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Association Between Early Fluid Overload and Mortality in Critically Ill Children

Kritik Hasta Çocuklarda Erken Sıvı Birikimi ile Ölüm Arasındaki İlişki

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Abstract

Introduction: Fluid therapy is essential during the resuscitation of critically ill children. However, aggressive resuscitation and additional fluids from medications and nutritional support often lead to fluid accumulation. Emerging evidence indicates that fluid buildup may negatively affect outcomes. This study aims to evaluate the relationship between early fluid accumulation and mortality in critically ill children.

Methods: This study enrolled 74 children in the pediatric intensive care unit (PICU) at Adam Malik, excluding those with prior renal impairment or a stay of less than 24 hours. Patients were categorized into survivors and non-survivors. Early fluid accumulation was calculated from the first 24 hours of fluid intake and output after admission.

Results: Out of 74 patients, 55.4% of whom were boys, with a median age of 31 months [interquartile range (IQR) 8-118 months]. The median first 24-hour fluid accumulation was 1.92% (IQR -48% to 20%). Fluid accumulation differed significantly between survivors and non-survivors (p=0.001), with non-survivors showing higher fluid accumulation (16%, IQR -10% to 27%) compared to survivors (-4%, IQR -20% to 4%). Bivariate analysis shows that fluid accumulation, vasoactive agent, mechanical ventilation, and pediatric logistic organ dysfunction-2 score have significant association with mortality (p<0.05). Multivariate analysis indicates that early fluid accumulation is linked to higher mortality [odds ratio (OR): 1.64; 95% confidence interval (CI): 1.22-2.19; p=0.001], while vasoactive agents are protective factors (OR: 0.28; 95% CI: 0.09-0.94).

Conclusion: Fluid accumulation is common in the PICU and significantly linked to mortality. These findings underscore the need to develop and evaluate strategies to mitigate the harmful effects of fluid accumulation.

Keywords: Critically ill children, early fluid accumulation, mortality

Öz

Giriş: Kritik derecede hasta çocukların resüsitasyonu sırasında sıvı tedavisi esastır. Ancak agresif resüsitasyon ve ilaçlardan ve beslenme desteğinden gelen ek sıvılar sıklıkla sıvı birikimine yol açar. Ortaya çıkan kanıtlar, sıvı birikiminin sonuçları olumsuz etkileyebileceğini göstermektedir. Bu çalışma, kritik derecede hasta çocuklarda erken sıvı birikimi ile mortalite arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntemler: Bu çalışmaya Adam Malik'teki çocuk yoğun bakım ünitesinde (ÇYBÜ) böbrek yetmezliği olanlar veya 24 saatten az süre kalanlar hariç olmak üzere 74 çocuk dahil edildi. Hastalar sağ kalanlar ve sağ kalmayanlar olarak kategorize edildi. Erken sıvı birikimi, kabulden sonraki ilk 24 saatlik sıvı alımı ve çıkışından hesaplandı.

Bulgular: Yetmiş dört hastanın %55,4'ü erkekti ve ortanca yaşları 31 ay [çeyrekler arası aralık (ÇAA) 8-118 ay] idi. Ortanca ilk 24 saatlik sıvı birikimi %1,92 idi (ÇAA -%48-20). Sıvı birikimi sağ kalanlar ve sağ kalmayanlar arasında önemli ölçüde farklılık gösterdi (p=0,001), sağ kalmayanlar sağ kalanlara kıyasla daha yüksek sıvı birikimi gösterdi (%16, ÇAA -%10 ile %27) (-%4, ÇAA -%20-%4). İki değişkenli analiz, sıvı birikiminin, vazoaktif ajanın, mekanik ventilasyonun ve pediatrik lojistik organ disfonksiyon-2 skorunun mortalite ile önemli bir ilişkisi olduğunu göstermektedir (p<0,05). Çok değişkenli analiz, erken sıvı birikiminin daha yüksek mortalite ile bağlantılı olduğunu [olasılık oranı (OO): 1,64; %95 güven aralığı (GA): 1,22-2,19; p=0,001] ve vazoaktif ajanların koruyucu faktör olduğunu (OO: 0,28; %95 GA: 0,09-0,94) göstermektedir.

