Original article

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Positive cumulative fluid balance is a risk factor of mortality in critically septic patients

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Abstract

***Objective*: Excessive fluid administration may increase septic patient mortality. Cumulative fluid balance is an easy, cheap, and non-invasive method of monitoring fluid therapy. Our study aimed to analyze the association between cumulative fluid balance and mortality in critically septic patient.**

***Design*: This was an observational analytic study with a retrospective cohort design.**

***Setting*: This study was conducted in intensive care unit of Mohammad Hoesin Hospital in 2017.**

***Patients and participants*: All adult septic patients from January to December 2017 were included. All patients who did not have completed medical record data were excluded.**

***Interventions*: Data on the mortality and cumulative fluid balance of septic patients were obtained through secondary medical record data and were analyzed using SPSS Statistics version 22.0 (IBM, New York, US).**

***Measurement and results*: Positive cumulative fluid has a very significant association with mortality (relative risk [RR] 3.41; 95% confidence interval [CI] 1.98-5.87; p<0.001). Mean cumulative fluid balance (ml) were greater in non-survivor than survivor group (1937.5±1692.6 vs 877.2±1228). The probability of survival in 28 days was affected by cumulative fluid balance (p=0.001) after being tested with Mantel Haenszel log-rank test. This cumulative fluid balance had a sensitivity of 81.8% and specificity of 89.2% as a predictor of mortality in septic patients.**

***Conclusions*: Positive cumulative fluid balance can be considered as the risk factor to septic patient mortality.**

Key words: Cumulative fluid balance, mortality, sepsis.

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Introduction

Sepsis is one of the most often diagnosis in the Intensive Care Unit (ICU). (1) European studies have found that septic patient have 1.15 times more risk for death than non-septic patients. (2) Epidemiological data from hospitals in Indonesia also show high septic mortality rates. The mortality rate of septic patients in Dr. Soetomo Surabaya Hospital was 16.7%. (3) Studies in Prof. Dr. RD Kandou Manado Hospital showed 65.7% mortality rate. (4)

The main cause of death in sepsis is hypoperfusion and shock. Fluid resuscitation is the first-line therapy in sepsis and septic shock to maintain hemodynamic stability. (5) Previous fluid strategies, that was early goal directed therapy (EGDT), had a tendency to overly aggressive fluid resuscitation. (6) Three recent randomized controlled trial (RCT) studies from ARISE, PRoCESS, and ProMISE

found that this strategy could not reduce mortality, so those studies made fluid therapy strategy controversial. (7-9) The latest guideline from Sepsis Bundle 2018 recommends giving crystalloid 30 ml/kg in the first one hour. (10) This amount of fluid differs only slightly from the median amount of fluid given by EGDT strategy.

Excessive fluid can cause interstitial, intravascular, and intercellular fluid accumulation, which results in tissues edema. (11) In septic patients there can be impaired fluid mobilization, a condition of global increased permeability syndrome (GIPS), and multiorgan dysfunction. (12) Therefore, excess fluid can cause increased mortality in septic patients. (13) One easiest technique for monitoring interstitial fluid accumulation is cumulative fluid balance. (12) This study was a continuation of the previous one. Various studies showed that cumulative fluid balance had an important role in determining the prognosis of septic patients. Septic patients with positive fluid balance had a higher mortality rate. (14,15) The patient's cumulative fluid balance is easy, cheap, and non-invasive tools for monitoring fluid therapy. This study aimed to assess the relationship of cumulative fluid balance and septic patients mortality treated in the ICU.

Materials and methods

This was a single center retrospective analytic observational cohort study conducted at Mohammad Hoesin Hospital Palembang, Indonesia. This study samples were all septic patients treated in ICU and recorded in the medical record for the period January to December 2017. The sampling technique in this study was total sampling, which took all medical records of septic patients treated at ICU during the period of time. In this study, 103 septic patient data were obtained that met the inclusion critera (18 years old or above). All patients who did not have complete medical record data were not included in the study. The study was approved by the Health Research Ethics Committee of Mohammad Hoesin Hospital and the Faculty of Medicine Universitas Sriwijaya, Palembang, Indonesia (No. 191/kepkrsmhfkunsri/2018).

