Research Square

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Differential Effects of Early Fluid Overload on Acute Kidney Injury and Mortality in Critically Ill Children: A Prospective Cohort Study with Convergent Causal-Inference Methods

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Abstract

Background.

Fluid overload (FO) is reported to increase mortality in critically ill children, but whether its effects differ across renal and mortality outcomes — and whether any mortality association reflects direct effect, confounding, or mediation via acute kidney injury (AKI) — is unresolved. We applied convergent causal-inference methods.

Methods.

In a prospective cohort of 360 children (1 month–18 years) admitted ≥ 24 h to a tertiary paediatric intensive care unit, early FO (first 24 h, Goldstein formula) was dichotomised at ≥ 5%. Primary outcome: AKI (AKI Network criteria); secondary outcomes: PICU mortality, mechanical-ventilation duration, length of stay. Analyses: sequential multivariable regression, restricted cubic splines, propensity-score matching, additive/multiplicative interaction, incremental discrimination, and exploratory mediation, all adjusted for the Pediatric Risk of Mortality III (PRISM III) score.

Results.

FO ≥ 5% occurred in 23.1%, AKI in 24.7%, mortality 19.4%. FO predicted AKI (adjusted OR 4.45; propensity-matched 2.72), with a non-linear dose-response inflecting at 2–5%. FO did not predict mortality: the crude association disappeared on AKI adjustment, the adjusted spline was flat, the matched estimate was null (OR 1.36), and FO added negligibly to PRISM III discrimination (ΔAUC 0.007). AKI dominated mortality (11.3% to 77.8% stagewise); the FO×AKI interaction was sub-additive; mediation attributed FO's small effect to AKI. FO prolonged PICU stay and ventilation.

Conclusions.

Early FO has differential effects: a dose-dependent, modifiable renal insult that prolongs intensive care but not an independent cause of death once severity and AKI are considered. Preventing FO-associated AKI should be the clinical priority; PRISM III remains the mortality-prognostic tool.

Introduction

Fluid therapy is among the most common interventions in the paediatric intensive care unit (PICU), yet after initial resuscitation critically ill children frequently accumulate fluid, and fluid overload — however defined — affects roughly one-third of this population [1]. In the largest contemporary synthesis, comprising 120 studies and more than 44,000 children, fluid accumulation was associated with a more than four-fold increase in mortality (odds ratio [OR] 4.36) together with significant increases in acute

kidney injury (AKI), prolonged mechanical ventilation, and length of intensive care stay [1]. An earlier meta-analysis in general PICU populations reported a near-identical mortality association and a 6% rise in the odds of death for every 1% increase in fluid overload after adjustment for illness severity [2], and comparable associations have been described in critically ill neonates [3] and in children with severe sepsis and septic shock [4]. Collectively, this evidence has shifted practice toward restrictive resuscitation and active de-resuscitation [5], and randomised trials of restrictive fluid strategies in ventilated children are now under way [6].

Despite this consistency, the causal architecture of the fluid overload–outcome relationship remains poorly defined. Most prior studies relied on unadjusted or minimally adjusted analyses, and even those that accounted for severity typically limited adjustment to age, ventilation status, or a single composite score [1, 2]. This is a critical gap, because children with greater illness severity receive more aggressive fluid resuscitation and also carry a higher baseline risk of death — a structural confounding pattern difficult to separate from a genuine causal effect. This distinction is not academic: if the association is largely confounded, lowering fluid overload may not improve survival, whereas if it is mediated by AKI, fluid stewardship becomes a renal-protective intervention. A second and distinct possibility is that the mortality association of fluid overload operates indirectly through AKI, an intermediate outcome that affects roughly a quarter of critically ill children and independently doubles the risk of death [7]. If this mediation hypothesis holds, fluid overload should be reconceptualised as a nephrotoxin whose clinical priority is the prevention of AKI rather than of death itself. Consistent with such a pathway, recent work has shown that early fluid overload precedes and can mask creatinine-based AKI in paediatric acute respiratory distress syndrome, implying that fluid accumulation contributes to subsequent renal injury rather than acting as an independent terminal insult [8].

We therefore conducted a prospective cohort study of critically ill children with three aims: first, to quantify early fluid overload during the first 24 hours of PICU admission and its association with AKI defined by AKI Network criteria; second, to determine whether early fluid overload independently predicts mortality after adjustment for illness severity using the Pediatric Risk of Mortality III (PRISM III) score [9] and for AKI; and third, to quantify its independent associations with prolonged mechanical ventilation and length of stay. To distinguish a direct effect of fluid overload on death from an effect mediated through AKI, we complemented conventional multivariable regression with restricted cubic splines, propensity score matching, and causal mediation analysis. By applying these complementary approaches within a single, prospectively characterised cohort, we sought to establish whether early fluid overload is a direct cause of death or acts predominantly through the kidney.

Methods

Study design and setting. This prospective observational cohort study was conducted in the Pediatric Intensive Care Unit (PICU) of SMS Medical College and the attached Sir Padampat Mother and Child Health Institute, Jaipur, India — a tertiary-care referral centre — between June 2020 and November 2021. The Institutional Ethics Committee approved the protocol (Ref. 388/MC/EC/2021; approved 13 February

2021), and written informed consent was obtained from a parent or legal guardian of every enrolled child. Reporting follows the STROBE guideline for observational cohort studies.

