

Original Article

# Positive Fluid Balance as a Prognosis Predictor in Pediatric Sepsis Patients: A Retrospective Cohort Study

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## ARTICLE INFO

### Keywords:

Fluid Balance; Sepsis; Children; Mortality;

### How to cite:

Gosal AA., Lawang SA., Ganda IJ., Angriani H., Artati RD., Jusli. (2023). Positive Fluid Balance as a Prognosis Predictor in Pediatric Sepsis Patients: A Retrospective Cohort Study. Nusantara Medical Science Journal, 8(1), 1-9

### DOI:

10.20956/nmsj.v8i1.23615

## ABSTRACT

**Introduction:** Sepsis is one of the leading causes of infant and child morbidity and mortality worldwide. Fluid administration is an important way to reduce morbidity and mortality in septic patients with low blood flow and shock, since sepsis is often linked to low blood volume. The purpose of this study was to investigate the relationship between positive fluid balance and the outcome of pediatric sepsis patients. **Methods:** A retrospective cohort analysis of 80 pediatric patients diagnosed with sepsis using the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria. The positive fluid balance value was obtained from medical records and was evaluated using the Receiver Operating Characteristic (ROC) curve method. **Results:** Positive fluid balance was found to have a significant link with the outcome of pediatric sepsis patients ( $p < 0.05$ ). The positive fluid balance value of  $\geq 4.61\%$  was associated with mortality in pediatric patients with sepsis, with a sensitivity value of 62.79%, specificity of 62.16%, negative predictive value of 58.95%, and positive predictive value of 65.85%. The value of fluid balance in the first 24 hours of Pediatric Intensive Care Unit (PICU) care was higher in septic pediatric patients who died compared to those who improved, but not significantly ( $p = 0.37$ ). The value of total

*fluid balance during PICU care was higher in septic pediatric patients who died compared to those who improved ( $p < 0.01$ ).*

**Conclusions:** *Positive fluid balance with a cut-off value of 4.61% can be used as a prognostic factor in pediatric patients with sepsis.*

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## 1. INTRODUCTION

Recent research suggests that the prevalence of pediatric sepsis is growing. Sepsis causes significant morbidity and mortality. Severe sepsis and septic shock accounted for 4% of all children who are admitted to hospitals and 8% of all children who are admitted to PICU. The in-hospital mortality rate for severe sepsis in children ranges from 9 to 21 percent<sup>[1]</sup>

International recommendations and studies recommend intravenous fluid resuscitation delivered prior for the treatment of sepsis or septic shock. The reestablishment of an adequate intravascular volume with aggressive and prompt delivery of fluids can save lives. However, critically ill patients appear to develop positive fluid balance (FB) or fluid overload with relative ease. Critically sick children frequently get varied quantities of "mandated" fluids as part of their management, apart from fluid therapy aiming at resuscitation (ie, nutrition, medication, and maintenance fluids). Frequently, the cumulative fluid administration surpasses fluid loss, resulting in a positive fluid balance<sup>[1,2]</sup>

Fluid balance provided in excess of 10% of body weight, or "fluid overload," is associated with organic dysfunction, death, PICU stay, mechanical ventilation (MV) duration, and renal replacement therapy use (RRT)<sup>[3]</sup>. There is accumulating evidence that fluid accumulation after first resuscitation poses a risk for significant morbidity and mortality<sup>[1]</sup>. In a research of over 4000 cases of suspected sepsis conducted by Mullan PC, et al. (2020), a faster intravenous fluid bolus administration rate was associated with a substantial increase in the 30-day chance of death, which was maintained in an adjusted model<sup>[4]</sup>.

Our aim was to prove the relationship between positive fluid balance and outcomes in pediatric patients with sepsis. It is important to determine the optimal cut-off limit to assess the patient's prognosis, so as to reduce the risk of mortality due to fluid overload in the management of sepsis in children.

