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ORIGINAL INVESTIGATION

Assessment of the components of fluid balance in patients with septic shock: a prospective observational study

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Abstract

Background: The optimal amount for initial fluid resuscitation is still controversial in sepsis and the contribution of non-resuscitation fluids in fluid balance is unclear. We aimed to investigate the main components of fluid intake and fluid balance in both survivors and non-survivor patients with septic shock within the first 72 hours.

Methods: In this prospective observational study in two intensive care units, we recorded all fluids administered intravenously, orally, or enterally, and losses during specific time intervals from vasopressor initiation: T1 (up to 24 hours), T2 (24 to 48 hours) and T3 (48 to 72 hours). Logistic regression and a mathematical model assessed the association with mortality and the influence of severity of illness.

Results: We included 139 patients. The main components of fluid intake varied across different time intervals, with resuscitation and non-resuscitation fluids such as antimicrobials and maintenance fluids being significant contributors in T1 and nutritional therapy in T2/T3. A positive fluid balance both in T1 and T2 was associated with mortality ($p = 0.049$; $p = 0.003$), while nutritional support in T2 was associated with lower mortality ($p = 0.040$). The association with mortality was not explained by severity of illness scores.

Conclusions: Non-resuscitation fluids are major contributors to a positive fluid balance within the first 48 hours of resuscitation. A positive fluid balance in the first 24 and 48 hours seems to independently increase the risk of death, while higher amount of nutrition seems protective. This data might inform fluid stewardship strategies aiming to improve outcomes and minimize complications in sepsis.

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Introduction

Sepsis is a worldwide public health problem with more than 40 million cases per year and 11 million deaths worldwide.[1] Adequate treatment for sepsis includes early recognition and rapid administration of antimicrobial agents, source control and hemodynamic resuscitation.[2,3] In hemodynamic resuscitation, fluid administration is fundamental as hypovolemia is frequent and can contribute to hypoperfusion and organ dysfunction. The Surviving Sepsis Campaign[3] recommends fluid resuscitation with 30 mL.kg^{-1} of body weight in patients with signs of hypoperfusion, however, there are still controversial issues such as the amount of fluids to be infused.[4] Fluid overload can trigger adverse events, with unfavorable clinical outcomes being shown in observational studies.[5–9] Nonetheless, assessment of causalities is challenging as more severely ill patients usually need aggressive resuscitation. Moreover, recent randomized studies failed in showing improved patient-centered outcomes with restrictive strategies.[10–14]

Although fluid therapy is fundamental to correct hypovolemia and to reduce hypoperfusion, the administration of unnecessary fluids should be avoided. Previously, resuscitation fluids constituted a major part of the total amount given to a septic patient,[15] however, our current practice has changed to a more conservative use of fluids. More recent studies suggested that non-resuscitation fluids might be major contributors to a positive fluid balance.[16] In this scenario, the current controversy around initial fluid resuscitation might be inopportune as the relative contribution of resuscitation fluids is smaller.

Both the components of fluid intake and the timing of resuscitation are relevant. Patients with shock, once properly resuscitated, might benefit from better fluid stewardship.[17,18] The recent randomized trials on restrictive strategies did not collect detailed data on the components of fluid intake given as non-resuscitation fluids in different time points within the first days of resuscitation. Observational studies have inconsistent results.[6,9,19] A better understanding of fluid administration patterns might help to implement prescription strategies to improve fluid stewardship.

Thus, our primary objective was to evaluate the components of fluid balance, both in survivors and non-survivors in different time points of resuscitation. We aimed to assess, after starting vasopressors, the relative contribution of both resuscitation and non-resuscitation fluids in the fluid balance. Our secondary objectives were to assess if the fluid balance and its components in different time points would be associated with mortality.

Methods

This is a prospective, observational study conducted in two general intensive care units (ICU) in Brazil. Both ICUs have a multidisciplinary team, daily visits by intensivist physicians and well-implemented routines with a mixed profile of patients, both clinical and surgical. The Universidade Federal de São Paulo Research Ethics Committee approved the study under the number (CAAE: 54538116.2.0000.5505). After identifying the eligible patients, the study team obtained an informed consent either directly with the patients, if they were able to consent, or with their legal representative. After consent, the study team retrieved all the information from the electronic medical records.

