ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2022;93(4):528-534
DOI: 10.32641/andespediatr.v93i4.4043

ORIGINAL ARTICLE

# Asociation between fluid overload and mortality in pediatric patients in the intensive care unit

## Asociación entre sobrecarga de fluidos y mortalidad en pacientes hospitalizados en una unidad de cuidados intensivos pediátricos

**Alexi Chávez-Valdivia[a], Paola Rojas-Vivanco[a], Alejandra Castañeda[a], María del Carmen Valdivia-Tapia[b], Nilton Yhuri Carreazo[a,b]**

[a]Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas. Lima, Perú.
[b]Unidad de Cuidados Intensivos, Hospital de Emergencias Pediátricas. Lima, Perú.

Received: September 20, 2021; Approved: March 4, 2022

**What do we know about the subject matter of this study?**

Although fluid overload is related to adverse outcomes in the pediatric intensive care unit, it is unclear whether it is a direct cause or is associated with factors that lead to it.

**What does this study contribute to what is already known?**

Fluid overload is a risk factor for mortality independent of the severity of the pediatric patient.

## Abstract

**Objective:** To assess the association between fluid overload (FO) and other risk factors in the mortality of patients admitted to the Pediatric Intensive Care Unit (PICU). **Patients and Method:** A historical cohort study was conducted. Pediatric patients older than one month and younger than 18 years who were hospitalized in the PICU for more than 48 hours during 2016 were included. Demographic and clinical data were recorded. FO was calculated as [Sum of daily (fluid in − fluid out)/weight at ICU admission] × 100. Poisson regression analysis was performed to determine factors associated with mortality. **Results:** 171 patients were included. The median age was 31 months (RIQ 8; 84). Mortality was 8.18%. FO in the surviving population was 7% and 11.5% in the deceased patients ($p < 0.05$). The adjusted analysis identified FO as a major risk factor for mortality with a Relative Risk 1.32 (1.24 - 1.40); age and Glasgow Coma Scale were protective factors. **Conclusion:** Fluid overload is an independent risk factor for mortality in the analyzed PICU cohort.

**Keywords:**
Fluid Overload;
Resuscitation;
Hemodynamics;
Mortality;
Intensive Care Units;
Pediatrics

Correspondence:
Nilton Yhuri Carreazo
yhuroc@gmail.com

Edited by:
Pablo Cruces Romero

How to cite this article: Andes pediatr. 2022;93(4):528-534. DOI: 10.32641/andespediatr.v93i4.4043

## Introduction

Fluid therapy is the cornerstone of resuscitation in critically ill patients and is one of the most commonly used strategies in these patients[1,2]. Fluids are an essential element in hemodynamic management, and administering adequate volume through early replacement can save lives[3,4]. Worldwide, there are several guidelines and protocols for the administration of fluids in Intensive Care Units (ICU), which provide information and guidance to health personnel on administering them to critically ill patients[5,6]. However, how they are administered varies widely between and even within ICUs, often depending on the specific criteria of each professional and availability, especially in situations with limited resources[1,7,8].

Beyond fluid therapy aimed at resuscitation, patients often receive varying amounts of fluids as part of their management (nutrition, medications, and maintenance fluids). This leads to fluid accumulation that often exceeds fluid elimination, resulting in a positive fluid balance[9,10]. Studies indicate that there are a series of complications and repercussions derived from the excess volume of perfused fluid, among the main ones are heart failure, acute pulmonary edema, and cerebral edema[6,11-12]. Additionally, evidence suggests an association between fluid overload and increased mortality in critically ill pediatric patients[2,11,13-14].

It is uncertain whether fluid overload (FO) is a direct cause of mortality or is associated with factors leading to it[15]. In general, these mechanisms are still under review and are poorly understood in clinical settings in which, in addition to FO, other factors such as the presence of comorbidities are present[15-16]. Given this background, our objective was to determine the association between FO and mortality in a cohort of patients admitted to a pediatric ICU (PICU), hypothesizing that cumulative fluid overload would increase mortality in critically ill children.