Sonuç: ÇYBÜ'de sıvı birikimi yaygındır ve ölümle önemli ölçüde bağlantılıdır. Bu bulgular, sıvı birikiminin zararlı etkilerini azaltmak için stratejiler geliştirme ve değerlendirme ihtiyacının altını çizmektedir.

Anahtar Kelimeler: Kritik derecede hasta çocuklar, erken sıvı birikimi, ölüm oranı

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Introduction

Fluid therapy is a crucial component in the resuscitation of critically ill children. Early aggressive fluid administration can adequately restore intravascular volume and is vital for saving lives. In addition to resuscitative fluid therapy, critically ill children are frequently administered other forms of "mandatory" fluids as part of their management, such as nutritional fluids, supportive medications, and maintenance fluids. This cumulative fluid administration frequently exceeds fluid losses, resulting in fluid overload (FO).[1,2]

Recent studies have shown that FO following initial resuscitation can substantially influence mortality in children.[3-5] Early FO has received considerable attention, as it appears to play a more critical role in predicting survival than late FO. This is because the peak severity of illness often manifests within the first few days of admission, after which the cumulative fluid balance curve flattens.[4,6] A threshold of 10% FO has been linked to increased mortality in some studies, with higher percentages correlating with even greater mortality rates.[5,7-10] At present, a clear definition of FO and a uniform threshold for predicting adverse outcomes, such as death or complications, in severely ill pediatric patients have yet to be established.

Materials and Methods

This study's data were collected from medical records until the required sample size was reached in both groups. The study population included all patients admitted to the pediatric intensive care unit (PICU) at Adam Malik Hospital, a major tertiary teaching hospital, between January and December 2022. Our PICU is a 10-bed, tertiary-level, university-affiliated PICU that combines medical and surgical (non-cardiac) and is staffed by board-certified pediatric intensivists, 24-hour residents, and one-to-one nursing care. Our PICU is equipped with ventilators, non-invasive ventilation such as continuous positive airway pressure and high flow nasal cannula, and continuous renal replacement therapy (CRRT). During the study period, our PICU did not adhere to a rigid protocol for net fluid balance; however, volume resuscitation was generally guided by the Surviving Sepsis Campaign guidelines.[1] In addition, local practice included the early administration of vasoactive drugs to ensure renal perfusion, as well as the early use of diuretics, hemodialysis, CRRT, and restricted fluid therapy to manage FO. Eligibility criteria included PICU admission for either medical or surgical reasons and an age range of 1 month to 18 years. Patients were excluded if they met any of the following criteria: 1) pre-existing acute or chronic kidney disease prior to PICU admission, 2) PICU stay of less than 24 hours, or 3) incomplete medical records. For patients with multiple PICU admissions during the study period, only the first admission was analyzed. Ethical approval for the study was granted by the University of Sumatra Utara Research Ethics Board (decision no: 457/KEPK/USU2023, date: 29.05.2023).

Data were collected from medical records using a consecutive sampling technique in both groups to achieve the required sample size. The sampling frame was derived from the mortality and admission registers of the PICU at Adam Malik Hospital. The independent variable in this study was early FO, while the dependent variable was mortality. Early FO was defined as FO within the first 24 hours of PICU admission.

