OBSERVATIONAL STUDY

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Associations Between Volume of Early Intravenous Fluid and Hospital Outcomes in Septic Patients With and Without Heart Failure: A Retrospective Cohort Study

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OBJECTIVES: To evaluate the relationship between early IV fluid volume and hospital outcomes, including death in-hospital or discharge to hospice, in septic patients with and without heart failure (HF).

DESIGN: A retrospective cohort study using logistic regression with restricted cubic splines to assess for nonlinear relationships between fluid volume and outcomes, stratified by HF status and adjusted for propensity to receive a given fluid volume in the first 6 hours. An ICU subgroup analysis was performed. Secondary outcomes of vasopressor use, mechanical ventilation, and length of stay in survivors were assessed.

SETTING: An urban university-based hospital.

PATIENTS: A total of 9613 adult patients were admitted from the emergency department from 2012 to 2021 that met electronic health record-based Sepsis-3 criteria. Preexisting HF diagnosis was identified by the *International Classification of Diseases* codes.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: There were 1449 admissions from patients with HF. The relationship between fluid volume and death or discharge to hospice was nonlinear in patients without HF, and approximately linear in patients with HF. Receiving 0–15 mL/kg in the first 6 hours was associated with lower likelihood of death or discharge to hospice compared with 30–45 mL/kg (odds ratio = 0.61; 95% CI, 0.41–0.90; $p = 0.01$) in HF patients, but no significant difference for non-HF patients. A similar pattern was identified in ICU admissions and some secondary outcomes. Volumes larger than 15–30 mL/kg for non-HF patients and 30–45 mL/kg for ICU-admitted non-HF patients were not associated with improved outcomes.

CONCLUSIONS: Early fluid resuscitation showed distinct patterns of potential harm and benefit between patients with and without HF who met Sepsis-3 criteria. Restricted cubic splines analysis highlighted the importance of considering nonlinear fluid outcomes relationships and identified potential points of diminishing returns (15–30 mL/kg across all patients without HF and 30–45 mL/kg when admitted to the ICU). Receiving less than 15 mL/kg was associated with better outcomes in HF patients, suggesting small volumes may be appropriate in select patients. Future studies may benefit from investigating nonlinear fluid–outcome associations and a focus on other conditions like HF.

KEYWORDS: fluid therapy; heart failure; intensive care units; regression analysis; sepsis

Sepsis frequently leads to hospitalization and carries a significant mortality rate of 10–20% across all hospitalized patients, and up to 20–50% for the critically ill (1–5). IV fluid therapy plays a key role in management (6).

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KEY POINTS

Question: Does the response to a range of early IV fluid volumes for sepsis treatment differ between patients with and without heart failure?

Findings: This retrospective cohort study, using logistic regression with restricted cubic splines and propensity score adjustment in a Sepsis-3 population, found that heart failure patients receiving 0–15 mL/kg of fluids had a lower likelihood of death or hospice discharge compared with those receiving 30–45 mL/kg. The relationship was near-linear in heart failure patients and nonlinear in patients without heart failure.

Meaning: Smaller resuscitation fluid volumes may be appropriate in heart failure. Distinct patterns of benefit and harm by heart failure status and at different fluid volumes suggest that personalized fluid targets may be reasonable.

However, three recent trials have revealed no difference between restrictive and liberal fluid strategies in septic shock (7–9), leaving uncertainty about the best approach for fluid therapy. This uncertainty is particularly pronounced in patients prone to hypervolemia, such as those with heart failure (HF).

Prior studies examining the relationship between mortality and fluid volumes administered in patients with HF have yielded conflicting results. Some suggest that HF patients benefit from receiving at least 30 mL/kg (10, 11). However, these studies have limitations. Defining fluid volume as a binary variable may lead to loss of valuable predictive information. Additionally, these studies were conducted using criteria predating Sepsis-3 (12). Focusing on a 30-mL/kg target also limits the clinical utility of the results in select situations. Clinicians may hesitate to administer this volume when there are risk factors for volume overload, like HF. Interestingly, a prior study in septic shock found a U-shaped association between fluid volume and outcomes, where receiving either more or less fluid than expected was associated with worse outcomes (13). However, this pattern did not hold for patients with comorbidities associated with receiving smaller fluid volumes.

This study aimed to investigate associations between IV fluid volumes and hospital outcomes, including a primary composite outcome of death in-hospital or discharge to hospice, in a broad sample of adult patients meeting Sepsis-3 criteria, with or without compensated HF, including a subgroup analysis of ICU admissions. Novel statistical methods were used to investigate the potential nonlinear patterns of benefit and harm.

MATERIALS AND METHODS

Design

We performed a retrospective cohort study using electronic health record (EHR) data at an urban academic hospital. This hospital has approximately 30,000 emergency department (ED) encounters annually and has used an Epic-based EHR (Epic 2017, Epic Systems Corporation, Verona, WI) since June 2012. Clinical and administrative data were extracted from Clarity, Epic's data warehouse. This study was approved by the UCSF Committee on Human Research on October 5, 2022 (study number 16-20956; titled Sepsis Cohort Study) with waiver of informed consent. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975.

Patients

The target population was adults hospitalized in acute care wards and ICUs who met Sepsis-3 criteria and were without clinical evidence of volume overload on presentation. Patients admitted from the ED between June 2012 and June 2021 greater than or equal to 18 years with suspected sepsis (14), defined as blood cultures ordered and IV antibiotics administered within 24 hours of presentation (**Fig. 1**), were included. Patients were also required to meet previously published Sepsis-3 criteria based on EHR data (1). These criteria require a Sequential Organ Failure Assessment (SOFA) score of at least two, and either four continuous days of antibiotics or a sepsis billing code at discharge (1, 12, 15). Patients who died or were discharged to hospice before receiving 4 days of antibiotics were included. Patients who received no fluids in the first 6 hours were included to avoid overestimating fluid volumes.

