Fluid Resuscitation in Sepsis: "Get the Balance Right"*

When you think you've got a hold of it all, you haven't got a hold at all. (from "Get the Balance Right", Depeche Mode)

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On the one hand, fluid administration represents a mainstay of therapy in hemodynamically unstable patients and is probably the most common intervention in critical care overall. Accordingly, the upgraded recommendations of the surviving sepsis guideline favor an aggressive fluid resuscitation for as long as the patient continues to improve hemodynamically (1). On the other hand, it is well known that a positive fluid balance represents an independent predictor of mortality in critically ill patients (2, 3). Probably because of this quandary, fluid resuscitation is currently one of the most intensively discussed topics in critical care. Already in 2000, Alsous et al (4) hypothesized based on a small retrospective study in pediatric patients "that negative fluid balance achieved in any of the first 3 days of septic shock portends a good prognosis." More recently, it was proposed that early positive fluid balance and late negative balance are positively associated with survival (5). But how to achieve a negative fluid balance? The majority of studies and debates currently focus on fluid input: assessing how to restrict fluid volumes, identifying the variables that are most reliable to guide fluid resuscitation, testing different solutions, and evaluating varying methods to determine fluid responsiveness. But there is another component of fluid balance, namely the fluid output.

In this issue of *Critical Care Medicine*, Sakr et al (6) present the very interesting results of their planned substudy of an observational multinational prospective audit, the so called "Intensive Care Over Nations database" (7). The authors concluded that a "higher cumulative fluid balance at day 3 but not in the first 24 hours following ICU admission was independently associated with an increase in the hazard of death." At first sight, these findings support the current approach to stabilize the patient with "aggressive" fluid resuscitation initially and then be restrictive as soon as possible. However, this conclusion is put in perspective by a closer look at the data: Fluid input on day 1 with less than 3.5 L was relatively low suggesting that hemodynamic stabilization took already place before ICU admission. The authors attributed this issue to an increased awareness for sepsis, a circumstance that has also been discussed as a potential reason for the failure of "early goal-directed therapy" as proclaimed by Rivers et al (8) in the recent randomized, controlled trials (9–11). Nevertheless, the relevance of a negative fluid balance within the first three ICU days for the patients' outcome is reinforced by the present study.

The second major finding is that the reduced fluid balance in survivors was exclusively caused by higher fluid outputs, whereas there was no difference in fluid input between survivors and nonsurvivors. This discovery raises (at least) two questions: what are the reasons for the reduced fluid output (summarizing diuresis, extracorporeal fluid elimination, and drainage fluid in the present study) and how does this information influence clinical practice? With regard to the first question, the authors tried to adjust for differences in renal function by including Sequential Organ Failure Assessment renal subscores in the multivariable analysis. Trusting this valid statistical approach, there must have been additional factors contributing to the reduced fluid output in nonsurvivors such as insufficient perfusion pressures and/or a lack of intravascular volume. Based on the observational design and the high number of participating centers worldwide, the applied strategies and goal variables for hemodynamic therapy probably differed substantially throughout the study. Unfortunately, the authors did not provide information about differences between survivors and nonsurvivors in respect to vasopressor support and hemodynamic parameters. As a consequence, we can only speculate on the role of perfusion pressures as a potential cause for the lower fluid output. However, one would assume that mean arterial pressure was probably comparable between both groups.

Under the premise that renal function, vasopressor support, and hemodynamics were comparable between survivors and nonsurvivors, the most conclusive explanation would be differences in capillary leakage. The increased vascular permeability does not only lead to a reduction of intravascular volume but

*See also p. 386.

Key Words: critical ill; fluid output; intensive care unit

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also increases intercellular edema formation. Both finally result in an impairment of urine output. This assumption is supported by the fact that the absolute differences in fluid output and fluid balance, respectively, are already present on day 1 and remain almost constant during the following days.

Regarding the second question, the impact of the proposed study on clinical practice primarily exists in an additional prognostic factor in septic patients: the cumulative fluid balance at day 3. Contrary to most of the recent studies that focus on the initial resuscitation bundle (1-, 3-, and 6-hr periods), the present results emphasize the role of the "management bundle" beyond day 1. Furthermore, the awareness for fluid output as important component of fluid balance is reinforced. Whether this knowledge leads to new therapeutic strategies remains to be determined. Just increasing fluid output in every septic patient will probably be associated with detrimental consequences. But preventing or attenuating vascular leakage would be desirable. In this context, highly selective vasopressin-1a-receptor agonists have been reported not only to stabilize cardiovascular hemodynamics but also to attenuate endothelial permeability (12, 13). However, clinical trials are required to verify these experimental studies. For now, let us close with the title of the above referred to song that nicely summarizes the most important rule for fluid resuscitation in sepsis: "Keep the balance right."

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Septic Cardiomyopathy: Getting to the Heart of the Matter*

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Sepsis is often accompanied by profound changes in the cardiovascular system, classically described as an initial hypodynamic state prior to resuscitation, followed by a hyperdynamic state with high cardiac output and low systemic vascular resistance. However, some patients also suffer from a reversible myocardial stunning known as "septic cardiomyopathy," which manifests primarily as a depression in both right and left ventricular contractility (1). This septic cardiomyopathy is difficult to study since native physiologic variables are often augmented by clinical interventions such as fluid resuscitation and inotropes/vasopressors. Further, due to the obvious difficulty in sampling the heart directly, most studies on the underlying pathophysiology have focused on either circulating cytokines in a clinical setting, or on cellular or animal models (2). These prior studies have suggested that the dysregulated immune response in sepsis may be coupled to myocardial changes in nitric oxide production and signaling, mitochondrial function, and/or calcium-regulated contractility.

