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Positive fluid balance within the first 72 hours in the intensive care unit is associated with higher mortality in adult patients

O balanço hídrico positivo nas primeiras 72 horas na unidade de terapia intensiva está associado a maior mortalidade em pacientes adultos

El balance de líquidos positivo en las 72 horas en la unidad de cuidados intensivos se asocia con una mayor mortalidad en pacientes adultos

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Abstract
Objective: To identify the association between cumulative fluid balance in the first 72 hours of ICU stay and outcomes. *Methodology:* retrospective observational cohort with data analysis of adult patients hospitalized in an ICU of a tertiary teaching hospital. *Results:* a total of 86 patients who remained in the ICU for more than 72 hours were evaluated. The fluid balance in the first 72 hours was higher in the subgroup of patients who died in the ICU (5210.3 ± 2787.7 *vs*. 3017.4 ± 2847.2 mL, p = 0.004). The fluid balance in the first 72 hours was an independent factor directly associated with death in the ICU (OR: 1,000; p = 0.009). The area under the ROC curve was 0.7119 (95% CI: 0.58-0.84, p = 0.005). The optimal cutoff point for the fluid balance in the first 72 hours as a predictor of death in the ICU was + 3.900mL and the relative risk of death among those who presented a fluid balance higher than this value was 1.702 (95% CI: 1, 15-2.53, p = 0.009). *Conclusion:* an association was identified between the cumulative value in the fluid balance in the first 72 hours of ICU stay and the highest risk of death, which is an independent factor of the patient's severity at admission.
Keywords: Water-electrolyte balance; Fluid therapy; Mortality; Intensive care units; Critical care; Prognosis.

Resumo
Objetivo: Identificar a associação entre o balanço hídrico cumulativo nas primeiras 72 horas de internação na UTI e os desfechos. *Metodologia:* coorte observacional retrospectiva com análise de dados de pacientes adultos internados em uma UTI de um hospital universitário terciário. *Resultados:* foram avaliados 86 pacientes que permaneceram na UTI por mais de 72 horas. O balanço hídrico nas primeiras 72 horas foi maior no subgrupo de pacientes que morreram na UTI (5210,3 ± 2787,7 vs. 3017,4 ± 2847,2 mL, p = 0,004). O balanço hídrico nas primeiras 72 horas foi um fator independente diretamente associado ao óbito na UTI (OR: 1.000; p = 0,009). A área sob a curva ROC foi de 0,7119 (IC 95%: 0,58-0,84, p = 0,005). O ponto de corte ideal para o balanço hídrico nas primeiras 72 horas como preditor de óbito na UTI foi de + 3,900mL e o risco relativo de óbito entre aqueles que apresentaram balanço hídrico superior a este valor foi 1,702 (IC 95%: 1, 15-2,53, p = 0,009). *Conclusão:* foi identificada associação entre o valor cumulativo no balanço hídrico nas primeiras 72 horas de internação na UTI e o maior risco de óbito, fator independente da gravidade do paciente na admissão.
Palavras-chave: Equilíbrio eletrolítico-hídrico; Fluid therapy; Mortalidade; Unidades de terapia intensiva; Cuidados intensivos; Prognóstico.

Resumen

Objetivo: Identificar la asociación entre el balance de líquidos acumulado en las primeras 72 horas de estadía en la UCI y los resultados. *Metodologia:* cohorte observacional retrospectiva con análisis de datos de pacientes adultos hospitalizados en una UCI de un hospital universitario de tercer nivel. *Resultados:* se evaluó a un total de 86 pacientes que permanecieron en la UCI por más de 72 horas. El balance de líquidos en las primeras 72 horas fue mayor en el subgrupo de pacientes que fallecieron en la UCI (5210,3 ± 2787,7 vs. 3017,4 ± 2847,2 mL, p = 0,004). El balance de líquidos en las primeras 72 horas fue un factor independiente directamente asociado con la muerte en la UCI (OR: 1.000; p = 0,009). El área bajo la curva ROC fue 0,7119 (IC del 95%: 0,58-0,84, p = 0,005). El punto de corte óptimo para el balance hídrico en las primeras 72 horas como predictor de muerte en UCI fue + 3.900mL y el riesgo relativo de muerte entre quienes presentaron un balance hídrico superior a este valor fue 1.702 (IC 95%: 1, 15-2,53, p = 0,009). *Conclusión:* se identificó asociación entre el valor acumulado en el balance hídrico en las primeras 72 horas de estancia en UCI y el mayor riesgo de muerte, que es un factor independiente de la gravedad del paciente al ingreso.