## 2. METHODS

### Research Design and Setting

We used a retrospective cohort study. This research was conducted at Dr. Wahidin Sudirohusodo Makassar's hospital using data from medical records of children with sepsis who were treated in the PICU of Dr. Wahidin Sudirohusodo Makassar. This research was carried out starting in December 2021 until Mei 2022. This research plan was given the permission number 220/UN4.6.4.5.31/PP36/2022 by the Health Research Ethics Commission of the Faculty of Medicine at Hasanuddin University.

### Participant

The Inclusion criteria for this study were age 1 month to 18 years, having clinical signs and laboratory markers of sepsis (routine blood, peripheral blood smear, IT ratio, procalcitonin, CRP, and blood culture), meeting the criteria for sepsis based on IPSCC 2005, a length of stay of 24 hours, and complete medical record data. This study excluded patients with heart disease, kidney disease, malnutrition type kwashiorkor, and negative fluid balance.

There were 127 children who enter the PICU treatment room at Dr. Wahidin Sudirohusodo. Of 112 patients who met the criteria for sepsis, 80 patients met the inclusion criteria, while 32 patients did not match the inclusion criteria for this study, they were excluded. Because 5 patients were treated within 24 hours, 3 patients suffered from heart failure, 3 patients suffered from kidney disease, and 12 patients had negative fluid balance.

### Data collection

Medical records were used to record the patient's name, register number, age, gender, weight, height, nutritional status, vital signs (blood pressure, pulse, respiration, temperature, and level of consciousness), clinical symptoms, routine laboratory tests, sepsis markers, total daily fluid intake, total daily fluid output, and daily fluid balance. A Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score will be made for all patients who meet the IPSCC 2005 criteria for sepsis. This score is used to predict patient mortality. While in treatment, research subjects were observed until an effect (outcome) occurred, i.e., the sepsis patient improved (was allowed to go home or changed to usual care) or died (during treatment in the PICU).

The result of calculating the percentage of daily fluid accumulation divided by the number of lengths of treatment and having a result of more than 10% is also called a positive fluid balance. [3].

$$\% \text{ Daily fluid balance} = \frac{(\text{Total daily fluid input (L)} - \text{Total daily fluid output(L)})}{\text{The patient's weight at the time of admission to the PICU}} \times 100\%$$

### Analysis Data

Data processing was carried out using SPSS v. 26. Test for normality using the Kolmogorov-Smirnov test. The unpaired student t test was used to compare the mean value of positive fluid balance in sepsis patients with the outcome. To determine the relationship between prognostic factors and outcome, the chi square test was used. The Receiver Operator Curve (ROC) curve was created to determine the optimal cut-off point for fluid balance in predicting outcomes. On the ROC curve, we searched for the highest intersection point between the sensitivity variable and 1-specificity.

## 3. RESULTS

### Subject Characteristics

The features of the group of pediatric participants in this study who had sepsis and a positive fluid balance are shown in Table 1. Of the 80 pediatric patients with sepsis, there were more males than females. The age group of 5 years outnumbers the age group of > 5 years. There were 43 deaths and 37 recoveries among patients with sepsis and positive fluid balance.

**Table 1. Subject Characteristics**

<b>Variable</b>	<b>Frequency (n)</b>	<b>Percentage (%)</b>
<b>Sex</b>		
Male	46	57.5
Female	34	42.5
<b>Age</b>		
<5 years	61	76.3
> 5 years	19	23.8
<b>Breathing Device</b>		
Nasal cannula	16	20
High Flow Nasal	2	2.5
Simple Mask	1	1.3
Non Rebreathing Mask	9	11.3
Mechanical Ventilator	52	65
<b>Bolus Fluid Administration</b>	27	33.7
<b>Use of Vasopressor Drugs</b>	45	56.3
<b>Primary Diagnosis</b>		
Allergy	1	1.3
Gastroenterhepatology	7	8.8
Hematology	12	15
Infection	6	7.5
Cardiology	6	7.5
Neurology	14	17.5
Nephrology	1	1.2
Respirology	13	16.2
Surgery	20	25
<b>Reason for Entering PICU</b>		
Respiratory Distress/Failure	40	50
Loss of consciousness	20	25
Hemodynamic Instability	3	3.7
Other	17	21.3
<b>Outcome</b>		
Recover	37	46.2
Death	43	53.8

### **Determination of the Optimal Point of Positive Fluid Balance**

In Figure 1, the value of the positive fluid balance assessed is above the diagonal line leading to the upper left corner, with the largest area under curve (AUC), which is the cut-off point at the limit value of  $\geq 4.61\%$ . The value at this point of intersection is the best predictor value for determining the outcome.

