OBSERVATIONAL STUDY

OPEN

Early Albumin Infusion Is Associated With Greater Survival to Discharge Among Patients With Sepsis/Septic Shock Who Develop Severe Acute Kidney Injury Among Patients With Sepsis/Septic Shock Who Develop Severe Acute Kidney Injury

Karthik Raghunathan, MD, MPH[1]
Jordan A. Kempker, MD, MSC[2]
E. Anne Davis, PharmD, MS[3]
Navreet S. Sindhwani, MD[3]
Santosh Telang, MS[4]
Kunal Lodaya, MD[4]
Greg S. Martin, MD, MSc[2]

IMPORTANCE: Adults hospitalized with sepsis/septic shock commonly develop acute kidney injury (AKI) which imposes a significant burden on the healthcare system. The administration of early human albumin in this patient population may yield more efficient healthcare resource utilization.

OBJECTIVES: To examine the association between early use of albumin and time to discharge in adults who develop severe AKI while hospitalized with sepsis/septic shock.

DESIGN: Retrospective cohort study using de-identified electronic health records from a national database (Cerner Health Facts; Cerner Corp., Kansas City, MO).

SETTING AND PARTICIPANTS: Patients (n = 2,829) hospitalized between January 2013 and April 2018 with a diagnosis of sepsis/septic shock (identified using *International Classification of Diseases*, 9th Revision and 10th Revision codes) who developed severe AKI (stage 3 according to Kidney Disease Improving Global Outcomes criteria) during hospitalization (n = 2,845 unique encounters).

MAIN OUTCOMES AND MEASURES: Patients were grouped according to timing of albumin exposure: within less than or equal to 24 hours of admission ("early albumin") or unexposed/exposed late ("nonearly albumin"). A cause-specific hazard model, censoring for death/discharge to hospice, was used to examine the association between "early albumin" and the rate of hospital discharge with clinical stability.

RESULTS: Albumin was administered early in 8.6% of cases. Cases with early albumin administration had a median time to discharge of 13.2 days compared with 17.0 in the nonearly group (Log-rank $p < 0.0001$). An adjusted analysis showed that the rate of hospital discharge with clinical stability increased by 83% in the early albumin group compared with the nonearly group (hazard ratio, 1.832; 95% CI, 1.564–2.146; $p < 0.001$ nonearly group.

CONCLUSIONS AND RELEVANCE: The use of albumin within 24 hours of hospital admission was associated with a shorter time to discharge and a higher rate of discharge with clinical stability, suggesting an improvement in healthcare resource utilization among patients with sepsis/septic shock who developed stage 3 AKI during hospitalization.

KEY WORDS: acute kidney injury; human serum albumin; length of stay; sepsis; septic shock

Approximately 1.7 million adults in the United States are diagnosed with sepsis annually (1, 2). Sepsis contributes to an estimated 270,000 deaths every year, with one in three hospital deaths occurring in patients with sepsis (3). Sepsis can lead to acute kidney injury (AKI) (4–6) and is the most

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KEY POINTS

- **Question:** The goal of this retrospective study was to evaluate the impact of albumin administration within 24 hours of hospital admission (early albumin) among patients with sepsis/septic shock who develop stage 3 acute kidney injury.
- **Findings:** We used a cause-specific hazard model to determine the rate of hospital discharge with clinical stability and found that early albumin administration (≤ 24 hr of admission) increased the rate of hospital discharge with clinical stability by 83% with statistical significance, when censoring for death and hospice discharge.
- **Meanings:** Our findings suggest that early administration of albumin may improve healthcare resource utilization in this unique yet critically ill patient population.

common cause of AKI in critically ill patients, accounting for nearly half of all cases seen in the ICU (7, 8). Patients with sepsis/septic shock who develop severe AKI during hospitalization have longer hospital stays, fewer ventilator-free days, and increased mortality when compared with nonseptic patients with AKI (7–10).