We included a convenient sample of patients over 18 years old with a confirmed diagnosis of septic shock admitted to one of the participating ICU, after signing the informed consent. We defined septic shock as the presence of life-threatening hypotension secondary to the presence of proven or presumed infection, requiring vasopressor to maintain mean blood pressure above 65 mmHg in the presence of an intravascular volume status considered appropriate by the attending physician, regardless of lactate levels after fluid replacement. Patients with shock of undefined etiology or not fully attributable to sepsis were excluded. We also excluded those who developed shock in another hospital, with chronic kidney disease in renal replacement therapy (RRT), advanced liver disease (Child C), under end-of-life care, as well as those previously included in the study.

Study protocol

We recorded all resuscitation or non-resuscitation fluids received by the patients intravenously, and the non-resuscitation fluids received by oral or by enteral route as well as all fluid output to allow the calculation of fluid balance for 72 hours. We considered as time zero the moment of the installation of shock, meaning the start of vasoactive drug, namely, noradrenaline, adrenaline, dopamine, or vasopressin. We defined the time periods as follows: T0 (6 hours before shock to time 0), T1 (up to 24 hours after shock), T2 (24 to 48 hours after shock), T3 (48 to 72 hours after shock).

We classified the fluids according to the following categories: vasoactive drugs (noradrenaline, adrenaline, dopamine, vasopressin and dobutamine); sedatives and analgesics (propofol, fentanyl, midazolam, dexmedetomidine, tramadol and neuromuscular blockers); antimicrobials, considering all classes of antimicrobial agents, antifungals, and antivirals; and others, comprising the other medications administered intravenously, oral or by enteral tube. Intravenous fluids for resuscitation and non-resuscitation fluid given for maintenance therapy, as well as blood products were also computed. As nutritional therapy, we considered oral diet, enteral, parenteral nutrition, and water.

We also recorded all fluids lost resulting from urine output, ultrafiltration, nasogastric tube, and drains. We did not consider insensitive losses, and gastrointestinal losses were computed only in the presence of important diarrhea (> 3 episodes/day). We calculated the total intake and loss, and defined fluid balance as the subtraction between them.

We obtained demographic and clinical data from the medical records. The study team did not influence the patient's treatment and, in general, the assistant team followed the institution sepsis protocols based on the recommendations of the Surviving Sepsis Campaign. We collected the severity scores Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiological score (SAPS3) at ICU admission. We followed the patients up to hospital discharge to determine the length of hospital stay and in-hospital mortality.

Statistical analysis

Given the descriptive nature of our primary objective and in the absence of studies assessing the components of fluid

intake according to survivorship, we did not perform a formal sample size calculation. We opted to specify a period for data collection of a convenient sample of patients.

We used percentages to describe categorical variables and median and interquartile range (IQR) or mean and standard deviation to describe continuous variables. For comparisons of survivors and non-survivors, we used Student's *t*-test and Mann-Whitney test for continuous variables with a normal or non-normal distribution. Categorical variables were compared with Pearson's Chi-Square test.

We assessed the association with hospital mortality using a logistic regression model considering all significant variables in the univariate analysis in each of the time intervals.[20] To mitigate redundancy within the model, we excluded variables that were components of the scores such as diabetes mellitus, mechanical ventilation, and renal replacement therapy (RRT). We evaluated collinearity observing Pearson's dispersal matrix and correlation coefficient for continuous variables, and cross-tabulation for categorical variables. We maintained the most clinically relevant variable in the model. We ran alternative models using 1) Only variables from the first 24 hours; 2) Aggregated variables in the 72 hours. The results were expressed in odds ratios (OR) and their respective confidence intervals (CI) of 95%.

We also ran a post roc analysis to further explore the association we found between the fluid balance and mortality. We constructed a mathematical model based on the first and third quartiles for SOFA and SAPS3 creating two hypothetical severity profiles (less severe: SOFA = 7 plus SAPS3 = 51; more severe: SOFA = 11 plus SAPS3 = 68) and we

Table 1 Main characteristics of the study population according to survival status.

