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**Original Article**

# The Association of Cumulative Fluid Balance and Sepsis Patient Mortality During Treatment in the Intensive Care Unit

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**ABSTRACT**

***Introduction:*** *Fluid management in sepsis patients is crucial, especially in the first three hours after sepsis diagnosis is established. However, excessive fluid administration will increase patient mortality. This study's purpose is to determine the correlation among cumulative fluid balance and mortality in patients with sepsis and/or septic shock admitted to the Intensive Care Unit (ICU) of Dr. Wahidin Sudirohusodo Central Hospital, Makassar.* ***Methods:*** *This comes about as an analytical observational study with a retrospective method. The population involved in this study was patients diagnosed with sepsis and septic shock who were treated in the ICU of Dr. Wahidin Sudirohusodo Central Hospital, Makassar from January to December 2021 with a total sample of 56 people. Data were analyzed using Mann-Whitney and Chi-Square statistical tests with a significance level of α=0.05. Data were studied using SPSS 25.0 (SPSS, Inc. Chicago, IL).* ***Results:*** *The mean cumulative fluid balance in septic patients was -1299.51±5228.34 ml. Based on the fluid balance category, 24 people (42.9%) had a positive balance and 32 people (57.1%) had a negative balance. There was a correlation among cumulative fluid balance and mortality in sepsis patients hospitalized in the ICU of Dr. Wahidin Sudirohusodo Central Hospital (p < 0.001),*

*out of 24 patients with a positive balance, the non-survivors percentage was 66.7% and 33.3% of patients survived, while out of 32 patients with a negative balance, the percentage of non-survivors was 18.7% and 81.3% of patients survived.* ***Conclusions:*** *There is a correlation among cumulative fluid balance and mortality of septic patients in the ICU. A positive cumulative fluid balance will cause a higher mortality rate or risk of death compared to a negative cumulative fluid balance.*



## 1. INTRODUCTION

Nowadays, sepsis is still the leading cause of death in the Intensive Care Unit. Sepsis is a dysregulated inflammatory response to infection with excessive morbidity and mortality rate.[1] The deficit in effective blood volume is frequent in patients with sepsis. Thereby, rational immediately fluid resuscitation has been advised the cornerstone for the therapy of patients with sepsis and septic shock. The principle of resuscitation in sepsis-induced hypoperfusion patients should point out a definite target and be worked on as soon as possible.[2] Studies have recommended that liberal fluid management is accomplished at some stages in the resuscitation and optimization phase of sepsis, while exaggerated fluid overload is evaded during the stabilization and de-escalation stages.[1,2] Evidence also demonstrates that intravenous fluid administration in high volume might lead to unfavorable effects, such as tissue edema, elevated cardiac preload, and harm to the kidneys and liver.[3]

Sepsis is a complicated syndrome with a collection of systemic signs and symptoms in response to infection.[4] It includes inflammatory, pro-coagulant processes, and immunosuppressive symptoms. Inflammatory mediators such as TNF-α, IL-1, thromboxane, and nitric oxide will alter capillary permeability, damage the endothelium, trigger micro thrombosis, and vasodilation so the patient will undergo shock condition.[4,5] Fluid resuscitation should be initiated immediately when signs of hypoperfusion and shock are noted. One method of fluid resuscitation is Early Goal-Directed Therapy (EGDT).[6] EGDT could reduce mortality in sepsis patients. However, according to Mouncey et al in 2015, the administration of EGDT did not provide a significant difference in mortality rates with ordinary fluid resuscitation.[7] The same results were reported by a study from The Australian Resuscitation in Sepsis Evaluation (ARISE) and Protocolized Care for Early Septic Shock (ProCESS).[8,9]

A study by Cordemans, et al in 2012 reported that interstitial fluid accumulation could be depicted from the cumulative fluid balance of sepsis patients.[10] Various studies have shown that cumulative fluid balance played a critical function in the mortality of sepsis patients. According to Sirvent, et al in 2015, the cumulative fluid balance was a crucial element in figuring out the prognosis of sepsis patients.[11] A study in America by Brotfain, et al in 2016 reported that out of 247 sepsis patients in the ICU, 213 (86%) people had a positive fluid balance after being discharged from the ICU.[12] A study by Huang, et al in 2019 found that 72 hours of fluid balance was linked with the likelihood of developing multiple organ dysfunction syndromes and of mortality in septic patients.[13]