## Patients and Method

A historical cohort study that included patients older than one month and younger than 18 years admitted for at least 48 hours to the PICU of the Pediatric Emergency Hospital between January 01 and December 31, 2016. This facility is a tertiary health center with pediatric subspecialties. The PICU has two pediatric wards (eight beds) and cares for surgical and non-surgical patients, with approximately 300 patients seen annually. The most frequent pathologies are traumatic brain injury, pneumonia, septic shock, and meningitis. Those with incomplete clinical history were excluded. These were followed up from their admission until their discharge or death.

To calculate the sample size, the information by Sutawan et al.[11] was used, which reports a mean fluid overload of 7.9 (SD ± 12.9) observed in the deceased patients, while in those who survived a mean of -1.4 (SD ± 8.2). A confidence level of 99% was considered, and a sample size ratio of 4:1, obtaining a sample size of 135 patients. Assuming a 10% margin of error due to lost or incomplete medical records, the final sample size was 149 patients. The type of sampling was by census.

Fluid overload (FO) was defined as[17,11] [Fluid administered (L) - Fluid eliminated (considering calculated insensible losses) (L) / weight at admission (Kg) x 100] expressed as a percentage.

In our unit, a detailed hourly water balance recorded by the nursing staff is performed. Fluid intake is at the treating physician's discretion according to the patient's pathology and context; no hydration protocol established.

The treating physician performs water balances every 6, 12, and 24 hours. Insensible losses were calculated based on age as follows: in children under one year of age in a range of 24 to 33 ml/Kg/d depending on whether the patient was on mechanical or spontaneous ventilation.,In comparison, in patients over one year of age the range was 300 ml/m2/d to 400 ml/m2/d, respectively. We did not calculate the maximum fluid overload[18].

The study outcome variable was PICU mortality, defined as patient death during the days of hospitalization in the unit as reported in the medical record. The variable fluid overload is obtained from the division between the accumulated fluid (fluid balance over a period) and the weight on admission to the PICU. [Fluid administered (L) - Fluid eliminated (L) / weight on admission (kg) x 100] expressed as a percentage[2,10]. A cut-off of ≥ 10% was considered since it has been associated in previous research with higher morbidity as higher oxygenation index (OI), longer duration of mechanical ventilation, acute kidney injury (AKI) requiring renal replacement therapy (RRT), longer PICU stay, and increased mortality[13].

Pediatric Index of Mortality 2 (PIM-2) was used to estimate mortality risk[2]. The arterial blood gas values (PaO2, FiO2, and base excess) were obtained from the laboratory data of the first hour after patient admission and recorded in the clinical history. The ventilatory support variable was considered positive in patients with endotracheal intubation. The Glasgow scale value was assessed according to what was recorded in the clinical history but was not calculated for sedated patients. Finally, the fluid bolus variable was defined as the rescue therapy used to improve the patient's blood volume in the short term and was defined as the administration of any fluid bolus (crystalloid or colloid) in less than two hours.

For data collection, a data recording sheet was used, recording all our study variables. The recording sheet was completed systematically, and a database was created in Microsoft® Office Excel 2013® (Microsoft Corporation-S). Quality data control was performed by double typing. The Ethics Committee of the *Universidad Peruana de Ciencias Aplicadas* (UPC) approved the study.

Each researcher verified that the information obtained was complete and imported into STATA 13.0 statistical software, which was used for data analysis. Regarding the statistical analysis, for the numerical variables, normality was evaluated using the Shapiro Wilk test the median was used as a summary measure of central tendency, and the interquartile range was used as a measure of dispersion. Categorical variables were expressed as frequencies and percentages. In the bivariate analysis, for the numerical variables, the assumptions of homogeneity of variances and normality were tested with the Levene and Shapiro Wilk tests, respectively. The nonparametric Wilcoxon test was used to analyze categorical variables with numerical variables, Fisher's test was used for comparing categorical variables. Finally, the Poisson regression model with robust variance was used for the crude and adjusted analysis, an accepted method for multivariate analysis of dichotomous dependent variables[19]. For the adjusted analysis, confounding variables were included that were considered when a value $p < 0.05$ was obtained in the bivariate analysis (mortality risk according to PIM-2) or by pathophysiological relationship[20-22], obtaining the relative risk (RR) of each variable. The fluid bolus variable was not included due to collinearity with exposure; likewise, the mechanical ventilation variable was excluded, as it was included in the PIM-2 scale. A 95% confidence interval and a p-value $< 0.05$ were considered significant for all tests.