FO was assessed based on the total fluid intake and output over a 24-hour period. Intake included all enteral and parenteral fluids, such as maintenance infusions, medications, nutritional products, and blood products. Output encompassed urine, blood loss, stool, nasogastric aspirates, and drainage. Urine output was measured either by weighing diapers or directly collecting urine via an indwelling urethral catheter. The percentage of FO was calculated using the following formula: [total fluid intake (L) - total fluid output (L)/body weight at PICU admission (kg)] × 100.[6,9,11]

To pinpoint independent predictors of mortality, we analyzed patient information gathered during the first 24 hours after PICU admission. This evaluation encompassed demographic data (including age, gender, body weight, and height), nutritional status, and clinical indicators, such as the pediatric organ logistic dysfunction (PELOD)-2 score and the presence of acute kidney injury (AKI). Additionally, data on PICU length of stay, use of diuretics and vasoactive medications, and net fluid balance were considered. The analysis also incorporated the earliest laboratory test results obtained during this period.

Statistical Analysis

Data analysis was conducted using SPSS software (version 25.0). For continuous variables, values were summarized as medians along with interquartile ranges (IQR), depending on the distribution pattern of the data. Group comparisons were made using the t-test for data with a normal distribution and the Mann-Whitney U test when the data were not normally distributed. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Stepwise multivariate logistic regression analysis was conducted to identify factors potentially associated with mortality. To examine associations with PICU mortality, multivariate binary logistic regression was performed, yielding odds ratios (OR) along with 95% confidence intervals (CI). A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

This study analyzed a total of 74 patients, evenly divided between the survival (n=37) and non-survival (n=37) groups. Respiratory conditions were the most frequent reason for PICU admission, accounting for 37.8% of cases. Other causes included postoperative status (20.3%), neurological disorders (18.9%), shock (10.8%), cardiac conditions (9.5%), and miscellaneous diagnoses (2.7%). Detailed sample characteristics are presented in Table 1. No statistically significant differences were found between the two groups in terms of age, gender, nutritional classification, diuretic usage, presence of AKI, or duration of PICU stay. In contrast, notable differences were observed in the administration of vasoactive medications, the use of mechanical ventilation, and early FO status, as shown in Table 2.

A bivariate analysis was first carried out to assess if early FO during the initial 24 hours of PICU admission independently correlates with increased mortality risk in critically ill pediatric patients, exploring associations between individual variables and mortality. Variables yielding a p-value below 0.25 in this initial analysis (see Table 2) were identified as potential confounders and were subsequently included in a multivariate binary logistic regression model, which used the backward elimination method.

In the multivariate logistic regression analysis, early FO (FO in the first 24 hours) was significantly associated with mortality (OR: 1.64; 95% CI: 1.22-2.19; p=0.001). The use of vasoactive agents was also significantly associated with mortality, acting as a protective factor (OR: 0.28; 95% CI: 0.09-0.94; p=0.039). However, no significant associations were found between sex (OR: 0.9; 95% CI: 0.26-3.12; p=0.877), use of mechanical ventilation (OR: 0.29; 95% CI: 0.05-1.54; p=0.147), or disease severity, as assessed by the PELOD-2 score (OR: 1.02; 95% CI: 0.99-1.05; p=0.075), and mortality in critically ill children (Table 3).

Table 1. Baseline characteristics of subjects

Variables	Total (n=74)
Age (months), median (IQR)	31 (8-118)
Gender (male), n (%)	41 (55.4)
24h fluid overload (%), median (IQR)	1.92 (-48-20)
Nutritional status, n (%)	
Severe wasted	20 (27)
Wasted	18 (24.3)
Normal	33 (44.6)
Overweight	2 (2.70)
Obese	1 (1.4)
Diuretic, n (%)	9 (12.2)
Vasoactive, n (%)	37 (50)
Mechanical ventilation, n (%)	49 (66.2)
PELOD-2 score, median (IQR)	4 (3-6)
AKI, n (%)	8 (10.8)
LOS (day), median (IQR)	6 (3-15)

IQR: Interquartile range, PELOD-2: Pediatric organ logistic dysfunction-2, AKI: Acute kidney injury, LOS: Length of stay