Participants. Eligible children were aged 1 month to 18 years, admitted to the PICU for at least 24 hours, and either required mechanical ventilation or were haemodynamically unstable. We excluded children with a PICU stay shorter than 24 hours or death within the first 24 hours, an uncertain prior fluid history or treatment at another facility, inter-hospital transfer, unexpected discharge for economic reasons, known acute or chronic kidney disease, PICU readmission, refusal of consent, or incomplete fluid-balance data. Two of these exclusions were deliberately chosen to support causal interpretation. Excluding pre-existing renal disease allowed the admission creatinine to serve as a clean baseline, so that any AKI subsequently observed was genuinely incident rather than prevalent; excluding deaths within the first 24 hours ensured that the 24-hour exposure window was fully observed before any outcome could occur. The required sample size was 364, calculated for 95% confidence, an expected early-FO prevalence of 17%, and 4% absolute precision; 360 children were ultimately analysed, and the observed FO prevalence of 23.1% exceeded the planning assumption, yielding more outcome events than anticipated.

Data collection. Demographic, clinical, and laboratory data were recorded on a standardized pro forma during the first 24 hours of admission by the study investigator. Variables included age, sex, weight, admission diagnosis classified by organ system, arterial blood-gas values and admission biochemistry (the first available values within 24 hours), and the clinical parameters shock, septic shock, MODS, oliguria, dehydration, and inotrope, diuretic, and ventilation use.

Exposure. Early fluid overload was calculated over the first 24 hours using the Goldstein formula: %FO = [total input (L) − total output (L)] / baseline body weight (kg) × 100. Input comprised intravenous fluids, medications, boluses, blood products, and enteral intake; output comprised urine and surgical-drain losses, with insensible and faecal losses excluded. Urine output was quantified by weighing disposable diapers or via an indwelling catheter. Significant fluid overload was defined a priori as ≥ 5%.

Outcomes. The primary outcome was AKI during the PICU stay, defined by AKI Network criteria as a ≥ 50% rise in serum creatinine from the admission baseline or urine output < 0.5 mL/kg/hour for 6 hours, and staged 1 to 3 by standard criteria. Secondary outcomes were PICU mortality, mechanical-ventilation duration, prolonged ventilation (> 48 hours), and PICU length of stay. Illness severity was quantified by the PRISM III score from 16 parameters collected during the first 24 hours.

Statistical analysis. Continuous variables, all of which departed from normality (Shapiro–Wilk $p < 0.05$), are summarised as median (interquartile range) and compared with the Mann–Whitney U or Kruskal–Wallis test; categorical variables are compared with the χ^2 or Fisher exact test. Unadjusted associations are expressed as odds ratios (OR) with 95% confidence intervals (CI). The independent association of FO with each binary outcome was examined by multivariable logistic regression using a pre-specified sequential strategy: FO was entered first, and PRISM III, mechanical ventilation, AKI, and the remaining covariates (age, sex, shock) were added in successive steps to observe how the FO estimate behaved as

confounders and the candidate mediator were introduced. Model calibration was assessed with the Hosmer–Lemeshow test. Length of stay was modelled with multivariable linear regression. Non-linearity in the FO–outcome relationships was examined with restricted cubic splines using four knots, adjusted for PRISM III, age, and ventilation. To reduce confounding by indication, we performed 1:1 propensity-score matching on PRISM III, age, sex, weight, shock, ventilation, and inotrope use, judging covariate balance by standardized mean differences below 0.10. The incremental discriminatory value of FO beyond PRISM III for mortality was quantified by the change in area under the curve (DeLong test), the net reclassification improvement, and the integrated discrimination improvement. Effect modification between FO and AKI on mortality was assessed on the multiplicative scale (interaction term) and the additive scale (relative excess risk due to interaction, RERI). Finally, the hypothesis that AKI mediates the FO–mortality relationship was explored by causal mediation analysis using a counterfactual mediation framework with 1000 bootstrap resamples for the indirect effect, pre-specified as exploratory and hypothesis-generating. PRISM III could not be computed for two patients, who were omitted from models containing that score. A two-sided $p < 0.05$ defined significance; analyses used R version 4.5.2.

Results

Cohort characteristics. Between June 2020 and November 2021, 360 children fulfilled the eligibility criteria and had complete fluid-balance data; their baseline characteristics are summarised in Table 1. The cohort spanned infancy to adolescence with a roughly even age distribution (median age 48 months) and a male predominance of nearly two to one. Sepsis was the single commonest reason for admission, accounting for more than a third of cases, followed by neurological and pulmonary disorders. Illness severity was high: three-quarters of children were in shock, three-fifths required mechanical ventilation, and two-fifths received inotropes, with a median PRISM III score of 6. Early fluid overload of at least 5% occurred in 83 children (23.1%), acute kidney injury developed in 89 (24.7%) — most often stage 1 — and 70 children (19.4%) died. Acute kidney injury onset clustered on the second to fourth PICU days, after the 24-hour window in which the exposure was measured (Supplementary Table S1), establishing the temporal ordering on which the later mediation analysis depends.

