Published in final edited form as:

J Crit Care. 2015 December ; 30(6): 1338–1343. doi:10.1016/j.jcrc.2015.07.009.

Impact of Late Fluid Balance on Clinical Outcomes in the Critically Ill Surgical and Trauma Population

Kathryn A. Elofson, PharmD^{a,1}, Daniel A. Eiferman, MD^a, Kyle Porter, MAS^a, and Claire V. Murphy, PharmD, BCPS^a

^aThe Ohio State University Wexner Medical Center; Doan Hall, Room 368, 410 West 10th Avenue Columbus, OH 43210, USA

Abstract

Purpose—Management of fluid status in critically ill patients poses a significant challenge due to limited literature. This study aimed to determine the impact of late fluid balance management following initial adequate fluid resuscitation on in-hospital mortality for critically ill surgical and trauma patients.

Materials and Methods—This single center retrospective cohort study included 197 patients who underwent surgical procedure within 24 hours of surgical intensive care unit (SICU) admission. Patients with high fluid balance on post-operative day 7 (>5L) were compared to those with a low fluid balance (<5L) with a primary endpoint of in-hospital mortality. Subgroup analyses were performed based on diuretic administration, diuretic response and type of surgery.

Results—High fluid balance was associated with a significantly higher in-hospital mortality (30.2 vs 3%, $p<0.001$) compared to low fluid balance; this relationship remained after multivariable regression analysis. High fluid balance was associated with increased mortality, independent of diuretic administration, diuretic response and type of surgery.

Conclusions—Consistent with previous literature, high fluid balance on post-operative day 7 was associated with increased in-hospital mortality. Patients who received and responded to diuretic therapy did not demonstrate improved clinical outcomes which questions their use in the post-operative period.

Keywords

Fluid balance; postoperative period; fluid therapy; general surgery; diuretics; critical illness

Introduction

Management of fluid status continues to be challenging in the critically ill patient. Adequate initial fluid resuscitation is essential to avoid an imbalance in systemic oxygen delivery and

Corresponding Author: Claire V. Murphy, The Ohio State University Wexner Medical Center, Doan Hall, Room 368, 410 West 10th Avenue, Columbus, OH 43210, Claire.Murphy@osumc.edu.

¹Present Address: Huntsman Cancer Institute at the University of Utah; 1950 Circle of Hope, Salt Lake City, UT 84112, USA

Financial Support:

Authors have no financial disclosures or conflicts of interest to report.

oxygen demand, which can result in hypoperfusion and subsequent shock. However, emerging data suggests that positive fluid balance is associated with poor clinical outcomes including prolonged duration of mechanical ventilation, ICU and hospital length of stay, anastomotic leak and increased mortality [1, 2, 3, 4, 5, 6]. While the mechanism behind the association with poor clinical outcomes is unknown, aggressive, large-volume resuscitation may increase pulmonary edema, decrease lung compliance and increase workload for respiration [7, 8].

In surgical and trauma patient populations there is limited evidence on effects of positive fluid balance in both the initial resuscitative period as well as the immediate period following this acute phase [9, 10, 11, 12, 13]. Excessive initial fluid administration in trauma patients is proposed to increase risk for worsened hemorrhage due to potential dislodgement of clots and dilutional coagulopathy [9]. Poor clinical outcomes, including increased mortality and intra-operative blood loss, acute lung injury, compartment syndrome and prolonged duration of mechanical ventilation, have been observed in both penetrating and blunt trauma patients receiving aggressive initial fluid resuscitation [9, 10, 11, 12, 13]. The majority of these trials, however, were conducted in the pre-hospital setting and may not directly apply to management of trauma patients in the emergency department or following hospital admission.

Currently, there is inadequate literature to guide fluid balance management following the acute resuscitative period in the critically ill trauma and surgical populations. While available literature does suggest positive fluid balance is associated with worse clinical outcomes, the majority of studies have focused on septic and acute lung injury patients. The few published studies assessing fluid balance in the surgical and trauma populations suggest a similar negative influence of liberal fluid strategies on clinical outcomes, including increased rates of pneumonia, pulmonary edema, hospital length of stay and post-operative complications [14, 15]. However, these studies are limited to the immediate post-operative period and primarily reflect initial resuscitation rather than post-operative management. The objective of this study is to determine the impact of late (post-operative day (POD) 7) fluid balance following adequate initial fluid resuscitation on in-hospital mortality for critically ill surgical and trauma patients. It was hypothesized that patients with high fluid balance in the late post-operative period have worse clinical outcomes compared to those with low fluid balance.