Patients transferred from other institutions were excluded. Patients who were volume overloaded on presentation (defined as receiving IV diuretics within 6 hr

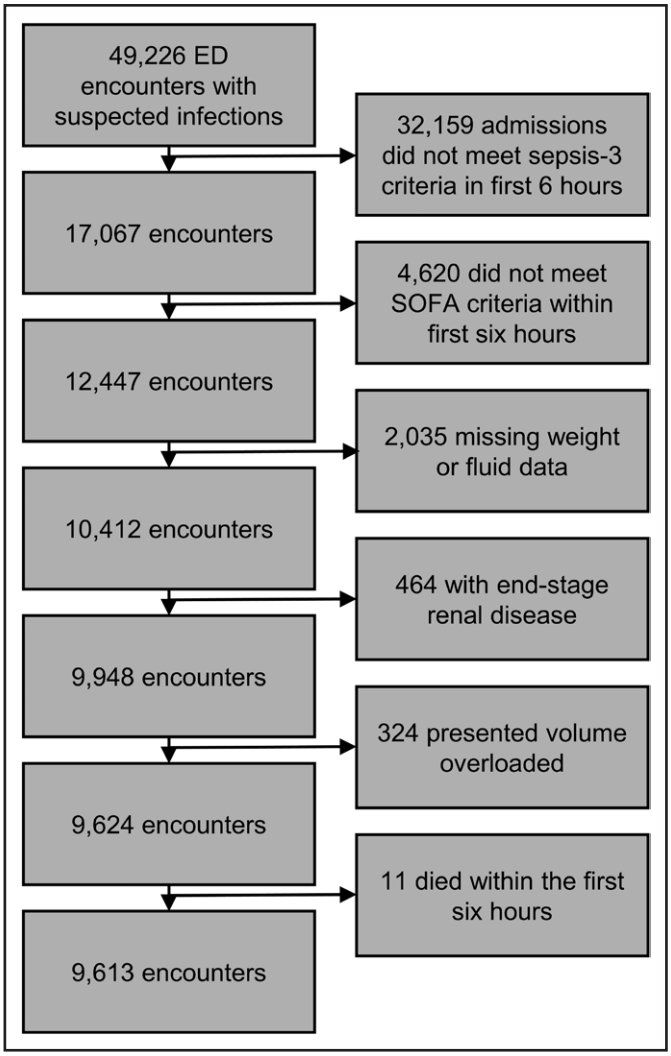

Figure 1. Cohort selection flow diagram. All patients in the initial population were adults (≥ 18 yr) presenting to the emergency department (ED) of an urban academic medical center between June 2012 and June 2021. Suspected infection was defined as having blood cultures ordered and IV antibiotics administered within 24 hours of presentation. End-stage renal disease patients were dependent on dialysis before admission. Volume overload was defined as receiving IV diuretics in the first 6 hours from ED presentation. SOFA = Sequential Organ Failure Assessment.

of presentation) and patients with dialysis-dependent end-stage renal disease before admission were excluded, as these were considered strong indications to limit fluid administration. Patients who died within 6 hours (n = 11) were excluded to avoid bias from censoring during the fluid administration timeframe.

A diagnosis of HF was identified using the *International Classification of Diseases* codes according to the Elixhauser comorbidity algorithm (**eTable 1**, http://links.lww.com/CCX/B331) (16). A random sample of 70 patients (~5%) with HF was selected for a chart review planned a priori. The most recent transthoracic echocardiogram within the index admission was reviewed by a single study author (A.J.B.). Patients were categorized as having left ventricular ejection fractions of less than 40%, 40–50%, or greater than 50%. If greater than 50%, earlier echocardiograms were reviewed to assess if the ejection fraction had recovered from less than 50% at an earlier assessment.

Measures

Demographic characteristics, components of the SOFA score, comorbidities, triage vital signs, laboratory results, fluid administration records, and clinical outcomes, including death or discharge to hospice, were extracted from Clarity. SOFA scores were calculated using previously described methods (14), which included estimating Pao_2 from oxygen saturation values to estimate Pao_2:Fio_2 ratios (**eTable 2**, http://links.lww.com/CCX/B331) (17). Timestamps for all SOFA components were collected, allowing for accurate identification of when Sepsis-3 criteria were met (12).

The volume of fluid received within the first 6 hours of ED presentation was weight-adjusted using the first recorded patient weight in kg within the index admission. Fluids were administered in either bolus or continuous forms. Both crystalloid and colloid solutions were included. Patients who received over 100 mL/kg of fluid within the first 6 hours of presentation (~0.02% of admissions) were recorded as having received 100 mL/kg.

The primary outcome of this study was a composite measure of death during hospitalization or discharge to hospice six or more hours after ED presentation. Discharge to hospice was included to account for mortality related to the sepsis admissions that occurred after discharge. Secondary outcomes were also assessed, including mechanical ventilation six or more hours after presentation, requiring vasopressors six or more hours after presentation, and length of stay (LOS) among patients who survived hospitalization (LOS). Patients who required mechanical ventilation (n = 473) or vasopressors (n = 907) within 6 hours were excluded from the corresponding analyses since associations between fluid volumes and synchronous or preceding outcomes were considered unlikely to be causal.

Statistical Analyses

Two-sided t-tests for normally distributed continuous data, Wilcoxon rank-sum tests for non-normal continuous data, and chi-square tests for categorical data were used to test cohort characteristics for bivariate associations with HF status. Histograms were used to depict fluid volume distributions.