Management of sepsis commonly includes fluid resuscitation guided by measures of volume responsiveness, vasopressor therapy, and, when indicated, renal replacement therapy (RRT), including in cases with severe AKI (2). Although crystalloids are more widely used for fluid resuscitation than colloids of all types, the proportion of resuscitation episodes specifically using human-derived colloid solutions (i.e., albumin) has increased (11). Albumin has been found to have a favorable safety profile and, when compared with crystalloids, is slightly more efficacious as a plasma volume-expander and less likely to reduce renal blood flow from hyperchloremia (which can occur with the use of chloride-liberal solutions like isotonic saline) (12, 13). However, some studies have indicated that albumin increases costs and its impact on mortality is unclear (14, 15). The timing of albumin treatment in sepsis/septic shock may be an important determinant of its utility, as early treatment with albumin has been associated with a significantly higher cardiac index than treatment with crystalloids (16).

The strategy for managing patients who present with both sepsis and AKI involves early recognition and intervention. Early antimicrobial therapy and resuscitation is the mainstay of treatment to prevent further kidney damage (17). The effect of early treatment with albumin in patients with sepsis/septic shock who develop severe AKI has not been studied, particularly in the context of healthcare resource utilization.

A recent study evaluating Medicare inpatient admissions reported that mean length of stay (LOS) increased significantly across sepsis severity, ranging from 4.5 days for sepsis to 16.5 days for septic shock (18). Furthermore, an Australian multicenter study of adult ICU admissions found that patients with sepsis complicated by AKI had increased hospital and ICU LOS compared with those with sepsis alone (19).

We sought to examine the association between timing of albumin infusion and time to hospital discharge as well as the rate of hospital discharge with clinical stability among patients who develop stage 3 AKI while hospitalized for sepsis/septic shock.

METHODS

Study Design

We used the Cerner Health Facts database (Cerner Corp., Kansas City, MO) to extract real-world data from electronic health records (EHRs) across greater than 700 participating clinical facilities and hospital systems across the United States. Western Institutional Review Board (Puyallup, WA) approved our study without the need for informed consent as the data are deidentified and HIPAA compliant (Ref. no. 1-1193960-1; approved June 17, 2019). Procedures were conducted in accordance with the ethical standards of the review board and the Helsinki Declaration of 1975.

We identified all inpatient encounters of adults (≥ 18 yr old) admitted with a diagnosis of sepsis/septic shock between January 1, 2013, and April 30, 2018, who developed severe AKI during the hospitalization. Sepsis and septic shock were identified using *International Classification of Diseases*, 9th Revision and 10th Revision codes (**eTable 1,** http://links.lww.com/CCX/B87) (20, 21). Severe AKI was defined as stage 3 AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (22). KDIGO characterizes stage 3 AKI as a greater than or equal to three-fold increase

in baseline serum creatinine (SCr) within 7 days, an increase in SCr to greater than or equal to 4 mg/dL within 48 hours, or the initiation of RRT.

We considered the SCr value closest to hospital admission using a 90-day lookback period as the baseline value; if unavailable, we used the first SCr during the visit (**eTable 2**, http://links.lww.com/CCX/B87). Urine output data for KDIGO staging were unavailable within the database. We excluded hospitalizations that met the following criteria: 1) LOS less than or equal to 48 hours and greater than 90th percentile (25.2 d); 2) the patient was transferred from another hospital; 3) no receipt of antibiotics; 4) no SCr measurements; 5) missing or incomplete demographic data; 6) nonacute hospital status; 7) admission type other than "urgent" or "emergent"; 8) patient had a history of end-stage renal disease or chronic kidney disease stage 5; and 9) no fluid resuscitation. Fluid resuscitation was defined as the receipt of albumin or noncarrier crystalloids (i.e., crystalloids in containers > 250 mL, thus excluding crystalloid solutions used as carriers for various drugs).

Exposures and Outcomes

Based on time-stamped data for albumin administration and hospital admission, we classified patients as either exposed to "early albumin" or not. Early albumin was defined as albumin infusion starting less than or equal to 24 hours of hospital admission. Patients in the nonearly group were those who received albumin greater than 24 hours after hospital admission or no albumin at all. We defined albumin administration as the use of any formulation regardless of concentration, generic or brand name. We measured the time to hospital discharge with clinical stability as time in hours between hospital admission and discharge, censoring for death and discharge to hospice.

Statistical Analyses

We compared baseline patient and hospital characteristics using descriptive statistics, counts and percentages for binary or categorical variables, and means with SDs for continuous variables. Standardized mean differences were used to assess effect size of baseline severity of chronic and acute illness indices, such as Charlson Comorbidity Index (19) and Acute Physiology Score (APS), as well as baseline SCr and albumin levels.