In this issue of *Critical Care Medicine*, Matkovich et al (3) report on a genome-wide expression profiling study of

Higher Fluid Balance Increases the Risk of Death From Sepsis: Results From a Large International Audit*

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Objectives: Excessive fluid therapy in patients with sepsis may be associated with risks that outweigh any benefit. We investigated the possible influence of early fluid balance on outcome in a large international database of ICU patients with sepsis.

Design: Observational cohort study.

Setting: Seven hundred and thirty ICUs in 84 countries.

Patients: All adult patients admitted between May 8 and May 18, 2012, except admissions for routine postoperative surveillance. For this analysis, we included only the 1,808 patients with an admission diagnosis of sepsis. Patients were stratified according to quartiles of cumulative fluid balance 24 hours and 3 days after ICU admission.

Measurements and Main Results: ICU and hospital mortality rates were 27.6% and 37.3%, respectively. The cumulative fluid balance increased from 1,217 mL (–90 to 2,783 mL) in the first 24 hours after ICU admission to 1,794 mL (–951 to 5,108 mL) on day 3 and decreased thereafter. The cumulative fluid intake was similar in survivors and nonsurvivors, but fluid balance was less positive in survivors because of higher fluid output in these patients. Fluid balances became negative after the third ICU day in survivors but remained positive in nonsurvivors. After adjustment for possible confounders in multivariable analysis, the 24-hour cumulative fluid balance was not associated with an increased hazard of 28-day in-hospital death. However, there was a stepwise increase in the hazard of death with higher quartiles of 3-day cumulative fluid balance in the whole population and after stratification according to the presence of septic shock.

Conclusions: In this large cohort of patients with sepsis, higher cumulative fluid balance at day 3 but not in the first 24 hours after ICU admission was independently associated with an increase in the hazard of death. (*Crit Care Med* 2017; 45:386–394)

Key Words: fluid administration; fluid output; outcome; septic shock

***See also p. 555.**

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Drs. Sakr and Rubatto Birri designed the study, extracted, and analyzed the data and drafted the article. Drs. Sakr, Kotfis, Nanchal, Shah, Kluge, Schroeder, Marshall, and Vincent participated in the original Intensive Care Over Nations study and reviewed the article for critical content. All authors read and approved the final article.

Additional members of the Care Over Nations Investigators are listed in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C246).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

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Sepsis frequently leads to death in ICU patients (1–3), with most deaths occurring as a result of cardiovascular or multiple organ failure (4). Fluid resuscitation is an essential component of treatment for patients with sepsis, but optimal hemodynamic targets and strategies are difficult to define. Preload optimization often necessitates administration of substantial amounts of fluid to compensate for the relative hypovolemia induced by generalized vasodilatation and increased capillary leak. But generous fluid administration can have deleterious effects, including tissue edema. Although positive fluid balance has been associated with a higher risk of death in septic and other populations of critically ill patients (5–11), optimal fluid balance targets beyond the initial resuscitation period remain unclear.

The aim of this study was to investigate possible associations between fluid balance and outcome in patients with sepsis using data from a large international database of ICU patients. We hypothesized that positive fluid balance after the initial 24-hour resuscitation period would be independently associated with mortality.

METHODS

This was a planned substudy of the Intensive Care Over Nations (ICON), a multicenter, worldwide audit. Full details of the methodology have been provided previously (3), and a list of participating ICUs is provided in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C246). Institutional recruitment for participation was by open invitation and was voluntary, with no financial incentive. Institutional review board approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not required because of the observational and anonymous nature of data collection. The ICON audit included all 10,069 adult patients (more than 16 yr old) admitted to the participating centers between May 8 and May 18, 2012. The organizational characteristics of these centers are shown in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C246). For the purposes of the current analysis, only those patients with a diagnosis of sepsis at admission to the ICU were considered ($n = 1{,}808$). Patients were followed up until death, hospital discharge, or for 60 days.

Data Management

Data were collected prospectively and were electronically introduced by the investigators using an internet-based website. Data collection at admission included demographic data and comorbid diseases. Clinical and laboratory data for Simplified Acute Physiology Score (SAPS) II (12) and Acute Physiology and Chronic Health Evaluation II (13) scores were recorded as the worst values within 24 hours after admission. Microbiologic and clinical infections were recorded daily, as well as the antibiotics administered. Daily evaluation of organ function according to the Sequential Organ Failure Assessment (SOFA) score (14) was performed. Data were collected for a maximum of 28 days in the ICU.

Definitions

Full details of the definitions have been published elsewhere (3). Infection was defined according to the International Sepsis Forum definitions (15). Only infections requiring administration of antimicrobial agents were considered. Sepsis was defined as the presence of infection with the concomitant occurrence of at least one organ failure, defined as a SOFA score of more than 2 for the organ in question. Septic shock was defined as sepsis associated with cardiovascular failure (cardiovascular SOFA score > 2). Lactate levels were not considered in the diagnosis of septic shock as they were not expected to be available in all patients. Surgical admissions were defined as patients who had had surgery in the 4 weeks preceding admission.