All study data were taken from secondary data in the form of medical records in physical form that were recorded by nurse or doctor at the ICU. Variables taken included sex, age, diagnosis of sepsis, patient outcome, cumulative fluid balance, and sequential organ failure assessment (SOFA) score.

The diagnosis of sepsis was divided into two groups. If the patient was diagnosed with sepsis due to a previous disease, then the patient was categorized as medical, and if the patient was diagnosed with sepsis due to the operation carried out, it was categorized as surgical. The patient outcome was recorded within 28 days, whether they survived or not survived. The cumulative fluid balance was the sum of daily fluid balance (the amount of fluid given per day minus the amount of fluid output per day) of septic patients treated in the ICU during treatment day (at most 28 days) and categorized as positive or negative. The SOFA score was recorded on the last day in the ICU and grouped into ≥12 or <12.

The study data was presented in tabular form to be processed and analyzed by SPSS version 22. Data analysis was carried out in two stages, univariate and bivariate analyses. Categorical variables were presented in the form of absolute and relative frequencies. Data normality was tested using the Kolmogorov-Smirnov test. If the data was normally distributed then mean value + 2 standard deviation (SD) would be used, otherwise we used the median value (min-max).

The collected data was processed and analyzed to determine the relationship between cumulative fluid balance and septic patient mortality using the chi-square test. In addition, the 28-day survival probability of septic patients affected by cumulative fluid balance were analyzed using the Kaplan Meier method with the Mantel-Haenszel log-rank test analysis. Finally, the cumulative fluid balance variable was analyzed with the receiver operating curve (ROC) curve to obtain the sensitivity and specificity of cumulative fluid balance to the risk of mortality for septic patients.

Results

After excluding 29 patients due to incomplete medical record data or under the age of 18 years, 103 patients were included in the analyses. The majority of septic patients in Mohammad Hoesin Hospital had positive fluid balance (62.1%) and only 39 patients (37.9%) had negative fluid balance (**Figure 1**).

The mortality rate of septic patient during 28 days of ICU treatment was still relatively high at 64.1%. Non-survivor tended to be older with an average age of 55.1 years compared to 47.7 years in the survivor group. Most patients in the study were male, surgical diagnosis, positive cumulative fluid balance, and had SOFA score <12 (**Table 1**). Non-survivor patient tended to have more positive cumulative fluid balance (ml). Although both groups had positive fluid cumulative balance, non-survivor group had more higher fluid cumulative balance than survivor group (1937.5±1692.6 vs 877.2±1228). The same thing was found in the group of patients with nega-

tive cumulative fluid balance. In non-survivor group, they had a greater cumulative fluid balance than the survivor group (-2067±1605.7 vs 2438.7±2865.4) (**Table 1**).

The results of bivariate analyses found that positive cumulative fluid balance was significantly associated with septic patient mortality (relative risk [RR]=3.41; p=0.001) and SOFA score (RR=2.23; p=0.036) (**Table 2**). Cumulative fluid balance had a significant effect on the 28-day survival probability. **Figure 2** shows the survival of septic patients who had a positive cumulative fluid balance having a much lower 28-day survival rate than patients who had a negative fluid balance. After being analyzed statistically using the Mantel-Haenszel log-rank test, the cumulative fluid balance could be used as septic mortality predictor (p=0.001). A figure model with area under the curve (AUC) (95% CI) =0.863 with a significance of 0.0001 obtained a cumulative fluid balance with 81.8% sensitivity and 89.2% specificity value as a sepsis mortality predictor (**Figure 3**).