Fluid management in sepsis patients is crucial if the diagnosis is established. Until now, fluid therapy with EGDT is still allowed in the International Guidelines for Management of Sepsis and Septic Shock 2016 (Survival Sepsis Campaign).[5] However, a study by Acheampong and Vincent in 2015 reported that excessive fluid administration will increase patient mortality.[14] As stated by a study by Malbrain, et al in 2014 that proper understanding of fluid management regulation might reduce mortality and organ dysfunction in sepsis patients.[10] A previous study conducted by Lestari et al in 2013 reported that fluid overload in sepsis patients admitted to the ICU could be assessed by observing the cumulative fluid balance and became related to an elevated risk of death.[5,15]

Currently, there is an increase of evidence that fluid management affects the patient's condition, both critically and during and after surgery.[16] Therefore, from various aspects, there have been many researchers who are interested in fluid management as their goal of studies, both in basic and clinical research over the last few years.[17,18]

This study focuses to assess the association between fluid overload and mortality in patients with sepsis and septic shock admitted to the ICU who accepted both liberal and conservative fluid therapy.

## 2. METHODS

This study was designed for an analytical observational with a retrospective approach. The collected data were medical records of patients diagnosed with sepsis and septic shock, whether the patients survived (transferred to the general ward) or did not survive, in the Intensive Care Unit (ICU) of Dr. Wahidin Sudirohusodo Central Hospital, Makassar from January to December 2021. SOFA score is measured on the first day the patients admitted in ICU. 56 subjects met the criteria and were divided into a survivor and non-survivor groups. Data were analyzed using Mann-Whitney and Chi-Square statistical tests with a significance level of $\alpha=0.05$. The cumulative fluid balance was calculated for each group and was analyzed for its relationship with patient mortality. Fluid overload was calculated using the formula = (total fluid intake – total fluid output) (L)/body weight during admission to ICU (kg) x 100%. Data were analyzed using SPSS 25.0 (SPSS, Inc. Chicago, IL).

## 3. RESULTS

### Sample Characteristics

Sample characteristics for both groups including age, body weight, body height, and body mass index (BMI) are outlined in Table 1.

**Table 1.** Age, body weight, body height, and BMI based on mortality

| Characteristic | Mortality | | | | p-Value |
|---|---|---|---|---|---|
| | Survivors (n=34) | | Non-survivors (n=22) | | |
| | Mean±SD | Median | Mean±SD | Median | |
| **Age (years)** | 46.74±15.72 | 45.50 | 50.00±16.25 | 54.50 | 0.461 |
| **Body Weight** | 59.03±8.78 | 60.00 | 63.77±12.68 | 64.50 | 0.104 |
| **Body Height** | 157.62±5.69 | 159.00 | 151.41±34.79 | 156.50 | 0.310 |
| **BMI** | 23.75±3.24 | 24.13 | 24.11±6.60 | 24.24 | 0.786 |

Table 1 shows that the data, based on age, weight, height, and BMI, were homogeneous.

**Table 2.** Gender characteristics based on mortality

| Gender | Mortality | | | | p-Value |
|---|---|---|---|---|---|
| | Survivors | | Non-survivors | | |
| | n (34) | % (100) | n (22) | % (100) | |
| Male | 13 | 38.2 | 9 | 40.9 | 1.000 |
| Female | 21 | 61.8 | 13 | 59.1 | |

Table 2 shows that gender distribution was homogenous statistically.

## Fluid Balance

**Table 3.** Overview of fluid balance in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Fluid Balance | Mean ± SD | Median |
|---|---|---|
| Cumulative Fluid Balance | -1299.51±5228.34 | -325.50 |
| Fluid Overload | -1.95±8.15 | -0.54 |
| **Fluid Balance** | **n** | **%** |
| Positive | 24 | 42.9 |
| Negative | 32 | 57.1 |

Based on Table 3, the mean cumulative fluid balance was -1299.51±5228.34 ml and the mean fluid overload (fluid balance/body weight) was -19.46±81.48 ml. As for fluid balance categories, 24 people (42.9%) had positive fluid balance and 32 people (57.1%) had negative fluid balance.

**Table 4.** Correlation of fluid balance and mortality in sepsis patients

| Fluid Balance | Mortality | | | | p-Value |
|---|---|---|---|---|---|
| | Survivors (n=34) | | Non-survivors (n=22) | | |
| | Mean (mL) | Min-Max | Mean (mL) | Min-Max | |
| **Cumulative** | -628.50 | -8472 – 7271 | 1864.00 | -11912 – 7271 | <0.001 |
| **Fluid Overload (%)** | -1.24 | -0.284 – 1.8 | 2.57 | -0.183 – 14.3 | <0.001 |

Table 4 shows that the mean cumulative fluid balance of the survivors group was -628.5 ml, and in the non-survivors group, the mean was 1864.0 ml. Based on statistical analysis, there was a strong association ($p < 0.001$). The mean fluid overload of the survivors group was -1.24% and the non-survivors group was 2.57%. Based on statistical analysis, fluid overload has a significant effect on the death to sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital ($p< 0.001$).

