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Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock☆

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ABSTRACT

Purpose: The purpose of this study is to assess whether late positive fluid balances are associated with acute kidney injury and mortality in severe sepsis and septic shock.
Methods: In this retrospective study, fluid balances were calculated at 3 different time points: the onset of organ dysfunction attributed to sepsis, sepsis diagnosis, and vasopressors initiation. Data were analyzed in logistic regression models for mortality and acute kidney injury as outcomes.
Results: We included 116 patients. A RIFLE score F, diuresis less than 0.9 L from the second day after the first organ dysfunction, and fluid balance more than 3 L between the 24th and the 48th hour after diagnosis were independently associated with higher mortality, whereas in the subgroup with shock, only the latter parameter and diuresis less than 0.85 L on the first day of shock were independent risk factors. After adjusting for age, creatinine more than 1.2 mg/dL, a nonrenal Sequential Organ Failure Assessment greater than or equal to 7.5 on the first day and urine output less than 1.3 L on the first day after organ dysfunction were independent risk factors for RIFLE F. No relationship was found between fluid balance and acute kidney injury.
Conclusion: Late positive fluid balance is an independent risk factor for mortality in severe sepsis. Positive fluid balances are not associated with either protection against or risk for acute kidney injury.

1. Introduction

Severe sepsis and septic shock are among the most challenging conditions in medicine. Despite major advances, these syndromes remain major causes of death in intensive care units (ICUs), with an increasing incidence as seen in observational studies [1,2].

Since the landmark Early Goal-directed Therapy study, several recommendations have been issued concerning fluid management, mainly consisting of large-volume fluid resuscitation, especially during the first 6 hours after sepsis onset [3,4]. It is widely acknowledged that a lack of adequate fluid resuscitation during these crucial first hours can result in tissue hypoperfusion and associated hazardous consequences [5,6]. In contrast, liberal fluid resuscitation also results in large fluid balances, and it is uncertain how long this strategy should be maintained. Recent evidence also suggested that fluids in excess can have adverse effects and can worsen outcomes [6]. A large randomized trial of patients with acute lung injury showed that a restrictive fluid management strategy resulted in fewer days on mechanical ventilation [7]. Positive fluid balances have been associated with higher morbidity and mortality in several observational studies with different clinical contexts, including septic shock [8-16].

It is also a matter of debate how fluid management influences outcomes regarding acute kidney injury. Oliguria is a common trigger of fluid administration, and it is not clear whether fluid loading is effective in protecting the kidneys from failing. There are observational data showing that positive fluid balances might not be protective against, and might even be associated with, worse outcomes [8,14,17].

Therefore, we hypothesized that large-volume resuscitation, resulting in positive fluid balances after the first 6 hours from the onset of the disease, would be associated with mortality in severe sepsis and septic patients. We also tested the hypothesis that a positive fluid balance would not be protective against acute kidney injury.

2. Methods

This was a retrospective analysis of a previously published prospective cohort study conducted in a 35-bed ICU at a university teaching hospital [18]. We included patients older than 18 years old with diagnoses of severe sepsis or septic shock, in accordance with the current definitions. Briefly, sepsis-induced organ dysfunction was considered one of the following: hypotension, Pao_2/oxygen inspiratory fraction (Fio_2) ratio less than or equal to 300, lactate level greater than or

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equal to 1.5 times the reference value and base deficit more than 5, bilirubin level more than 2 times the reference value, urine output less than or equal to 0.5 mL/kg per hour after adequate volume replacement or the need for renal replacement therapy, platelet count less than or equal to 100 000 mm^3 or a decrease of 50% from the previous 3 days' values, and reduced level of consciousness. *Septic shock* was defined as volume-refractory hypotension with a need for vasopressors. The exclusion criteria were pregnancy and expectancy of death within less than 24 hours after admission to the ICU.

The study was approved by the Research Ethics Committee of Hospital São Paulo under number 1477/06, and all of the patients or their legal representatives signed informed consent forms.