Discussion

This study showed that septic patients with positive cumulative fluid balance had a higher mortality risk compared with patients with negative cumulative fluid balance. The results of this study found that there were significant differences in the amount of fluid balance between the groups of patients with positive cumulative fluid balance and negative cumulative fluid balance (1804.9±1671.5 ml vs -2343.6±2586 ml; p=0.004). After being analyzed, positive cumulative fluid balance could increase mortality risk of septic patients by 3.41 times. The results of this study were in line with several previous studies, which stated that the more positive the cumulative fluid balance, the higher the mortality risk of septic patients. (15-17) Even though the patients had the same fluid intake, positive cumulative fluid balance could still increase the mortality risk. (18) Study from Shen et al. showed that positive fluid balance in the first 24-hour was not related to mortality, but the second 24-hour fluid balance during treatment could increase the risk of patient death. They concluded that negative fluid balance could reduce mortality if the patient's hemodynamic condition was stable. (19)

In septic shock, capillary leakage and pathological vasoplegia cause fluid deficiency. However, continuing fluid administration can cause intravascular fluid to move into the interstitial space, causing tissue edema and interfering oxygenation. (5) This occurs because of an imbalance between the total filtration of transcapillary fluid and the fluid released from the tissue through the lymphatic system. In multiorgan dysfunction syndrome, edema often occurs in severe sepsis with or without acute kidney injury. The reason is due to the release of complement factors, cytokines, and prostaglandin, which alter microcirculation in various organs. (17,20) Positive fluid balance can also increase the amount of water in the extravascular lung, prolonged use of ventilators, and contribute to the incidence of ventilator acquired pneumonia (VAP). (17)

Some septic patients do not reach the flow phase (fluid mobilization), which is characterized by no increase in diuresis and no improvement in edema, and will experience global increased permeability syndrome (GIPS) and multiorgan dysfunction. The abdomen is a vital part of GIPS and compartment syndrome. Positive fluid balance has been recognized as one of the risk factor for intra abdominal hypertension (IAH), which will have an impact on organ dysfunction. (11) IAH will lead to the development of organ hypoperfusion, which will result in the final complication of multiorgan dysfunction. (21)

Fluid overload alone contributes to the deterioration of organ function due to various mechanisms. First, edema-affected tissue can interfere with absorption in the digestive tract or excretion by the kidneys. Fluid overload can also lead to increased abdominal pressure and renal vein congestion. Abdominal compartment syndrome is increased due to excessive fluid resuscitation, causing ascites and visceral edema. (17,20)

Several studies stated that there were various mechanisms that caused mortality in critically ill patients who had a positive fluid balance. Positive fluid balance affects various organ function in the body. Volume overload in the heart can cause a decrease in right ventricular function due to over stretched ventricles and increased left ventricular work due to increased preload. In the kidney, it can increase renal venous pressure and decrease glomerular filtration. In the lung fluid overload can induce pleural effusion and pulmonary edema. Increased extracellular fluid volume will be distributed directly to intravascular and interstitial. This causes multiorgan dysfunction, which is a predictor of mortality in septic patients. (22) Positive fluid balance can cause venous congestion that characterized by peripheral edema and increase in central venous pressure (CVP). (23) High CVP can increase hydrostatic pressure, thereby worsening edema. (20)

Evidence of excessive fluid balance can cause multiorgan dysfunction is shown by the patient's SOFA score. SOFA scores can be used as a septic patient mortality predictor. (24) Medam et al. found that

SOFA scores ≥12 increased the mortality risk in septic patients. (25) Recent study found that patients with fluid overload would have less improvement in SOFA scores during ICU treatment. (26) This study found a significant relationship between positive cumulative fluid balance and SOFA score (p=0.036). It can be concluded that a positive cumulative fluid balance can cause multiorgan dysfunction, which results in increased mortality of septic patients.

Limitations in this study were confounding factors that could cause bias in this study, including previous patient comorbid disease (heart disease, metabolic disease, cancer), pharmacology therapy (especially diuretic), fluid resuscitation that was not recorded before ICU admission, and other intervention by the healthcare workers. Further study can be conducted, which includes an analysis of variable that can affect the relationship (confounder) between cumulative fluid balance and septic patient mortality, so that the relationship can be stronger.

Conclusions

Positive cumulative fluid balance can increase the mortality risk by 3.41 times and significantly related to septic patient mortality. Cumulative fluid balance monitoring is important to reduce the mortality rate of septic patients in the ICU.

Competing interests

The author(s) declared no potential competing interest with respect to any patents, patent applications, or products in development or for market.