## Results

192 medical records were reviewed, of which 21 were incomplete and were excluded from the study. In the study period, 14 (8.18%) patients died during their stay in the PICU and 7.1% presented with fluid overload. Of the population, 53.8% were male and the median age was 31 months[8-84]. The median length of stay in PICU was five days (IQR: 3-9) and eight days from admission to discharge (IQR: 5-18). Table 1 shows the remaining characteristics of the study population.

The bivariate analysis observed that males died more than females, as did those patients to whom a fluid bolus was administered. The mortality risk calculated by PIM-2 was 14 times higher in the deceased population. Most of the patients who survived did not present shock. Among the dead, septic shock was the most prevalent cause and there were more cases than in the survivors. Likewise, it was observed that the most frequent diagnoses in the deceased group were sepsis and trauma and in those who survived, trauma headed the list of pathologies followed by respiratory pathology (table 2).

In the crude analysis, the variables with which an association was found were the risk of mortality by PIM-2 and the Glasgow scale value. Finally, in the adjusted analysis, all variables were associated with the outcome variable ($p < 0.05$). Fluid overload and PIM-2 had higher mortality risk while age and Glasgow scale value had lower (table 3). It was observed that each month older, there is 9% less mortality risk. On the other hand, it was found that there is a 15% higher mortality risk for each point of the PIM. Finally, it was observed that fluid overload increased the risk of mortality by 32%.

## Discussion

The main finding of our study was the association between fluid overload and mortality in pediatric PICU patients. Sutawan et al. performed a similar study whose results coincide with our findings[11]. Similar results have been found in studies conducted in pediatric populations with various comorbidities, such as acute renal injury, acute respiratory failure, and patients with cardiac surgery[23-26].

As previously mentioned, it is not known for sure whether fluid overload is a direct cause of mortality or if it is instead an epiphenomenon. It has been suggested that FO has harmful effects on the function of many organs, such as increased intra-abdominal pressure, and myocardial and pulmonary edema, so some propose that FO by itself can lead to organ dysfunction, inflammation, and tissue hypoperfusion. All this is because the edema caused in the organs distorts the tissue architecture, obstructing vascular flow and lymphatic drainage thus affecting oxygenation and diffusion of metabolites, leading to organ failure. In general, these mechanisms have not yet been completely defined, especially in patients with important comorbidities such as systemic inflammation, infection, or renal damage[15,27-28].

On the other hand, some data differ from previously described findings. In a prospective cohort study of 224 patients in the PICU of a hospital in Alabama, USA, FO was common in critically ill patients but was not an independent risk factor for mortality[29]. The results could differ due to variables included in the multivariate analysis, such as acute renal injury, vasopressors use, and organ failure that were not used in our study.

In our study population, age was an independent risk factor for mortality. Although there is some controversy in the literature, the tendency in most indicates that younger patients are at greater risk. Although there is no consensus on the reason for this higher mortality, it is suggested that the lesions described in younger patients are usually more severe, leading to a higher risk of mortality[30-32].

Likewise, we found a relationship between mortality and clinical parameters such as mechanical ventilation time[33], the use of fluid bolus, and the Glasgow scale value. A retrospective study by Yousefzadeh-Chabok et al. in a population similar to ours found that the lower the Glasgow scale value, the higher the mortality, coinciding with our research. This scale assesses three behavioral aspects (motor response, verbal response, and eye-opening) which combined determine the severity of brain damage, and therefore the lower the score, the worse the outcome[20]. The presence of mechanical ventilation was found to be a significant risk factor; however, in this study, this parameter was not analyzed in the univariate or bivariate analysis because it is included in the PIM-2 mortality risk scale. Our data showed that there is a 16% higher risk of mortality for each additional point in the score. This information will help encourage physicians to apply this scale more frequently, allowing a more objective evaluation for clinical decision-making[18].