We prospectively registered data on demographics, comorbid conditions, sources of infection, and organ dysfunction as well as compliance with the individual items of the Surviving Sepsis Campaign 6-hour bundle, Acute Physiologic and Chronic Health Evaluation II (APACHE II) during the first 24 hours of ICU admission, and the daily Sequential Organ Failure Assessment (SOFA) scores for the first week. The medical charts were retrospectively assessed to calculate the fluid balances and diuresis over the first 3 days. The fluid balances were calculated at 3 different time points: the onset of the first sepsis-induced organ dysfunction, the time when sepsis was diagnosed, and the time when vasopressors were started. To identify the time of organ dysfunction onset, the patient's chart was carefully reviewed to determine the first registration of hypotension, reduced level of consciousness, or low urine output as well as the first laboratory sampling time at which the results fulfilled the respiratory, metabolic, coagulation, or hepatic criteria for organ dysfunction. In patients admitted to the emergency department (ED) already with severe sepsis criteria, we used the time of triage. We defined *sepsis recognition* as the registration of a sepsis hypothesis in the patient's chart. *Duration of organ dysfunction* was defined as the time frame between the onset of dysfunction and its recognition. Starting from each of these time points, the fluid balances were calculated at the first 6, 12, and 24 hours and between the 24th and 48th hours. We calculated fluid balance by adding all of the fluid administered (intravenously, orally, and enteral) and subtracting diuresis and fluid loss from drains and tubes, without considering insensible water loss. The information on fluid administration and fluid loss are routinely registered by the nursing team in the patients' chart. Acute kidney injury was classified using the worst RIFLE score, considering either creatinine or diuresis, obtained during the first 5 days. The patients were followed up until ICU discharge or death. The end points were mortality at 60 days and a RIFLE score of F [19].

2.1. Statistical analysis

Categorical data are presented as percentages and were tested using Pearson χ^2 test and Fisher exact test, if applicable. Continuous variables were tested for normality with the Kolmogorov-Smimov test and are expressed as medians and interquartile ranges or as the mean ± SD as applicable. We compared these variables using the Mann-Whitney *U* test.

Fluid balances, diuresis, age, APACHE II score, SOFA score, δ SOFA, creatinine, and Pao_2/Fio_2 were categorized using receiver operator characteristic curves to predict mortality. The best cut-off values were calculated for all variables based on their sensitivity and specificity using Youden index. All of the variables in the univariate analysis that had *P* values less than .2 were included in the multivariate logistic stepwise forward regression models. In these analyses, we decided not to include variables with missing data for more than 10 patients because the lack of data would have resulted in serious inconsistencies. Three logistic regression models were generated. The first 2, using hospital mortality as the outcome, were composed of all of the patients as well as only the subgroup of patients with shock. We ran a third model analyzing the risk factors for the occurrence of a RIFLE score of F at any time during the first 5 days after admission. We excluded from this analysis only patients under previous renal replacement therapy. We included only variables from the first 24 hours after sepsis diagnosis and nonrenal SOFA score instead of the total SOFA score. The Hosmer-Lemeshow test was used to test the models' calibration, which was considered to be appropriate if *P* was higher than .10. The results were deemed significant if $P < .05$, and they are presented with their respective odds ratio (ORs) and 95% confidence intervals.

Statistics were analyzed with the SPSS (IBM, Chicago, Illinois, USA) software package, version 17.0 for Windows, and all of the tests were 2 tailed.

3. Results

From January 2007 to March 2009, a total of 176 patients were included in the original cohort study. In the present study, only 116 of those 176 patients were analyzed because 60 patients did not have sufficient data for fluid balance calculations or because the medical chart was not available. The main reason for these missing data is that fluid balances were properly registered in our institution only in the ICUs, and in some patients the first 6 hours occurred, while they were still in the ED or in the wards. Septic shock represented 73.2% of the cases. Median age was 60 years old (44-74), 63.5% were men, the median APACHE II score was 17 (13-26), and the median SOFA score was 8 (5-10). The mortality rate was 62.1% (Table 1).

In the univariate analysis of the whole population (n = 116), APACHE II greater than or equal to 22, age greater than or equal to 55, diabetes mellitus, SOFA scores (D1, D3, and D7), the need for renal replacement therapy, and RIFLE score of F were more frequent among nonsurvivors ($P < .05$). There were no differences between survivors and nonsurvivors regarding compliance with 6-hour bundle components. Nonsurvivors also had higher fluid balances at 24 hours (from the time of diagnosis and from shock onset) and between the 24th and 48th hours, irrespective of the starting point (first organ dysfunction, diagnosis, or shock) ($P < .05$). Nonsurvivors also had lower urine output (Table 1). The categorized variables, those related to fluid balance and diuresis and others, are presented in Table S1 of the supplementary electronic materials. The first logistic regression model, considering this whole population, showed that a RIFLE F, a fluid balance greater than 3 L between the 24th and the 48th hour after sepsis diagnosis, and a urine output less than 0.9 L on day 2 after the first organ dysfunction were independent risk factors for mortality. After adjusting for age and APACHE II score, only RIFLE F and a fluid balance greater than 3 L between the 24th and the 48th hour after sepsis diagnosis remained in the model (Table 2).