Materials and Methods

Patient Population

Mechanically ventilated patients ages 18 to 89 years old admitted to the surgical intensive care unit (SICU) between November 1, 2011 and October 1, 2013 who underwent a surgical procedure within 24 hours preceding or following SICU admission were eligible for evaluation. Patients were required to have adequate initial fluid resuscitation, defined as urine output $\geq 0.5\text{ml/kg/hr}$ for the initial 12-hour post-operative period, to be included. To primarily assess patients requiring more aggressive fluid resuscitation, patients admitted by the following services were included: trauma, acute care surgery, colorectal surgery, gastrointestinal surgery, bariatric surgery, gynecologic oncology, surgical oncology, thoracic

surgery, orthopedic surgery, plastic surgery, and transplant surgery. Exclusion criteria included incarceration, pregnancy, SICU length of stay less than 7 days or admission to any of the following services: neurosurgery, neurovascular, burn, otolaryngology, peripheral vascular surgery, oral maxillofacial surgery or post-partum obstetrics. While patients on the burn service require aggressive fluid administration, they were excluded from this analysis due to the use of a colloid based resuscitation protocol at our institution. For patients who underwent multiple surgical procedures, data collection was performed starting on POD 1 from the initial procedure occurring within 24 hours of SICU admission. During the study period there was no specific protocol or criteria for fluid or diuretic administration in the SICU. Determination of intravascular fluid balance and initiation of therapy (fluid vs. vasopressor vs. diuretic) was based on continuous analysis by the intensive care unit multi-disciplinary team. Goal directed fluid administration is provider specific with clinical decisions largely based on urine output and blood pressure, with utilization of lactate, central venous pressure (CVP), stroke volume, cardiac output (CO) and other assessments of fluid status dependent upon provider preference.

Study Design

A single-center retrospective cohort study was conducted at a large academic, level 1 trauma center, to assess the impact of late fluid status on in-hospital mortality in surgical and trauma patients after obtaining approval from The Ohio State University Institutional Review Board. Patients with low fluid balance on POD 7 were compared to those with high fluid balance with a primary endpoint of in-hospital mortality. For the purposes of this study, low fluid balance was defined *a priori* as a net balance of ≤ 5 L positive on POD 7, whereas high fluid balance was used to describe patients with > 5 L net balance on POD 7 to account for estimated insensible losses in this critically ill population[16]. This cutoff was estimated based on an average 70kg patient (10ml/kg/day) which would equate to approximately 5L at POD7. Secondary endpoints include duration of mechanical ventilation, SICU and hospital length of stay, and SICU and total hospital cost. Subgroup analyses were determined *a priori* and were performed for patients undergoing abdominal surgery and for those receiving diuretics within the 7-day postoperative period. The patient populations selected for subgroup analysis were determined based on typical characteristics of the abdominal surgery patient population and anticipated benefit of assessing these subgroups in answering our study question. Response to diuretic was defined as an increase in urine output of 50% or greater compared to the day prior to diuretic administration. In addition, survivors of hospital admission were compared to non-survivors based on daily fluid balance and cumulative fluid balance.

Data was collected retrospectively from the electronic medical record, including baseline characteristics (age, gender, comorbidities to calculate the Charlson Comorbidity Index Score, primary service, Simplified Acute Physiology Score (SAPS) II score, baseline calculated glomerular filtration rate (GFR) and serum creatinine), number of days hospitalized prior to SICU admission, surgical procedure(s) and whether emergent vs. elective operation, administration of any diuretic or vasopressor through POD 7, and lactate, CVP, and CO as available during 24 hours preceding or following SICU admission. Total hospital and SICU cost were obtained from the institutional finance department. Assessment

of fluid balance was based on all recorded intake (including bolus and maintenance fluids, enteral and parenteral nutrition, and blood products) and output (including urine, stool, blood and drain/tube output) while the patient was admitted to the SICU. Fluid status prior to transfer into the SICU, if applicable, was not included for purposes of analysis.