**Table 5.** Correlation of fluid balance with the Sequential Organ Failure Assessment (SOFA) score and length of stay (LOS) in sepsis patients at the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Variable | Correlation | |
|---|---|---|
| | R | P |
| Cumulative Fluid Balance vs SOFA score | 0.365 | 0.006* |
| Cumulative Fluid Balance vs length of stay | -0.613 | <0.001* |
| SOFA score vs length of stay | 0.315 | 0.069* |

*Pearson correlation

Based on correlation test results, it was found that the cumulative fluid balance and SOFA score have a strong association (p:0.006), where a positive fluid balance would cause the SOFA score to be higher (r:0.365). There was also a correlation with LOS patients ($p<0.001$), where a positive fluid balance would lead to a shorter LOS (r:-0.613). However, there was no correlation between SOFA score and LOS (p: 0.069).

**Table 6.** Overview of the LOS and mortality in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Variable | Mean ± SD (days) | Median |
|---|---|---|
| **Length of Stay** | | |
| Survivors | 4.79±3.95 | 4 (2-19) |
| Non-survivors | 7.90±4.95 | 8 (2-19) |
| **Mortality** | **n** | **%** |
| Survivors | 34 | 60.7 |
| Non-survivors | 22 | 39.3 |

Based on Table 6, the mean LOS in the survivors group was 4.79±3.95 days, and in the non-survivors group was 7.90±4.95 days. It means that dead patients require a longer hospital stay.

**Table 7.** Correlation between comorbidities and fluid balance with the LOS in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Variable | Length of Stay/ LOS (Days) | | p-Value |
|---|---|---|---|
| | Mean | Min-Max | |
| **Comorbid** | | | |
| None | 3.00 | 2.00-19.00 | 0.004 |
| Present | 7.00 | 2.00-19.00 | |
| **Fluid Balance** | | | |
| Positive | 2.50 | 2.00-4.00 | 0.007 |
| Negative | 4.00 | 2.00-19.00 | |

Table 7 shows that the mean LOS for patients with comorbidities and without comorbidities was 7 and 3 days, respectively. Based on statistical analysis, this is a significant association (p: 0.004). Likewise, the mean LOS for patients with positive and negative cumulative fluid balance was 2.5 and 4 days, respectively. There was an association of cumulative fluid balance with the LOS patients (p:0.007).

**Table 8.** Correlation between SOFA score and the LOS with mortality in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Variable | Mortality | | | | p-Value |
|---|---|---|---|---|---|
| | Survivors (n=34) | | Non-survivors (n=22) | | |
| | Mean | Min-Max | Mean | Min-Max | |
| **SOFA Score** | 2.00 | 2.00-6.00 | 10.00 | 2.00-16.00 | <0.001 |
| **Length of Stay** | 4.00 | 2.00-19.00 | 8.00 | 2.00-19.00 | 0.011 |

Table 8 shows that the mean SOFA score in the survivors and the non-survivors group was 2 and 10, respectively. It was discovered through statistical research that there was a correlation between SOFA score and mortality (p<0.001), where the higher the SOFA score, the higher the risk of death. There was also a correlation between the LOS and mortality (p< 0.001).

**Table 9.** Correlation of comorbid and cumulative fluid balance with mortality

| Variable | Mortality | | | | p-Value |
|---|---|---|---|---|---|
| | Survivors | | Non-survivors | | |
| | n (34) | % (100) | n (22) | % (100) | |
| **Comorbid** | | | | | |
| None | 24 | 70.6 | 1 | 4.5 | <0.001 |
| Present | 10 | 29.4 | 21 | 95.5 | |
| Cumulative Fluid Balance | | | | | |
| Positive | 8 | 23.5 | 16 | 72.7 | <0.001 |
| Negative | 26 | 76.5 | 6 | 39.3 | |

In Table 9, it could be seen that there was a correlation between comorbid presence and mortality ($p < 0.001$). There was also a correlation between fluid balance and mortality ($p < 0.001$). A positive fluid balance would cause a higher mortality rate or risk of death than a negative fluid balance.