Calculation of Fluid Balance

Fluid balance was calculated from the daily fluid intake (enteral or parenteral) and output (urinary output and other fluid losses, including drainage fluids and extracorporeal fluid elimination) recorded every 24 hours after ICU admission. Insensible fluid loss was not recorded and hence not considered in the calculation of fluid balance. The cumulative fluid balances in the first 24 hours, 3 days, and 7 days of the ICU stay were calculated. Patients were stratified according to quartiles of cumulative fluid balance at 24 hours and at 3 days after ICU admission to investigate the possible influence of early fluid balance on outcome in these patients. In patients who died or were discharged before 3 days in the ICU, the cumulative fluid balance during the ICU stay was considered as the 3-day fluid balance.

Data Management and Quality Control

Detailed instructions, explaining the aim of the study, data collection, and definitions for various items were available through a secure website for all participants. Validity checks were made concurrent with data entry on the electronic case record form, including plausibility checks within each variable and between variables. Data were further reviewed by the coordinating center for plausibility and availability of the outcome variables, and doubts were clarified with the corresponding ICU. We performed no other supplementary quality control measures.

Statistical Analysis

Data are summarized using means and SD, medians and interquartile ranges (IQRs), or numbers and percentages. The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify if there were significant deviations from the normality assumption of continuous variables. Difference testing between groups was performed using analysis of variance, Kruskal-Wallis test, Student's t test, Mann-Whitney test, chi-square test, or Fisher exact test as appropriate.

To determine the adjusted relative risk of hospital death, right censored at 28 days, according to quartiles of cumulative fluid balance at 24 and 72 hours following admission to the ICU, we developed a multivariable Cox proportional hazard model in the overall population and in patients stratified according to the presence of septic shock. The categories of fluid balance were included as categorical variables with the first quartile as the reference category. Full details of this analysis are given in Appendix 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/C246).

Data were analyzed using IBM SPSS Statistics software, version 20 for Windows (IBM, Armonk, NY). All reported p

TABLE 1. Characteristics of the Study Group at Admission to the ICU According to the Quartiles of Fluid Balance at 24 Hours

Characteristics	All Patients, *n* = 1,808	First Quartile, *n* = 452	Second Quartile *n* = 452	Third Quartile, *n* = 452	Fourth Quartile, *n* = 452	*p*
Age (yr), mean ± SD	62 ± 17	60 ± 16	62 ± 17	64 ± 17	63 ± 16	0.002
Men, *n* (%)	1,065 (59.6)	263 (58.6)	277 (62.1)	262 (58.9)	263 (58.8)	0.665
Severity scores, mean ± SD						
Simplified Acute Physiology Score II score	51.0 ± 17.0	46.8 ± 15.7	48.5 ± 16.0	52.8 ± 17.5	56.0 ± 17.3	< 0.001
Sequential Organ Failure Assessment score	9.5 ± 3.8	8.6 ± 3.4	9.0 ± 3.6	9.9 ± 3.8	10.6 ± 4.1	< 0.001
Referring facility, *n* (%)						0.267
Emergency room/ambulance	608 (33.6)	147 (32.5)	152 (33.6)	157 (34.7)	152 (33.3)	
Operating room/recovery	243 (13.4)	54 (11.9)	55 (12.2)	57 (12.6)	77 (17.0)	
Hospital floor	633 (35.0)	159 (35.2)	174 (38.5)	144 (31.9)	156 (34.5)	
Other hospital	180 (10.0)	60 (13.3)	41 (9.1)	44 (9.7)	35 (7.7)	
Others	144 (8.0)	32 (7.1)	30 (6.6)	50 (11.1)	32 (7.1)	
Type of admission, *n* (%)						0.006
Medical	1,125 (65.5)	287 (67.1)	287 (67.5)	289 (66.3)	262 (61.2)	
Surgical	536 (31.2)	127 (29.7)	116 (27.3)	137 (31.4)	156 (36.4)	
Trauma	47 (2.7)	11 (2.6)	18 (4.2)	10 (2.3)	8 (1.9)	
Others	9 (0.5)	3 (0.7)	4 (0.9)	0 (0.0)	2 (0.5)	
Comorbidities, *n* (%)						
Chronic obstructive pulmonary disease	290 (16.0)	82 (18.1)	72 (15.9)	79 (17.5)	57 (12.6)	0.051
Insulin-dependent diabetes mellitus	218 (12.1)	58 (12.8)	52 (11.5)	64 (14.2)	44 (9.7)	0.333
Heart failure (New York Heart Association Classification III–IV)	218 (12.1)	63 (13.9)	58 (12.8)	57 (12.6)	40 (8.8)	0.024
Chronic renal failure	216 (11.6)	54 (11.9)	64 (14.2)	56 (12.4)	42 (9.3)	0.154
Cancer	203 (11.2)	42 (9.3)	53 (11.7)	52 (11.5)	56 (12.4)	0.172
Immunosuppression	127 (7.0)	28 (6.2)	23 (5.1)	31 (6.9)	45 (10.0)	0.015
Steroid therapy	101 (5.6)	30 (6.6)	21 (4.6)	22 (4.9)	28 (6.2)	0.819
Cirrhosis	91 (5.0)	26 (5.8)	24 (5.3)	16 (3.5)	25 (5.5)	0.597
Metastatic cancer	73 (4.0)	14 (3.1)	23 (5.1)	14 (3.1)	22 (4.9)	0.423
Chemotherapy	69 (3.8)	12 (2.7)	20 (4.4)	16 (3.5)	21 (4.6)	0.207
HIV infection	23 (1.3)	6 (1.3)	3 (0.7)	6 (1.3)	8 (1.8)	0.398