Statistical Analysis

Patient characteristics were reported separately by late fluid balance status on POD 7 using mean and standard deviation or median and interquartile range for continuous variables and frequency and percentages for categorical variables. The groups were compared using t-tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. The primary hypothesis was tested using a multivariable logistic regression model, fit to the dichotomous outcome in-hospital mortality. Low versus high fluid balance on POD 7 was the primary independent variable. The model included covariates adjusting for age, gender, SAPS II (less age component), Charlson Comorbidity Index and abdominal surgery versus other surgery [17, 18]. Age was removed from the SAPS II score in the model as age was included as a separate covariate.

Secondary analyses included investigation of the primary hypothesis within subgroups based on type of surgery (abdominal or other) and administration of a diuretic within the 7-day post-operative period. The secondary outcomes of total duration of mechanical ventilation, SICU and hospital length of stay, and total hospital and SICU cost were compared between groups by linear regression models, adjusting for the same variables as the primary analysis. Duration of ventilation and both length of stay measures were right skewed and log-transformed for analysis. Logistic regression was used to compare in-hospital mortality and duration of mechanical ventilation in subgroups of abdominal surgery and other surgery and subgroups of diuretic recipients and non-recipients. All models included the same covariates as the primary analysis, with the exception of the abdominal surgery subgroups, which no longer included a covariate for abdominal surgery. Sensitivity analyses using fewer covariates were performed for the subgroup analyses. Two models were fit for each subgroup. The first adjusted only for age and SAPSII and the second was the univariable model for low versus high fluid balance. Statistical tests were performed at a Type I error rate of $\alpha=0.05$. All analyses were performed using SAS/STAT software, version 9.3.

Results

A total of 3,598 patients were screened, with 101 patients meeting inclusion criteria for the low fluid balance group and 96 patients for the high fluid balance group (Figure 1). Primary reasons for exclusion were length of stay in SICU <7 days, surgical service, or no surgical procedure within 24 hours of SICU admission. Baseline characteristics were similar between the groups, although the high fluid balance group had significantly higher rates of abdominal surgery, median Charlson Comorbidity Index and SAPS II scores (Table 1). The majority of patients were admitted to the SICU on their first day of hospitalization, and greater than 70% underwent emergent surgery. Upon admission to the SICU, the average lactate for all patients was greater than 3 mmol/L, with low rates of acute and chronic kidney dysfunction

in both groups. Patients included in the study had a high severity of illness, evidenced by a median SAPS II score > 40 in both groups, equating to > 25% predicted mortality [18].

The primary outcome of in-hospital mortality was significantly increased in the high fluid balance group compared to low fluid balance group (30.2% vs. 3.0%, $p < 0.001$; Figure 2). In the multivariable logistic regression model for in-hospital mortality, adjusting for covariates age, gender, SAPS II (less age component), Charlson Comorbidity Index, and abdominal surgery, this relationship remained with patients with a high fluid balance exhibiting a 12-fold higher odds of in-hospital mortality compared to those with low fluid balance on POD 7 (Table 2). When patients were categorized based on survival, patients in both groups were aggressively fluid resuscitated initially as reflected by a positive daily fluid balance for both survivors and non-survivors through POD 3 (Figure 2). However, between POD 3 and 4, a distinct separation was demonstrated between survivors and non-survivors in regards to fluid balance. Survivors had significantly lower daily fluid balance starting on POD3 ($p=0.02$) and significantly lower cumulative fluid balance beginning POD 4 ($p=0.02$, Figures 2 and 3). This separation remained throughout the study period to POD 7 ($p<0.001$). Patients with high fluid balance received significantly more bolus fluids and blood products throughout the 7-day post-operative period (Table 3). There were no differences between groups in the proportion of patients administered vasopressor therapy during the 7-day post-operative period, with the exception of POD2 when significantly more patients in the high-fluid balance group were administered vasopressor agents (Table 4).

In adjusted analysis, patients with high fluid balance had significantly longer total duration of mechanical ventilation compared to patients with low fluid balance by about 2 days ($p = 0.02$; Table 5). There was no difference in SICU or hospital length of stay, SICU or total hospital costs between groups (Table 5).

Abdominal Surgery Subgroup Analyses

High fluid balance on POD 7 was significantly associated with increased in-hospital mortality, both for patients undergoing abdominal surgery and other types of surgery (abdominal surgery: adjusted OR = 17.9 (95% CI = 2.3, 140.0), $p = 0.01$; other surgery: adjusted OR = 8.8 (1.5, 51.0), $p = 0.02$). Sensitivity analyses with fewer covariates produced similar results. Duration of mechanical ventilation did not differ significantly by type of surgery (8 days for abdominal surgery versus 9.3 days for other surgery, $p = 0.08$).