Table 2. Bivariate analysis between variables and mortality

Variables	Survivors (n=37)	Non-survivors (n=37)	p-value
Age (months), median (IQR)	48 (13-140)	17 (7-109)	0.394[a]
Gender (male), n (%)	23 (62.16)	18 (48.64)	0.242[b]
24h fluid overload (%), median (IQR)	-4 (-20-4)	16 (-10-27)	0.001[c]
Nutritional status, n (%)			0.670[b]
Severe wasted	9 (24.33)	11 (29.73)	
Wasted	11 (29.73)	7 (18.92)	
Normal	15 (40.54)	18 (48.65)	
Overweight	1 (2.7)	1 (2.7)	
Obese	1 (2.7)	0 (0)	
Diuretic, n (%)	6 (16.21)	3 (8.1)	0.286[b]
Vasoactive; n (%)	12 (32.43)	25 (67.56)	0.003[b]
Mechanical ventilation, n (%)	16 (43.24)	33 (89.18)	0.000[b]
PELOD-2 score, median (IQR)	3 (1-4)	6 (4-7)	0.000[a]
AKI; n (%)	3 (8.10)	5 (13.51)	0.454[b]
LOS (day), median (IQR)	6 (3-15)	6 (3-15)	0.665[a]

[a]: Independent t-test, [b]: Chi-square, [c]: Mann-Whitney U test, IQR: Interquartile range, PELOD-2: Pediatric organ logistic dysfunction-2, AKI: Acute kidney injury, LOS: Length of stay

Table 3. Multivariate analysis between variables and mortality

Variables	OR (95% CI)	p-value
Gender	0.9 (0.26-3.12)	0.877
24-h fluid overload	1.64 (1.22-2.19)	0.001
Vasoactive	0.28 (0.09-0.94)	0.039
Mechanical ventilation	0.29 (0.05-1.54)	0.147
PELOD-2 score	1.02 (0.99-1.05)	0.075

OR: Odds ratio, CI: Confidence interval, PELOD-2: Pediatric organ logistic dysfunction-2

Discussion

Children in critical condition are especially vulnerable to developing FO, notably within the initial 24 to 48 hours of care, due to the need for additional fluids for hemodynamic resuscitation, blood transfusion, medications, and capillary leak conditions.[12] Although no clinical trials have yet evaluated the impact of conservative fluid therapy or de-resuscitation strategies in children, recent recommendations for septic shock and acute respiratory distress syndrome (ARDS) suggest the use of a conservative fluid approach to prevent FO and associated complications.[13]

Findings from this study showed that the non-survival group had a higher FO compared to the survival group [median (IQR) FO in the first 24 hours for non-survivors and survivors: -4 (-20-4) and 16 (-10-27), respectively]. These findings suggest that a fluid restriction approach may have been applied more frequently in the survival group compared to the non-survival group. A study by Rameshkumar et al.[14] assessing cumulative FO over 7 days in the PICU, using a fluid restriction approach, found that a 3% FO did not significantly correlate with mortality or morbidity in critically ill children compared to a more aggressive resuscitation approach.

Fluid administration is a routine intervention in pediatric critical care, particularly during resuscitation. However, excessive fluid delivery can harm the vascular lining by disrupting the glycocalyx and damaging the endothelium. For this reason, intravenous fluids should be treated similarly to medications, each with its own clear indications, risks, and limitations. In 2014, Malbrain et al.[15] introduced a comprehensive framework for fluid stewardship, inspired by the principles used in antibiotic regulation. This framework includes the "4D" approach: considering the type of fluid, appropriate dosage, treatment duration, and timely reduction, as well as guidance on the initiation and cessation of both fluid therapy and fluid removal. The strategy also defines four clinical purposes for fluid use (resuscitation, maintenance, replacement, and nutrition) and categorizes therapy into four sequential stages, summarized by the ROSE acronym: resuscitation, optimization, stabilization, and evacuation.[16]

