Balance on ARDS Day 3

Boxplots of cumulative fluid balance on ARDS day 3, stratified by PICU survival and the presence or absence of acute kidney injury (AKI) on day 3. No Day 3 AKI and survived, n=175. No day 3 AKI and died, n=17. Day 3 AKI and survived, n=51. Day 3 AKI and died, n=17.

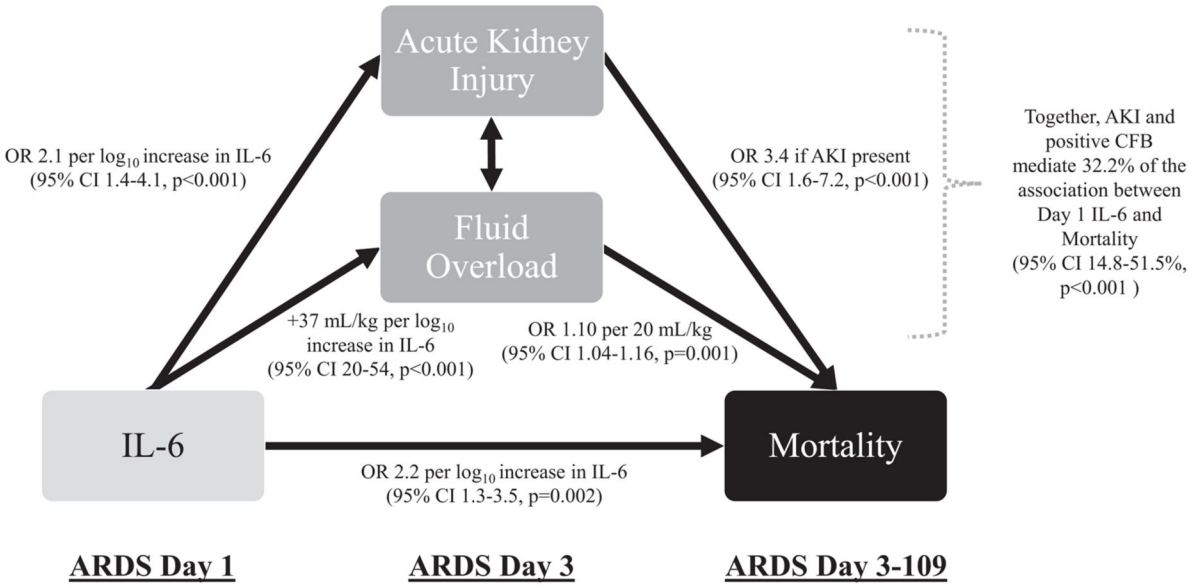

Figure 5). Concept Diagram Associating Day 1 IL-6, Day 3 AKI and Fluid Overload, and Mortality in Pediatric ARDS

Day 1 IL-6 is associated with the development of Day 3 AKI, the development of Day 3 positive CFB, and the development of PICU mortality. Day 3 AKI and Day 3 positive CFB are also each associated with PICU mortality. The association between Day 1 IL-6 and PICU mortality is partially mediated by the interval development of Day 3 AKI and Day 3 positive CFB.

Table 1)