In the subgroup of shock patients (n = 85), APACHE II greater than or equal to 22, age greater than or equal to 55, RIFLE F, renal replacement therapy and higher SOFA scores were more frequent among nonsurvivors in the univariate analysis. Fluid balance between the 24th and 48th hours were higher in nonsurvivors irrespective of the starting point (first organ dysfunction, diagnosis or shock). Urine output was lower in nonsurvivors at all of the time points. There was no difference in compliance with the 6-hour bundle components. The results of univariate analysis are presented in Tables S3 and S4 in the electronic supplementary materials. In the multivariate analysis, fluid balance between the 24th and 48th hours from the onset of shock greater than 3.4 L and urine output on the first day of shock less than 0.85 L were independent risk factors for death, regardless of adjustment for age or APACHE II score (Table 2).

The univariate analysis for the risk factor for RIFLE F during the first 5 days is presented in Tables S5 and S6 in the supplementary materials. Three patients were excluded because they were already on dialysis. Creatinine greater than 1.2 mg/dL at baseline, nonrenal SOFA greater than or equal to 7.5 on the first day, and urine output less than 1.3 L on the first day after organ dysfunction were independent risk factors. After adjusting for age and APACHE II score, there was no relevant change in our results (Table 3).

4. Discussion

In this study, we demonstrated that a higher positive fluid balance between 24 and 48 hours after the diagnosis of sepsis and the presence of kidney dysfunction were associated with mortality in patients with

Table 1
Main characteristics of the whole population according to survival

Variable	Whole cohort (n = 116)	Survivors (n = 44)	Nonsurvivors (n = 72)	P^*
Age (y)	60 (44-74)	57 (35-83)	63 (56-87)	.024
Sex				.605
Female	42 (36.5)	17 (38.6)	25 (34.7)	
Male	74 (63.5)	27 (59.0)	47 (65.2)	
APACHE II	17 (23-26)	15 (11-20)	18 (14-25)	.026
Comorbidities				
Arterial hypertension	50 (46.1)	15 (34.0)	35 (48.6)	.125
CKD	11 (9.4)	4 (9.0)	7 (9.7)	.910
Immunosuppression	12 (10.3)	3 (6.8)	9 (12.5)	.330
Diabetes mellitus	22 (18.9)	4 (9.0)	18 (25)	.034
Alcohol	10 (8.6)	4 (9.0)	6 (8.3)	.877
COPD	13 (11.2)	6 (13.6)	7 (9.7)	.517
Cancer	30 (25.8)	13 (29.5)	17 (23.6)	.479
Admission category				.292
Medical	60 (43.1)	20 (45.4)	40 (55.6)	
Surgical	56 (48.2)	24 (54.5)	32 (44.4)	
Sepsis category				.570
Severe sepsis	46 (39.6)	16 (36.4)	30 (41.7)	
Septic shock	70 (40.3)	28 (63.6)	42 (58.3)	
Infection category				.917
Community	31 (26.7)	12 (27.3)	19 (26.4)	
Nosocomial	85 (73.3)	32 (72.7)	53 (73.6)	
Infection site				.568
Lung	68 (58.8)	26 (59.1)	42 (58.3)	
Abdominal	27 (23.2)	8 (18.2)	19(26.4)	
Urinary tract	7 (6.0)	4 (9.0)	3(4,2)	
Others	14 (12.0)	6 (13.6)	8 (11.1)	
Organ dysfunction (n)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	.138
Duration of dysfunction (h)	5.7 (0-10.9)	5.28 (0.0-10.8)	5.7(0.0-10.8)	.649
Mechanical ventilation	92 (79.3)	35 (79.5)	57 (79.1)	.961
Pao_2/Fio_2	209 (160-289)	219 (170-300)	202 (154-261)	.292
SOFA				
D0	8 (5-10)	7(5-9)	8 (6-10)	.170
D1	9 (6-11)	8 (6-10)	10 (7-13)	.010
D3	8 (5-10)	6 (4-8)	9 (6-11)	<.001
D7	7 (3-10)	4 (1-5)	10 (7-13)	<.001
δ SOFA				
D3-D0	−1(−5 to 2,5)	−3 (−6 to −1)	0 (-2- 4)	<.001
D7-D0	0 (0-1)	−3 (−6 to −1)	0 (-2- 4)	<.001
Creatinine				
D0	1.2 (0.7-2.0)	1.0(0.6-2.8)	1.6(0.8-2.0)	.247
D1	1.4 (0.7-2.2)	1.0(0.5-2.4)	1.6(0.8-2.1)	.065
D2	1.4 (0.7-2.4)	1.0 (0.6-2.4)	1.6 (0.8-2.3)	.039
RIFLE F or worse	65 (56)	14 (31.8)	51 (70.8)	<.001
Hemodialysis	34 (29.3)	5 (11.3)	29 (40)	.001
Compliance with 6-hour bundle				
Lactate	28 (24.1)	9 (20.4)	19 (26.3)	.469
Blood cultures	44 (37.9)	14 (31.8)	30 (41.6)	.289
Antibiotic therapy	52 (44.8)	16 (36.3)	36 (50.0)	.152
Fluids/vasopressor	114 (98.2)	44 (100.0)	70 (97.2)	.257
CVP optimization	40 (34.4)	13 (29.3)	27 (37.5)	.257
$Svco_2$ optimization	35 (30.1)	13 (29.3)	22 (30.5)	.838