Table 1
Baseline characteristics, clinical profile, and outcomes of the cohort (N = 360)

Characteristic	Value
Demographics	
Age, months — median (IQR)	48 (12–120)
Age group, n (%): ≤1 y / 1–5 y / 6–10 y / >10 y	106 (29.4) / 83 (23.1) / 102 (28.3) / 69 (19.2)
Male sex, n (%)	231 (64.2)
Weight, kg — median (IQR)	12.8 (8.2–24.0)
Admission diagnosis, n (%)	
Sepsis / Neurologic / Pulmonary / Cardiovascular	134 (37.2) / 72 (20.0) / 66 (18.3) / 30 (8.3)
MIS-C / Haem-oncologic / Gastrointestinal / Endocrine	16 (4.4) / 15 (4.2) / 14 (3.9) / 10 (2.8)
Poisoning / Surgical	2 (0.6) / 1 (0.3)
Illness severity	
PRISM III — median (IQR); mean ± SD	6 (4–9); 7.52 ± 4.89
Clinical features, n (%)	
Shock / Septic shock	272 (75.6) / 129 (35.8)
MODS / Oliguria / Dehydration	35 (9.7) / 51 (14.2) / 10 (2.8)
Inotrope use / Diuretic use	146 (40.6) / 148 (41.1)
Mechanical ventilation / Prolonged MV (> 48 h)	218 (60.6) / 147 (40.8)
Laboratory, first 24 h — median (IQR)	
PaO_2 / $PaCO_2$ (mmHg)	76 (56–112) / 35 (33–45)
HCO_3 (mEq/L) / pH	21 (18.7–22.3) / 7.3 (7.3–7.4)
Albumin (g/dL) / Creatinine (mg/dL) / Urea (mg/dL)	3.4 (2.9–3.8) / 0.5 (0.4–0.6) / 42 (33–45)
Sodium / Potassium / Chloride (mEq/L)	139 (134–143) / 4.3 (3.4–4.7) / 108 (102–111)
Glucose (mg/dL)	98.5 (92–109)
Fluid parameters — median (IQR)	
Fluid input (mL) / Fluid output (mL)	1233 (880–1620) / 767 (550–1023)
Fluid overload (%); mean ± SD	2.3 (1.2–4.5); 3.06 ± 2.61
Urine output (mL/kg/h)	2.3 (1.7–3.0)

Characteristic	Value
Outcomes, n (%)	
Fluid overload ≥ 5%	83 (23.1)
AKI, any	89 (24.7)
AKI stage 1 / 2 / 3	58 (16.1) / 18 (5.0) / 9 (2.5)
MV duration, days — median (IQR) [ventilated, n = 218]	3 (2–4)
PICU length of stay, days — median (IQR)	5 (4–6)
PICU mortality	70 (19.4)

Determinants of early fluid overload. Fluid overload was not distributed at random. Its frequency varied significantly across age groups, being highest in 1–5-year-olds and lowest in infants, and it was associated with markers of aggressive resuscitation and impaired fluid clearance — oliguria, inotrope use, mechanical ventilation, and diuretic use — as well as with hypoalbuminaemia, but not with the presence of shock itself (Supplementary Table S1). This profile is consistent with fluid accumulation driven by resuscitation requirements and reduced excretion rather than by haemodynamic instability per se, and it identifies the variables for which the subsequent multivariable models adjust.

Fluid overload and acute kidney injury (primary outcome). Early fluid overload was associated with acute kidney injury consistently and across every analytic approach (Table 2). In unadjusted analysis, AKI occurred more than twice as often in children with FO ≥ 5% as in those below that threshold. Critically, the association did not weaken on adjustment; after accounting for illness severity it strengthened modestly to an adjusted odds ratio of 4.45 — a suppression pattern indicating that the FO–AKI relationship is not an artefact of sicker children receiving more fluid — and modelling FO continuously showed that each one-percent increment raised the odds of AKI by roughly a fifth. The effect was directionally consistent across all four age strata and was reproduced in the propensity-score-matched cohort, in which matching on illness severity and treatment intensity removed measured confounding by indication. Restricted cubic spline modelling demonstrated a significant non-linear dose–response (Fig. 1A): AKI risk rose steeply between approximately 2% and 5% fluid overload and then plateaued, an inflection that provides empirical support for the conventional 5% threshold rather than presupposing it.

Table 2
Association of early fluid overload (≥ 5%) with acute kidney injury — convergent analyses (primary outcome)

Analysis	Effect estimate (95% CI)	p
Bivariate (unadjusted) OR	3.73 (2.13–6.55)	< 0.001
AKI incidence: FO ≥ 5% vs < 5%	45.8% vs 18.4%	—
Adjusted OR (+ PRISM III)	4.45 (2.45–8.08)	< 0.001
Fully adjusted OR (+ PRISM III, age, sex, shock, MV)	4.45 (2.43–8.17)	< 0.001
Continuous FO, per 1% increment (adjusted)	1.22 (1.10–1.36)	< 0.001
Mantel–Haenszel OR, pooled across age strata	3.57 (2.09–6.09)	< 0.001
Propensity-score-matched OR (79 matched pairs)	2.72 (1.33–5.69)	0.005
RCS — overall FO effect (adjusted)	$\chi^2 = 20.82$	0.0001
RCS — non-linearity (risk rises 2–5%, then plateaus)	$\chi^2 = 6.48$	0.039
Mean FO%: AKI vs no AKI	4.36 ± 2.46 vs 2.64 ± 2.53	< 0.001
RCS C-statistic 0.795. Age-stratified estimates are detailed in Supplementary Table S2.		