Based on Figure 2, the acquisition of the sensitivity and specificity cut-off point is at the 39th point, which, if converted to a fluid balance value, is the optimal positive fluid balance cut-off value of 4.61. The cut-off point value is  $\geq 4.61\%$ , which has a sensitivity of 62.79% and a specificity of 62.16% with an Area Under the Curve (AUC) of 0.745. As a result, the positive fluid balance value of  $\geq 4.61\%$  was used as the cut-off point for the positive fluid balance value in the sepsis group with death and recovery outcomes.

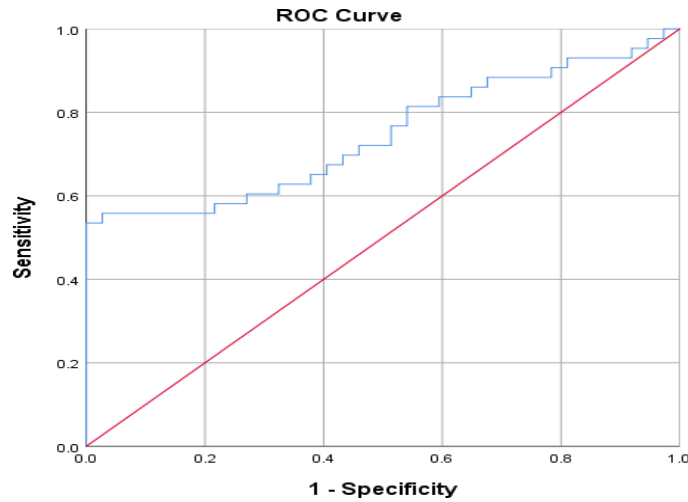


Figure 1. Receiver operating characteristic (ROC) curve for positive fluid balance

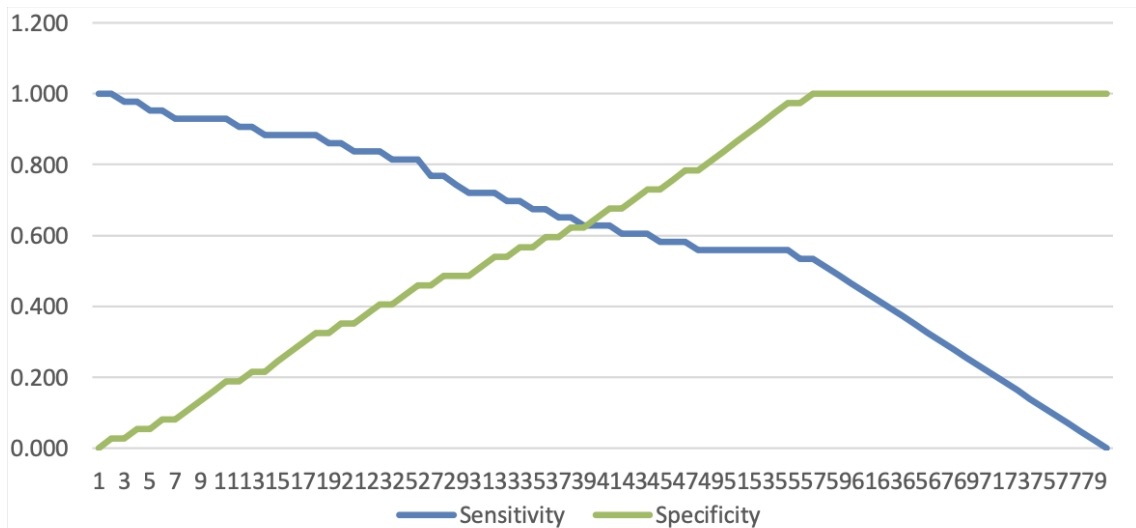


Figure 2. Receiver operating characteristic (ROC) curve for positive fluid balance