Palabras clave: Equilibrio agua-electrolitos; Terapia de fluidos; Mortalidad; Unidades de cuidados intensivos; Cuidado crítico; Pronóstico.

1. Introduction

Volume resuscitation is an essential component of critical care. Large amounts of fluid are commonly used for the replacement of intravascular volume deficit and to minimize secondary complications (Rivers et al., 2001). In circulatory shock, adequate fluid replacement is crucial for the maintenance of perfusion pressure and, more importantly, tissue blood flow (Ospina-Tascon et al., 2010).

Fluids, however, should be administered based on guiding premises (Cecconi et al., 2014). If, on the one hand, according to the Frank-Starling principle, as preload increases, cardiac output also increases, we know, on the other hand, that venous and pulmonary hydrostatic pressures also increase and may promote fluid leaking into the bloodstream. Tissue edema impairs the diffusion of oxygen and metabolites, distorts tissue architecture, and reduces capillary blood flow and lymphatic drainage (Marik et al., 2011).

Distinguishing normal and abnormal fluid balance in medical practice can be challenging (Bouchard et al., 2019). Even if an initial fluid resuscitation is required, subsequent approaches aiming for neutral and negative fluid balance can be required (Roumelioti et al., 2018).

There is a growing body of literature suggesting that patients who receive excessive fluid, culminating with positive fluid balance, are likely to develop complications related to fluid overload and organ edema (Murugan et al., 2012), particularly, the lungs and the kidneys (Bouchard et al., 2009; Prowle et al., 2013; Rhodes et al., 2017).

In the face of all this, we sought to validate the findings previously mentioned in this study, as well as objectively identify a cumulative value in the fluid balance capable of discriminating outcomes.

2. Methodology

This is a retrospective observational cohort study, in which data from hospitalized patients were consecutively analyzed between September 2014 and February 2015 in an adult ICU with 8 beds from a tertiary hospital.

Data from all admitted patients who remained for more than 72 hours at the unit were included. The analysis included demographic data (age and sex), clinical information (APACHE II severity score, organ dysfunction at admission), perfusion status (arterial serum lactate, base excess and central venous oxygen saturation) and outcomes (time on mechanical ventilation, length of ICU stay, development of renal dysfunction and ICU death).

Records from the nursing staff were used to analyze the amount of fluids administered, diuresis and the calculated fluid balance in the first 72 hours. The insensible losses of body water and the endogenous production of water were not quantified or calculated.

Data were subjected to descriptive statistical analyzes of a univariate nature for continuous variables (measures of frequency, position and dispersion) and categorical (relative frequencies). The p-value ≤ 0.05 was adopted as an index of significance. Simple and multiple linear regression analyzes using the retrograde elimination procedure, one at a time (backward stepwise), were performed to evaluate the relationship between the outcome length of ICU stay with independent variables. Simple logistic regression was used to evaluate the independent contribution of covariates associated with death in the ICU. Then all variables that presented a p-value <0.25 by the Wald test in simple logistic regression were included in a multiple logistic regression model. The ROC (Receiver Operating Characteristic) curve was constructed to identify the cutoff point of the variable fluid balance in the first 24 hours, predicting death in the ICU and calculating the relative risk of death by this value.

This study, approved by the Research Ethics Committee of the institution (CAAE 465084115.3.0000.5040), being in accordance with Resolution 466/12 of the National Health Council and the Declaration of Helsinki.

3. Results

A total of 108 patients were admited to the ICU during the study period. Of these, 86 of these remaining for more than 72 hours in the ICU and were included in the analysis. The demographic, clinical characterization and outcomes of the patients studied are described in Table 1.