Fluid overload and mortality (secondary outcome). The relationship between fluid overload and death followed an entirely different pattern (Table 3, Panel A). The unadjusted association was statistically significant but modest, and it proved fragile under adjustment. In sequential modelling the odds ratio remained significant after adjustment for illness severity and ventilation but lost all significance the moment acute kidney injury entered the model — the characteristic signature of an effect operating through, rather than independently of, AKI. This null was then reproduced by every advanced method: the adjusted spline was flat with no evidence of non-linearity (Fig. 1B), the propensity-score-matched estimate was non-significant, and fluid overload added negligibly to the discrimination already provided by PRISM III, improving the area under the curve by less than one percentage point and correctly reclassifying only about 5% of patients (Fig. 2A). Although the overall unadjusted association was significant, it disappeared within every individual disease category (Fig. 2B); this within-subgroup non-significance is most parsimoniously read as the expected behaviour of an underpowered stratified analysis once confounding is removed, and therefore corroborates the null rather than independently establishing it.

Table 3. Association of early fluid overload with mortality, and the mediating role of AKI (secondary outcome and mechanism)

Panel A — Fluid overload (≥5%) and mortality, across methods

Analysis	Effect estimate (95% CI)	p
Bivariate (unadjusted) OR	2.22 (1.20–4.05)	0.005
Adjusted (+ PRISM III)	3.01 (1.26–7.20)	0.013
Adjusted (+ PRISM III, MV)	2.62 (1.04–6.60)	0.042
Adjusted (+ PRISM III, MV, AKI)	1.45 (0.51–4.15)	0.488
Full model (+ age, shock)	1.94 (0.61–6.18)	0.264
Propensity-score-matched OR	1.36 (0.64–2.91)	0.481
RCS — overall FO effect (adjusted)	$\chi^2 = 2.32$	0.508
RCS — non-linearity	$\chi^2 = 0.97$	0.616
Incremental value over PRISM III: ΔAUC (0.921→0.928)	DeLong	0.245
Net reclassification / integrated discrimination improvement	5.3% / 0.0087	—
Disease-stratified (Mantel–Haenszel): overall, NS within every category	2.20 (1.19–4.01)	0.007

Panel B — Acute kidney injury as the dominant driver of mortality

Analysis	Effect estimate (95% CI)	p
Mortality by AKI stage: none / 1 / 2 / 3	11.3% / 37.9% / 55.6% / 77.8%	<0.001
AKI (any) → mortality, unadjusted OR	8.38 (4.57–15.65)	<0.001
AKI in full mortality model, adjusted OR	2.83 (1.00–8.04)	0.050
FO × AKI multiplicative interaction (sub-additive)	OR 0.06 (0.01–0.50)	0.009
FO × AKI additive interaction (RERI)	−12.20	0.008
Mediation FO→AKI→mortality: proportion mediated (exploratory)	≈ 89%	NS

The mediation estimate is exploratory: the total, direct, and indirect effects did not reach significance and the direct effect of FO was essentially null, so the proportion mediated is unstable and is not interpreted quantitatively. PRISM III was the dominant mortality predictor across all models (Supplementary Table S2).

Acute kidney injury as the dominant driver of mortality. Acute kidney injury, by contrast, was strongly and gradedly related to death (Table 3, Panel B). Mortality climbed steeply with AKI stage, from approximately one in nine children without AKI to more than three-quarters of those with stage 3 injury, and AKI remained an independent predictor of death in the fully adjusted model. The interaction between

fluid overload and AKI was sub-additive on both the multiplicative and additive scales, meaning that fluid overload conferred no further mortality risk once AKI was present. Exploratory causal mediation analysis was consistent with this picture, attributing the majority of fluid overload's small total effect on mortality to the AKI pathway (Fig. 3) while the direct effect of FO was essentially null; the formal mediation estimates did not, however, reach statistical significance, and this analysis is presented as hypothesis-generating. Across the mortality models the PRISM III score was the dominant predictor, a primacy underscored by the steep gradient of mortality across its tertiles (Supplementary Table S2).

Secondary outcomes. Fluid overload was independently associated with a more prolonged intensive-care course (Supplementary Table S3). After adjustment, each one-percent increment predicted roughly one-fifth of a day of additional PICU stay, and in the matched cohort children with FO ≥ 5% remained about 2.3 days longer. Fluid overload was likewise associated with prolonged mechanical ventilation. Among children with FO ≥ 5%, diuretic use was associated with substantially lower mortality and with lower attained fluid overload but with no reduction in AKI, suggesting that any benefit operated through fluid removal rather than renal protection — although selection bias cannot be excluded in this observational comparison. Finally, total fluid input was almost identical in survivors and non-survivors, whereas net positive balance was significantly higher in children who developed AKI (Supplementary Table S3), reinforcing the interpretation that fluid overload in this cohort reflected impaired excretion rather than excessive administration. Taken together, the two confirmed independent effects of early fluid overload were on the kidney and on the duration of intensive care, not on survival.

Discussion

In this prospective cohort of critically ill children, early fluid overload was an independent, dose-dependent risk factor for acute kidney injury and for a more prolonged intensive-care course, but it was not an independent predictor of death once illness severity and AKI were taken into account. Acute kidney injury, by contrast, was the dominant determinant of mortality, and the apparent association between fluid overload and death was both confounded by severity and mediated through AKI. These findings support reconceptualising early fluid overload as a modifiable renal insult whose clinical danger lies in the kidney injury and prolonged support it produces rather than as a direct cause of death.