Variable	Global (n = 139)	Survivors (n = 65)	Non survivors (n = 74)	*p*-value
Age (years)	70 [60–82]	70 [57–81.5]	73.5 [62.75–82]	0.32
Gender (female)	66 [47.5]	33 [50.8]	33 [44.6]	0.50
Body mass index (kg.m^{-2})	24.2 [21.9–27.7]	23.9 [21.0–27.1]	24.2 [22.5–28.5]	0.19
Charlson Comorbidity Index	2 [0–3]	1 [0–2]	2 [1–3]	0.02
Comorbidities				
Hypertension	100 [71.9]	43 [66.2]	57 [77]	0.18
Diabetes mellitus	51 [36.7]	17 [26.2]	34 [45.9]	0.02
Congestive heart failure	33 [23.7]	12 [18.5]	21 [28.4]	0.23
COPD	12 [8.6]	6 [9.2]	6 [8.1]	~1
SAPS3	61.8 ± 14.3	58.7 ± 12.7	64.5 ± 15.2	0.02
SOFA score (ICU admission)	5 [3–8]	4.5 [3–6]	6 [3–9]	0.046
ICU admission source				0.38
Emergency room	54 [38.8]	28 [43.1]	26 [35.1]	
Hospital floor	41 [29.5]	17 [26.2]	24 [32.4]	
Operation room	27 [19.4]	10 [15.4]	17 [23]	
Others	17 [12.2]	10 [15.4	7 [9.5]	
Type of admission				0.12
Medical	108 [77.7]	52 [80]	56 [75.7]	
Elective surgery	15 [10.8]	9 [13.8]	6 [8.1]	
Emergency surgery	16 [11.5]	4 [6.2]	12 [16.2]	
Infection site				0.12
Lung	70 [50.4]	35 [53.8]	35 [47.3]	
Abdominal	19 [13.7]	7 [10.8]	12 [13.7]	
Genitourinary	23 [16.5]	11 [16.9]	12 [16.2]	
Others	27 [19.4]	12 [18.4]	15 [20.3]	
SOFA score (vasopressor onset)	9 [7–11]	8 [7–10.5]	9 [8–11]	0.04
Time lengths				
Hospital admission to ICU admission (h)	43.8 [8.3–237.0]	34.9 [6.7–213.0]	54.3 [9.0–244.5]	0.62
Organ dysfunction to vasopressor (h)	2.2 [0.3–8.8]	2.1 [0.2–12.8]	2.2 [0.5–8.0]	0.81
Hypotension to vasopressor (h)	1.0 [0.0–3.0]	1.0 [0.0–3.2]	0.5 [0.0–2.2]	0.23
Hospital admission to vasopressor (h)	43.8 [8.3–237.0]	34.9 [6.7–213.0]	54.3 [9.0–244.5]	0.62
Lactate ≥18 mg.dL^{-1}	64 [49.2]	26 [43.3]	38 [54.3]	0.21
Lactate (mg.dL^{-1})	16.5 [12–25]	14.5 [11–24]	18 [12–25]	0.24
Use of invasive support				
Mechanical ventilation	114 [83.8]	44 [69.8]	70 [95.9]	< 0.001
Renal replacement therapy	27 [19.9]	6 [9.5]	21 [28.8]	0.005
ICU length of stay (days)	12.5 [6.5–24.8]	11.6 [6.2–18.1]	13.9 [6.9–26.8]	0.28
Hospital length of stay (days)	22.6 [6.3–42.1]	21.8 [13.7–42.0]	22.6 [12.5–42.8]	0.92

COPD, Chronic Obstructive Pulmonary Disease; SAPS3, Simplified Acute Physiological Score; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; Results are expressed as mean ± SD, median [IQR] or n (%). Mechanical ventilation and renal replacement therapy (n = 136).

generated the death probability estimates for fluid balance up to 24 hours and 72 hours for the two profiles with their respective 95% CI.

In all tests, we considered the results significant if the *p*-value was less than 0.05. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 19.0 program and statistical software R 3.4.4 (R Core Team, 2018). The graphics were constructed using the ggplot2 package.

Results

From May 2016 to January 2017, we included 139 patients diagnosed with septic shock. The mean age was 70 (60–82) years and the majority were clinical patients admitted from emergency services or wards with a severe profile as depicted by high severity scores and hospital mortality (53.2%). The main characteristics of patients are available in Table 1.

The amount of fluids received in the first hours of shock was high with 795 (425–1422 mL) in T0, 3412 (2502–4488 mL) on T1, 2846 (2234–3654 mL) on T2 and 2626 (1975–3465 mL) in T3. In the first 24 hours (T1), the main sources of fluids were antimicrobials (550 [330–950] mL), resuscitation fluids (500 [0–1250] mL) and maintenance fluids (520 [0–1032] mL). In T2 and T3, fluids from nutritional therapy constituted the main source (704 [82–1478] mL and 1045 [467–1477] mL). Fluid balance was positive in the first 72 hours after vasopressor onset (T1: 1976 [1081–3329] mL; T2: 1348 [437–2319] mL; T3: 799 [0–1860] mL). Figure 1A shows intake and loss according to the distinct categories of fluids, considering all patients. Detailed data is available in Table 2.