Recent literature suggests that FO is more related to fluid output than intake and that delaying fluid removal may worsen outcomes. In this study, diuretic use was higher in the survival group (16.21%) compared to the non-survival group (8.1%). This is likely associated with the early fluid deficit in the survival group, indicating fluid loss, compared to the non-survival group. These findings align with previous studies that suggest patients may benefit from fluid removal strategies such as diuretic use or hemofiltration.[4]

FO not only indicates that but also causes AKI. A meta-analysis of observational studies showed that the degree of FO correlates with mortality, with a 19% increased risk for every liter of fluid accumulated and a 6% increased risk for each percentage increase in FO. FO is also associated with a higher risk of AKI in critically ill children. A FO threshold >10% has been suggested as clinically significant for initiating RRT.[17] The renal angina index (RAI) is a tool used to assess the risk of AKI development in critically ill children, including FO in its analysis. Higher FO percentages lead to higher RAI scores. Studies have shown that an RAI value >8 can predict AKI on day 3 with a sensitivity of 43.7% and specificity of 79%.[18,19] This highlights that FO is an important factor in predicting AKI risk in critically ill children. In this study, the non-survival group had greater FO and a higher incidence of AKI (13.1%) compared to the survival group (8.1%), though the difference was not statistically significant (p=0.454). Further studies are needed to evaluate the direct relationship with FO.

In this study, no significant association was found among age, sex, and mortality in critically ill children. Research by Castañuela-Sánchez et al.[20] on post-cardiac surgery children showed that younger age was associated with FO, as younger children are more prone to hemodynamic instability, which increases their need for additional fluids to restore systemic perfusion.

Fluid resuscitation is the first step in early goal-directed therapy (EGDT) for managing children with sepsis or septic shock, which often requires intensive care. The administration of vasoactive and inotropic medications is the next step in cases where resuscitation does not respond to fluid therapy. EGDT has been shown to reduce mortality by up to one-third. The vasoactive-inotropic score (VIS) is a modality used to assess cardiovascular involvement that is associated with mortality in critically ill children, based on the maximum doses of vasoactive and inotropic drugs used. This study found a significant difference in vasoactive use between the non-survival and survival groups. Vasoactive agents were more frequently used in the non-survival group (67.56%) compared to the survival group (32.43%). These findings are consistent with research conducted at the Adam Malik Hospital PICU in 2021, which evaluated the relationship between VIS and

mortality. In this study, the VIS at 48 hours of PICU admission was higher in the non-survival group, compared to the survival group.[21] A VIS value >11 showed 78.87% sensitivity and 72.22% specificity in predicting mortality.[22] In this study, after multivariate analysis, vasoactive use was found to be a protective factor for mortality (OR: 0.28; p=0.039). This study did not analyze further the dosage, duration of vasoactive use, or VIS values, but it is hypothesized that vasoactive use as continuation therapy in cases unresponsive to fluid therapy may explain its protective role in mortality in this study. Furthermore, this study includes critically ill pediatric patients in general, without specifically targeting sepsis or septic shock cases. As a result, the use of inotropic agents in this study is not restricted to shock cases but may also apply to cardiovascular and other conditions. Further research is needed to assess the dose and duration of vasoactive drugs and their relationship to mortality and FO in critically ill children, considering that diagnosis classification may influence mortality outcomes.

Studies on ARDS and the latest consensus recommendations suggest that conservative fluid strategies with neutral or negative fluid balance can improve lung function and shorten PICU stay. In this study, the percentage of mechanical ventilation use was significantly higher in the non-survival group (89.19%) compared to the survival group (43.24%), (p=0.000). A meta-analysis indicated that FO >10% in the first 24 hours of PICU admission increases mortality, mechanical ventilation use, and length of PICU stay.[23] In this study, there was no significant difference in length of stay between survivors and non-survivors (p=0.665) - with a median stay of 6 days (IQR 3-15 days).