The association between fluid overload and AKI in our cohort was stronger and more consistent than in pooled estimates, in which fluid accumulation has been linked to AKI with odds ratios of roughly 2.0 in the largest meta-analysis [1] and 2.4 in an earlier synthesis [2]. The larger effect we observed, and its persistence — indeed strengthening — after adjustment for severity, most likely reflects our measurement of early fluid overload and of genuinely incident AKI in a cohort from which pre-existing renal disease was excluded. The restricted cubic spline identified an inflection in AKI risk between 2% and 5%, providing empirical support for the conventional 5% threshold; this dovetails with the multinational AWARE analysis by Selewski and colleagues, in which fluid overload of at least 5% by the end of the first ICU day was already associated with adverse outcomes [10]. This dose–response applied to the risk of *developing* AKI rather than to its severity: mean fluid overload did not increase

monotonically across AKI stages (Supplementary Table S2), so early fluid accumulation is better interpreted as a marker of incident renal injury than as a determinant of its grade, and the spline should not be read as a severity gradient. Our observation that AKI onset followed the fluid-overload window is concordant with evidence that early fluid overload precedes and can mask creatinine-defined AKI in children [8]. The incidence of AKI in our cohort — approximately one quarter — matched the burden reported across critically ill children [7, 11], and the clinical correlates of fluid overload that we identified (oliguria, inotrope and ventilator use, and hypoalbuminaemia, but not shock itself) are consistent with accumulation driven by resuscitation requirements, impaired excretion, and capillary leak rather than by haemodynamic instability alone. This determinant profile — dominated by hypoalbuminaemia, mechanical ventilation, oedema, and impaired excretion rather than shock — aligns with other paediatric cohorts in which the same markers of capillary leak independently predicted both fluid accumulation and incident AKI [12], and in which hypoalbuminaemia and younger age were associated with greater accumulation and its sequelae [13]. The age distribution we observed, with fluid overload most frequent in 1–5-year-olds and least frequent in infants, has been examined directly in few cohorts and is not fully concordant across them [13], so age-related differences in fluid handling warrant dedicated study. That net positive balance, rather than total fluid administered, distinguished children who developed AKI echoes evidence that the achieved balance and its trajectory — not the volume infused — drive renal outcomes [14], including the observation that a more positive net balance during continuous kidney replacement therapy is associated with fewer kidney-recovery days [15].

The relationship with mortality stood in sharp contrast. Our crude fluid overload–mortality odds ratio (2.22) lay at the lower end of the four-fold associations reported by meta-analyses [1, 2], and it disappeared once AKI entered the model. This apparent discrepancy is readily explained. Most prior studies relied on unadjusted or minimally adjusted analyses, and even the pooled adjusted estimate — a 6% increase in the odds of death per 1% fluid overload — did not account for AKI as an intermediate [1, 2]. When we removed confounding by illness severity and treatment intensity through sequential regression, restricted cubic splines, and propensity-score matching, and tested incremental value against PRISM III, every approach converged on a null, with fluid overload improving discrimination beyond PRISM III by less than one percentage point. Our result aligns closely with a prospective Indian PICU cohort managed with a restrictive fluid protocol, in which fluid balance was not associated with mortality (19.6% vs 16.8%) but was associated with a longer stay [16], and with the AWARE finding that mild fluid overload predicted morbidity whereas only more severe accumulation (≥ 10%) predicted death [10]. It is also consistent with adult randomised trials in which restricting resuscitation fluid did not reduce mortality [17]. Notably, within the sepsis subgroup — the commonest diagnosis — early fluid overload showed no association with death, in contrast to the report by Wong and colleagues that cumulative fluid overload accrued over five days predicted mortality in paediatric severe sepsis [4]; this contrast suggests that the duration and trajectory of accumulation, rather than a single early measurement, may underlie the mortality signal seen in some cohorts. Taken together, the meta-analytic mortality signal most plausibly reflects residual confounding by severity combined with the indirect renal pathway rather than a direct causal effect on death.

In contrast to the mortality findings, fluid overload was independently associated with prolonged mechanical ventilation and a longer PICU stay, and these associations were robust to propensity-score matching. They replicate the wider literature — prolonged ventilation (odds ratio 2.14) and longer intensive-care stay in pooled analyses [1, 2], and fewer ICU- and ventilator-free days in the AWARE cohort [10] — and our matched estimate of approximately 2.3 additional PICU days is virtually identical to the pooled mean difference of 2.29 days [1]. That fluid overload reliably lengthens intensive care even where it does not independently increase mortality identifies a tangible, modifiable harm with direct resource implications [16].

Two features of our data favour mediation through AKI over confounding alone. First, the temporal architecture: fluid overload and PRISM III were measured within the first 24 hours, AKI onset clustered on days 2–4, and death occurred later, so the exposure preceded the mediator, which preceded the outcome — an ordering that mediation requires and that reverse causation cannot produce, mirroring the demonstration that early fluid overload precedes creatinine-based AKI [8]. Second, AKI was the dominant determinant of death, with mortality rising steeply across AKI stages and AKI retaining independence in the full model, consistent with the AWARE programme and with reviews identifying higher AKI stages as independently associated with mortality [7, 11]. The sub-additive fluid overload × AKI interaction indicates that fluid overload contributes no additional mortality risk once AKI is established. These inferences are tempered by the exploratory nature of the formal mediation estimates, which did not reach significance — so that the proportion mediated is itself unstable and is not interpreted quantitatively — and by the likelihood of a parallel respiratory pathway: diuretic use was associated with lower mortality without a reduction in AKI, implying that fluid removal may benefit survival through mechanisms beyond the kidney; indeed, prolonged ventilation was itself strongly associated with death while fluid overload predicted prolonged ventilation, delineating a plausible pulmonary route operating in parallel with the renal one. This dissociation between the diuretic effect on survival and its absence on AKI is concordant with a paediatric randomised trial in which a furosemide infusion lowered fluid balance but did not prevent progression of early acute kidney injury [18], supporting the interpretation that diuretics relieve fluid accumulation rather than confer renal protection. To our knowledge, few paediatric studies have formally partitioned the fluid overload–mortality association into direct and AKI-mediated components or quantified additive-scale interaction — a gap that recent consensus work identifies as a priority for clarifying fluid-overload pathophysiology [14] — so our exploratory estimates are best read as hypothesis-generating signals for larger, purpose-designed cohorts.