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Table1. Patient characteristic

Characteristic	Survivor	Non-survivor	p
Patients, n (%)	37 (35.9)	66 (64.1)	
Age (year), mean (SD)	47.7 (14.9)	55.1 (16.5)	0.026*
Gender - Male, n (%) - Female, n (%)	 22 (21.4) 15 (14.5)	 39 (37.9) 27 (26.2)	0.971**
Diagnosis - Medical, n (%) - Surgical, n (%)	 17 (16.5) 20 (19.4)	 30 (29.1) 36 (35.0)	0.962**
Cumulative fluid balance (ml) - Positive, mean±SD - Negative, mean±SD	 877.2±1228 -2438.7±2865.4	 1937.5±1692.6 -2067±1605.7	0.000*
SOFA score - <12, n (%) - ≥12, n (%)	 35 (34.0) 2 (2.0)	 40 (38.8) 26 (25.2)	0.000**

Legend: SD=standard deviation; SOFA=sequential organ failure assessment.
*Independent t-test; **Chi-square test; ***Man-Whitney test.

Table 2. Cumulative fluid balance with outcome and SOFA score

		Outcome		p*	RR (95% CI)	SOFA score		p*	RR (95% CI)
		Not survived	Survived			≥12	<12		
Cumulative fluid balance	Positive n (%)	56 (54.4)	8 (7.8)	0.001	3.41 (1.98-5.87)	22 (21.4)	42 (40.8)	0.036	2.23 (0.994-5.023)
	Negative n (%)	10 (9.7)	29 (28.2)			6 (5.8)	33 (32)		
	Total n (%)	66 (64.1)	37 (35.9)			28 (27.2)	75 (72.8)		

Legend: SOFA=sequential organ failure assessment; RR=relative risk; CI=confidence interval.
*Chi-square test.