A Kaplan-Meier analysis was conducted to examine time to hospital discharge with clinical stability, censoring for in-hospital mortality and discharge to hospice. A Log-rank test was used to compare the rates of achieving clinical stability and hospital discharge between patients who received early albumin and those who did not (nonearly group). Descriptive statistics for time to clinical stability from the Kaplan-Meier analysis were also evaluated.

We explored the effect of several covariates on the time to hospital discharge censoring for death and discharge to hospice, by using a multivariable cause-specific hazard model with 95% CIs at a significance threshold of p value of less than 0.05. Covariates of interest included albumin administration timing (early vs nonearly), baseline SCr, volume of crystalloid resuscitation, as well as frequent comorbidities and complications of sepsis/septic shock, such as cirrhosis, the need for mechanical ventilation, vasopressor use, and RBC transfusions (to indicate severe anemia). Longer and shorter times to hospital discharge were indicated by hazard ratios (HRs) less than 1 and greater than 1, respectively. SAS Version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

We identified 2,845 unique hospitalizations for patients with sepsis/septic shock who developed stage 3 AKI and met other study selection criteria (**Fig. 1**). Hospitalizations concerning stage 1/2 AKI or no AKI were excluded from our study (n = 26,374). Baseline/clinical characteristics and outcomes for all 2,845 encounters are shown in **Table 1**. The overall mean (± SD) age was 64.3 ± 15.2 years, and 47.5% (n = 1,351) were female. The unadjusted overall median hospital LOS was 10.8 days and included cases of mortality and discharge to hospice. Among the 1,535 cases 54% of 2,845 where albumin was administered, the median dosage was 19.8 g/d.

Albumin infusion was administered within 24 hours of admission (defined as "early albumin") in 245 cases (8.6%) at a median of 23.3 g/d (compared with 19.5 g/d in the nonearly group). Lower proportions of patients who were greater than 65 years old, women, or identified as African American were administered early albumin, whereas higher proportions of patients who identified as Hispanic were in the early albumin group. The mean (± SD) APS in the early albumin group was 56.3 ± 26.9 compared with 45.4 ± 26.9 in the nonearly group with a standardized mean difference