Our study has some limitations. First, this study collected data from a single center; however, the sample represents well the general population since this is a specialized pediatric center that receives critical patients from different cities of the country. Similarly, the definition of fluid overload used is not an accurate measure since it is known that this should include the daily weight of the patient for a more precise determination; however, this is an impractical measure because determining weight in critically ill patients is very difficult due to the instability and supportive treatment they receive, in addition to not having accessible scales in all services. Some authors analyzed this observation and have determined that the results using or not using daily weight are quite similar[2,34] For this reason, the definition of FO based on water balance is an accepted and frequently used measure worldwide in critical patients for calculating FO. Another limitation is the insensible losses, which were calculated, being an inaccurate method with risk of errors.

Despite these limitations, the main finding of this study was that critically ill children with fluid overload are at a higher risk of death. Multicenter studies will be necessary to corroborate these results and to determine strategies to avoid fluid overload during PICU stay, such as maintenance fluid restriction calculated at 50% of basal requirements according to the Holliday-Segar formula, ensuring sufficient glucose load for normoglycemia; preparation of continuous drug infusions in the minimum recommended dilution volume; use of dynamic preload markers (invasive or noninvasive) to decide the administration of intravenous fluid boluses and titration of vasoactive drugs; early use of diuretics when hypovolemia has been ruled out, resuscitation goals achieved and diuresis is less than 0. 5 ml/kg/hr, and early initiation of enteral feeding[33].

**Table 1. Clinical and demographic characteristics**

| Variable | n = 171 (%) |
|---|---|
| Age (months)* | 31 [8;84] |
| Weight (Kg)* | 13 [7,8;25] |
| Gender | |
| Masculine | 97 (56,7%) |
| Fluid overload (%) * | 7,1 [4,2;11] |
| Bolus fluid administration | 56 (32,7%) |
| Length of stay PICU (days)* | 5 [3;10] |
| Length of stay PICU (days) | |
| > 5 | 93 (54,4%) |
| Length of stay hospital (days) | 5 [8;19] |
| Length of stay hospital (days) | |
| ≥ 8 | 98 (57,3%) |
| Mechanical ventilation | 137 (80,1%) |
| Diagnosis | |
| Sepsis | 17 (9,9%) |
| Cardiac | 4 (2,4%) |
| Respiratory | 50 (29,2%) |
| Trauma | 58 (33,9%) |
| Neurologic | 31 (12,3%) |
| Poisoning | 4 (2,4%) |
| Other | 17 (9,9%) |
| *Shock* | |
| No | 154 (90,1%) |
| Septic | 15 (8,7%) |
| Hypovolemic | 2 (1,2%) |
| Glasgow scale | |
| < 8 | 4 (7,0%) |

*Median and interquartile range. PICU: Pediatric Intensive Care Unit.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Table 2. Bivariate analysis of mortality risk factors**

| | Sobrevivientes (n = 157) | Fallecidos (n = 14) | p |
|---|---|---|---|
| | n (%) | n (%) | |
| Age (months)* | 32 (9;84) | 11 (4;72) | 0.25 |
| Weight (Kg)* | 13(8.2;25) | 9.6(4.5;22) | 0.15 |
| Gender | | | 0.28 |
| Masculine | 87 (55.4) | 10 (71.4) | |
| Bolus fluid administration | | | < 0.05 |
| Yes | 43 (27.4) | 13 (92.9) | |
| Mortality risk PIM 2*† | 2.8 (0.9; 8.2) | 25.1 (3.8; 55.8) | < 0.05 |
| Fluid overload* | 7.0 [4.0; 10.5] | 11.5 [9.2; 13.9] | < 0.05 |
| Fluid overload | | | 0.01 |
| >10% | 44 (28) | 9 (64.3) | |
| Length of stay hospital (days)* | 8 [6; 19] | 3 [3; 18] | 0.18 |
| Length of stay hospital (days) | | | 1.00 |
| ≥ 8 | 90 (57.3) | 8 (57.1) | |
| Length of stay PICU (days)* | 5 [3; 10] | 3 [3; 8] | 0.55 |
| Length of stay PICU (days) | | | 1.00 |
| ≥ 5 | 85 (54.1) | 8 (57.1) | |
| Mechanical ventilation | | | 0.07 |
| Yes | 123 (78.3) | 14 (100) | |
| Mechanical ventilation (days)* | 4 [2; 7] | 3 [3; 8] | 0.51 |
| Mechanical ventilation (days) | | | 0.04 |
| ≥ 3 | 72 (57.6) | 12 (85.7) | |
| Diagnosis | | | 0.13 |
| Sepsis | 13 (76.5) | 4 (23.5) | |
| Cardiac | 4 (100) | 0 (0) | |
| Respiratory | 48 (96) | 2 (4) | |
| Trauma | 55 (94.8) | 3 (5.2) | |
| Neurologic | 19 (90.5) | 2 (9.5) | |
| Poisoning | 4 (100) | 0 (0) | |
| Other | 14 (82.4) | 3 (17.6) | |
| Shock | | | < 0.05 |
| No | 148 (96.1) | 6 (3.9) | |
| Septic | 7 (46.7) | 8 (53.3) | |
| Hypovolemic | 2 (100) | 0 (0) | |
| Glasgow scale | | | < 0.05 |
| < 8 | 2 (3.6) | 2 (100) | |