Abbreviations: *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; CVP, central venous pressure; $Svco_2$, central venous oxygen saturation.
Results expressed as numbers (%) or medians and interquartile ranges (25%-75%).
* χ^2 and Mann-Whitney *U* tests (univariate analysis).

severe sepsis and septic shock. In patients with shock, we also found that fluid balance between 24 and 48 hours and reduced urinary output after shock onset were associated with mortality. Moreover, a positive fluid balance during the first 24 hours after diagnosis or after shock onset was not a protective factor against mortality. Positive fluid balances were also not associated with acute kidney injury, either as risk factors or protective factors.

It is well known that the earlier the timing of interventions, the better the results of the treatment will be for severe sepsis and septic shock [20]. The most important evidence of this relationship came from a single-center trial with the specificities of an ED population [3]. Notably, the interventions were restricted to the first 6 hours. Patients arriving at the ED likely did not have long time courses of organ dysfunction. Therefore, the efficacy of the interventions started during this 6-hour interval likely held true, but one cannot assume that these outcomes would also pertain for longer intervals, such as 12 or 24 hours. Earlier studies of hemodynamic resuscitation from shock failed to provide benefit, most likely because they did not consider the starting points of the diseases treated [21,22]. It has already been demonstrated that the duration of organ dysfunction can be very long [23]. Thus, even resuscitation strategies starting sooner after sepsis diagnosis could actually be considered late interventions. We might expect that a positive fluid balance during the first 6 hours, especially when measured from the onset of the first organ dysfunction, would be a protective strategy. However, we did not find this effect in our study. Another important marker would be the onset of shock, and it was also expected that fluid resuscitation would confer some benefit when considering this time point. We did not find this outcome in our study either. Fluid balances were not protective in any of the time windows analyzed. However, our limited sample size and the observational nature of the study limited our interpretations;

Table 2
Risk factors for mortality—multivariate analysis

Variable	*P*	OR	95% CI
Whole population (n = 101)			
Nonadjusted analysis			
RIFLE F or worse	.029	3.03	1.12-8.26
Fluid balance 24-48 h, >3000 mL[a]	.021	3.14	1.18-8.33
Urine output at day 2, <900 mL[a]	.037	4.46	1.09-18.1
Adjusted for age and APACHE II			
RIFLE F or worse	.034	2.95	1.08-8.06
Fluid balance 24-48 h, >3000 mL[a]	.021	3.19	1.19-8.54
Urine output at day 2, <900 mL[a]	.067	3.84	0.90-16.39
Patients with shock (n = 71)			
Nonadjusted analysis			
Fluid balance 24-48 h, >3400 mL[b]	.015	4.46	1.34-14.9
Urine output in day 1, <850 mL[b]	.005	19.6	2.40-16.6
Adjusted for age and APACHE II			
Fluid balance 24-48 h, >3400 mL[b]	.020	4.32	1.25-14.9
Diuresis in day 1, <850 mL[b]	.010	16.3	1.97-14.2