(*Continued*)

TABLE 1. (*Continued*). Characteristics of the Study Group at Admission to the ICU According to the Quartiles of Fluid Balance at 24 Hours

Characteristics	All Patients, *n* = 1,808	First Quartile, *n* = 452	Second Quartile *n* = 452	Third Quartile, *n* = 452	Fourth Quartile, *n* = 452	*p*
Procedures, *n* (%)						
Mechanical ventilation	1,284 (71.0)	330 (73.0)	284 (62.8)	332 (73.5)	338 (74.8)	0.095
Hemodialysis	123 (6.8)	30 (6.6)	35 (7.7)	29 (6.4)	29 (6.4)	0.707
Hemofiltration	133 (7.4)	33 (7.3)	27 (6.0)	31 (6.9)	42 (9.3)	0.212
Site of infection, *n* (%)						
Respiratory	1,159 (64.1)	318 (70.4)	274 (60.6)	308 (68.1)	259 (57.3)	0.002
Abdominal	435 (24.1)	70 (15.5)	100 (22.1)	115 (25.4)	150 (33.2)	< 0.001
Bloodstream	401 (22.2)	88 (19.5)	101 (22.3)	87 (19.2)	125 (27.7)	0.014
Wound	303 (16.8)	73 (16.2)	72 (15.9)	71 (15.7)	87 (19.2)	0.248
Urinary tract	283 (15.7)	66 (14.6)	66 (14.6)	76 (16.8)	75 (16.6)	0.284
Catheter	182 (10.1)	50 (11.1)	37 (8.2)	46 (10.2)	49 (10.8)	0.834
Other	234 (12.9)	53 (11.7)	55 (12.2)	67 (14.8)	59 (13.1)	0.347
Septic shock, *n* (%)	1,098 (60.7)	217 (48.0)	238 (52.7)	297 (65.7)	346 (76.5)	< 0.001
Geographic region, *n* (%)						0.001
West Europe	778 (43.0)	196 (43.4)	180 (39.8)	196 (43.4)	206 (45.6)	
East Europe	207 (11.4)	60 (13.3)	46 (10.2)	59 (13.1)	42 (9.3)	
East and south east Asia	246 (13.6)	57 (12.6)	73 (16.2)	58 (12.8)	58 (12.8)	
South America	204 (11.3)	42 (9.3)	46 (10.2)	53 (11.7)	63 (13.9)	
Middle east	104 (5.8)	29 (6.4)	21 (4.6)	32 (7.1)	22 (4.9)	
Oceania	82 (4.5)	27 (6.0)	18 (4.0)	17 (3.8)	20 (4.4)	
South Asia	79 (4.4)	22 (4.9)	35 (7.7)	17 (3.8)	5 (1.1)	
North America	89 (4.9)	18 (4.0)	27 (4.0)	13 (2.9)	31 (6.9)	
Africa	19 (1.1)	1 (0.2)	6 (1.3)	7 (1.5)	5 (1.1)	

Missing values: sex, 25; type of admission, 91; ICU mortality, 27; hospital length of stay, 80. Valid percentages are presented after excluding missing values.

values are two sided, and a *p* value less than 0.05 was considered to indicate statistical significance.

RESULTS

Of the 1,808 patients with sepsis at admission to the ICU, 1,098 (60.7%) had septic shock. The baseline characteristics of these patients are summarized in **Table 1**. The overall ICU and hospital mortality rates were 27.6% (*n* = 491) and 37.3% (*n* = 646), respectively, and the median ICU and hospital lengths of stay were 5 days (IQR, 2–10 d) and 13 days (IQR, 6–27 d).

Fluid intakes in the whole cohort were 3,325 (2,028–4,932), 9,399 (5,425–13,614), and 12,595 (6,065–20,673) mL at 24 hours, 3 days, and 7 days after ICU admission, respectively. The cumulative fluid balance increased from 1,217 mL (–90 to 2,783 mL) in the first 24 hours after ICU admission to 1,794 mL (–951 to 5,108 mL) mL at 3 days and decreased thereafter to reach 1,453 mL (–2,173 to 5,548 mL) at 7 days following ICU admission.