These data reframe the clinical target. If fluid overload acts predominantly through the kidney, the priority is to prevent fluid-overload–associated AKI by limiting accumulation — plausibly below the 2–5% range at which renal risk accelerates — through early, restrictive resuscitation and active de-resuscitation [5, 6]. This is consistent with adult evidence that limiting fluid and administering diuretics increases ventilator-free days [17] and with our own observation that diuretic-treated children with fluid overload had lower mortality and lower attained fluid overload. The harms of liberal bolus resuscitation demonstrated in the FEAST trial reinforce caution with early fluid loading [19]. For mortality risk stratification, however, PRISM

III rather than fluid overload should be used [9], and renal function warrants close monitoring during the first 72 hours, when fluid overload and AKI co-evolve.

Several features strengthen these inferences: the prospective design with a pre-specified primary outcome, adequate statistical power, and the convergence of multiple analytic strategies — any one of which is individually rebuttable but which together provide robust evidence. The exclusion of pre-existing renal disease enabled assessment of genuinely incident AKI, and measuring fluid overload and illness severity before AKI onset allowed the exposure, mediator, and outcome to be temporally separated. Several limitations temper these conclusions. This was a single-centre study in an Indian tertiary PICU, which may limit generalisability. As an observational study, residual confounding cannot be excluded despite propensity-score matching. Because urine output contributes to both the fluid-overload numerator and the urine-output criterion for AKI, part of the fluid overload–AKI association may reflect shared measurement; a creatinine-only sensitivity analysis would help quantify this and was not performed in the present study. By design, our conclusions about mortality apply to children surviving beyond the first 24 hours. The interaction and mediation analyses were exploratory, with thin cell counts and a relative-excess-risk estimate that is biased when outcomes are common. Finally, fluid overload was captured at a single time point, whereas the AWARE data indicate that accumulation on later days also carries prognostic weight [10].

Conclusions

Early fluid overload is a common, dose-dependent, and modifiable renal insult in critically ill children that independently prolongs mechanical ventilation and intensive-care stay, but it is not an independent cause of death once illness severity and acute kidney injury are taken into account. Its long-reported mortality association appears to be largely confounded by illness severity and to operate through acute kidney injury, the true dominant determinant of death in this population. The actionable message for the bedside is therefore to prevent and limit fluid accumulation — targeting a fluid overload below the 2–5% range at which renal risk accelerates — in order to protect the kidney and shorten hospitalisation, while continuing to rely on the PRISM III score for mortality prognostication. Confirmation in multicentre cohorts incorporating serial fluid-balance trajectories and creatinine-anchored AKI definitions is warranted.

Abbreviations

AKI, acute kidney injury; AKIN, AKI Network; AUC, area under the curve; CI, confidence interval; FO, fluid overload; IDI, integrated discrimination improvement; IQR, interquartile range; LOS, length of stay; MODS, multiorgan dysfunction syndrome; MV, mechanical ventilation; NRI, net reclassification improvement; OR, odds ratio; PICU, paediatric intensive care unit; PRISM III, Pediatric Risk of Mortality III; RCS, restricted cubic spline; RERI, relative excess risk due to interaction.

Declarations

Ethics approval This study was approved by the Institutional Ethics Committee of SMS Medical College and attached hospitals, Jaipur, India (Ref. 388/MC/EC/2021; approved 13 February 2021, certificate issued 25 March 2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from the parents or legal guardians of all enrolled children prior to study participation.

Consent for publication Not applicable. The manuscript does not contain any individual person's data in any form (including individual details, images or videos).

Clinical trial number Not applicable.

Data availability The de-identified datasets generated and analysed during the current study are available from the corresponding author on reasonable request, subject to institutional data sharing policies and ethical approval for secondary use.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions MB conceived the study, supervised the renal-medicine aspects of design and interpretation, and drafted and critically revised the manuscript. AM (corresponding author) supervised the overall study design, oversaw clinical conduct in the pediatric intensive care unit, contributed to interpretation, and critically revised the manuscript. AA performed patient enrolment, prospective data collection, and data curation, and contributed to manuscript preparation. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figures