Abbreviation: *CI*, confidence interval.
[a] Fluid balance and urine output calculated after the sepsis diagnosis.
[b] Fluid balance and urine output calculated after shock onset. Stepwise forward logistic regression. Whole population: Hosmer-Lemeshow for nonadjusted model, *P*= .61; and adjusted model, *P*= .707. Patients with shock: Hosmer-Lemeshow for nonadjusted model, *P*= .753; and adjusted model, *P*= .648. In the patients with shock, the following variables were not included due to missing data: fluid balance in the first 6 hours after dysfunction, fluid balance between the 24th and 48th hours after diagnosis, creatinine on the first and the second days, and SOFA score on the seventh day.

thus, we cannot exclude a protective effect of positive fluid balances during these time intervals. However, taken together, we might suggest that the therapeutic time window for the treatment of severe sepsis is very short, thus reinforcing the need for early detection and treatment.

Several researchers have suggested a burden of morbidity and mortality associated with positive fluid balances within multiple contexts [6,13-15]. We found an association between late (between the 24th and 48th hours after diagnosis and after the onset of shock) positive fluid balance and mortality. Our findings were consistent with the results of previous studies. We can hypothesize that fluid resuscitation outside of the therapeutic time window is not only a futile strategy but also exposes patients to harmful effects. [24,25]

Another important contribution was the finding of advanced acute kidney injury, defined as a RIFLE score of F, as a mortality risk factor [26]. This finding was also consistent with previous studies [27]. Acute kidney injury not only augments the risk of death, but it also makes patient management more complex, with the need for dialysis and its consequent toll on morbidity and its costs. Much emphasis has been placed on the need for preventive measures, but very little is known about what these measures should be. Traditionally, it has been recommended to maintain patients as euvolemic and hydrated. Our findings did not support a protective role for positive fluid balance or kidney function, even during the first 6 hours. Our findings were in accordance with those of other studies involving septic and nonseptic patients [8,14]. These findings are in agreement with the hypothesis that the pathophysiology of sepsis-related kidney dysfunction is complex and involves more than just hydration status and perfusion parameters. Therefore, oliguria and creatinine elevations per se might not be good indications for fluid challenges.

Table 3
Risk factors for acute kidney injury (RIFLE 3)—multivariate analysis

Variable	*P*	OR	95% CI
Nonadjusted			
Creatinine on day 0, >1.2	<.001	9.0	3.09-26.31
Nonrenal SOFA on day 1, >7.5	.021	3.69	1.21-11.2
Urine output on the first day, <1300 mL[a]	.010	3.75	1.37-10.20
Adjusted for age and APACHE II			
Creatinine D0, >1.2	<.001	8.92	3.07-26.31
Nonrenal SOFA on day 1, >7.5	.026	3.73	1.17-11.90
Urine output on the first day, <1300 mL[a]	.020	3.59	1.22-10.63

[a] After the first dysfunction. Stepwise forward logistic regression. Hosmer-Lemeshow for nonadjusted model, *P*= .992; and adjusted model, *P*= .620. Only baseline variables were considered.

Our study had some strengths. Our population was a consecutive prospective cohort with high disease severity. We established specific time windows to define early and late time points as well as important starting points (eg, detection of the first sepsis-related organ dysfunction, the time of sepsis diagnosis, and the onset of shock). We could also prospectively assess compliance with the 6-hour Surviving Sepsis Campaign bundle. Because there were no differences in compliance among the groups, for either survival or RIFLE status, it is unlikely that these variables would have affected the relationships between fluid balance and the outcomes studied.

This study also had several limitations. Because this was an observational study, we could not infer any causal relationships. The observational design and that it was a single-center study also reduced its external validity. Another important limitation was the absence of data from 60 patients, which might have biased our results. We also need to recognize that some of our variables are correlated, such as urine output and fluid balance. This might cause some instability in our multivariate regression model. However, our results suggest that low urine output and positive fluid balances are both independent risk factor for mortality. Our results should also be interpreted bearing in mind the small sample size; thus, the absence of associations between early fluid balance and survival might have been due to a lack of statistical power. However, even with such a small sample size, we could establish that late positive fluid balance was an independent risk factor for mortality, suggesting that this finding was consistent and most likely stronger than the hypothetical survival benefit of an early positive balance.