In the univariate analysis, we observed differences in the number of components of fluid intake between survivors and non-survivors. The volume received as vasoactive drugs was higher in non-survivors in all observed times (T1 – survivors: 153 [73–337], non-survivors: 283 [140–579] mL, $p = 0.01$; T2 – survivors: 91 [12–271], non-survivors: 334 [108–707] mL, $p < 0.001$; T3 – survivors: 31 [0–114], non-survivors: 191 [35–565] mL, $p < 0.001$), with no difference in the amount received as resuscitation fluid in the first 24 hours after shock (T1 – survivors: 500 [0–1000], non-survivors: 1000 [0–1500] mL, $p = 0.054$). More fluids were administered as maintenance in non-survivors in T2 (survivors: 0 [0–563], non-survivors: 346 [0–946] mL), $p = 0.01$, while nutrition therapy had a greater contribution in surviving patients (T1 = survivors: 330 [8–955] mL, non-survivors: 30 [0–717] mL), $p = 0.02$; T2 = survivors: 933 [374–1662] mL, non-survivors: 483 [0–1000] mL, $p = 0.001$). This data is available in Figure 1B. There was a significant difference between survivors and non-survivors in the total volume infused within the first 24 hours (T1 – survivors: 3133 [3238–3925] mL, non-survivors: 3947 [2758–5080] mL, $p = 0.006$) and in the fluid balance (T1 – survivors: 1560 [664–2472], non-survivors: 2486 [1765–4114] mL, $p < 0.001$) (Fig. 2). The amount of diuresis was lower in non-survivors in all periods analyzed and the fluid balance on the second day after shock was significantly higher in non-survivors (Table 2).

In the first multivariable logistic regression model, we observed a higher mortality rate in patients with a positive fluid balance both at T1 (OR = 1.025 [95% CI 1.001–1.052], $p = 0.049$) and T2 (OR = 1.050 [95% CI 1.018–1.086], $p = 0.003$) (Table 3). Interestingly, higher nutrition intake in T2 was associated with lower mortality (OR = 0.941 [95% CI 0.886–0.996], $p = 0.040$). On the alternative models, only the fluid balance in T1 (OR = 1.045 [95% CI 1.021, 1.072]; $p < 0.001$) and the total fluid balance OR = 1.026 (95% CI 1.014, 1.040]; $p < 0.001$) remained as significant factors associated with higher mortality (Table 3).

Considering only the variables up to 24 hours, our mathematical model to predict death based on the first and third quartiles values for SAPS and SOFA scores, generated curves with superposed 95% CI suggesting that the association between death and the fluid balance in T1 is not modified by the severity of the patient (Fig. 3A). We found similar results when we considered the aggregate fluid variables up to 72 hours (Fig. 3B).

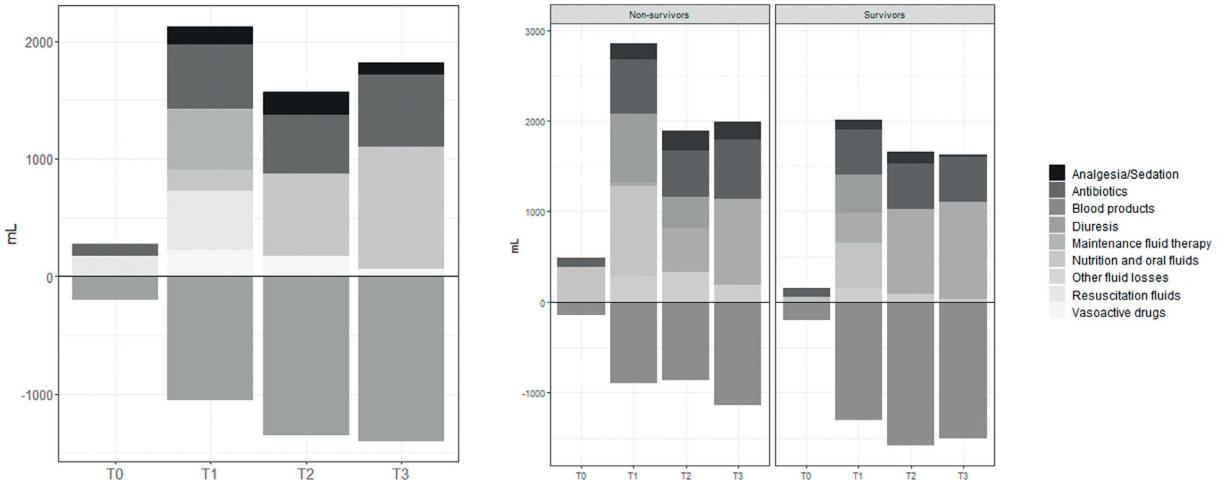

Figure 1 Fluid intake and output considering all patients and according to hospital survival status. (A) Total population. (B) According to survival status. T0 (6 hours before shock to time 0), T1 (from 0:01 to 24 hours after shock), T2 (from 24:01 to 48 hours after shock), T3 (from 48:01 to 72 hours after shock).