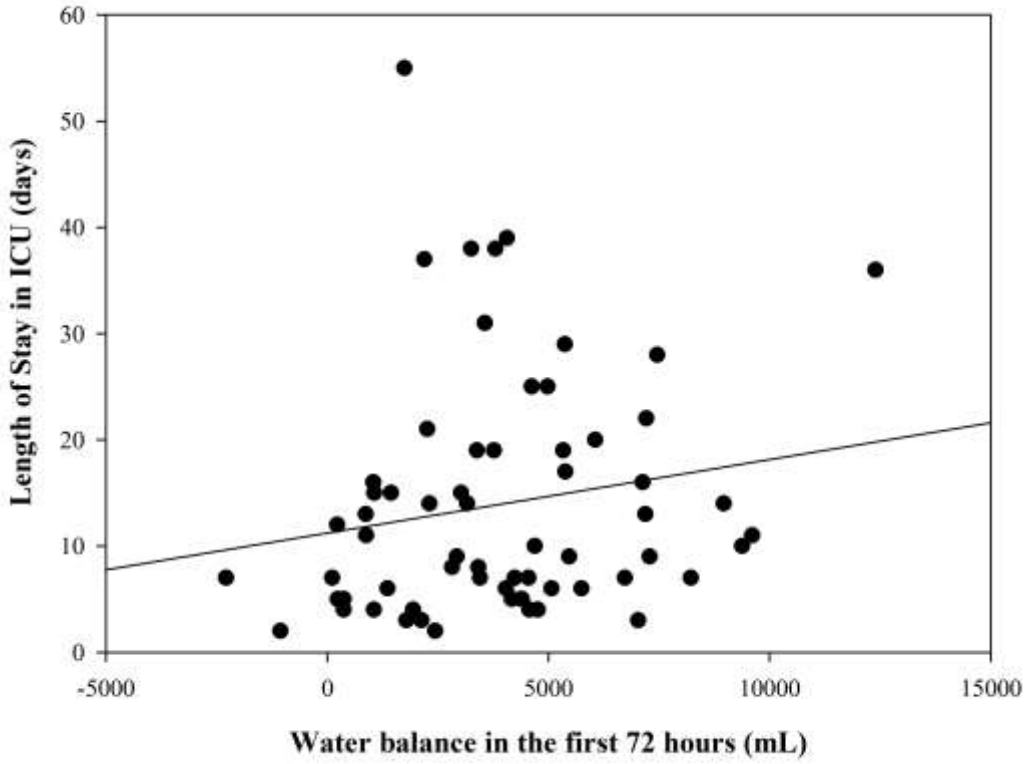
Table 1. Demographic and clinical characterization of the patients studied (N = 86).

Characteristics	Values
Demographic data	
Age (years)*	54.9 ± 19.5
Female (%)	51.5
Clinical hospitalization (%)	78.5
Disease severity markers	
APACHE II score *	15.2 ± 7.0
Number of organ dysfunctions at ICU admission**	2.0 (1.0 – 3.0)
Perfusion parameters on the first day of ICU	
Central venous saturation of O_2 (%)*	70.8 ± 10.8
Arterial lactate (mg/dL)**	1.5 (1.0 – 3.0)
Base excess**	-2.6 [(-7.8) – (-0.1)]
Fluid supply and fluid balance	
Fluid received within the first 72 hours (mL)**	5849.5 (4650.5 – 7910.3)
Diuresis in the first 72 hours (mL)*	4097.2 ± 3308.1
Fluid balance in the first 72 hours (mL)*	3727.9 ± 2990.1
Outcomes	
Time on mechanical ventilation (days)**	6.0 (2.3 – 15.0)
Renal dysfunction after ICU admission (%)	13.2
Length of ICU stay (days)**	9.5 (5,3 – 19.0)
ICU death (%)	32.8

Note: *Average ± standard deviation; **Median (percentiles 25 e 75%). Source: Authors.

Simple linear regression analysis of the variable length of ICU stay, using the independent variables age, APACHE II score, number of admission dysfunctions, central venous oxygen saturation at admission, lactate at admission, baseline admission and fluid balance in the first 72 hours were performed. These analyzes revealed that the APACHE II severity score had a positive relation with the variable length of ICU stay (R2 = 0.498, p = 0.026), as well as the fluid balance in the first 72 hours (R2 = 0.00105, p = 0.044). The patients with higher fluid balance in the first 72 hours had a bigger length of ICU stay (Figure 1). However multiple linear regression analysis revealed that these variables did not remain independent in predicting the length of ICU stay.

Figure 1. Association between fluid balance in the first 72 hours and length of ICU stay (N = 86).