**Table 10.** Correlation between mortality and fluid balance in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

| Variable | Cumulative Fluid Balance | | | | p-Value |
|---|---|---|---|---|---|
| | Positive | | Negative | | |
| | n (24) | % (100) | n (32) | % (100) | |
| Mortality | | | | | |
| Survivors | 8 | 33,3 | 26 | 81,3 | <0.001 |
| Non-survivors | 16 | 66,7 | 6 | 18,7 | |

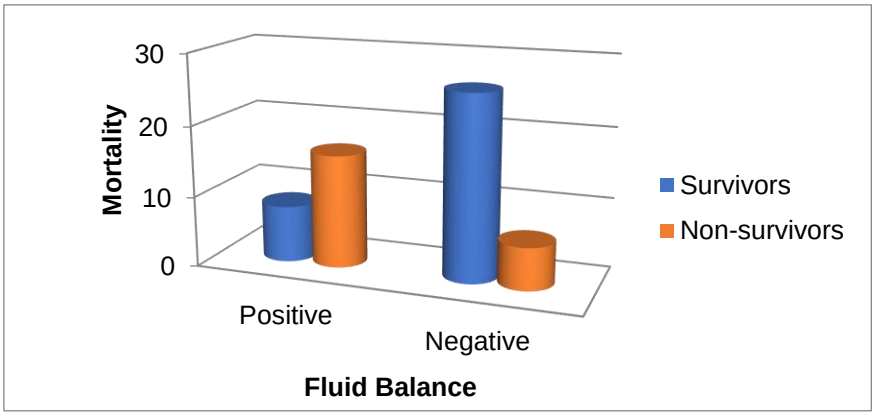


**Figure 1.** Comparison of mortality rates with fluid balance in sepsis patients in the ICU of Dr. Wahidin Sudirohusodo Central Hospital

Based on Table 10 and Figure 1, it could be seen that there was a correlation between mortality and fluid balance in sepsis patients ($p < 0.001$), where patients with a positive cumulative fluid balance had a mortality percentage of 66.7% and those in negative cumulative fluid balance the mortality percentage was only 18.7%.

## 4. DISCUSSIONS

Our study analysis shows that from 56 sepsis and/or septic shock in the ICU of Dr.Wahidin Sudirohusodo Central Hospital, the mortality rate is 39.3% (22 patients) while the survivors are 60.7% (34 patients). Although overall the mean cumulative fluid balance in patients showed a negative number (-1299.51±5228.34 ml), if they were classified into survivors and non-survivors, it shows that the group of survived patients (-628.50 ml) had a more negative cumulative fluid balance than the dead patient's group (1864.00 ml).

The existence of past comorbid diseases such as diabetes mellitus, hypertension, heart disease, and acute or chronic kidney disease can all contribute to a high risk of death in sepsis patients in the ICU. All of these factors will have an impact on the patient's disease progression.[19] Even if there are disparities in comorbidity and

SOFA score between the two groups in this study, there is still a strong association between positive cumulative fluid balance and mortality of patients.

This result was consistent with several previous studies. In a multi-centered prospective observational study in Finnish by Vaara, et al in 2012 in 76 patients diagnosed with sepsis with a positive fluid balance, 45 of them did not survive (59.2%).[17] Similar to an observational study in San Diego California by Bouchard, et al in 618 adult patients with critical illness, a higher percentage of fluid accumulation was found in dead patients (7.1±9.1%) compared to the survivors' group (4.9±8,4%). The study also shows that fluid overload correlates with mortality in AKI patients.[17,18]

Our study result combined with the results of previous studies showed the critical role of fluid monitoring in critically ill patients in the ICU. Adequate fluid monitoring performed to avoid fluid overload should be one of the crucial focuses to preventing morbidity and mortality in critically ill patients in the ICU.

The important thing to note is the response to fluid therapy and fluid balance. Organ dysfunction might progress to reversal and unresolved shock.[1] When unresolved shock occurs, the release of anti-inflammatory cytokines, persistent capillary leakage, and increased organ failure occur and might lead to globally increased permeability syndrome (GIPS) which causes fluid loss and might lead to death.[10] Patients who respond poorly and progress to GIPS will result in a positive fluid balance, leading to organ dysfunction and death. These patients require a restrictive fluid strategy and even fluid removal guided by hemodynamic monitoring.[3,20]

The limitation of our study is the amount of fluid accumulated in patients before being admitted to ICU cannot be known with certainty. Another limitation is the summation of fluid balance obtained from the patient's intake and output medical record, manual error can occur during calculation. Even though the issue had been minimized by conducting a recount of all data collected. In addition, our study was a retrospective, single-centered study with all the limitations of a retrospective study.

## 5. CONCLUSION

Hemodynamic monitoring to assess the condition of critical patients in the ICU must be conducted early, which includes assessing the patient's response to fluid administration. This is important to maintain the patient's fluid balance and to prevent excess fluid accumulation that is directly related to organ dysfunction and ultimately increases the mortality rate. However, excessive fluid removal should also be avoided because it will cause adverse effects.

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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.