Diuretic Subgroup Analyses

Incidence of diuretic administration during the 7-day post-operative study period was similar between the low and high fluid balance groups (Table 1). A total of 66 patients received at least one dose of diuretic within the 7-day post-operative period. Of these 66 patients, 54.8% in the low and 45.7% in the high fluid group received a diuretic prior to the third post-operative day. The remainder of patients only received diuretics between post-operative days 4 and 7. The majority of patients in the diuretic subgroup, 80.6% in the low and 74.3% in the high fluid group, received more than 1 dose of diuretic within the 7 day post-operative period.

High fluid balance was associated with increased in-hospital mortality in all patients, regardless of whether or not they received diuretics within the 7-day post-operative period (diuretics adjusted OR, 11.5; 95% CI, 1.3–101.2, $p = 0.03$; no diuretics adjusted OR; 13.8, 2.9–65.8, $p = 0.001$). Sensitivity analyses with fewer covariates produced similar results. There was no difference in duration of mechanical ventilation for patients receiving diuretics compared to those that did not (9.4 days vs. 8.1 days, respectively, $p=0.13$).

Patients who met criteria for response to diuretic therapy did not have improved clinical outcomes compared to those who did not respond to diuresis. Of the 66 patients receiving at least one dose of diuretic, 59.4% were classified as responders. Twenty patients (52.6%) who responded to diuretic therapy met criteria for the low fluid balance group, compared to fourteen (53.9%) non-responders. Mortality was also similar between groups: 15.8% mortality for responders compared to 15.4% for those failing to demonstrate diuretic response. In adjusted analysis, accounting for age, gender, SAPS II minus age, Charlson comorbidity index, and abdominal surgery, there was no difference in fluid balance category [OR = 1.02 (95% CI: 0.98, 1.06), $p = 0.71$] or mortality [OR = 1.42 (95% CI: 0.28, 7.13), $p = 0.67$] based on diuretic response. Duration of mechanical ventilation did not differ between responders and non-responders (geometric mean 9.0 for responders and 10.4 for non-responders, $p = 0.68$).

Discussion

This retrospective analysis of critically ill surgical and trauma patients found significantly increased mortality in patients with a fluid balance greater than 5L on post-operative day 7; this relationship remained after adjusting for multiple potential confounders. These results support previous studies suggesting that patients with a high fluid balance have worse clinical outcomes, including increased mortality and prolonged duration of mechanical ventilation, independent of severity of illness. Subgroup analysis comparing patients that received diuretics to those that did not failed to find a difference in mortality or duration of mechanical ventilation. Similarly, patients demonstrating diuretic response in the post-operative period were not more likely to meet criteria for low fluid balance, have shorter duration of mechanical ventilation or have decreased risk for mortality. Thus, diuretic administration within this 7-day post-operative period may not alter poor clinical outcomes associated with a high fluid balance.

This was the first study to assess the effect of fluid balance in a broad critically ill surgical and trauma population in the late post-operative phase, following adequate initial fluid resuscitation. Guidance for the management of late fluid balance is extrapolated from limited evidence, primarily in the septic shock and acute lung injury populations. In patients with septic shock, Boyd and colleagues demonstrated that a positive fluid balance at both 12 hours and 4 days was associated with significantly higher mortality [10]. In a similar analysis in patients with septic shock and acute lung injury, significantly decreased mortality was found in patients achieving both adequate initial early fluid resuscitation (< 20 ml/kg prior to vasopressors and CVP < 8 within 6 hours) and conservative late fluid management, defined as even to negative fluid balance on 2 days within 7 days of septic shock onset ($p<0.001$) [2].