For the main analysis, logistic regression was used to first model the unadjusted association between the composite outcome of death or discharge to hospice (dependent variable) and the volume of IV fluid given in the first 6 hours after ED presentation (independent variable). Restricted cubic spline (RCS) transformation of the fluid volume with three knots was performed (18–20). This method was selected to allow the relationship between fluids and the outcome to be nonlinear. The unadjusted logistic regression was then stratified by HF status.

To account for confounding by indications for fluids (21), the model was then adjusted for a patient's propensity to receive a given volume of fluid. This propensity score was estimated based on presenting characteristics likely to influence fluid decisions by clinicians, using the generalized propensity score method with balancing property testing by T-test to assess for baseline characteristic balance across fluid volume quartiles (21–23). These presenting characteristics included baseline demographics (admission year, age, gender, limited English language proficiency), comorbidities (liver disease, hypertension, malignancy, or diabetes), triage vital signs (fever, hypothermia, heart rate, mean arterial pressure, respiratory rate, Sao_2:FIO_2 ratio), and laboratory values (leukocytosis, leukopenia, creatinine, platelets, first lactate value). The propensity score reflected the specific volume of fluid a patient would receive in typical clinical care at the study institution based on these characteristics. Owing to inherent differences in clinician heuristics for fluid strategy in patients with and without HF, propensity score estimations were performed separately for patients with and without HF. Missing data for vital signs and laboratory values were recorded as normal. Total bilirubin was not included in propensity score estimation as it was missing in 9.9% of patients (**eTable 3**, http://links.lww.com/CCX/B331). Patients missing gender and limited English proficiency (n = 11) were excluded from the main analysis.

Goodness-of-fit was compared between models with and without the RCS transformation for fluid volume using the likelihood ratio test and Akaike's information criterion (AIC) (24). All main analysis components were planned a priori.

Repeated admissions from the same patient were treated as independent. All data preparation and analyses were performed in STATA 16 (StataCorp, College Station, TX). Two-tailed p values of less than 0.05 were considered significant.

The main analysis was repeated within a subgroup of patients who were admitted directly to the ICU. Receipt of at least 30 mL/kg of fluid was tested for association with the initial level of care (ICU or non-ICU) using the chi-square test; this was performed with all patients and stratified by HF status. The ICU subgroup analysis was planned a priori.

An exploratory analysis of secondary outcomes was performed. The main analysis procedure and ICU subgroup analysis were repeated for three secondary outcomes: requiring vasopressors six or more hours after ED presentation, requiring mechanical ventilation six or more hours after presentation, and LOS among survivors. Secondary outcomes analysis was planned a priori.

A post hoc analysis was then performed to assess concordance between the main analysis results and results from logistic regression with a categorical fluid predictor, a commonly applied method in previous studies. Fluid volume was categorized into 15 mL/kg strata to calculate odds ratios (ORs) for associations between fluid volume strata and the primary outcome. This analysis was performed separately in patients with and without HF using the 30–45 mL/kg stratum as a reference for both groups and then adjusted for propensity to receive a given volume of fluid.

Four post hoc sensitivity analyses were performed. First, the results were tested for sensitivity to defining the fluid propensity score with a model using a binary dependent variable (i.e., propensity to receive more than 30 mL/kg). Second, the main findings were tested for sensitivity to the number of knots used in the RCS analysis (three vs. four vs. five). Third, sensitivity to changes in measures of hypoperfusion (hypotension and lactate) within the 6-hour timeframe of the study, which might influence decisions to administer more fluid after an initial bolus, was tested. Lactate values and hypotension at the first vital sign assessment were

expressed instead as the fraction of the 6-hour timeframe in which the values were abnormal (lactate > 2.0 mmol/L; mean arterial pressure < 65 mm Hg) and then included in the propensity analysis described above. Fourth, to evaluate sensitivity to inclusion of multiple admissions by the same patient, one admission for each patient (n = 7598) was selected using a random number generator, and the main analysis was repeated.

RESULTS

There were 9613 admissions included (Fig. 1), of which 1449 (15.1%) were from patients with HF (**Table 1**). There were 2351 (24.6%) admissions to the ICU; 480 of 1449 (33.3%) among HF patients versus 1871 of 8164 (23.0%) in patients without HF ($p < 0.001$). HF patients were typically older and more frequently identified as Black/African American. They also had higher Elixhauser mortality comorbidity indices and higher rates of hypertension and diabetes. HF patients tended to present with more abnormalities in triage vital signs and initial laboratory values. Patients with HF died or were discharged to hospice in 296 of 1449 admissions (20.4%), compared with 1224 of 8164 (15.0%) among those without HF ($p < 0.001$). HF patients also had higher rates of mechanical ventilation, vasopressor usage, and longer LOS (**Table 2**). Characteristics of the ICU subgroup are presented in **eTable 4**, http://links.lww.com/CCX/B331. Of 64 patients with HF randomly selected for a chart review who had available echocardiograms, the most recent ejection fraction was less than 40% in 19 patients (29.7%) (**eTable 5**, http://links.lww.com/CCX/B331).

Across all admissions, a weight-adjusted median of 19 mL/kg (interquartile range [IQR] 11–32 mL/kg) of fluid was administered in the first 6 hours, with 2774 of 9613 (28.9%) receiving at least 30 mL/kg (**eTable 6**, http://links.lww.com/CCX/B331). HF patients received significantly less fluid than those without HF, a median of 13 mL/kg (IQR 6–23 mL/kg) versus a median of 20 mL/kg (IQR 12–34, $p < 0.001$). Weight-adjusted fluid volume distributions stratified by HF status and in the ICU subgroup are shown in **eFigure 1** (http://links.lww.com/CCX/B331).