The cumulative fluid intake was similar in survivors and nonsurvivors. However, fluid output was significantly less in nonsurvivors leading to a more positive fluid balance in these patients. Nonsurvivors were more likely to have received synthetic colloid solutions, including hydroxyethyl starch and gelatin, than survivors and received more vasopressor/inotropic support (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246). Fluid balance remained positive over time in the nonsurvivors but became negative in the survivors after the third day of the ICU stay (**Fig. 1**). Patients with septic shock had greater fluid intake during the first 4 days in the ICU

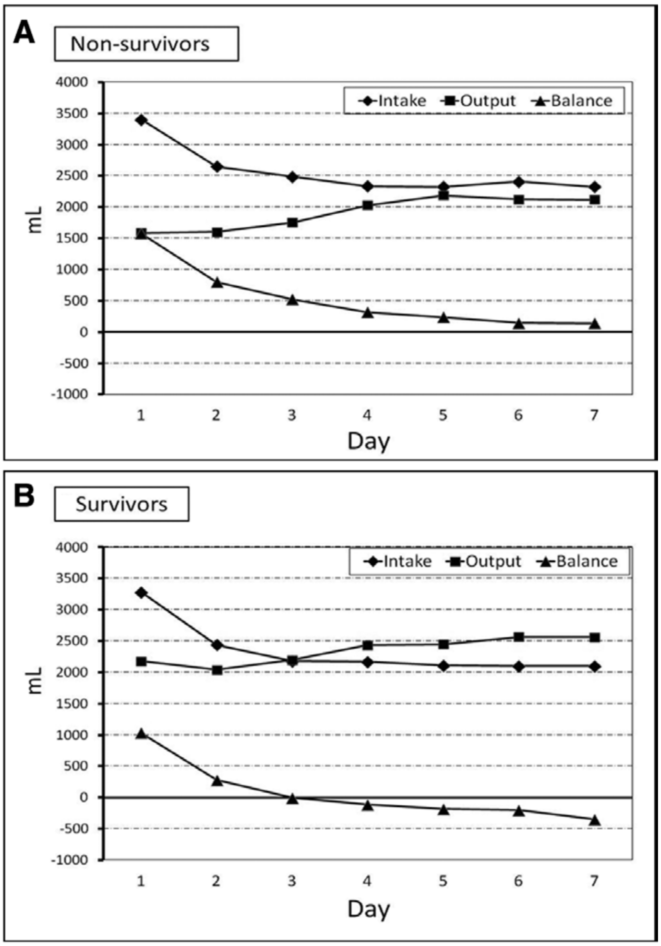

Figure 1. Median fluid intake, output, and balance over the first week in the ICU in hospital nonsurvivors (**A**) and survivors (**B**).

and more positive fluid balance during the first 3 days compared with those without shock (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246; and **Fig. S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246).

Characteristics and Outcome According to the Cumulative Fluid Balance at 24 Hours and 3 Days After ICU Admission

The characteristics of patients at ICU admission, stratified according to quartiles of 24- and 72-hour cumulative fluid balance, are presented in Table 1 and **Table S3** (Supplemental Digital Content 1, http://links.lww.com/CCM/C246). SAPS II and SOFA scores at admission to the ICU, the degree of organ failure during the ICU stay as assessed by the SOFA maximum and SOFA mean, and the need for renal replacement therapy and vasopressors and inotropes during the ICU stay increased stepwise with increasing quartiles of 24-hour cumulative fluid balance (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246). Although ICU and hospital lengths of stay were similar among the quartiles of 24-hour fluid balance, there was a stepwise increase in ICU and hospital mortality rates within increasing quartiles (Table S4, Supplemental Digital Content 1, http://links.lww.com/CCM/C246; and **Fig. S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246).

Similar patterns were observed with the 3-day quartiles (**Table 2**), with ICU and hospital mortality rates increasing more than two-fold from the lowest to the highest quartile. The hospital length of stay was shorter in the higher quartiles than in the lowest quartile (Table 2).

Multivariable Adjustment

After adjustment for possible confounders in a multivariable Cox proportional hazard analysis, cumulative 24-hour fluid balance was not associated with an increased hazard of death in the whole cohort or in patients with septic shock (**Table 3**; **Fig. 2**; and **Fig. S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C246). However, there was a stepwise increase in the hazard of death with increasing 3-day cumulative fluid balance quartile.

DISCUSSION

The main findings of our study are as follows: 1) fluid balance was more positive in nonsurvivors than in survivors despite similar fluid intakes; 2) these differences were more marked on the third day following admission; and 3) after adjustment for possible confounders, there was a stepwise increase in the hazard of death with increasing 3-day cumulative fluid balance quartile but not with 24-hour quartiles.

Optimal targets for fluid resuscitation in patients with sepsis are not fully established and probably require the integration of multiple variables. In our study, differences in fluid balance were primarily the result of lower fluid output in nonsurvivors than in survivors; hence, the inability to excrete excess fluid may be an important factor. Some experimental data have suggested that high-volume resuscitation in septic animals may increase mortality (16). Several retrospective clinical studies support this hypothesis (1, 8, 17). Shum et al (17) showed that in critically ill patients who stayed in the ICU for 3 days or more, fluid balance on the second plus third ICU days and total fluid balance during the ICU stay were positively associated with hospital death, whereas a positive fluid balance on the first ICU day was negatively associated with hospital mortality. This study, however, included a relatively small number of patients and was not confined to patients with sepsis. In a large database of critically ill patients admitted to ICUs in 24 European countries, we previously reported that cumulative fluid balance within the first 72 hours following the onset of sepsis was an independent risk factor for ICU death (1). More recently, a post hoc analysis of the Vasopressin in Septic Shock Trial showed that a more positive fluid balance, both early in resuscitation and cumulatively over 4 days, was associated with an increased risk of mortality in septic shock (8). Acheampong and Vincent (6) also recently showed, in a prospective observational study, that positive fluid balance was independently associated with higher ICU mortality.