Results of previously published literature suggest worsened clinical outcomes with positive late post-operative fluid balance, however application of this data and guidance for practice is limited by significant exclusion criteria and short study durations [9, 10, 11, 12]. A meta-analysis assessing clinical outcomes of trauma and surgical patients found significantly higher rates of pneumonia, pulmonary edema and hospital length of stay with liberal resuscitative fluid management, although the analysis attributed differences in fluid balance to increased volume administered during the intraoperative period [15]. Of note, the majority of studies included in this analysis enrolled patients undergoing elective surgeries, and aimed to exclude trauma and sepsis patients. A recent study assessing the effect of positive fluid balance in the critically ill non-cardiac surgical population found no association between fluid balance and in-hospital mortality [19]. However, for patients with APACHE II scores ≥ 20 , non-survivors had significantly higher fluid balance compared to those that survived hospitalization. The study only assessed fluid balance through POD 2, and excluded trauma and transplant patients, limiting application to a more diverse SICU populations. Brandstrup and colleagues demonstrated that patients undergoing colorectal resection treated with a restrictive intra-operative and postoperative fluid strategy utilizing diuretics, had significantly fewer cardiopulmonary and tissue-healing complications compared to those receiving standard fluid management through POD 6 [14]. Finally, a recently published prospective observational study showed significantly lower mortality for critically ill acute care surgery patients that achieved and maintained a negative fluid balance day 5 or discharge from ICU [20]. In addition, those achieving negative fluid balance by day one had significantly lower overall and infection related complications. However, 68.8% of the 144 patients included were trauma patients with the majority younger than 60 years old, which significantly limits extrapolation to other critically ill surgical populations. Additionally, fluid status assessment was based on day of ICU admission rather than in relation to surgical procedure(s), which may impact fluid balance and outcomes. As the utilization of diuretic therapy was not assessed in the study, the sole intervention clinicians can apply based on these results is limiting administration of fluid in the post-operative period. This is consistent with the data presented from our institution. Although the high fluid balance and low fluid balance group were not similar in baseline characteristics, it is logical that patients with more severe illness received a greater amount of fluid administered. Patients whose illness and subsequent inflammatory response did not require high amounts of fluid resuscitation to maintain perfusion to the visceral organs would be expected to have better outcomes. Our data demonstrate that regardless of the etiology of the need for high volume resuscitation, worse outcomes can be expected when greater interventions are necessary to maintain perfusion.

In contrast to prior literature, this study included a primarily emergent surgery population and did not have such strict exclusion criteria in an attempt to evaluate a more diverse SICU population. This analysis also assessed all intake and output during the post-operative period, including amount of blood products and bolused fluids, which has been omitted in previous studies. By extending the study period through post-operative day 7, our study provides information regarding effects of fluid balance in the late phase, to better guide fluid management following the acute resuscitation period.

Despite literature consistently demonstrating the relationship between positive fluid balance and poor clinical outcomes, there is little evidence to guide practice in regards to whether or not diuretics should be utilized to facilitate achievement of euvolemia in a post-surgical population. Administration of diuretics in the critically ill population continues to be controversial, particularly in regards to which patients will benefit, the optimal time point to initiate diuretics following fluid resuscitation and the most appropriate endpoint for therapy. Potential risks of diuretic administration in the ICU population are substantial, including hemodynamic compromise, electrolyte abnormalities and renal dysfunction. A recent study concluded that administration of furosemide is safe and effective for stable, critically ill trauma patients, however this study has significant limitations which prevent extrapolation to other critically ill patients [21]. The results of our study suggest diuretics do not alter clinical outcomes associated with fluid balance on POD 7, as poor outcomes were significantly increased in patients with high fluid balance regardless of whether or not they received diuretics. In addition, these clinical outcomes did not change even if patients were deemed to have a response to diuretic therapy. While this data suggests that forced diuresis is not beneficial in this critically ill population, assessment of diuretic administration was not the primary aim of this study. A recent retrospective study in trauma patients showed patients receiving furosemide within 14 days of ICU admission had significantly higher urine output and less 24 hour fluid accumulation without resulting in hemodynamic instability or laboratory abnormalities [21]. However, this study failed to demonstrate a relationship between diuretic administration and improved clinical outcomes. Patients receiving furosemide had significantly longer duration of mechanical ventilation, ICU and hospital length of stay. Extrapolation of these results to the critically ill surgical and trauma population is limited, as patients receiving diuretics had a very high median fluid balance of greater than 16 liters on day of diuretic initiation and patients with any pre-existing renal dysfunction, defined as a serum creatinine of > 1.5 mg/dL, were excluded from analysis.. In addition, a recent study compared goal-directed continuous infusion furosemide in critically ill trauma patients to a historic cohort receiving intermittent furosemide administration[22]. Patients receiving continuous infusion diuretic were significantly more likely to achieve negative fluid balance with no difference in potassium or serum creatinine levels. The authors did not find any difference in ICU or hospital LOS, ventilator-free days or mortality. The study included a total of only 55 patients and a very specific patient population, limiting extrapolation to a broad critically ill population. Additional studies are necessary to determine whether or not diuretics are appropriate for management of fluid balance in this population