Admissions with missing data for propensity score estimation (n = 11) were excluded from logistic regression analyses, yielding a sample of 9602 admissions, 8157 from patients without HF, and 1445 from patients with HF. A nonlinear relationship between volume and the likelihood of death or discharge to hospice was observed across all patients in the unadjusted regression (**Fig. 2*A***).

Propensity score adjustment attenuated the association between fluid volume received and the primary outcome of death or discharge to hospice (**Fig. 2*B***). In the unadjusted regression stratified by HF status, HF patients demonstrated a linear increase in expected probability of the primary outcome with larger fluid volumes (**Fig. 2*C***). In contrast, this relationship remained nonlinear for patients without HF, with decreasing expected probability of the primary outcome up to approximately 15–30 mL/kg and increasing probability at volumes larger than this range. After adjustment for propensity to receive a given fluid volume, there was a nonlinear relationship between volume and the primary outcome in patients without HF, and a near-linear relationship in patients with HF (**Fig. 2*D***). At smaller fluid volumes, probability of death or discharge to hospice increased with larger fluid volumes for patients with HF and decreased for patients without HF. The lowest propensity-adjusted probability estimates for the primary outcome in patients without HF occurred around 15–30 mL/kg for all patients (Fig. 2*D*). T-testing showed the balancing property to be satisfied for patients with and without HF (both $p = 0.01$).

The inclusion of RCS fluid transformation improved model goodness-of-fit for the propensity-adjusted regression in patients without HF (AIC with RCS 6874.5 vs. 6881.0 without RCS; $p = 0.003$), but for patients with HF, including RCS transformation did not improve model fit compared with a logistic regression without RCS ($p = 0.44$). Logistic regression results using a continuous fluid predictor without RCS transformation are presented in **eTable 7** (http://links.lww.com/CCX/B331).

A similar pattern was seen in the ICU subgroup after propensity adjustment (**Fig. 3*B***). The lowest propensity-adjusted predicted mortality in patients without HF admitted to the ICU occurred around 30–45 mL/kg (Fig. 3*B*). ICU patients were more likely to receive at least 30 mL/kg than non-ICU patients (44.6% vs. 28.9%, $p < 0.001$).

The association between fluid volumes and the secondary outcome of mechanical ventilation six or more hours after ED presentation revealed a pattern similar

TABLE 1.
Characteristics Overall and by Heart Failure Status for 9613 Admissions From Patients Meeting Sepsis-3 Criteria

Cohort characteristics	Overall (*n* = 9613)	No HF (*n* = 8164)	HF (*n* = 1449)	*p*
Demographic characteristics				
Age, yr, mean ± SD	64.7 ± 17.9	63.1 ± 17.9	73.5 ± 15.4	< 0.001
Female gender, *n* (%)	4190 (43.6%)	3584 (43.9%)	606 (41.8%)	0.14
Race/ethnicity, *n* (%)				
White/Caucasian	4285 (45.1%)	3649 (45.2%)	636 (44.6%)	< 0.001
Asian	2439 (25.7%)	2072 (25.7%)	367 (25.7%)	
Black/African American	1013 (10.7%)	818 (10.1%)	195 (13.7%)	
Hispanic/Latino	1081 (11.4%)	962 (11.9%)	119 (8.3%)	
Other	686 (7.2%)	576 (7.1%)	110 (7.7%)	
Limited English proficiency, *n* (%)	1914 (19.9%)	1580 (19.4%)	334 (23.1%)	0.001
Elixhauser Mortality Comorbidity Index, mean ± SD	12.4 ± 11.5	10.9 ± 10.9	20.6 ± 11.4	< 0.001
Liver disease, *n* (%)	1432 (14.9%)	1218 (14.9%)	214 (14.8%)	0.88
Hypertension, *n* (%)	3009 (31.3%)	2240 (27.4%)	769 (53.1%)	< 0.001
Malignancy, *n* (%)	2291 (23.8%)	2071 (25.4%)	220 (15.2%)	< 0.001
Diabetes, *n* (%)	2589 (26.9%)	2044 (25.0%)	545 (37.6%)	< 0.001
Heart failure, *n* (%)	1449 (15.1%)	NA	NA	NA
Year of admission, *n* (%)				
2012–2013	1594 (16.6%)	1399 (17.1%)	195 (13.5%)	< 0.001
2014–2015	2519 (26.2%)	2180 (26.7%)	339 (23.4%)	
2016–2017	2386 (24.8%)	1963 (24.0%)	423 (29.2%)	
2018–2019	1959 (20.4%)	1659 (20.3%)	300 (20.7%)	
2020–2021	1155 (12.0%)	963 (11.8%)	192 (13.3%)	
Vital signs at triage				
Fever, temperature ≥ 38°C, *n* (%)	2093 (21.8%)	1853 (22.7%)	240 (16.6%)	< 0.001
Hypothermia, temperature < 36°C, *n* (%)	467 (4.9%)	353 (4.3%)	114 (7.9%)	< 0.001
Heart rate, beats/min, mean ± SD	104 ± 23	105 ± 23	98 ± 24	< 0.001
Mean arterial pressure, mm Hg, mean ± SD	89 ± 19	89 ± 19	89 ± 21	0.65
Hypotension, systolic < 90 mm Hg, *n* (%)	1007 (10.5%)	840 (10.3%)	167 (11.5%)	0.16
Respiratory rate, breaths/min, mean ± SD	20 ± 6	20 ± 5	21 ± 6	< 0.001
Spo_2:FIO_2 ratio, mean ± SD	371 ± 128	378 ± 125	334 ± 139	< 0.001
Laboratory values				
Leukopenia, < 4 cells × 10^9/L, *n* (%)	1020 (10.6%)	923 (11.3%)	97 (6.7%)	< 0.001
Leukocytosis, > 12 cells × 10^9/L, *n* (%)	4546 (47.3%)	3883 (47.6%)	663 (45.8%)	0.20
Creatinine, mg/dL, median (IQR)	1.1 (0.8–1.6)	1.0 (0.8–1.5)	1.3 (0.9–1.9)	< 0.001
Platelets, ×10^9 platelets/L, median (IQR)	199 (124– 286)	199 (122–288)	199 (136–277)	0.38
Total bilirubin, mg/dL, median (IQR)	1.0 (0.6–1.7)	1.0 (0.6–1.7)	1.0 (0.7–1.6)	0.74
Lactate, mmol/ L, median (IQR)	2.0 (1.3–3.1)	2.0 (1.3–3.0)	2.3 (1.5–3.5)	< 0.001