Figure1. Sample recruitment chart

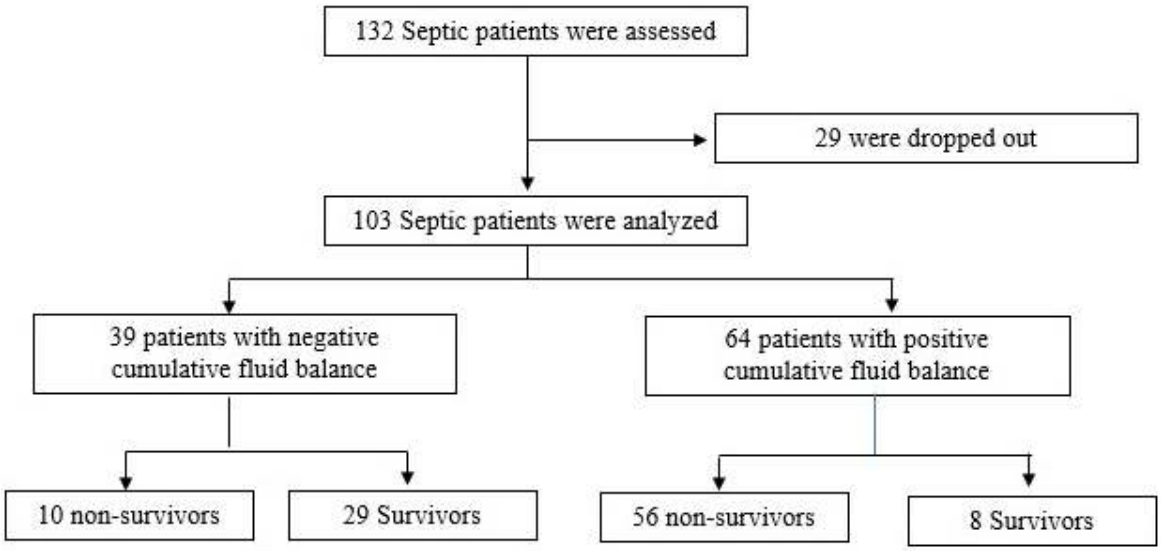


Figure 2. Survival function

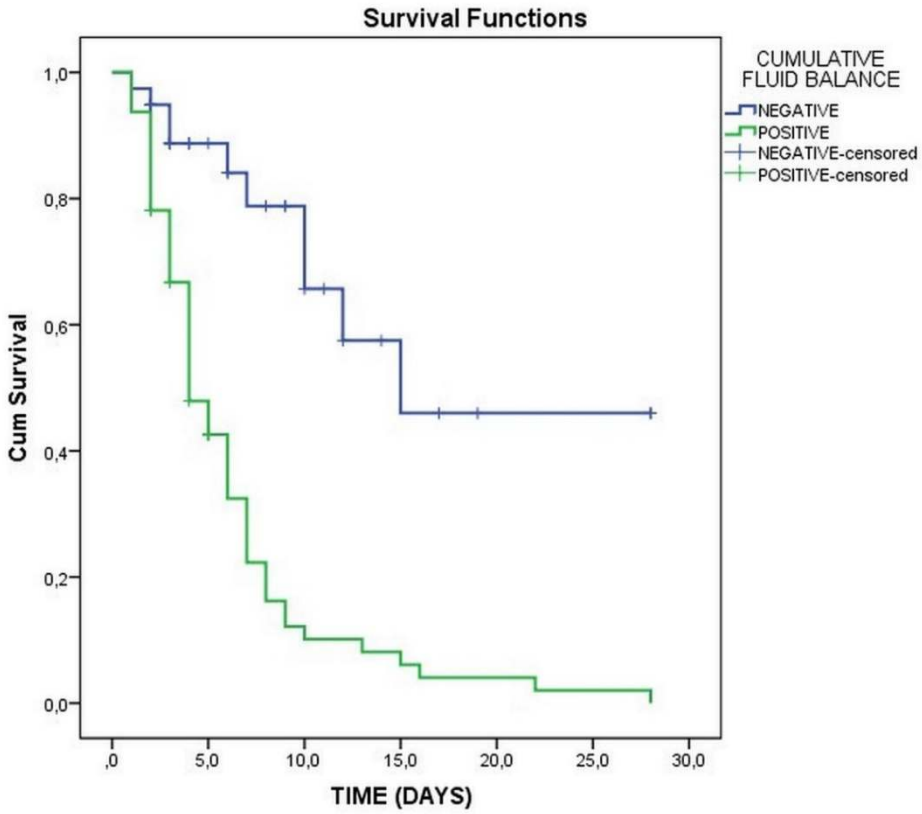
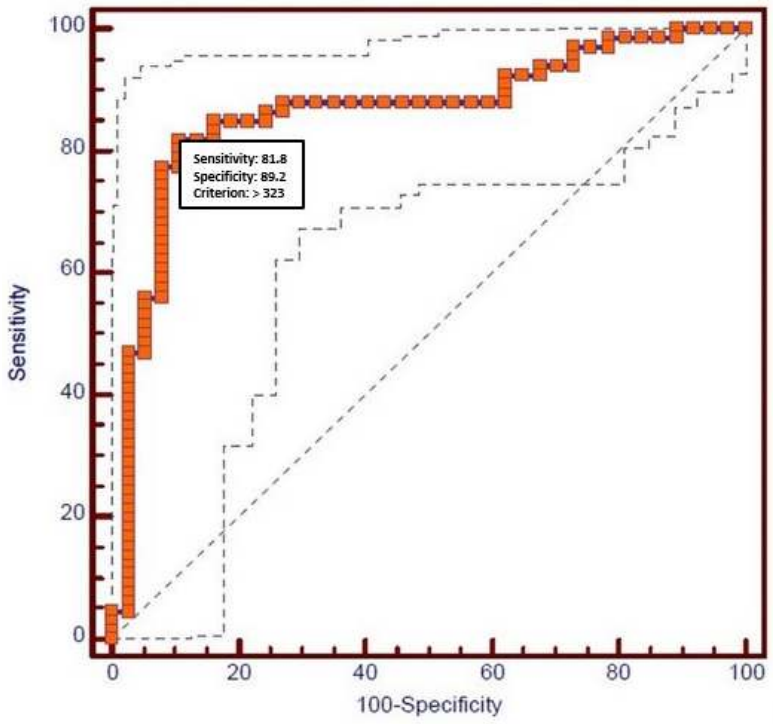


Figure 3. Cumulative fluid balance ROC and sepsis mortality



Legend: ROC=receiver operating curve.