There are several limitations of our study that should be noted. First, the single center, retrospective nature of the study design and reliance on documentation in the electronic medical record limited our ability to identify secondary complications that may have impacted clinical outcomes or determine rationale for fluid administration during the 7-day study period. The retrospective nature also prevents us from establishing a true causal relationship between fluid balance and clinical outcomes. The large increase in risk of mortality with high fluid balance could simply be a marker of disease severity despite our attempts to adjust for baseline severity of illness. It should be noted that a limitation to our study is the presence of significant differences between groups at baseline. However, we

attempted to account for these differences by adjusting for markers of both acute and chronic severity of illness in multivariable analysis. In addition, our study population was restricted to patients with SICU LOS of at least 7 days, which could limit application to patients with extremes of illness (i.e. those who did not survive 7 days and those who required < 7 days ICU LOS). Fluid balance for this study did not include fluids administered prior to the ICU setting due to high potential for inaccuracies in documentation of fluid administration in the ED or pre-hospital setting. While this omission may have impacted fluid balance, both groups would have been equally impacted. Finally, diuretic therapy prior to admission was not assessed, preventing analysis to determine whether this subgroup may benefit from diuretic therapy.

Conclusions

High fluid balance on post-operative day 7 is associated with increased mortality and prolonged duration of mechanical ventilation in critically ill surgical and trauma patients, consistent with previous literature in other patient populations. Based on our results, diuretic administration during the post-operative period did not attenuate mortality risk associated with high fluid balance, suggesting that forced diuresis may not improve clinical outcomes. Additional trials are needed to determine optimal management of late fluid status in this population.

Acknowledgments

The project described was supported by Award Number Grant UL1TR001070 from the National Center For Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Advancing Translational Sciences or the National Institutes of Health.

References

1. Marjanovic G, Villain C, Juettnner E, et al. Impact of different crystalloid volume regimes on intestinal anastomotic stability. *Ann Surg*. 2009; 249(2):181–185. [PubMed: 19212167]
2. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest*. 2009; 136(1):102–109. [PubMed: 19318675]
3. Riddez L, Johnson L, Hahn RG. Central and regional hemodynamics during crystalloid fluid therapy after uncontrolled intra-abdominal bleeding. *J Trauma*. 1998; 44(3):433–439. [PubMed: 9529168]
4. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001; 345(19):1368–1377. [PubMed: 11794169]
5. Sadaka F, Juarez M, Naydenov S, et al. Fluid Resuscitation in Septic Shock: The Effect of Increasing Fluid Balance on Mortality. *J Intensive Care Med*. 2013; 29(4):213–217. [PubMed: 23753235]
6. Schnuriger B, Inaba K, Wu T, et al. Crystalloids after primary colon resection and anastomosis at initial trauma laparotomy: excessive volumes are associated with anastomotic leakage. *J Trauma*. 2011; 70(3):603–610. [PubMed: 21610349]
7. D'Orio V, Mendes P, Carlier P, et al. Lung fluid dynamics and supply dependency of oxygen uptake during experimental endotoxic shock and volume resuscitation. *Crit Care Med*. 1991; 19(7):955–962. [PubMed: 2055085]
8. D'Orio V, Wahlen C, Rodriguez LM, et al. Effects of intravascular volume expansion on lung fluid balance in a canine model of septic shock. *Crit Care Med*. 1987; 15(9):863–868. [PubMed: 3621962]

9. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med.* 1994; 331(17):1105–1109. [PubMed: 7935634]
10. Boyd JH, Forbes J, Nakada TA, et al. 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):259–265. [PubMed: 20975548]
11. Guidry C, Gleeson E, Simms ER, et al. Initial assessment on the impact of crystalloids versus colloids during damage control resuscitation. *J Surg Res.* 2013; 185(1):294–299. [PubMed: 23816247]
12. Kasotakis G, Sideris A, Yang Y, et al. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: an analysis of the Glue Grant database. *J Trauma Acute Care Surg.* 2013; 74(5):1215–1221. discussion 1221–1212. [PubMed: 23609270]
13. Wang CH, Hsieh WH, Chou HC, et al. Liberal versus restricted fluid resuscitation strategies in trauma patients: a systematic review and meta-analysis of randomized controlled trials and observational studies*. *Crit Care Med.* 2014; 42(4):954–961. [PubMed: 24335443]
14. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg.* 2003; 238(5):641–648. [PubMed: 14578723]
15. Corcoran T, Rhodes JE, Clarke S, et al. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg.* 2012; 114(3):640–651. [PubMed: 22253274]
16. Cox P. Insensible water loss and its assessment in adult patients: a review. *Acta Anaesthesiol Scand.* 1987; 31(8):771–776. [PubMed: 3324617]
17. Charlson ME, Sax FL, MacKenzie CR, et al. Morbidity during hospitalization: can we predict it? *J Chronic Dis.* 1987; 40(7):705–712. [PubMed: 3110198]
18. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993; 270(24):2957–2963. [PubMed: 8254858]
19. Shim HJ, Jang JY, Lee SH, et al. The effect of positive balance on the outcomes of critically ill noncardiac postsurgical patients: a retrospective cohort study. *J Crit Care.* 2014; 29(1):43–48. [PubMed: 24140168]
20. Barmparas G, Liou D, Lee D, et al. Impact of positive fluid balance on critically ill surgical patients: a prospective observational study. *J Crit Care.* 2014; 29(6):936–941. [PubMed: 25085510]
21. Yeh DD, Tang JF, Chang Y. The use of furosemide in critically ill trauma patients: A retrospective review. *J Emerg Trauma Shock.* 2014; 7(2):83–87. [PubMed: 24812452]
22. Yeh DD, Van Der Wilden GM, Cropano C, et al. Goal-directed diuresis: A case - control study of continuous furosemide infusion in critically ill trauma patients. *J Emerg Trauma Shock.* 2015; 8(1):34–38. [PubMed: 25709251]

Figure 1.
Development of Study Cohort

Figure 2.
Daily Fluid Balance Based of Survivors vs Non-Survivors through Post-Operative Day 7

POD	Survivors (mL)	Non-Survivors (mL)
1	3258	3692
2	5124	5763
3	5596	7539
4	4784	8948
5	5508	10740
6	5142	12093
7	4882	14439

Figure 3.
Cumulative Balance Based of Survivors vs Non-Survivors through Post-Operative Day 7

Table 1

Baseline Demographics and Characteristics of Study Population comparing Low vs High Fluid Balance on Post-Operative Day 7

	Low Fluid Balance (n=101)	High Fluid Balance (n=96)	p-value
Age, mean $\pm$ SD	53.4 $\pm$ 17.3	59.2 $\pm$ 16.5	0.02
Female Gender	32 (31.7%)	39 (40.6%)	0.19
BMI, mean $\pm$ SD	28.2 $\pm$ 8.1	29.2 $\pm$ 9.1	0.4
CKD	7 (6.9%)	11 (11.5%)	0.27
Charlson Comorbidity Index, median [IQR]	2 [0–4]	4 [2–6]	<0.001
SAPS II, mean $\pm$ SD	42.7 $\pm$ 12.7	46.6 $\pm$ 15.0	0.048
Surgical Service			
Trauma/Acute Care	54 (53.5%)	42 (43.8%)	0.17
Colorectal	3 (3.0%)	6 (6.3%)	0.27
Gastrointestinal	10 (9.9%)	16 (16.7%)	0.16
Gynecology Oncology	2 (2.0%)	5 (5.2%)	0.22
Surgical Oncology	1 (1.0%)	10 (10.4%)	0.004
Thoracic Surgery	14 (13.9%)	7 (7.3%)	0.14
Orthopedic Surgery	9 (8.9%)	6 (6.3%)	0.48
Other ^a	8 (3.0%)	5 (3.1%)	0.95
Surgery Type			
Abdominal	47 (46.5%)	70 (72.9%)	<0.001
Thoracic	22 (21.8%)	13 (13.5%)	0.13
Ortho Lower Extremity	14 (13.9%)	8 (8.3%)	0.22
Spinal	14 (13.9%)	6 (6.3%)	0.08
Other ^b	12 (11.9%)	4 (4.2%)	0.048
Trauma	32 (31.7%)	13 (13.5%)	0.002
Penetrating	2 (2.0%)	1 (1.0%)	0.86 ^c
Blunt	30 (29.7%)	12 (12.5%)	
Emergent Surgery	77 (76.2%)	74 (77.1%)	0.89
Hospital Day to ICU, median [IQR]	1.0 [1.0–2.5]	1.0 [1.0–2.0]	0.1
Baseline SCr, mcg/dL median [IQR]	0.6 [0.5–0.8]	0.6 [0.5–0.8]	0.86
Baseline Creatinine Clearance > 60 ml/min	90 (89.1%)	79 (82.3%)	0.17
Lactate, mean $\pm$ SD	3.7 $\pm$ 2.4, n=61	3.4 $\pm$ 2.6, n=75	0.48
CVP, mean $\pm$ SD	12.1 $\pm$ 5.5, n=37	11.5 $\pm$ 5.6, n=51	0.62
Diuretic POD 1–7	31 (30.7%)	35 (36.5%)	0.39