Table 2 Components of fluid intake, output, and fluid balance in the time points according to survival status.

Variable	Global (n = 139)	Survivors (n = 65)	Non survivors (n = 74)	*p*-value
Sedation and analgesia				
T0	0 (0 – 20)	0 (0 – 21)	0 (0 – 20)	0.72
T1	153 (26 – 300)	102 (7.5 – 311)	180 (40 – 295)	0.35
T2	200 (0 – 348)	132 (0 – 284)	217 (30 – 410)	0.02
T3	102 (0 – 309)	25 (0 – 198)	190 (21 – 386)	0.005
Vasoactive drugs				
T0	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.34
T1	225 (106 – 452)	153 (73 – 337)	283 (140 – 579)	0.01
T2	170 (40 – 494)	91 (12 – 271)	334 (108 – 707)	<0.001
T3	59 (0 – 306)	31 (0 – 114)	191 (35 – 565)	<0.001
Antimicrobial agents				
T0	100 (0 – 200)	100 (0 – 201)	100 (0 – 148)	0.32
T1	550 (330 – 950)	500 (330 – 925)	600 (337 – 952)	0.51
T2	500 (330 – 850)	500 (300 – 840)	510 (400 – 893)	0.32
T3	608 (335 – 870)	500 (505 – 800)	660 (400 – 906)	0.12
Nutrition				
T0	0 (0 – 200)	0 (0 – 185)	0 (0 – 200)	0.44
T1	180 (0 – 880)	330 (8 – 955)	30 (0-717)	0.02
T2	704 (82 – 1478)	933 (374 – 1662)	483 (0 – 1000)	0.001
T3	1045 (467 – 1477)	1070 (660 – 1479)	944 (30 – 1481)	0.11
Maintenance fluids				
T0	0 (0 – 125)	0 (0 – 86)	0 (0 – 167)	0.56
T1	520 (0 – 1032)	423 (0 – 942)	761 (0 – 1187)	0.08
T2	0 (0 – 902)	0 (0 – 563)	346 (0 – 946)	0.01
T3	0 (0 – 609)	0 (0 – 321)	0 (0 – 879)	0.18
Resuscitation fluids				
T0	173 (0 – 1000)	50 (0 – 1000)	382 (0 – 1000)	0.70
T1	500 (0 – 1250)	500 (0 – 1000)	1000 (0 – 1500)	0.054
T2	0 (0 – 225)	0 (0 – 0)	0 (0 – 500)	0.04
T3	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.66
Others[a]				
T0	30 (7 – 110)	30 (10 – 120)	30 (0–87)	0.68
T1	230 (80 – 530)	180 (60 – 448)	285 (100 – 544)	0.08
T2	236 (82 – 492)	213 (73 – 404)	260 (100 – 548)	0.41
T3	250 (93 – 422)	230 (67 – 389)	255 (127 – 466)	0.12
Overall fluid intake[b]				
T0	795 (425 – 1422)	810 (426 – 1391)	745 (417 – 1463)	0.87
T1	3412 (2502–4488)	3133 (2338 – 3925)	3947 (2758 – 5080)	0.006
T2	2846 (2234–3654)	2642 (2079 – 3382)	3042 (2337 – 3740)	0.06
T3	2626 (1975–3465)	2532 (1809 – 3358)	2713 (2021 – 3603)	0.41
Diuresis				
T0	200 (0 – 450)	200 (0–450)	150 (0–420)	0.57
T1	1050 (605 – 1550)	1300 (812–1700)	900 (545–1435)	0.01
T2	1350 (725 – 1850)	1585 (1150–2040)	865 (456–1660)	<0.001
T3	1400 (763 – 2350)	1500 (1100 – 2700)	1145 (468 – 2000)	0.01
Overall fluid output[b]				
T0	250 (0 – 500)	230 (10 – 475)	250 (0 – 524)	0.88
T1	1200 (735 – 1705)	1325 (875 – 1925)	1000 (604 – 1535)	0.02
T2	1550 (900 – 2010)	1700 (1430 – 2225)	1138 (588 – 1878)	0
T3	1700 (1100–2500)	1800 (1255 – 2745)	1575 (844 – 2180)	0.056
Fluid balance[c]				
T0	500 (130-1150)	532 (198 – 1141)	498 (58 – 1157)	0.65
T1	1976 (1081-3329)	1560 (664 – 2472)	2486 (1765 – 4114)	<0.001
T2	1348 (437-2319)	1111 (161 – 1701)	1799 (726 – 2611)	0.001
T3	799 (0-1860)	695 (-99 – 1507)	910 (0 – 2269)	0.056
Total fluid intake within 72 hours	14692 (12659-19031)	13988 (11833–17256)	15840 (13100–20547)	0.02
Total fluid output in 72 hours	4860 (3320–6450)	5505 (4045–7050)	4105 (2740–6121)	<0.001
Total fluid balance	10370 (7095–14257)	8299 (6622–11320)	12010 (8735–16821)	<0.001