(*Continued*)

TABLE 1. (*Continued*)

Characteristics Overall and by Heart Failure Status for 9613 Admissions From Patients Meeting Sepsis-3 Criteria

Cohort characteristics	Overall (*n* = 9613)	No HF (*n* = 8164)	HF (*n* = 1449)	*p*
ICU admission[a], *n* (%)	2351 (24.6%)	1871 (23.0%)	480 (33.3%)	< 0.001
Sequential Organ Failure Assessment score, median (IQR)	5 (4–8)	5 (4–7)	6 (4–9)	< 0.001

HF = heart failure, IQR = interquartile range, NA = not applicable.

[a]Proportion of admissions where the first admission level of care was ICU.

Includes all 9613 admissions. *p* values are for comparisons of patients with HF vs. patients without HF. Missing data are reported in eTable 3, http://links.lww.com/CCX/B331. Values shown here do not include the normal values recoded from missing for the propensity score analysis. A table describing these characteristics for the ICU subgroup is presented in eTable 4, http://links.lww.com/CCX/B331.

to that seen for the primary outcome among those without HF (**eFig. 2**, http://links.lww.com/CCX/B331). For vasopressor administration six or more hours after ED presentation, there was no association at lower volumes in the overall cohort (**eFig. 3**, http://links.lww.com/CCX/B331). For LOS in patients admitted to the ICU, the predicted LOS decreased with increasing fluid volumes until about 30–45 mL/kg in patients without HF (**eFig. 4**, http://links.lww.com/CCX/B331).

In the propensity-adjusted logistic regression using a categorical fluid volume predictor, patients with HF were less likely to die or be discharged to hospice when receiving 0–15 mL/kg of fluid versus 30–45 mL/kg (OR = 0.61; 95% CI, 0.41–0.90; $p = 0.01$) (**Table 3**). In contrast, there was no difference between these two fluid strata for patients without HF (OR = 0.95 for 0–15 vs. 30–45 mL/kg; 95% CI, 0.80–1.14; $p = 0.58$).

In sensitivity analyses, the main results differed significantly when using a propensity score estimated from a model with binary fluid volume as the dependent variable (**eFig. 5**, http://links.lww.com/CCX/B331) but were insensitive to RCS transformations using four or five knots (**eFig. 6**, http://links.lww.com/CCX/B331). Expressing the lactate and mean arterial blood pressure as the fraction of time during the 6-hour window in which they were abnormal for the propensity score estimation did not significantly alter the main findings (**eFig. 7**, http://links.lww.com/CCX/B331). The results did not differ significantly after including only one randomly selected admission for each patient (**eFig. 8**, http://links.lww.com/CCX/B331).

DISCUSSION

This study investigated the relationship between early fluid resuscitation volume and hospital outcomes in hospitalized adults meeting EHR-based Sepsis-3 criteria, comparing patients with and without HF. Distinct patterns were identified by HF status. Patients with HF experienced a near-linear increase in the likelihood of death or discharge to hospice as fluid volumes increased. Conversely, patients without HF exhibited a U-shaped association between fluid volume and this outcome, with the lowest rates of death or discharge to hospice observed at fluid volumes around 15–30 mL/kg. Logistic regression using a categorical fluid predictor showed that patients with HF had a lower estimated risk of death or hospice discharge when receiving 0–15 mL/kg compared with 30–45 mL/kg of fluid. Similarly, distinct associations were noted for secondary outcomes like mechanical ventilation, vasopressor use, and LOS.

Evaluating the relationship between fluids and outcomes nonlinearly revealed key volume ranges beyond which the benefits of additional fluids may diminish, highlighting the potential value of a judicious approach to fluid management, particularly in patients with HF. Until approximately 15–30 mL/kg of fluid, larger fluid volumes were associated with a reduced likelihood of death or discharge to hospice across all hospitalized patients. This may reflect the adverse effects of hypoperfusion. However, beyond this point, larger volumes were associated with a higher probability of death or discharge to hospice. This suggests that excessive volumes may be harmful even among patients without preexisting HF, perhaps due to sepsis effects like acute cardiomyopathy and kidney injury. In ICU patients without HF, a similar threshold was observed around 30–45 mL/kg. While ICU patients with HF displayed a pattern of decreasing mortality rates with higher fluid

TABLE 2.
Outcomes Overall and by Heart Failure Status for 9613 Admissions From Patients Meeting Sepsis-3 Criteria, Including a Subgroup of 2351 ICU Admissions