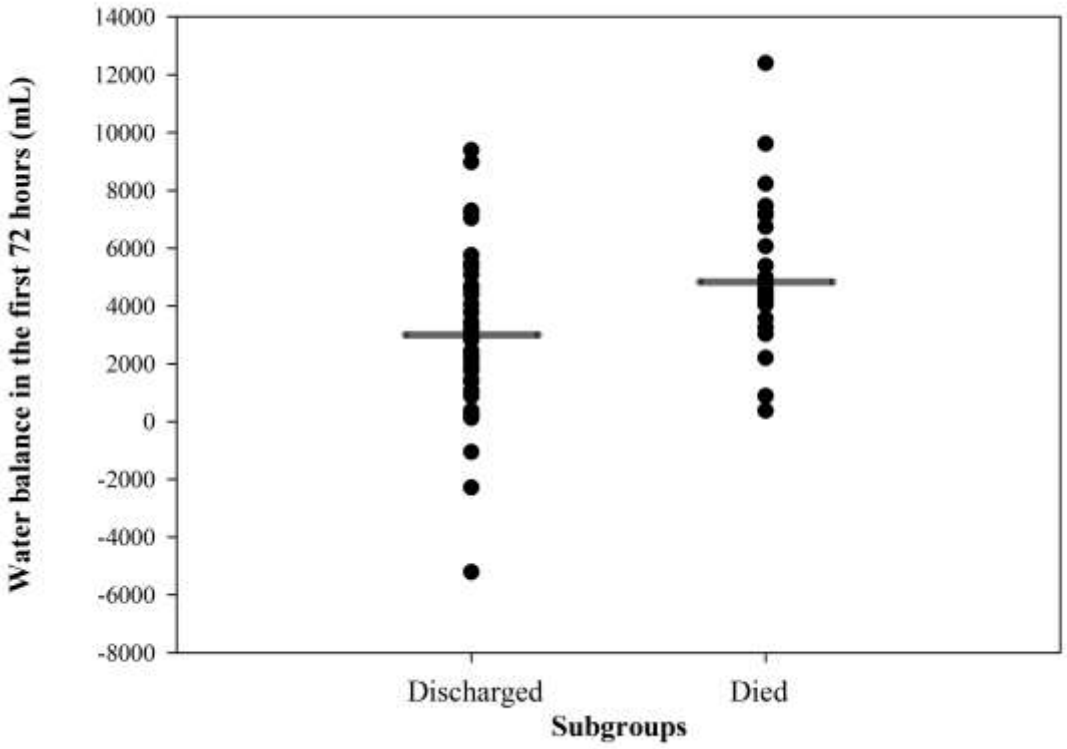


Note: Dispersion diagram between the fluid balance in the first 72 hours and the length of ICU stay. Length of stay in ICU = 10.324 + (0.00105 x Fluid balance in the first 72 hours); R^2 = 0.0603; p-value = 0.044. Source: Authors.

Simple linear regression analysis revealed that the fluid balance in the first 72 hours was not related to time on mechanical ventilation (p-value = 0.105).

The fluid balance in the first 72 hours was higher in the subgroup of patients who died in the ICU than in the subgroup of surviving patients (5210.3 ± 2787.7 vs. 3017.4 ± 2847.2 mL, p = 0.004), what can be seen in Figure 2.

Figure 2. Water balance in subgroups of patients who were discharged or died in the ICU (N=86).



Note: t-Student test, p-value = 0.004. Source: Authors.

Multiple logistic regression models were constructed in which the following variables were included: age, APACHE II score, number of admission dysfunctions and fluid balance in the first 72 hours; it was verified that the fluid balance was an independent factor directly associated with ICU death (Table 2).

Table 2. Multiple logistic regression models of the variables associated with death in the ICU (N = 86).

Variables	Coefficient	SD	OR	p-value
Age	0.0169	0.0164	1.017	0.302
APACHE II score	0.0335	0.0526	1.034	0.524
Number of organ dysfunctions at admission	0.244	0.241	1.276	0.312
Fluid balance in the first 72 hours	0.000234	0.000120	1.000	0.049

Note: SD (Standard desviation); OR (Odds ratio); Hosmer-Lemershow (p = 0.437). Source: Authors.

The area under the ROC curve for the fluid balance in the first 72 hours was 0.7119 with 95% confidence interval = 0.58-0.84 and p = 0.005. The optimal cutoff point for the fluid balance in the first 72 hours as a predictor of death in the ICU was + 3.9 liters (sensitivity = 72.7%, specificity = 65.1%, likelihood ratio = 2.0851 and likelihood ratio negative = 0.4188).

The relative risk of ICU death among patients who presented a fluid balance in the first 72 hours above + 3.9 liters compared to those who had a balance equal to or less than this value was 1.702 (95% confidence interval = 1.15 – 2.53, p = 0.009).