PIM2: Pediatric Index of Mortality 2. PICU: Pediatric Intensive Care Unit. Variables analyzed with Fisher's test unless otherwise indicated. *Variable analyzed with the Mann-Whitney U test, data presented as median and interquartile range.

**Tabla 3. Análisis multivariado de Factores de riesgo para mortalidad**

| | Análisis Crudo RR (95% IC) | Análisis Ajustado RR (95% IC) |
|---|---|---|
| Sobrecarga de fluido (%) | 1.00 (0.99;1.00) | 1.32 (1.24;1.40) |
| Edad (meses) | 0.99 (0.98;1.00) | 0.91 (0.90;0.91) |
| Riesgo de mortalidad por PIM2 (%) | 1.04 (1.03;1.06) | 1.16 (1.14;1.18) |
| Escala de Glasgow (puntaje) | 0.47 (0.36;0.61) | 0.08 (0.08;0.09) |

PICU: Pediatric Intensive Care Unit. Multivariate mortality analysis adjusted for all variables. (RR, Relative risk; 95% IC, confidence interval 95%).

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

## References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.
2. Alobaidi R, Morgan C, Basu RK, et al. Association Between Fluid Balance and Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. JAMA Pediatr. 2018;172(3):257-68.
3. Garnacho-Montero J, Fernández-Mondéjar E, Ferrer-Roca R, et al. Cristaloides y coloides en la reanimación del paciente crítico. Med Intensiva. 2015;39(5):303-15.
4. Davis AL, Carcillo JA, Aneja RK, et al. The American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock: Executive Summary. Pediatr Crit Care Med. 2017;18(9):884-90.
5. Powell-Tuck J, Gosling P, Lobo DN, et al. Summary of the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients. GIFTASUP. Journal of the Intensive Care Society. 2009;10(1):13-5.
6. Pottecher T, Calvat S, Dupont H, et al. SFAR/SRLF workgroup. Hemodynamic management of severe sepsis: recommendations of the French Intensive Care Societies (SFAR/SRLF) Consensus Conference, 13 October 2005, Paris, France. Crit Care. 2006;10(4):311.
7. Wooldridge G, O'Brien N, Muttalib F, et al. Challenges of implementing the Paediatric Surviving Sepsis Campaign International Guidelines 2020 in resource-limited settings: A real-world view beyond the academia. Andes pediatr. 2021;92(6):954-62
8. Cruces P. Sepsis desde la perspectiva de países de medianos y bajos ingresos. Andes pediatr. 2021;92(6):829-30
9. Abulebda K, Cvijanovich NZ, Thomas NJ, et al. Post-ICU admission fluid balance and pediatric septic shock outcomes: a risk-stratified analysis. Crit Care Med. 2014;42(2):397-403.
10. Bhaskar P, Dhar AV, Thompson M, et al. Early fluid accumulation in children with shock and ICU mortality: a matched case-control study. Intensive Care Med. 2015;41(8):1445-53.
11. Sutawan I, Kanya Wati D, Suparyatha I. Association of fluid overload with mortality in pediatric intensive care unit. Crit Care Shock. 2016;19(1):8-13.
12. Flori HR, Church G, Liu KD, et al. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. Crit Care Res Pract. 2011;2011:854142.
13. Ketharanathan N, McCulloch M, Wilson C, et al. Fluid Overload in a South African Pediatric Intensive Care Unit. J Trop Pediatr. 2014;60(6):428-33.
14. Sankar J, Singh A, Sankar MJ, et al. Pediatric Index of Mortality and PIM2 scores have good calibration in a large cohort of children from a developing country. Biomed Res Int. 2014;2014:907871.
15. Butcher BW, Liu KD. Fluid Overload in AKI - Epiphenomenon or Putative Effect on Mortality? Curr Opin Crit Care. 2012;18(6):593-8.