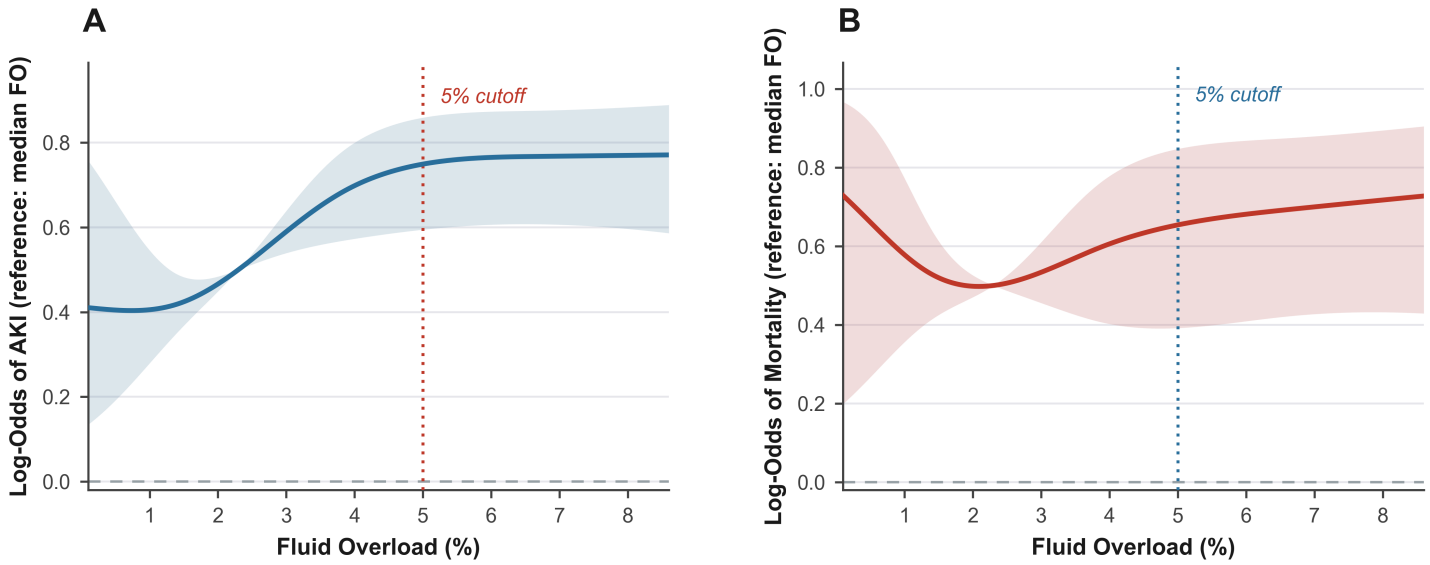


Figure 1

Restricted cubic spline dose-response of early fluid overload with acute kidney injury (Panel A) and PICU mortality (Panel B). Models use restricted cubic splines with four knots, adjusted for PRISM III, age, and mechanical ventilation; reference is the median fluid overload. Shaded bands indicate 95% confidence intervals. The vertical dotted line marks the conventional 5% clinical threshold. For AKI (A), a significant non-linear inflection between 2% and 5% (overall p=0.0001; non-linearity p=0.039) empirically validates the 5% cutoff. For mortality (B), the adjusted dose-response is flat (overall p=0.508; non-linearity p=0.616), indicating no independent association after adjustment.

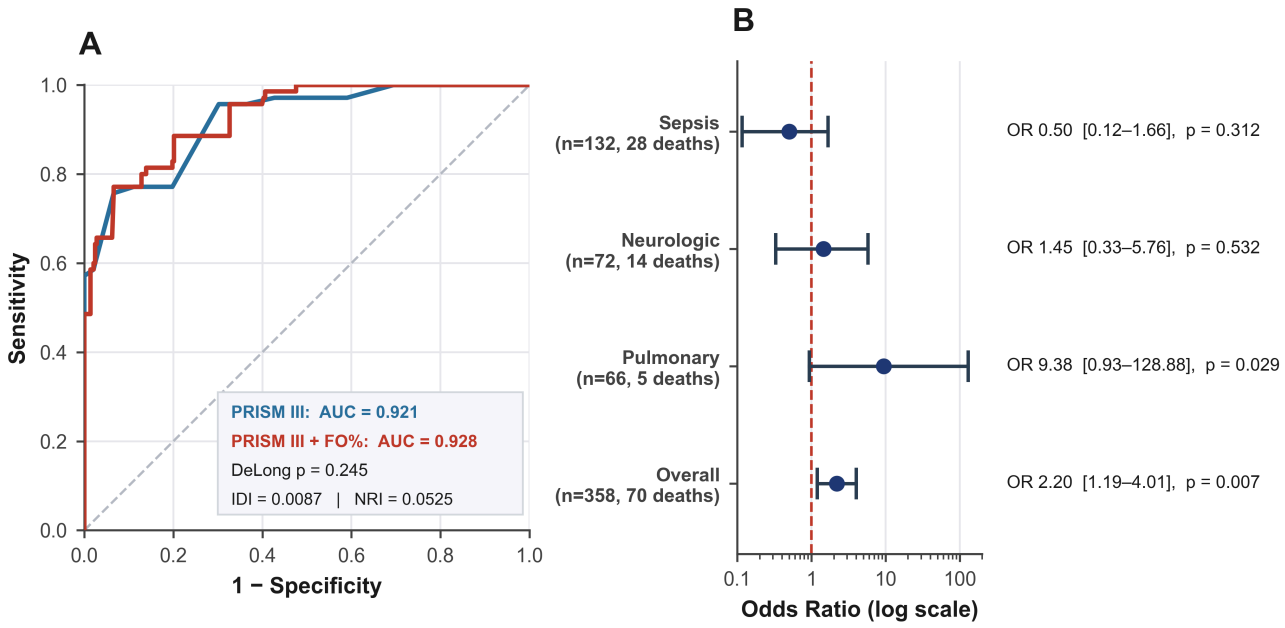


Figure 2

Incremental predictive value and subgroup heterogeneity. (A) Receiver operating characteristic curves for PICU mortality using PRISM III alone (AUC 0.921) versus PRISM III plus fluid overload percentage (AUC 0.928); incremental gain is not statistically significant (DeLong p=0.245; IDI 0.009; NRI 5.3%). (B) Subgroup analysis of fluid overload ≥5% and PICU mortality by primary admission organ system (unadjusted odds ratios with 95% CI on log scale); no individual subgroup shows a significant fluid overload-mortality association. The pulmonary estimate is unstable due to only 5 deaths in that subgroup.