4. Discussion

In this retrospective cohort, the fluid balance was an independent predictor of mortality. Associated with other prognostic predictors, such as the APACHE II score and the number of admission dysfunctions in the ICU, the 72-hour fluid balance was an isolated factor, directly associated with the ICU death outcome.

Recent studies on patients with sepsis have shown benefit in more conservative fluid use. They emphasize caution with the positive fluid balance, especially after the perfusion is restored (Yealy et al., 2014; Peake et al., 2014; Mouncey et al., 2015). Some studies have also shown this relationship of fluid accumulation with increased mortality (Acheapong et al, 2015; Alsous et al., 2000).

A mechanism that possibly explains for the increased mortality and morbidity in these patients is the development of interstitial edema (Jacob et al, 2009). In inflamed patients, the destruction of the glycocalyx and the changes in the forces of the Frank-Starling mechanism lead to an altered distribution of the plasma proteins and, consequently, to interstitial edema. The accumulation of fluid in the interstitial compartment has been described as one of the causes of organic function impairment in these individuals (Schrier, 2010).

Different from what we expected, our study found no association between the cumulative fluid balance of the first 3 days and the time of MV. This association was identified in the work of Widderman and Upadya et al., the negative fluid balance was a predictor of success in withdrawal of the MV (Wiedermann et al., 2006; Upadya et al., 2005). In our study, the retrospective character and the influence of ventilatory parameters may have prevented the identification of this association.

In our study, patients who died had a higher positive fluid balance. It would be possible to question whether the greatest number of deaths happened because of the greater severity of the patients, however, the cumulative fluid balance was an independent factor, directly associated with the death outcome, regardless of age, APACHE II score and number of organ dysfunctions. In this way, the higher mortality can also be explained by the positive balance.

Ralib et al shown that survivors demonstrated smaller positive fluid balance over the first week. In univariate logistic regressions, fluid balance on day 3 was associated independently with 30-day mortality (Ralib et al., 2005). Contrary evidence comes from a randomized trial published in 2018, in which 3,000 patients were randomly assigned to a restrictive or liberal fluid strategy during and after major abdominal surgery (Myles et al, 2018).

The identification of a cutoff of +3.9 liters of cumulative fluid balance in the first 72 hours after admission to the ICU as an ideal value to predict the death in this unit was a differential of our work. Another study involving surgical patients found the cut-off point of +2.0 liters as an independent factor associated with mortality (Silva et al, 2013). These paatients have a risk 1.702 higher of death.

Our study presented some limitations. It was performed in a single center, with secondary data collected retrospectively, involving a heterogeneous population. In addition, the types of fluids administered to patients were not discriminated in the analyzes. Despite these limitations, the present study is valid because it strengthens the associations of positive fluid balance with unfavorable outcome, emphasizing the importance of a more rational use of fluids, and identifying a cutoff point of fluid balance from which the risk of death in the ICU becomes higher.

5. Conclusion

This study identified an association between the cumulative value in the fluid balance in the first 72 hours of ICU stay and the highest risk of death, which is an independent factor of patient's severity of illness at admission. Fluid administration, besides being guided by goals, should consider fluid overload and its clinical repercussions.

Future research will be needed to define the ideal tool to guide the administration of these fluids in the ICU, as well as monitor positive balance damage

References

Acheampong, A., Vincent, J. L. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care. 2015 Jun 15;19:251. DOI: 10.1186/s13054-015-0970-1

Alsous, F., Khamiees, M., DeGirolamo, A., Amoateng-Adjepong, Y., Manthous, C. A. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. Chest. 2000 Jun;117(6):1749-54. DOI: 10.1378/chest.117.6.1749

Bouchard, J., Granado, R. C. D., Mehta, G. R. (2019) Components of fluid balance and monitoring. Critical Care Nephrology 3:816-821.

Bouchard, J., Soroko, S. B., Chertow, G. M., Himmelfarb, J., Ikizler, T. A., Paganini, E. P. et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009 Aug;76(4):422-7. DOI: 10.1038/ki.2009.159.

Cecconi, M., Arulkumaran, N., Kilic, J., Ebm, C., Rhodes, A. Update on hemodynamic monitoring and management in septic patients. Minerva Anestesiol. 2014 Jun;80(6):701-11. Epub 2013 Nov 26.