16. Arikan A, Zappitelli M, Goldstein SL, et al. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatric Care Med. 2012;13(3):253-8.
17. Sánchez Torres DF, Tlacuílo Morales A, Arias González A. Sobrecarga de fluidos en pacientes hospitalizados en una institución de segundo nivel en México. Rev CONAMED 2020;25(3):107-14.
18. Diaz F, Benfield M, Brown L, et al. Fluid overload and outcomes in critically ill children: A single center prospective cohort study. J Crit Care. 2017;39:209-13.
19. Lee J, Tan CS, Chia KS. A practical guide for multivariate analysis of dichotomous outcomes. Ann Acad Med Singap. 2009;38(8):714-9.
20. Gandhi J, Sangareddi S, Varadarajan P, et al. Pediatric index of mortality 2 score as an outcome predictor in pediatric Intensive Care Unit in India. Medicine Indian J Crit Care Med. 2013;17(5):288-91.
21. Yousefzadeh-Chabok S, Kazemnejad-Leili E, Kouchakinejad-Eramsadati L, et al. Comparing Pediatric Trauma, Glasgow Coma Scale and Injury Severity scores for mortality prediction in traumatic children. Ulus Travma Acil Cerrahi Derg. 2016;22(4):328-32.
22. Cicero MX, Cross KP. Predictive Value of Initial Glasgow Coma Scale Score in Pediatric Trauma Patients. Pediatr Emerg Care. 2013;29(1):43-8.
23. Valentine SL, Sapru A, Higgerson RA, et al. Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network, Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet). Fluid balance in critically ill children with acute lung injury. Crit Care Med. 2012;40(10):2883-9.
24. Hazle MA, Gajarski RJ, Yu S, et al. Fluid overload in infants following congenital heart surgery. Pediatr Crit Care Med. 2013;14(1):44-9.
25. Seguin J, Albright B, Vertullo L, et al. Extent, risk factors, and outcome of fluid overload after pediatric heart surgery. Crit Care Med. 2014;42(12):2591-9.
26. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. Pediatr Crit Care Med. 2014;15(2):131-8.
27. Reyes-Bahamonde J, Raimann JG, Thijssen S, et al. Fluid overload and inflammation - a vicious cycle. Semin Dial. 2013;26(1):31-5.
28. Li Y, Wang J, Bai Z, et al. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. Eur J Pediatr. 2016;175(1):39-48.
29. Sinitsky L, Walls D, Nadel S, et al. Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. Pediatr Crit Care Med. 2015;16(3):205-9.
30. Morrison WE, Arbelaez JJ, Fackler JC, et al. Gender and age effects on outcome

after pediatric traumatic brain injury. Pediatr Crit Care Med. 2004;5(2):145-51.
31. Naghib S, Van der Starre C, Gischler S, et al. Mortality in very long-stay pediatric intensive care unit patients and incidence of withdrawal of treatment. Intensive Care Med. 2010; 36(1):131-6.
32. Nupen T, Argent A, Morrow B. Characteristics and Outcome of Long-Stay Patients in a Paediatric Intensive Care Unit in Cape Town, South Africa. S Afr Med J. 2016;107(1):70-5.
33. Díaz F, Nuñez MJ, Pino P, et al. Implementation of preemptive fluid strategy as a bundle to prevent fluid overload in children with acute respiratory distress syndrome and sepsis BMC Pediatr. 2018;18(1):207.
34. Lombel RM, Kommareddi M, Mottes T, et al. Implications of different fluid overload definitions in pediatric stem cell transplant patients requiring continuous renal replacement therapy. Intensive Care Med. 2012;38(4):663-9.