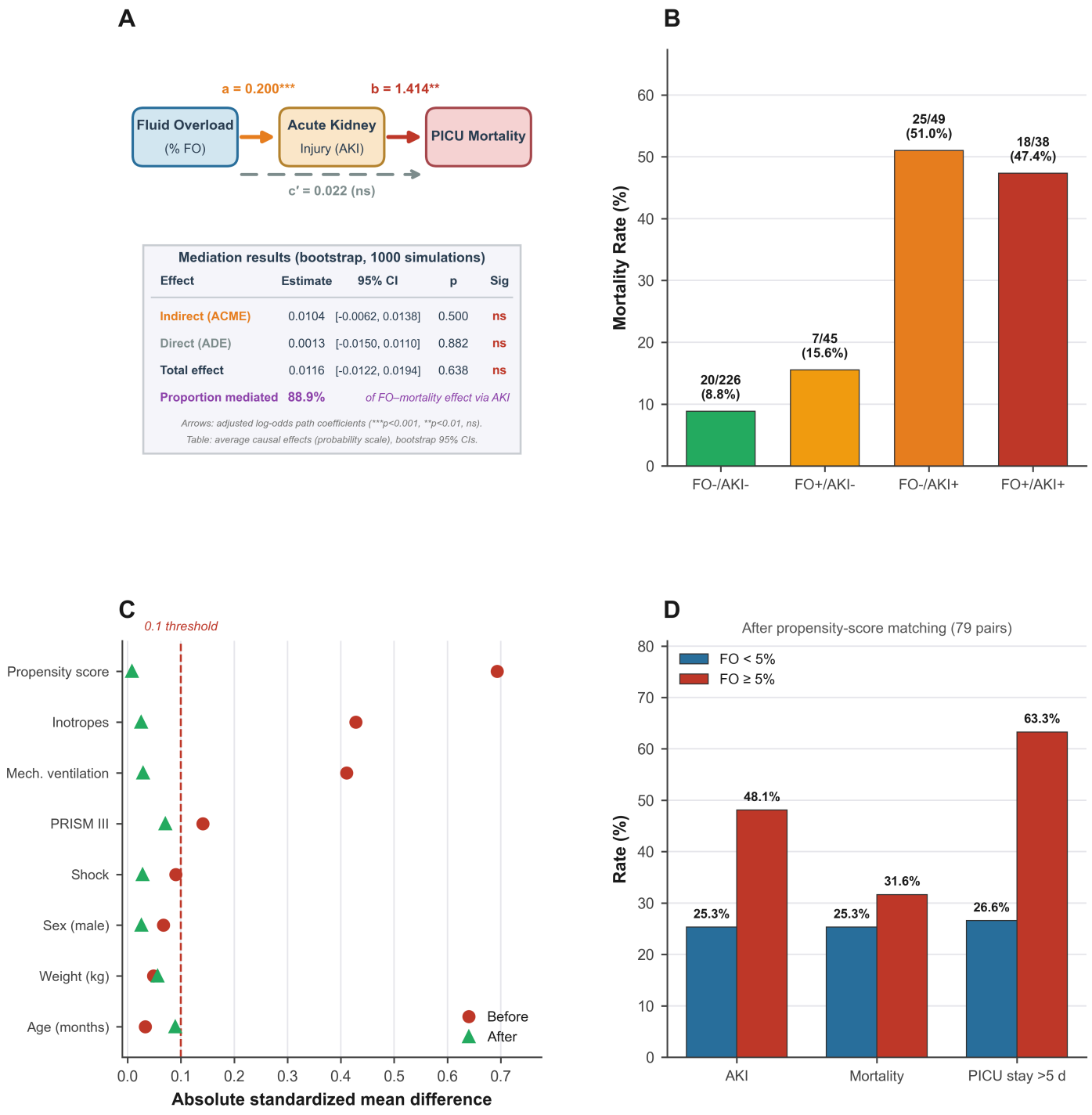


Figure 3

Causal-inference architecture of the fluid overload, acute kidney injury, and PICU mortality relationship. (A) Mediation analysis (counterfactual mediation framework, 1000 bootstrap iterations): the indirect path FO → AKI → mortality carries the majority of FO's total effect on mortality, while the direct effect is essentially null (this exploratory mediation estimate did not reach statistical significance). (B) Stratified PICU mortality by combined fluid overload and AKI status; the FO × AKI interaction is sub-additive (RERI = -12.20; p=0.008). (C) Standardized mean differences for matching covariates before (red circles) and after (green triangles) 1:1 propensity score matching (79 matched pairs; caliper 0.2 SD); all post-match

SMDs <0.10. (D) Outcomes in matched pairs by fluid overload status; FO ≥5% independently increases AKI and prolongs PICU stay >5 days but does not increase mortality (OR 1.36, p=0.481).

Supplementary Files

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- AdditionalFile1SupplementaryTables.docx