Data reported as n(%) unless otherwise noted; SD= standard deviation, IQR= inter-quartile range, BMI= body mass index, kg/m², CKD = chronic kidney disease, CVP = central venous pressure, SAPS = Simplified Acute Physiology Score

^aIncluding bariatric surgery, transplant surgery and orthopedic surgery

^bIncluding upper extremity orthopedic, gynecologic and transplant

^cPenetrating versus Blunt

Table 2

Multivariable Regression for In-Hospital Mortality

Variable	Odds Ratio (95% CI)	p-value
High fluid balance	12.7 (3.5, 45.8)	<0.001
Age (5 year increase)	1.1 (0.9, 1.2)	0.39
Male	1.1 (0.5, 2.7)	0.80
SAPS ^a II minus age (5 point increase)	1.2 (1.0, 1.4)	0.04
Charlson Comorbidity Index (1 point increase)	1.0 (0.9, 1.2)	0.60
Abdominal surgery	0.9 (0.3, 2.2)	0.78

^aSAPS = Simplified Acute Physiology Score

Table 3

Administration of Bolus Fluids and Blood Products by Post-Operative Day

Low Fluid Balance (n=101)				High Fluid Balance (n=96)				
Post-op Day	geometric mean	LCL	UCL	geometric mean	LCL	UCL	p-value	
Bolus Fluids (mL)								
1	9.98	4.52	20.82	122.59	55.23	270.60	<.001	
2	1.24	0.42	2.55	15.83	6.97	34.54	<.001	
3	0.61	0.14	1.29	8.16	3.59	17.29	<.001	
4	0.83	0.24	1.70	3.43	1.40	7.18	.02	
5	0.35	0.01	0.81	2.75	1.09	5.74	.002	
6	0.52	0.09	1.13	4.21	1.75	8.87	.001	
7	0.50	0.09	1.08	3.72	1.59	7.62	.001	
Blood Products (mL)								
1	2.51	1.11	4.83	7.23	3.31	14.71	.04	
2	1.24	0.47	2.42	6.19	2.85	12.42	.002	
3	0.67	0.21	1.31	3.83	1.80	7.31	.002	
4	0.53	0.12	1.08	2.70	1.23	5.14	.004	
5	0.52	0.12	1.06	1.15	0.42	2.25	.17	
6	0.58	0.16	1.15	2.08	0.87	4.08	.03	
7	0.19	0.00	0.44	2.42	1.06	4.69	<.001	

Table 4

Vasopressor Use by Post-Operative Day

Post-Operative Day	Low Fluid Balance (n=101)	High Fluid Balance (n=96)	p-value
1	19 (18.8%)	26 (27.1%)	0.17
2	14 (13.9%)	24 (25.0%)	0.048
3	10 (9.9%)	13 (13.5%)	0.43
4	6 (5.9%)	9 (9.4%)	0.36
5	6 (5.9%)	9 (9.4%)	0.36
6	6 (5.9%)	6 (6.3%)	0.93
7	5 (5.0%)	7 (7.3%)	0.49

Table 5

Secondary Outcomes for Low vs High Fluid Balance on Post-Operative Day 7

	Low Fluid Balance (n=101)	High Fluid Balance (n=96)	p-value
Total duration of mechanical ventilation, days	7.6 (6.3, 9.0)	9.6 (7.9, 11.6)	0.02
ICU Length of Stay, days	16.0 (14.5, 17.6)	17.7 (15.6, 20.0)	0.15
Hospital Length of Stay, days	21.8 (20.0, 23.8)	22.8 (20.2, 25.8)	0.54
Median Total Hospital Cost, dollars	108,300.63	101,129.13	0.78
Median Total SICU Costs, dollars	61,893.42	66,310.61	0.44

Data reported as geometric mean (95% Confidence Interval)