From our data, we cannot determine the mechanisms underlying the observed association between fluid balance and

TABLE 2. Fluid Balance, Severity of Illness, and Outcome According to Quartiles of Fluid Balance at 72 Hours After Admission to the ICU

Variable	First Quartile, *n* = 452	Second Quartile, *n* = 452	Third Quartile, *n* = 452	Fourth Quartile, *n* = 452	*p*
Fluid balance (mL), median (IQR)					
First 24 hr	2,252 (1,250 to 3,325)	2,444 (1,404 to 3,632)	3,709 (2,602 to 4,894)	5,398 (3,910 to 7,111)	< 0.001
Cumulative 3 d	−3,714 (−6,536 to −2,301)	456 (−137 to 1,110)	3,241 (2,556 to 4,059)	7,904 (6,293 to 10,744)	< 0.001
Cumulative 7 d	−5,360 (−9,849 to −2,686)	286 (−554 to 1,153)	3,339 (2,164 to 4,495)	8,781 (6,209 to 12,951)	< 0.001
ICU cumulative	−5,375 (−11,949 to −2,358)	187 (−532 to 1,168)	3,050 (1,977 to 4,291)	8,307 (5,616 to 14,498)	< 0.001
Simplified Acute Physiology Score II score, mean ± SD	46.1 ± 15.4	49.5 ± 17.1	52.6 ± 17.0	56.0 ± 16.9	< 0.001
SOFA scores, mean ± SD					
SOFA maximum	10.5 ± 4.0	10.5 ± 4.1	11.5 ± 4.3	13.0 ± 4.4	< 0.001
SOFA mean	7.4 ± 3.2	8.1 ± 3.6	8.7 ± 4.2	9.6 ± 4.3	< 0.001
SOFA admission	8.9 ± 3.4	9.0 ± 3.6	9.7 ± 4.0	10.5 ± 3.9	< 0.001
Procedures in the ICU, *n* (%)					
Mechanical ventilation	366 (81.0)	316 (69.9)	352 (77.9)	778 (83.6)	0.067
Hemodialysis	54 (11.9)	59 (13.1)	77 (17.0)	102 (22.6)	< 0.001
Hemofiltration	70 (15.9)	60 (13.3)	71 (15.7)	122 (27.0)	< 0.001
Vasopressors/inotropes[a]					
Norepinephrine (μg/kg/min), *n* (%)	246 (54.4)	225 (49.8)	281 (62.2)	336 (74.3)	< 0.001
Median (IQR)	0.2 (0.1–0.49)	0.18 (0.1–0.67)	0.27 (0.12–0.79)	0.25 (0.12–0.79)	0.003
Epinephrine (μg/kg/min), *n* (%)	28 (6.2)	23 (5.1)	30 (6.6)	54 (11.9)	0.001
Median (IQR)	0.13 (0.1–0.29)	0.32 (0.01–1)	0.52 (0.16–2.7)	0.24 (0.1–1.08)	0.009
Dopamine (μg/kg/min), *n* (%)	48 (10.6)	59 (13.1)	68 (15.0)	79 (17.5)	0.002
Median (IQR)	5 (3–8.2)	7 (4–16.3)	7 (5–11.1)	8 (5–12.5)	0.168
Dobutamine (μg/kg/min), *n* (%)	59 (13.1)	44 (9.7)	47 (10.4)	84 (18.6)	0.015
Median (IQR)	5 (3–7)	4.3 (2.5–6.9)	5 (3–9)	5 (2.9–8)	0.356
Vasopressin (IU/kg/min), *n* (%)	12 (2.7)	22 (4.9)	24 (5.3)	40 (8.8)	< 0.001
Median (IQR)	0.05 (0.03–1.2)	0.55 (0.04–2.4)	1.4 (0.04–2.4)	0.29 (0.04–2)	0.288
Mortality rates (%)[b]					
ICU mortality	68 (15.3)	98 (21.1)	146 (32.6)	179 (40.2)	< 0.001
In-hospital mortality	111 (25.8)	138 (30.5)	179 (40.8)	218 (50.6)	< 0.001
Length of stay (d), median (IQR)					
ICU	5 (3–10)	4 (2–8)	4 (2–9)	7 (3–14)	0.210
In-hospital	16 (8–30)	12 (5–26)	12 (5–28)	14 (4–26)	< 0.001

IQR = interquartile range, SOFA = Sequential Organ Failure Assessment.
[a]Median doses during the ICU stay are based on the maximum daily dosage.
[b]Valid percentages are presented after excluding missing values.

outcome in patients with septic shock. The impact of renal function on the results was considered in the multivariable analysis by adjustment for the SOFA renal subscores, so that renal function may not be the only factor explaining the association between fluid balance and outcome in these patients. We can speculate that excess fluid administration may lead to increased tissue edema and worsening of organ function. These effects may be more pronounced in encapsulated organs, such as the kidney and liver, which may not be able to accommodate excess volume without an increase in interstitial pressure,