Characteristics of Pediatric ARDS Patients on Day 1 of ARDS

Characteristic	All Patients (n=260)	PICU Survivors (n=226)	PICU Non-Survivors (n=34)	Significance
Age (median years, IQR)	5.0 (1.1-11.9)	4.9 (1.1-11.6)	6.8 (1.9-14.1)	p=0.345
Sex (% male)	54.6%	53.1%	64.7%	p=0.205
Race				p=0.548
American Indiana/Alaskan	0.8%	0.4%	2.9%	
Asian/Pacific Islander	6.2%	6.6%	2.9%	
Black or African-American	7.1%	7.1%	11.8%	
White	62.7%	63.3%	58.8%	
Other/Unknown	22.7%	22.6%	23.5%	
Ethnicity				
Latino/Hispanic	38.9%	38.9%	38.2%	p=0.931
Past Medical History				
None	32.0%	34.0%	21.0%	p=0.091
Chronic Kidney Disease	3.5%	3.6%	2.6%	p=0.859
Malignancy	10.0%	7.5%	26.5%	**p=0.001**
Hematopoietic Cell Transplant	8.5%	5.8%	26.5%	**p<0.001**
Either Malignancy Or HCT	15.8%	12.4%	38.2%	**p<0.001**
Nutrition				p=0.617
None	61%	61.6%	52.9%	
Parenteral only[a]	17%	16.1%	26.5%	
Enteral[b]	22%	22.3%	20.6%	
ARDS Etiology				p=0.720
Pneumonia	59.1%	60.0%	52.9%	
Aspiration	3.6%	3.6%	2.9%	
Sepsis	21.2%	20.0%	29.4%	
Trauma	5.0%	5.3%	2.9%	
Multiple Transfusions	1.9%	2.2%	0.0%	
Other	9.3%	8.9%	11.8%	
P/F Ratio (day 1 median, IQR)[c]	133.5 (88.2-218.3)	145.0 (88.6-242.5)	115.0 (76.0-156.4)	**p=0.018**
PRISM III (median, IQR)[d]	12 (7-19)	11 (6-18)	17 (10-21)	**p<0.001**
Plasma IL-6 (median pg/mL, IQR)[e]	76 (23-281)	69 (16-233)	194 (60-3810)	**p=0.003**
Duration of Mechanical Ventilation (median days, IQR)[f]	6 (4-13)	6 (4-12)	10 (6-23)	**p=0.001**

Bolded p-values indicate statistical significance.

[a]Parenteral nutrition was defined as any PPN and/or TPN in the absence of enteral nutrition.

[b] Enteral nutrition was defined as any enteral nutrition, with or without concomitant parenteral nutrition.

[c] P/F ratio was calculable for n=230 patients and could not be calculated or estimated for n=30 patients due to absence of P_aO2 and/or $S_pO2 \geq 97\%$.

[d] Median duration between PICU admission and ARDS diagnosis was 1 day (IQR 0-2).

[e] Day 1 IL-6 levels from plasma were available in n=186 patients.

[f] Median ventilator free days in the first 28 days of ARDS were 22 overall (IQR 16-24, 21 for survivors (IQR 10-24), and 0 for nonsurvivors (IQR 0-0).

Table 2)

Cumulative Fluid Balance and AKI are each associated with PICU Mortality on ARDS Days 2 and 3.

	All Patients (n=260)	PICU Survivors (n=226)	PICU Non-Survivors (n=34)	Significance
Cumulative Fluid Balance (median mL/kg, IQR)				
ARDS Day 1	+26.8 (4.0-58.7)	+27.9 (4.0-54.7)	+23.8 (3.6-107.0)	p=0.518
ARDS Day 2	+47.7 (4.1-101.7)	+47.5 (4.1-88.5)	+80.2 (13.0-144.5)	p=0.059
ARDS Day 3	+48.6 (11.3-116.3)	+44.9 (10.0-111.3)	+90.1 (26.6-161.7)	p=0.008
Cumulative Fluid Balance (median mL/m^2, IQR)				
ARDS Day 1	+665 (92-1,411)	+665 (92-1,342)	+636 (164-2,054)	p=0.576
ARDS Day 2	+1,243 (134-2,251)	+1,224 (103-2,079)	+1,623 (435-3,525)	p=0.039
ARDS Day 3	+1,263 (358-2,744)	+1,193 (280-2,644)	+2,286 (965-3,863)	p=0.006
Acute Kidney Injury (n, %)				
ARDS Day 1	65 (25.1)	55 (24.4)	10 (29.4)	p=0.534
ARDS Day 2	72 (27.8)	57 (25.2)	15 (45.5)	p=0.015
ARDS Day 3	68 (26.2)	51 (22.6)	17 (50.0)	p=0.001

Cumulative fluid balance in mL/kg and mL/m^2 on ARDS days 1, 2, and 3 is shown for all patients, PICU survivors, and PICU non-survivors. Rates of AKI defined as pRIFLE “Injury” or “Failure” on ARDS days 1, 2, and 3 are shown for all patients, PICU survivors, and PICU non-survivors.