Outcomes	Overall	No HF	HF	*p*
All patients	*n* = 9613	*n* = 8164	*n* = 1449	
Primary outcome				
Death in hospital, *n* (%)	1102 (11.5%)	857 (10.5%)	245 (16.9%)	< 0.001
Death or discharge to hospice, *n* (%)	1520 (15.8%)	1224 (15.0%)	296 (20.4%)	< 0.001
Secondary outcomes				
Length of stay in survivors, d, median (IQR)	5.7 (3.7–9.7)	5.5 (3.7–9.2)	6.8 (4.2–11.9)	< 0.001
Mechanical ventilation, *n* (%)	1416 (14.7%)	1096 (13.4%)	320 (22.1%)	< 0.001
Time to mechanical ventilation[a]				
0–6 hr	473 (33.4%)	359 (32.8%)	114 (35.6%)	0.28
6–24 hr	521 (36.8%)	399 (36.4%)	122 (38.1%)	
24+ hr	422 (29.8%)	338 (30.8%)	84 (26.3%)	
Required vasopressors, *n* (%)	1736 (18.1%)	1318 (16.1%)	418 (28.8%)	< 0.001
Time to vasopressors[a]				
0–6 hr	907 (52.2%)	674 (51.1%)	233 (55.7%)	0.25
6–24 hr	602 (34.7%)	466 (35.4%)	136 (32.5%)	
24+ hr	227 (13.1%)	178 (13.5%)	49 (11.7%)	
ICU subgroup	*n* = 2351	*n* = 1871	*n* = 480	
Primary outcome				
Death in hospital, *n* (%)	569 (24.2%)	422 (22.6%)	147 (30.6%)	< 0.001
Death or discharge to hospice, *n* (%)	641 (27.3%)	485 (25.9%)	156 (32.5%)	0.004
Secondary outcomes				
Length of stay in survivors, d, median (IQR)	7.5 (4.8–13.2)	7.2 (4.6–12.4)	8.9 (5.9–16.7)	< 0.001
ICU length of stay[a], d, median (IQR)	3.1 (1.9–6.0)	3.0 (1.8–5.9)	4.0 (2.0–8.0)	< 0.001
Mechanical ventilation, *n* (%)	1056 (44.9%)	803 (42.9%)	253 (52.7%)	< 0.001
Time to mechanical ventilation[a]				
0–6 hr	466 (44.1%)	352 (43.8%)	114 (45.1%)	0.94
6–24 hr	435 (41.2%)	332 (41.3%)	103 (40.7%)	
24+ hr	155 (14.7%)	119 (14.8%)	36 (14.2%)	
Required vasopressors, *n* (%)	1336 (56.8%)	1004 (53.7%)	332 (69.2%)	< 0.001
Time to vasopressors[a]				
0–6 hr	838 (62.7%)	619 (61.7%)	219 (66.0%)	0.23
6–24 hr	421 (31.5%)	322 (32.1%)	99 (29.8%)	
24+ hr	77 (5.8%)	63 (6.3%)	14 (4.2%)	

HF = heart failure.
[a]First uses only.
p values are for comparisons of patients with HF vs. patients without HF.

volumes, the significant margin of error suggests this finding may be attributable to chance. These insights complement studies focusing on volumes exceeding or falling short of the 30 mL/kg guideline and underscore the importance of considering nonlinear relationships between fluid volumes and outcomes.