TABLE 3. Adjusted Hazard Ratios[a] of Death According to Quartiles of Cumulative Fluid Balance at 24 and 72 Hours After Admission to the ICU

	All Patients (n = 1,481)[b]		No Septic Shock (n = 568)[b]		Septic Shock (n = 913)[b]	
Variable	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	p
Cumulative fluid balance at 24 hr[c]						
First quartile	R	NA	R	NA	R	NA
Second quartile	1.08 (0.83–1.41)	0.572	1.10 (0.71–1.69)	0.674	1.06 (0.73–1.54)	0.749
Third quartile	1.05 (0.81–1.36)	0.742	1.31 (0.84–2.03)	0.228	0.98 (0.69–1.39)	0.895
Fourth quartile	1.17 (0.90–1.53)	0.240	1.51 (0.92–2.49)	0.105	1.07 (0.76–1.51)	0.687
Cumulative fluid balance at 72 hr[c]						
First quartile	R	NA	R	NA	R	NA
Second quartile	1.36 (1.03–1.80)	0.035	1.58 (0.99–2.52)	0.053	1.28 (0.87–1.87)	0.206
Third quartile	1.47 (1.12–1.92)	0.005	1.83 (1.16–2.88)	0.010	1.43 (1.01–2.03)	0.046
Fourth quartile	1.63 (1.25–2.12)	< 0.001	1.93 (1.19–3.12)	0.007	1.51 (1.08–2.12)	0.016

NA = not applicable, R = reference category.

[a]Adjusted in a Cox proportional hazard model with hospital death right censored at 28 d as the dependent variable. The covariates considered in the multivariable model included geographic region, ICU and hospital organizational characteristics, age, sex, comorbidities, Simplified Acute Physiology Score II score at admission to the ICU, type of admission, referring facility, Sequential Organ Failure Assessment subscores at admission to the ICU, site of infection, and the type of colloids.

[b]After exclusion of patients with missing values.

[c]Introduced alternately in separate multivariable models because of collinearity.

thereby compromising organ blood flow (18). In patients with acute lung injury, the Fluids and Catheters Treatment Trial study compared restrictive and liberal fluid management strategies (19) and showed no significant differences in mortality, but the conservative strategy of fluid management was associated with improved lung function and reduced duration of mechanical ventilation without increasing nonpulmonary organ failure. The inability to remove excess fluids may, therefore, play an important role in determining outcomes in critically ill patients, including those with sepsis, lung injury, and acute renal failure.

In our study, higher quartiles of cumulative fluid balance at 3 days after ICU admission but not at 24 hours were associated with a stepwise increase in the hazard of death. This finding suggests that accumulation of excess fluid beyond the initial resuscitation stage may be mechanistically linked to worse outcomes. It is possible that a cutoff value of fluid balance exists beyond which worse outcomes become apparent as evidenced by similar hazards of death in our 24-hour quartiles when positive fluid balance, even in the highest quartile, was less marked than on day 3 or 7. Boyd et al (8) reported that lower fluid balance as early as 12 hours following septic shock was independently associated with a lower 28-day hazard of survival. As our data were collected only every 24 hours, it is not possible to directly compare our results with those of Boyd et al (8) in this regard. Micek et al (20) in a retrospective analysis of 325 patients with septic shock found that nonsurvivors had a larger net fluid balance at 24 hours and 8 days after the onset of septic shock, and when using different quartiles, the highest quartile of net fluid balance on day 8 was associated with greater mortality in the multivariable analysis. Sadaka et al (21) retrospectively collected data from 350 patients with septic shock in 56 medical-surgical ICUs. They divided patients into groups based on the degree of excess fluid balance at 24 hours and observed that in-hospital mortality increased significantly with a higher degree of positive fluid balance. Taken together, these results support the four-phase salvage, optimization, stabilization, and deescalation approach to fluid administration (22, 23), suggesting that a more restrictive approach to fluid administration may be safe after initial resuscitation of septic patients.

The strengths of the current study are the large number of patients and variables included, allowing adjustment for a large number of factors. We also acknowledge some limitations. First, although we adjusted for severity of illness, organ failures, and other variables, we cannot discount the possible influence of unmeasured factors. Second, data collection was restricted to every 24 hours, so we could not control for the influence of patterns of fluid therapy during the early hours after sepsis onset, when they are perhaps most intense. We also did not collect data on fluid administration prior to ICU admission. Increased awareness of sepsis may have led to earlier fluid resuscitation prior to referral to the ICU and may explain the relatively low amount of fluid given to patients