Based on bivariate analysis, a significant association was found between PELOD-2 scores and mortality in critically ill children (p<0.001); the median PELOD-2 score in the non-survivor group (median 6, IQR 4-7) was higher than in the survivor group (median 3, IQR 1-4). However, multivariate analysis revealed no significant association between PELOD-2 scores and mortality in critically ill children (p=0.075). Thus, it can be concluded that FO is an independent factor influencing mortality in this study. In line with previous studies, this research supports the hypothesis that early FO is associated with mortality in critically ill children and underscores the importance of monitoring and evaluating fluid therapy in this population. Fluid boluses for perfusion disorders in limited-resource settings have been associated with increased mortality within the first 24-48 hours.[24] This study shows that early FO within the first 24 hours increases mortality by 1.64 times after adjusting for disease severity. These results align with a meta-analysis of pediatric observational studies, which reported that each 1% rise in FO was linked to a 6% increase in mortality risk, even after accounting for initial illness severity.[5] Meanwhile, a study conducted in China in 2016 demonstrated significant findings, indicating that each 1% rise in FO was associated with a 36% higher risk of mortality.[9] Meanwhile, in patients undergoing dialysis, a twofold increase in mortality was observed in those with FO at dialysis initiation compared to those without it. Fluid removal through CRRT was found to reduce mortality. A study conducted by Kim et al.[25] in Korea showed that maintaining FO <10% during CRRT was associated with a reduction in mortality rates. A study conducted in Makassar in 2023 showed that a positive fluid balance ≥4.61% was associated with mortality in children, with 62.79% sensitivity and 58.95% specificity.[26] Preventing FO through a conservative fluid therapy approach and fluid evacuation can have a positive impact on outcomes in critically ill children.

Study Limitations

This study acknowledges several limitations that must be considered when interpreting the results.

Lack of pre-PICU admission fluid balance and PICU cumulative fluid balance data: The study was unable to assess the fluid balance prior to PICU admission, implying that initial fluid resuscitation, pressor administration, and diuretic therapy administered before admission were not recorded. Due to existing limitations, we did not assess cumulative PICU balance. This absence of baseline fluid balance data and PICU cumulative balances may have influenced the analysis of FO and its relationship with mortality.

Limited sample size and potential recording bias: The relatively small sample size and the risk of inaccurate recording of fluid input and output during PICU admission could introduce bias into the findings. Despite recalculating all collected fluid administration data from medical records to minimize potential inaccuracies, the limited sample size still raises concerns about the generalizability of the results.

Retrospective design: This was a retrospective, single-center study, which inherently limits the ability to infer causality and introduces potential bias associated with retrospective data collection. Additionally, the retrospective nature means that the findings are dependent on the quality of historical medical records and documentation.

These limitations underscore the need for further prospective, multicenter studies with larger sample sizes, detailed pre-admission baseline data, and PICU cumulative FO assessments to validate and expand the findings of this research.

Conclusion

In conclusion, FO is a prevalent issue in the PICU and is significantly associated with increased mortality. These findings highlight the critical need to develop and assess strategies aimed at mitigating the detrimental effects of FO in

critically ill children. Implementing targeted fluid management approaches has the potential to enhance clinical outcomes while minimizing the likelihood of complications associated with excessive fluid retention.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the University of Sumatra Utara Research Ethics Board (decision no: 457/KEPK/USU2023, date: 29.05.2023).

Informed Consent: This study's data were collected from medical records until the required sample size was reached in both groups.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.W., R.A.C.S., A.P.P., S.M.L., H.W., J.H., Concept: M.A.W., R.A.C.S., A.P.P., Design: M.A.W., R.A.C.S., A.P.P., J.H., Data Collection or Processing: M.A.W., S.M.L., H.W., Analysis or Interpretation: M.A.W., R.A.C.S., A.P.P., J.H., Literature Search: M.A.W., S.M.L., H.W., Writing: M.A.W., R.A.C.S.

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