5. Conclusion

Positive fluid balance between the 24th and 48th hours after the diagnosis of severe sepsis and the onset of septic shock were independent risk factors for mortality. Earlier positive fluid balances were not associated with survival. Positive fluid balances were not associated with either protection or with the risk for acute kidney injury. Our results raise the hypothesis that a judicious fluid balance after early resuscitation might be a useful tool to improve outcomes in sepsis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2014.09.002.

References

[1] Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348(16):1546–54.
[2] Angus DC, Linde-Zwirble WT, Lindcker J, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29(7):1303–10.
[3] 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(19):1368–77.
[4] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):1394–6.
[5] Cinel I, Dellinger RP. Advances in pathogenesis and management of sepsis. Curr Opin Infect Dis 2007;20(4):345–52.
[6] Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136:102–9.
[7] National Heart, Lung, And Blood Institute Acute Respiratory Distress Syndrome (Ards) Clinical Trials Network, Wiedermann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564–75.
[8] Metha RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 2004;66(4):1613–21.

[9] Epstein CD, Peerless JR. Weaning readiness and fluid balance in older critically ill surgical patients. Am J Crit Care 2006;15(1):54–64.
[10] Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA. Fluid balance and weaning outcomes. Intensive Care Med 2005;31(12):1643–7.
[11] Rosenberg AL, Dechert RE, Park PK, Bartlet RH, N.I.H.N.H.L.B.I.A.R.D.S. Network. Review of a large clinical series: assosiation of cumulative fluid balance on outcome in acute lung injury: a retrospective review of ARDSnet trial volume study cohort. J Intensive Care Med 2009;24(1):35–46.
[12] Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinheart K, Gerlach H, et al. Sepsis in European intensive care units: results of the soap study. Crit Care Med 2006;34(2):344–53.
[13] Sakr Y, Vincent JL, Reinheart K, Groeneveld J, Michalopoulos A, Sprung CL, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest 2005;128(5):3098–108.
[14] Payen D, Pont AC, Sakr Y, Spies C, Reinhart K, Vincent J, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12:R74–80.
[15] Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39(2):259–65.
[16] Azevedo LC, Park M, Salluh JL, Rea-Neto A, Souza-Dantas VC, Varaschin P, et al. Clinical outcomes of patients requiring mechanical ventilator support in Brazilian intensive care units: a prospective, cohort study. Crit Care 2013;17(2):R63–74.
[17] Vaara ST, Korkhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012;16(5):R197–207.
[18] Machado FR, Salomao R, Rigato O, Ferreira EM, Schettino G, Mohovic T, et al. Late recognition and illness severity are determinants of early death in severe septic patients. Clinics (Sao Paulo) 2013;68(5):586–91.
[19] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute dialysis acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204–12.
[20] Westphal GA, Feijó J, Andrade PS, Trindade L, Suchard C, Monteiro MAG, et al. Early detection strategy and mortality reduction in severe sepsis. Rev Bras Ter Intensiva 2009;21(2):113–23.
[21] Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, et al. A trial of goal-oriented therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995;333(16):1025–32.
[22] Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl Med 1994;330(24):1717–22.
[23] Conde KA, Silva E, Silva CO, Ferreira E, Freitas FG, Castro I, et al. Differences in sepsis treatment and outcomes between public and private hospitals in Brazil: a multicenter observational study. PLoS One 2013;8(6):e64790–800.
[24] Lopes JA, Fernandes P, Jorge S, Resina C, Santos C, Pereira A, et al. Long-term risk of mortality after acute kidney injury in patients with sepsis: a contemporary analysis. BMC Nephrol 2010;11:9–18.
[25] Dalfino L, Tullo L, Ilaria D, Malcangi V, Brienza N. Intraabdominal hypertension and acute renal failure in critically ill patients. Intensive Care Med 2008;34(4):707–13.
[26] Prowle JR, Echeverri JE, Ligabo VE, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol 2010;6:107–15.
[27] Lopes JA, Jorge S, Resina C, Santos C, Pereira A, Neves J, et al. Prognostic utility of RIFLE for acute renal failure in patients with sepsis. Crit Care 2007;11(2):408.