T0 (six hours before shock to time 0), T1 (from 0:01 to 24 hours after shock), T2 (from 24:01 to 48 hours after shock), T3 (from 48:01 to 72 hours after shock). Results are in mL. Results are expressed as mean ± SD, median [IQR] or n (%).

[a] Other comprised any other medications administered intravenously, oral or by enteral tube.

[b] Overall means the sum of all fluids taken or lost in each time period. For losses we also computed ultrafiltration, nasogastric tube and drains.

[c] Fluid balance defined as the subtraction from total intake and output.

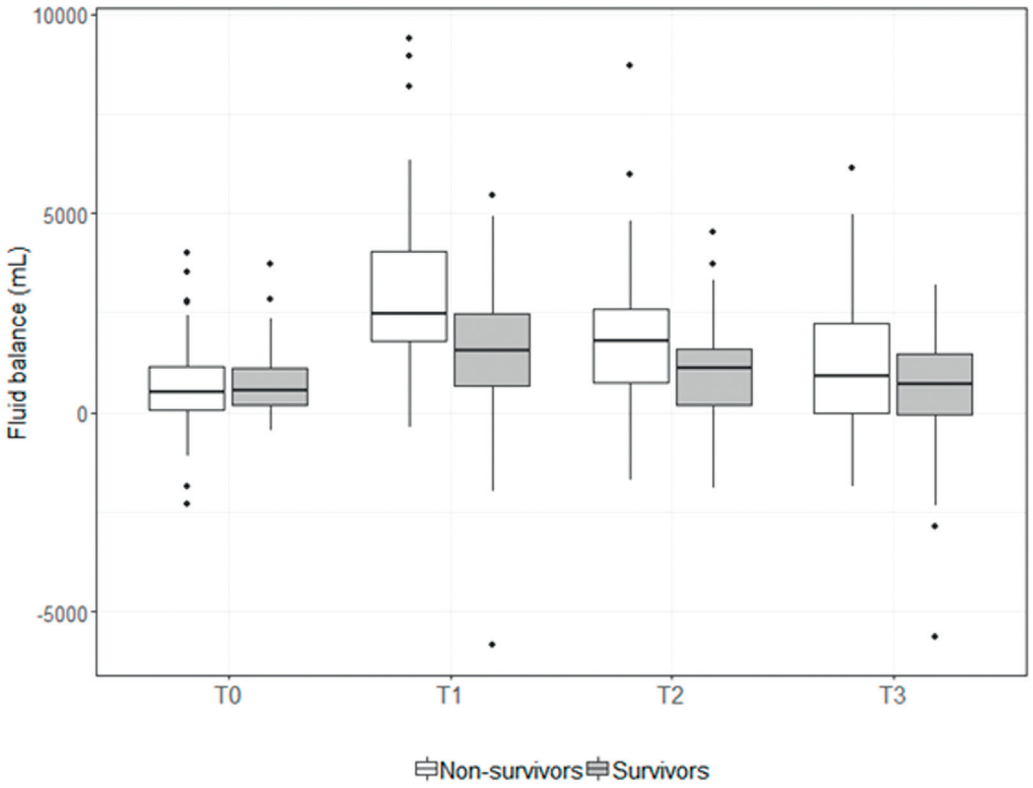

Figure 2 Fluid balance according to survival status. T0 (6 hours before shock to time 0), T1 (from 0:01 to 24 hours after shock), T2 (from 24:01 to 48 hours after shock), T3 (from 48:01 to 72 hours after shock). Survivors vs. non-survivors: T1 — $p < 0.01$; T2 — $p = 0.001$.