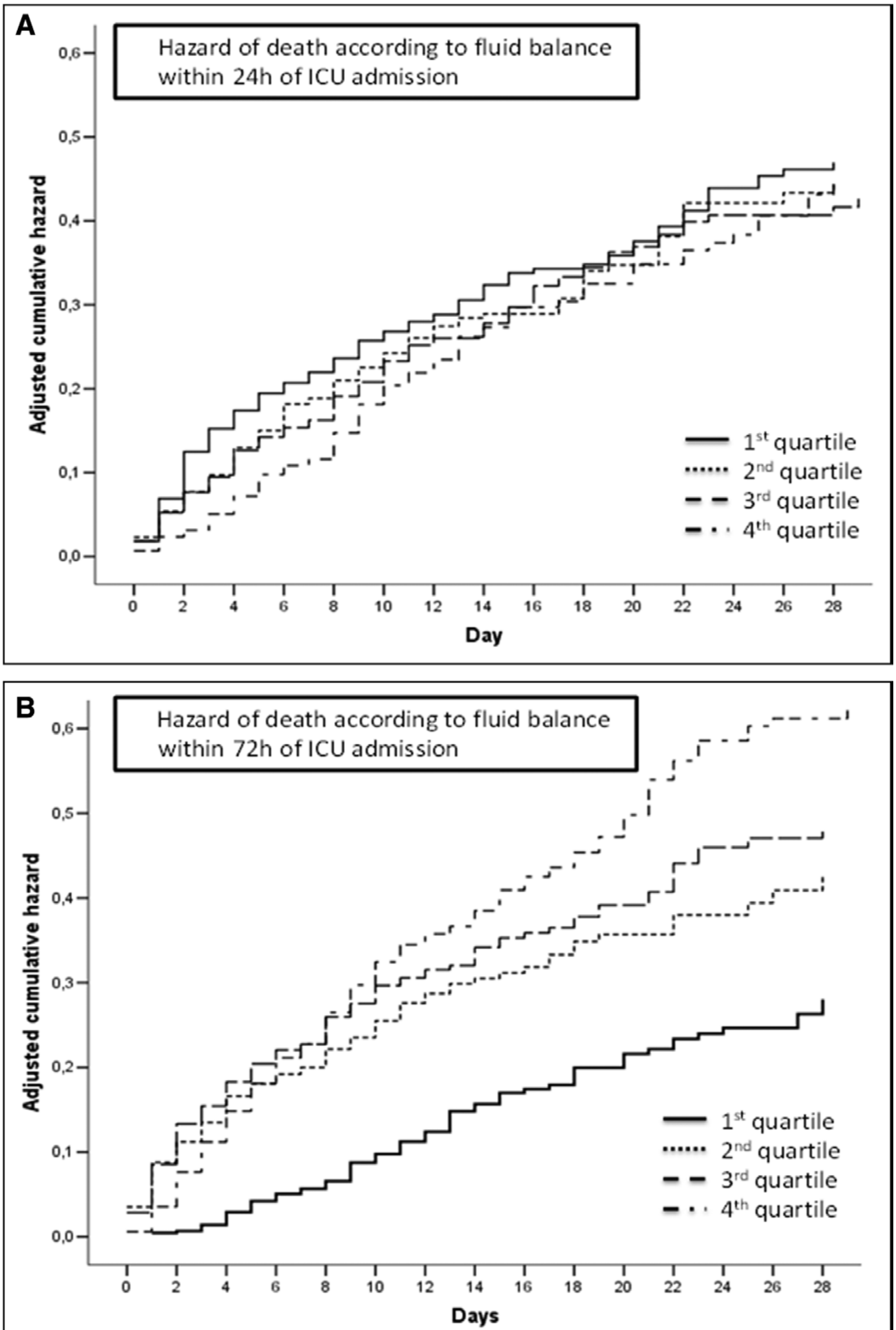

Figure 2. Adjusted cumulative hazard of in-hospital death right censored at 28 d in the whole cohort (n = 1,808) according to quartiles of cumulative fluid balance at 24 hr (**A**; $p = 0.656$) and 72 hr (**B**; $p = 0.003$) after admission to the ICU.

with sepsis in our cohort. Third, although we controlled for the use of colloid solutions, we do not have information on the choice of crystalloid solutions for resuscitation. The use of hyperchloremic crystalloid solutions can affect outcomes (24) and may have confounded our results. Fourth, data regarding hemodynamic targets for resuscitation, fluid responsiveness, adequacy of tissue perfusion, reasons for accumulation of fluid, diuretic use, and attempts to reduce fluid accumulation are unavailable. The use of vasopressor agents may also have influenced fluid resuscitation and balance. Nonetheless, the degree of cardiovascular dysfunction and vasopressor support, as assessed by the SOFA score, was considered in the multivariable adjustment. Finally, despite our demonstration of increasing hazard of death with progressive cumulative positive fluid balance, we are unable to discern whether there was a specific point at which the excess hazard developed or the optimal volume of fluid resuscitation. These are important questions that should be the target of future investigations.

CONCLUSIONS

In this large cohort of patients with severe sepsis, although the cumulative fluid intake was similar at 24 hours, 3 days, and 7 days after admission to the ICU, the corresponding cumulative fluid balance was lower in survivors than in nonsurvivors because of higher fluid output. After adjustment for possible confounders, higher quartiles of cumulative fluid balance at 3 days after ICU admission but not at 24 hours were associated with an increase in the hazard of death in the whole population and after stratification according to the presence of septic shock. Because of the retrospective nature of the analysis, we cannot elaborate on whether limiting fluid intake or enforcing fluid output would be the most effective approach to decrease fluid balance, probably a combination of both approaches is needed. These data are hypothesis generating and may provide a good basis for randomized controlled trials to investigate the possible influence of negative fluid balance and a restrictive approach to fluid therapy after initial resuscitation on the outcome of these patients.

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