D'Orio, V., Wahlen, C., Rodriguez, L. M., Halleux, J., Fossium, A., Juchmes, et al. Effects of intravascular volume expansion on lung fluid balance in a canine model of septic shock. Crit Care Med. 1987 Sep;15(9):863-8.

Jacob, M., Chappell, D., Rehm, M..The 'third space'--fact or fiction? Best Pract Res Clin Anaesthesiol. 2009 Jun;23(2):145-57. PMID: 19653435.

Marik, P. E., Monnet, X., Teboul, J. L. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care. 2011 Mar 21;1(1):1. DOI: 10.1186/2110-5820-1-1.

Mouncey, P. R., Osborn, T. M., Power, S., Harrison, D. A., Sadique, Z., Grieve, R. D. et al. Trial of early, goaldirected resuscitation for septic shock. N Engl J Med. 2015 Apr 2;372(14):1301-11. DOI: 10.1056/NEJMoa1500896.

Murugan, R., Kellum, J. A. (2012) Fluid balance and outcome in acute kidney injury: is fluid really the best medicine? Crit Care Med. 2012 Jun;40(6):1970-2. DOI: 10.1097/CCM.0b013e31824e1a1f.

Myles, P. S., Bellomo, R., Corcoran, T., Forbes, A., Peyton, P., Story, D. et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med 2018; 378:2263-2274. DOI: 10.1056/NEJMoa1801601.

Ospina-Tascon, G., Neves, A. P., Occhipinti, G., Donadello, K., Büchele, G., Simion, D. et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med. 2010 Jun;36(6):949-55. DOI: 10.1007/s00134-010-1843-3.

Peake, S. L., Delasney, A., Bailey, M., Bellomo, R., Cameron, P. A., Cooper, D. J. et al. Goal-directed resuscitation for patients with Early Septic Shock. N Engl J Med. 2014 Oct 16;371(16):1496-506. DOI: 10.1056/NEJMoa1404380.

Prowle, J. R., Kirwan, C. J., Bellomo, R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol. 2014 Jan;10(1):37-47. DOI: 10.1038/nrneph.2013.232.

Ralib, A. M., Hamzah, N., Nazir, M.S., Nor, M. B.M. The Impact of Fluid Balances in the First 48 Hours on Mortality in the Critically Ill Patients. Intensive Care Med. 2005 Dec;31(12):1643-7. DOI: 10.1007/s00134-005-2801-3.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblish, B. et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77. DOI: 10.1056/NEJMoa010307.

Roumelioti, M. E., Glew, R. H., Khitan, Z. J., Rondon-Berrios, H., Argyropoulos, C. P., Malhora, D. et al. Fluid balance concepts in medicine: principles and pratice. World J Nephrol. 2018 Jan 6;7(1):1-28. DOI: 10.5527/wjn.v7.i1.1.

Rhodes, A., Evans, L. E., Alhazzani, W, Levy, M. M., Antonelli, M., ferrer Ricard et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304-377. DOI: 10.1007/s00134-017-4683-6.

Schrier, R. W. (2010) Fluid administration in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol. 2010 Apr;5(4):733-9. DOI: 10.2215/CJN.00060110.

Upadya, A., Tilluckdharry, L., Muralidharan, V., Amoateng-Adjepong, Y., Manthous, C. A. Fluid balance and weaning outcomes. Intensive Care Med. 2005 Dec;31(12):1643-7. DOI:10.1007/s00134-005-2801-3

Silva, J. M. Jr, de Oliveira, A. M., Nogueira, F. A., Vianna, P. M., Pereira Filho, M. R., Dias, L. F. et al. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. Crit Care. 2013 Dec 10;17(6):R288. DOI: 10.1186/cc13151.

Silversides, J. A., Fitzgerald, E., Manickavasagam, U. S., Lapinsky, S. E., Nisenbaum, R., Hemmings, N. et al. Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness. Crit Care Med. 2018 Oct;46(10):1600-1607. DOI: 10.1097/CCM.0000000000003276.

Yealy, D. M., Kellum, J. A., Huang, D. T., Barnato, A. E., Weissfeld, L. A., Pike FR et al. A Randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370:1683-1693. DOI: 10.1056/NEJMoa1401602.

Wiedemann, H. P., Wheeler, A. P., Bernard, G. R., Thompson, B. T., Hayden, D., deBoisblanc, B. et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75. DOI:10.1056/NEJMoa062200