Table 3 Multivariable analysis of factors associated with hospital mortality.

Variable		95% confidence interval		
	Odds Ratio	Inferior limit	Superior limit	*p*-value
Full model with all time-points				
SOFA at vasopressor onset	1.058	0.905	1.241	0.48
SAPS 3	1.015	0.983	1.048	0.37
Fluid balance — T1 (per 100 mL)	1.025	1.001	1.052	0.049
Fluid balance — T2 (per 100 mL)	1.050	1.018	1.086	0.003
Nutrition — T2 (per 100 mL)	0.941	0.886	0.996	0.04
Model only with variables from the first 24 hours				
SOFA at vasopressor onset	1.042	0.899	1.212	0.581
SAPS3	1.025	0.996	1.055	0.094
Fluid balance — T1 (per 100 mL)	1.045	1.021	1.072	<0.001
Model with variables aggregated in 72 hours				
SOFA at vasopressor onset	1.045	0.901	1.216	0.56
SAPS3	1.025	0.996	1.057	0.097
Total fluid balance (per 100 mL)	1.026	1.014	1.040	<0.001

SOFA, Sequential Organ Failure Assessment; SAPS3, Simplified Acute Physiological score; T1 (from 0:01 to 24 hours after shock), T2 (from 24:01 to 48 hours after shock). In the full model, we included fluid balance (T1 and T2), resuscitation fluid (T2), vasoactive drugs (T1), diuresis (T1, T2 and T3), nutrition (T1 and T2), maintenance fluids (T2), analgesia/sedation (T2), SOFA at vasopressor onset, SAPS3 and Charlson index in the model only with variables from the first 24 hours, we included fluid balance (T1), vasoactive drugs (T1), diuresis (T1), nutrition (T1), SOFA at vasopressor onset, SAPS3 and Charlson index. In the model with variables aggregated in the 72 hours, we included the total fluid intake, total diuresis, total fluid balance, SOFA at vasopressor onset, SAPS3 and Charlson index. In all models we excluded variables with collinearity.

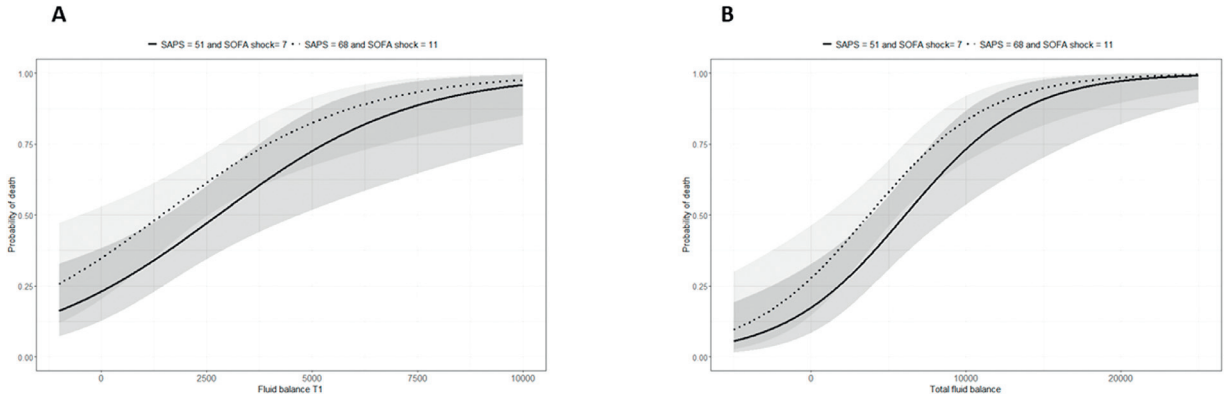

Figure 3 Mathematical model to predict mortality according to fluid balance in T1 and total fluid balance. (A) Fluid balance in T1. (B) Total fluid balance. The probability was calculated based on the second and third multivariable regression model (see Table 3) using the first and third quartile value for SAPS and SOFA score. The model generates curves with superposed 95% CI suggesting that the severity of illness does not modify the association between death and fluid balance.

Discussion

Our results show that the major source of fluid intake in the first 24 hours of sepsis is not restricted to resuscitation fluids but also includes non-resuscitation fluids such as antimicrobials and maintenance fluids. There was an association between higher mortality and positive fluid balance in the first 24 and 48 hours, while a higher amount of nutrition was associated with lower lethality. The total fluid balance in 72 hours was also associated with higher mortality. These associations do not seem to be clearly mediated by the severity of disease, at least as assessed by SOFA score and SAPS.