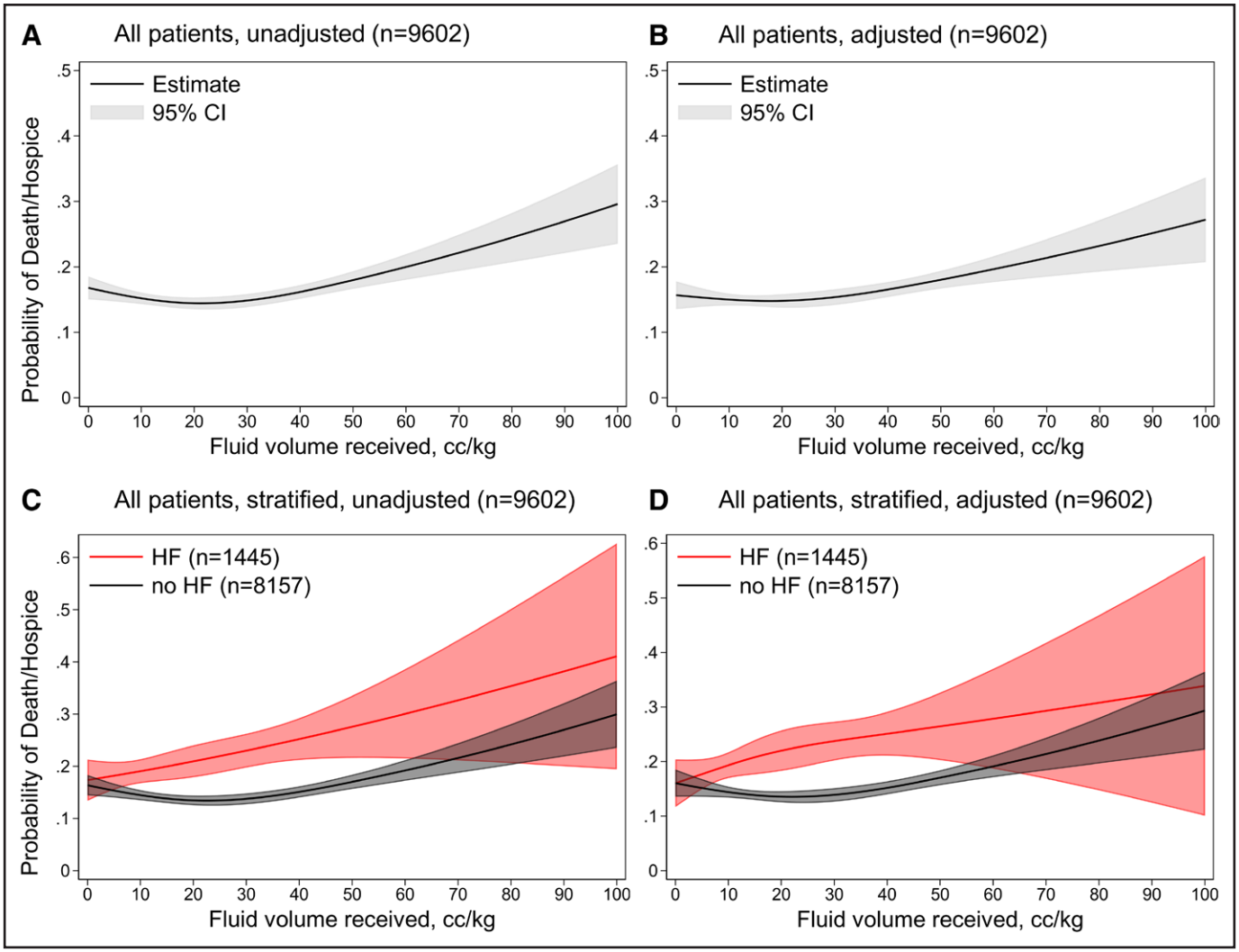

Figure 2. Death or discharge to hospice versus volume of early IV fluid in 9602 hospitalized patients with or without heart failure (HF) meeting Sepsis-3 criteria. **A**, Estimated probability of death in-hospital or hospice discharge as a function of IV fluid volume received in the first 6 hours after presenting to the emergency department. Logistic regressions included all 9602 patients who were not missing gender or limited English proficiency data for propensity score estimation. Fluid volume is the independent variable and was transformed using restricted cubic splines with three knots. The *line* represents the estimate, and the *shaded area* is the 95% CI for the estimate. **B**, Figure 2*A* adjusted for propensity to receive a given volume of fluid. **C,** Figure 2*A* stratified by HF status without adjustment. HF patients are shown in *red*, and patients without HF in *black*. **D,** Figure 2*C* adjusted for propensity to receive a given volume of IV fluid.

This study's findings echo recent literature emphasizing the need for a nuanced approach to fluid therapy in septic patients (25). This shifting perspective is reflected in the most recent Surviving Sepsis guidelines, which downgraded the strength of evidence for the 30 mL/kg recommendation and now emphasizes the importance of assessing hypoperfusion (6). Several studies have indicated that administering larger fluid volumes may not necessarily lead to improved outcomes in septic shock (26), which was also observed in our ICU subgroup analysis. Adjusting for the propensity to receive a given fluid volume reduces confounding by indication and increases the strength of this finding. Recent trials like CLASSIC and CLOVERS have helped to address the need for prospective studies of fluid therapy in patients with septic shock (7, 8). However, our study underscores the importance of including less severely ill patients to fully understand the interaction of illness severity and fluid therapy. Collectively, these trials and our findings suggest that smaller volumes may offer benefits, particularly for patients with HF, and possibly for those without HF. These benefits may be attributed to factors such as sepsis-induced cardiomyopathy or preexisting subclinical cardiomyopathy. Enhancing our understanding of the relationship between fluid volumes and outcomes

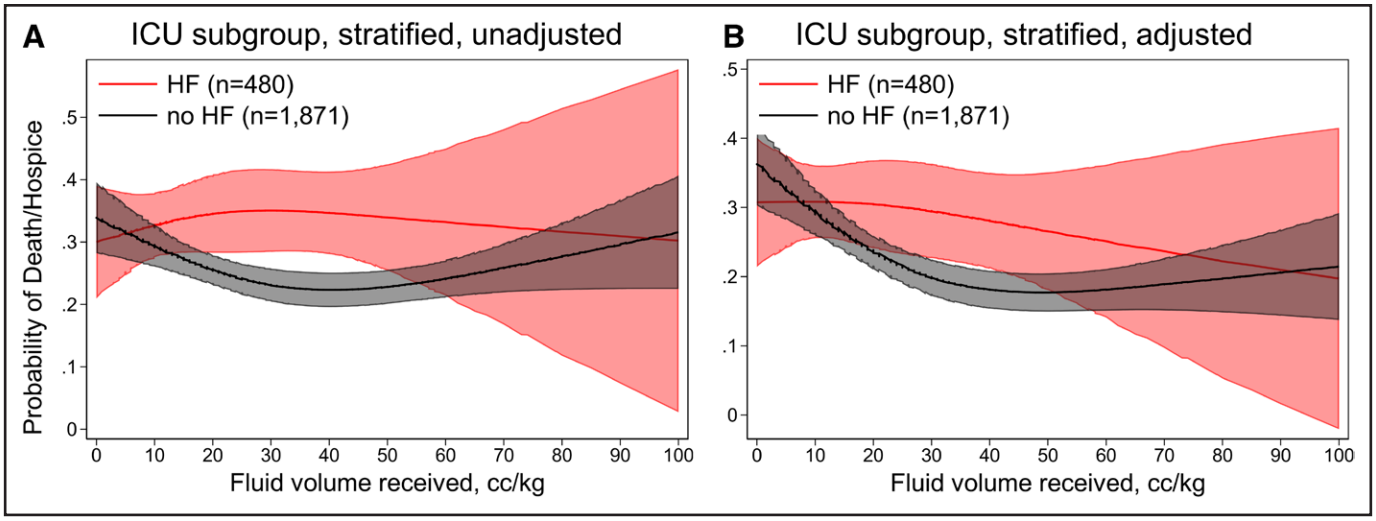

Figure 3. Death or discharge to hospice versus volume of early IV fluid in 2349 ICU patients with or without heart failure (HF) meeting Sepsis-3 criteria. **A**, Estimated probability of death in-hospital or hospice discharge as a function of IV fluid volume received in the first 6 hours after presenting to the emergency department among patients in the subgroup of patients whose first admission level of care was ICU. Logistic regression including 2349 patients who were not missing gender or limited English proficiency data for propensity score estimation. Fluid volume is the independent variable and was transformed using restricted cubic splines with three knots. The *line* represents the estimate, and the *shaded area* is the 95% CI for the estimate. **B**, Adjusted for propensity to receive a given volume of IV fluid.