References

1. Quenot JP, Binquet C, Kara F, Martinet O, Ganster F, Navellou J, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care 2013;17:R65.
2. Vincent J-L, Sakir Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
3. Irawan D, Hamidah, Purwati H, A. Triyono E, Bramantono, V. Arfianto, et al. PROFIL PENDERITA SEPSIS AKIBAT BAKTERI PENGHASIL ESBL. J Peny Dalam 2012;13: 63-8.
4. Tambajong RN, Lalenoh DC, Kumaat L. Profil penderita sepsis di ICU RSUP Prof. Dr. R. D. Kandou Manado Periode Desember 2014-November 2015. e-Clinic Journal 2016;4:452-7.
5. Bonanno LS. Early Administration of Intravenous Fluids in Sepsis: Pros and Cons. Crit Care Nurs Clin North Am 2018;30:323-32.
6. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy in The Treatment of Severe sepsis and Septic Shock. N Engl J Med 2001;345:1368-77.
7. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA. A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 2014;370: 1683-93.
8. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. N Engl J Med 2015;372:1301-11.
9. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. N Engl J Med 2014;371:1496-506.
10. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med 2018;44:925-8.
11. Malbrain MLNG, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014;46: 361-80.
12. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. Ann Intensive Care 2012;2(Suppl 1):S1.
13. Acheampong A, Vincent J-L. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19:251.
14. Lestari MI, Puspita Y, Zulkifli, Maas EM. Hubungan antara Kelebihan Cairan dengan Meningkatnya Angka Mortalitas Pasien Sepsis yang Dirawat di Ruang Intensive Care Unit (ICU). Majalah Anestesia dan Critical Care 2017;35:1-4.
15. Vaara ST, Korhonen A-M, Kaukonen K-M, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012; 16:R197.
16. Wang Y, Gu Y, Huang F, Liu D, Zhang Z, Zhou N, et al. Risk Factors for Sepsis Based on Sepsis-3 Criteria after Orthotopic Liver Transplantation. Mediators Inflamm 2018;2018: 8703172.
17. Koonrangsesomboon W, Khwannimit B. Impact of positive fluid balance on mortality and length of stay in septic shock patients. Indian J Crit Care Med 2015;19:708-13.
18. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, et al. Higher Fluid Balance Increases the Risk of Death from Sepsis: Results from a Large International Audit. Crit Care Med 2017;45:386-94.
19. Shen Y, Ru W, Huang X, Zhang W. Time-related association between fluid balance and mortality in septic patients : interaction between fluid balance and haemodynamics. Sci Rep 2018;8:10390.
20. Bouchard JE, Mehta RL. Fluid Balance Issues in the Critically Ill Patient. In: Ronco C, Constanzo MR, Bellomo R, Maisel AS, editors. Fluid Overload: Diagnosis and Management. Basel, Switzerland: Karger; 2010.
21. Sirvent J-M, Ferri C, Baró A, Murcia C, Lorencio C. Fluid balance in sepsis and septic shock as a determining factor of mortality. Am J Emerg Med 2015;33:186-9.
22. Danziger J. Positive Fluid Balance and Patient's Outcomes. In: Farag E, Kurz A, editors. Perioperative Fluid Management. Switzerland: Springer Cham; 2016.
23. Chen KP, Cavender S, Lee J, Feng M, Mark

RG, Celi LA, et al. Peripheral Edema, Central Venous Pressure, and Risk of AKI in Critical Illness. Clin J Am Soc Nephrol 2016;11:602-8.
24. Macdonald SPJ, Arendts G, Fatovich DM, Brown SGA. Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock. Acad Emerg Med 2014;21:1257-63.
25. Medam S, Zieleskiewicz L, Duclos G, Baumstarck K, Loundou A, Alingrin J, et al. Risk factors for death in septic shock: A retrospective cohort study comparing trauma and non-trauma patients. Medicine (Baltimore) 2017;96:e9241.
26. Chapalain X, Vermeersch V, Egreteau P-Y, Prat G, Alavi Z, Vicaut E, et al. Association between fluid overload and SOFA score kinetics in septic shock patients : a retrospective multicenter study. J Intensive Care 2019;7:42.

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