Fluids other than those for fluid resuscitation contributed to the positive fluid balance in the first 24 hours after vasopressor initiation. In this sense, the controversy on the administration of 30 mL.kg^{-1} of fluids for initial fluid resuscitation seems awkward as other non-perceivable sources are major contributors.[3,4] In our study, the amount of fluid received as resuscitation did not seem to be associated with higher mortality rates. Recent studies showed the relevance of non-resuscitation fluids.[16,21-23] Of note, maintenance fluids, which are not always clinically needed, played a major role,[6,22] which is in consonance to our findings of a similar amount of maintenance and resuscitation fluids in the first 24 hours. Another important finding was the high amount of fluids used for antimicrobials dilution and the volume received as vasopressor/inotropic and analgesia/sedation therapy. These results suggest that patients with septic shock may benefit from prescription concentration strategies and better fluid stewardship.

The association between more nutritional support and lower mortality even after adjustment for severity of illness is interesting. A direct effect of nutrition is unlikely as randomized studies comparing early with late nutrition and full nutritional therapy with permissive undernutrition did not demonstrate an effect of nutrition in outcomes of critically ill patients.[24,25] Nonetheless, observational studies showed an association between adequate nutritional therapy and improvement in outcomes.[26] These apparently conflicting results suggest that the inadequacy of nutritional therapy may be a marker of severity with no causality implication. In line with this hypothesis, the amount of maintenance fluids was higher in non-surviving patients. As maintenance fluids in the participating ICUs are routinely used only in fasting patients, it is possible that nutritional therapy is just a marker of less severity, given that more severe patients with signs of hypoperfusion would be fasting. Another interesting and possible explanation is that receiving nutrition would be a proxy for the absence of gastrointestinal dysfunction. The epidemiology and prognostic correlation for gastrointestinal dysfunction in sepsis is not well established and usually neglected in the assessment of severity. None of the severity scores used, SAPS3 and SOFA, contemplate this dysfunction. Another interesting finding was the lack of association of these classic severity scores with mortality. None of them remained in the final logistic regression model. Although our limited sample size might explain this finding, another explanation could be the high severity of the patients, generating high scores both for non-survivors and survivors.

Our study finding of an association between a positive fluid balance in the first 24 hours, 24th and 48th hours and the total fluid balance with increased mortality was expected, as more severe patients tend to receive more fluids and have, at the same time, higher mortality. Although this association does not mean causality, it remained significant even after adjusting for severity of illness. Along these lines, our mathematical models also suggest that the association persisted regardless of the severity of illness. This is in consonance with prior observational reports,[27,28] although there are controversial findings regarding the first 24 hours.[9,19] However, recent data from randomized trials were not able to show the association between a restrictive fluid strategy and improved outcomes reinforcing the limitation of an observational study in assessing causality. Meyhoff et al compared a restrictive fluid therapy with a standard intravenous fluid therapy for septic patients admitted to ICU. In this trial among patients with septic shock who were in ICU, intravenous fluid restriction did not result in fewer deaths at

90 days.[13] Shapiro et al. evaluated the effect of a restrictive or liberal fluid management for the first 24 hours of sepsis-induced hypotension and did not demonstrate a difference in 90-day mortality.[14]

Although our study has some strengths such as its prospective design and detailed data collection in a homogeneous sample, it has several limitations. This was an observational study; thus we were not able to assess causality. Our sample was small which might not represent adequately other populations. We did not perform a sample size calculation due to the descriptive nature of our primary objective which might have compromised our power regarding the comparison between survivors and non-survivors. We used a non-consecutive convenience sample of heterogeneous patients, with a potential loss of relevant patients. As we did not collect data on the compliance with the sepsis treatment bundles, we cannot assure that the patients received standard of care although in both units there are institutional sepsis protocols.

Conclusions

Non-resuscitation fluids such antimicrobials and maintenance fluids are major contributors to a positive fluid balance within the first 48 hours of resuscitation. A positive fluid balance, including the first 24 hours after shock, seem to be associated with higher mortality while receiving higher amounts of nutrition might be a proxy of lower severity and better outcomes. This data might inform fluid stewardship strategies, such as optimization of prescription strategies to reduce unnecessary fluids. Aiming to improve outcomes and minimize complications in sepsis.

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Declaration of competing interest

The authors declare no conflicts of interest.

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