TABLE 3.
Odds of Death or Discharge to Hospice by IV Fluid Volume Category Over 9602 Admissions in Patients With or Without Heart Failure Meeting Sepsis-3 Criteria

Fluids in First 6 hr (mL/kg)	*n* Died or Discharged to Hospice/Total (%)	Unadjusted			Propensity Adjusted[a]		
		OR	95% CI	*p*	OR	95% CI	*p*
HF (*n* = 1445)							
0–15	141/789 (17.9)	0.60	0.41–0.89	0.01	0.61	0.41–0.90	0.01
15–30	88/409 (21.5)	0.76	0.50–1.16	0.20	0.78	0.51–1.20	0.25
30–45	45/170 (26.5)	Reference	Reference	Reference	Reference	Reference	Reference
45+	22/77 (28.6)	1.11	0.61–2.03	0.73	1.09	0.60–2.00	0.78
No HF (*n* = 8157)							
0–15	416/2856 (14.6)	1.00	0.84–1.19	0.99	0.95	0.80–1.14	0.58
15–30	398/2778 (14.3)	0.98	0.82–1.17	0.82	1.01	0.85–1.21	0.87
30–45	228/1563 (14.6)	Reference	Reference	Reference	Reference	Reference	Reference
45+	182/960 (19.0)	1.37	1.10–1.70	0.004	1.32	1.06–1.64	0.01

HF = heart failure, OR = odds ratio.

[a]Adjusted for propensity to receive a given volume of IV fluid.

Logistic regressions were performed separately in patients with and without heart failure, using data from all 9602 admission that were not missing gender or limited English proficiency data for propensity score estimation ($n = 11$). Dependent variable is death in-hospital or discharge to hospice. Independent variable is the volume of IV fluid received in the first 6 hr from ED presentation, categorized into 15 mL/kg strata. The 30–45 mL/kg stratum was used as the reference for OR comparisons. Propensity score was the propensity to receive a given volume of fluid based on presenting patient characteristics.

in noncritically ill patients could ultimately decrease the incidence of decompensations requiring critical care.

Our study supports the notion that HF patients may respond differently to fluid resuscitation compared with patients without HF, an inadequately understood but clinically impactful topic (27, 28). Patients with HF may receive smaller fluid volumes that are administered more cautiously (27, 29, 30), even in septic shock (30), due to concerns about iatrogenic volume overload. It is plausible that HF patients have higher mortality and require interventions like mechanical ventilation more often when receiving excessive fluids. Indeed, excessive fluid administration in HF patients has been associated with an increased risk of mortality and the need for interventions like mechanical ventilation (28, 31), but studies are conflicting in their findings on the topic (32). Furthermore, fluid overload is associated with higher mortality rates in septic shock in various populations (33–35). Our study revealed a linear increase in the likelihood of death or discharge to hospice as fluid volume increased in HF patients. Propensity adjustment revealed that patients receiving minimal volumes may also have a lower probability of needing mechanical ventilation. This suggests that HF patients may benefit from individualized decisions to administer smaller fluid volumes. This interpretation aligns with the finding from Mansoori et al (13), which also reported a lack of a U-shaped association between mortality and fluid volume in patients with conditions associated with receiving less fluid, like HF.

The sensitivity analysis considering changes over time in assessments of hypoperfusion for the propensity analysis did not significantly affect the main findings, suggesting the effects of time-varying confounding may be limited in this case. This could be due to the short duration of the 6-hour early resuscitation period. Future studies could explore how patients respond to repeated fluid administrations over longer durations and in specific cases of persistent evidence of hypoperfusion. Such studies would benefit from using time-varying analytical methods to account for changes over time in the data available to clinicians administering fluids.

This study had several limitations, but efforts were made to address them and strengthen the findings. We relied on clinical coding data to identify HF patients, possibly introducing inaccuracies. However, we established that the ejection fractions in the chart-reviewed subset of HF patients were similar to estimates from hospitalized patients with HF (36). Nonetheless, further studies are needed to determine if these findings extend to all subtypes and severities of HF. This retrospective observational study aimed to estimate a treatment effect, which is best suited to a randomized trial design. Propensity adjustment was used to lessen confounding by indication, but residual confounding may exist. The EHR-based data did not allow for the extraction of bedside measures of hypoperfusion, such as capillary refill, which may introduce such residual confounding. However, lactate was included in the propensity analysis to account for hypoperfusion within these constraints. Although our study was conducted at a single center, the extensive database spanning over 10 years enabled us to link data components over time and develop novel statistical models. These models can be replicated in larger, multicenter confirmatory studies, enhancing generalizability.

CONCLUSIONS

This study identified a nonlinear relationship between a composite outcome of death or discharge to hospice and early IV fluid volume among patients without HF meeting EHR-based Sepsis-3 criteria. This finding remained after adjustment for clinician propensity to administer a given fluid volume and was present in a subgroup admitted to the ICU. Patients with HF had a near-linear increase in the primary outcome with increasing fluid volumes. The likelihood of death or discharge to hospice was lower for HF patients receiving less than 15 mL/kg in the first 6 hours compared with those receiving 30–45 mL/kg. Smaller volumes may be appropriate for early fluid resuscitation in select patients, particularly those with HF.

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