**The Relationship Between Positive Fluid Balance and Pediatric Sepsis Patients**

In children with sepsis who had a positive fluid balance value of  $\geq 4.61\%$ , it was found that more died than those who recovered. On the other hand, the group of children with sepsis who had a positive fluid balance  $< 4.61\%$  recovered more than died. Statistically, there was a significant relationship between positive fluid balance and outcome in pediatric patients with sepsis ( $p = 0.045$ ). A positive fluid balance value of 4.61% has a sensitivity value of 62.79% and a specificity of 62.16%, with a positive predictive value of 65.85% and a negative predictive value of 58.97% (Table 2).

**Table 2. Relationship of Positive Fluid Balance with Outcome of Pediatric Patients with Sepsis**

Variable	Outcome		P	OR (95% CI)	Sensitivity	Specificity	PPV	NPV	AUC
	Death (%)	Recover (%)							
<b>Positive Fluid Balance</b>									
≥ 4,61%	27 (65.9%)	14 (34.1%)	0.045	2.772 (1.119-6.871)	62.79	62.16	65.85	58.97	0.745
< 4,61%	16 (41.10%)	23 (59.0%)							
<b>Total</b>	<b>43 (53.8%)</b>	<b>37 (46.3%)</b>							

### Relationship of Risk Factors to the Outcome of Pediatric Patients with Sepsis

There were significant differences in the group of pediatric sepsis patients' death and recovery outcomes based on the use of vasopressor drugs, the use of mechanical ventilators, and the PELOD-2 score (table 3).

**Table 3. Relationship of Risk Factors to Outcome of Pediatric Patients with Sepsis**

Variable	Outcome		P	OR (95% CI)
	Death(%)	Recover (%)		
<b>Sex</b>				
Male	25 (54,3%)	21 (45,7%)	1,000	1,058 (0,435-2,574)
Female	18 (52,9%)	16 (47,1%)		
<b>Age</b>				
< 5 years	32 (52,5%)	29 (47,5%)	0,880	0,803 (0,284-2,271)
>5 years	11 (57,9%)	8 (42,1%)		
<b>Use of mechanical ventilator</b>				
Yes	42 (80,8%)	10 (19,2%)	0,000	113,400 (13,725-936,957)
No	1 (3,6%)	27 (96,4%)		
<b>Use of vasopressor drugs</b>				
Yes	40 (88,9%)	5 (11,1%)	0,000	85,333 (18,947 – 384,333)
No	3 (8,6%)	21 (91,4%)		
<b>PELOD-2 Score</b>				
< 7	32 (47,1%)	36 (52,9%)	0,011	12,375 (1,513-101,235)
≥ 7	11 (91,7%)	1 (8,3%)		

## 4. DISCUSSIONS

Sepsis is one of the most common clinical syndromes found in PICU care. This clinical syndrome is defined as the body's systemic response to dysregulation of infection due to an inflammatory and life-threatening process. Sepsis is a major cause of morbidity and mortality in pediatric patients<sup>[5,6]</sup>. Adequate fluid administration is one of the most important treatments for pediatric patients with sepsis. The amount of fluid administered is based on an estimate of the volume of the intravascular compartment, with the aim of maintaining intravascular volume and organ perfusion. However, aggressive fluid administration can lead to consequences from fluid overload. Recent

studies indicate that fluid overload is partly responsible for worsening the outcome of pediatric patients with sepsis<sup>[7,8]</sup>.

Our study shows that there is a significant relationship between positive fluid balance values and outcomes in pediatric patients with sepsis. We also determined the optimal cut-off point for positive fluid balance as a prognostic factor in pediatric patients with sepsis, namely  $\geq 4.61\%$ . In this study, positive fluid balance values below 4.61 percent were found in more patients who died, while positive fluid balance values above 4.61 percent were found in more patients who recovered. In line with the study of Wong JJ et al. (2019), the average value of total fluid accumulation in 116 pediatric sepsis patients was 3.6% in the improved group and 15.1% in the death group. And there is a significant difference in total fluid balance and patient outcome with a P value of 0.001. Positive fluid balance increases septic patient morbidity and mortality<sup>[9]</sup>. A retrospective study found that too much fluid (10% L/kg) prolonged multiorgan failure in persons with septic shock, as measured by the renal sub-SOFA score, and increased 90-day mortality<sup>[10]</sup>.

Although the exact mechanism by which increased fluid overload impacts septic shock patients' prognosis is still unclear, it is generally accepted that the accumulation of positive fluid balance is linked to the onset of systemic hypoperfusion, tissue edema, respiratory failure, and renal failure<sup>[3,9]</sup>. Severe vascular leakage and third space leakage may be related to higher fluid therapy or a more favorable fluid balance, but it is uncertain whether these factors are the actual cause of the elevated mortality. The dilution brought on by the rise in body volume brought on by a positive fluid balance and the onset of sepsis may be linked to the platelet decline. According to Ma Q, et al (2022), the probability of dying dropped by 0.2% for every increase in platelet units<sup>[11]</sup>.

The glycocalyx layer of the vascular endothelial cell membrane may rupture or suffer damage in the early stages of sepsis. Fluid resuscitation therapy, especially rapid infusions and transfusions that cause hypervolemia, might worsen the damage already done to the glycocalyx layer<sup>[12,13]</sup>. As a side consequence of fluid resuscitation therapy, the breakdown of the vascular endothelial cells that form the glycocalyx layer can result in capillary leakage, local tissue edema, and poor oxygen utilization, all of which may affect the patient's prognosis. The use of hypertonic fluids for small-volume resuscitation in patients with sepsis needs further research<sup>[11]</sup>.

We also assessed risk factors for the outcome of pediatric patients with sepsis. The use of mechanical ventilators ( $p < 0.001$ ), use of vasopressor drugs ( $p < 0.001$ ), and PELOD-2 score ( $p = 0.011$ ) seemed to affect patient outcomes. In patients using mechanical ventilation, 80.8% died, and in patients using vasopressor drugs also, 88.9% died. Acute respiratory distress syndrome (ARDS) is most often caused by sepsis, and it happens in more than 50% of people with severe sepsis or septic shock. The use of a mechanical ventilator is one of the most important treatments for sepsis and aims to minimize lung damage. However, patients with moderate to severe ARDS require invasive mechanical ventilation and have a poor prognosis<sup>[14]</sup>. In addition, the relationship between vasopressor dose and mortality in sepsis has previously been described in several other observational studies<sup>[15]</sup>. There was a significant difference between the PELOD-2 scores in the group of children with sepsis who died and recovered. In line with the research of Rusmawatingtyas et al. (2021),

there was a significant difference between PELOD 2 scores and patient outcomes with a  $P < 0.001$ . Children with sepsis are assessed for organ failure and mortality using the PELOD-2 score<sup>[16,17]</sup>.

Although our study can generally describe that positive fluid balance with an optimal cut point of 4.61 can be a predictor of the prognosis of pediatric sepsis patients, our study also has some limitations. First, we use secondary data from medical records, so the data may be incomplete or not according to what is needed. Second, due to the lack of data regarding daily fluid volume, drug dilution volume, and fluid resuscitation in patients who have been given this prior to admission to the PICU, it may confound the results of a positive fluid balance assessment, which would influence a positive fluid balance analysis as a predictor of prognosis in pediatric patients with sepsis.

## 5. CONCLUSION

Monitoring fluid balance in sepsis is important so that there is no positive fluid balance that can affect the outcome of pediatric patients with sepsis. The cut-off value of  $\geq 4.61\%$  can be used as a prognostic factor for pediatric patients with sepsis. However, further research is needed to determine other factors.

## ACKNOWLEDGMENTS

We sincerely thank everyone of the Hasanuddin University Department of Pediatrics academic members who contributed to this work.

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**Conflict of Interest Statement:**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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