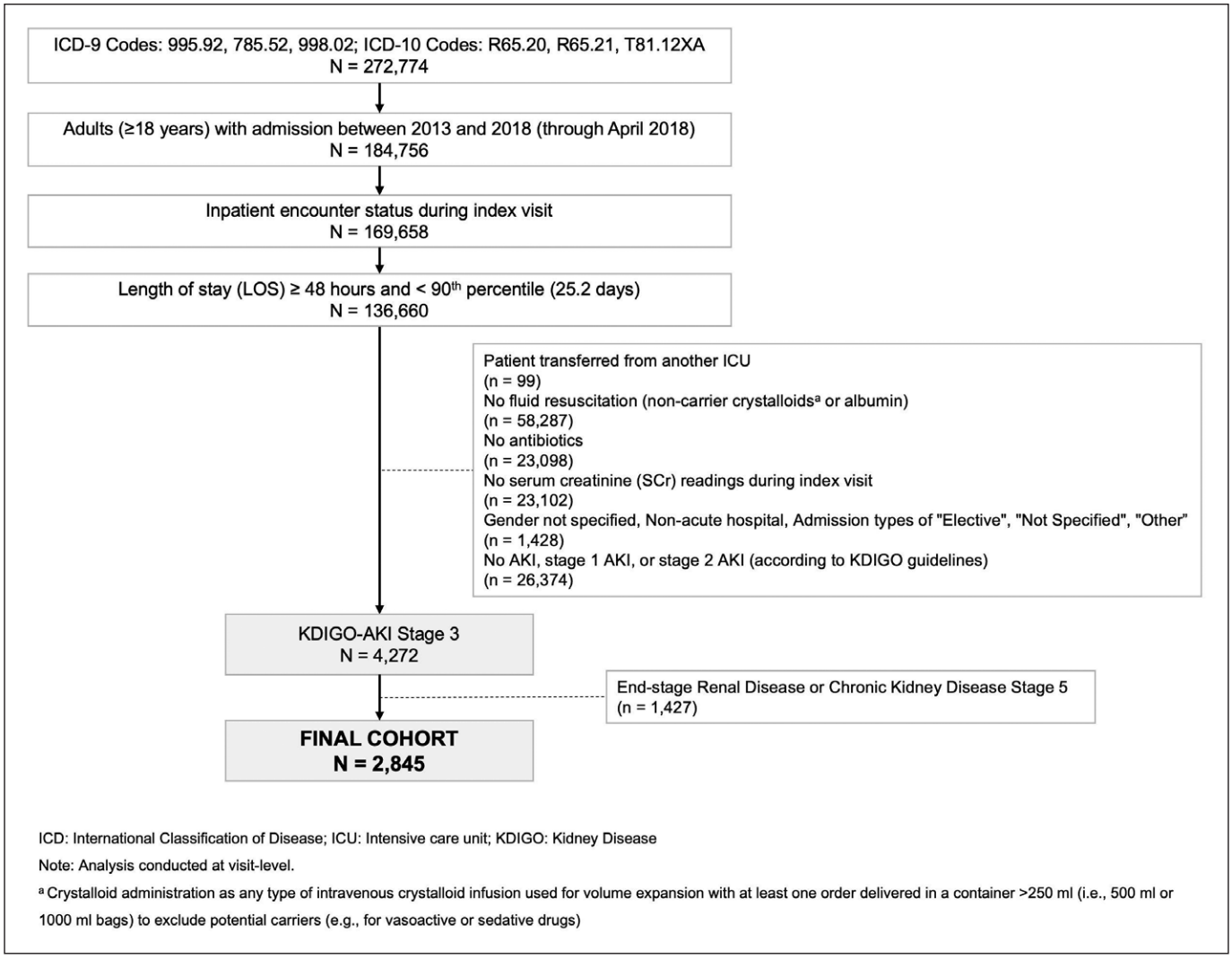

Figure 1. Flowchart of patient inclusion. AKI = acute kidney injury, KDIGO = Kidney Disease: Improving Global Outcomes, ICD-9 = *International Classification of Diseases*, 9th Revision, ICD-10 = *International Classification of Diseases*, 10th Revision, LOS = length of stay, SCr = serum creatinine.

TABLE 1.
Patient Characteristics

Characteristic	Overall (*N* = 2,845)	Early Albumin (*N* = 245)	Nonearly Albumin (*N* = 2,600)	Standardized Mean Difference
Age (yr)				−0.135
Mean ± SD	64.3 ± 15.2	62.4 ± 15.3	64.5 ± 15.2	
Median (p25–p75)	65.0 (55.0–76.0)	64.0 (54.0–72.0)	66.0 (55.0–76.0)	
18–29, *n* (%)	67 (2.4)	8 (3.3)	59 (2.3)	
30–49, *n* (%)	393 (13.8)	35 (14.3)	358 (13.8)	
50–64, *n* (%)	906 (31.9)	86 (35.1)	820 (31.5)	
65+, *n* (%)	1,479 (52.0)	116 (47.4)	1,363 (52.4)	
Female, *n* (%)	1,351 (47.5)	110 (44.9)	1,241 (47.7)	0.061

(Continued)

TABLE 1. (*Continued*).
Patient Characteristics

Characteristic	Overall (*N* = 2,845)	Early Albumin (*N* = 245)	Nonearly Albumin (*N* = 2,600)	Standardized Mean Difference
Ethnicity, *n* (%)				0.18
African American	382 (13.4)	27 (11.0)	535 (13.7)	
Asian/Pacific Islander	58 (2.0)	4 (1.6)	54 (2.1)	
Caucasian	2,157 (75.8)	186 (75.9)	1,971 (75.8)	
Hispanic	15 (0.5)	3 (1.2)	12 (0.5)	
Other[a]	204 (7.2)	22 (9.0)	182 (7.0)	
Unknown[b]	29 (1.0)	3 (1.2)	26 (1.0)	
Admission type, *n* (%)				−0.076
Emergency	2,580 (90.7)	218 (89.0)	2,362 (90.9)	
Urgent	265 (9.3)	27 (11.0)	238 (9.2)	
Baseline severity indices				
APS, mean (SD)	46.4 (27.1)	56.3 (26.9)	45.4 (26.9)	0.464
Median (p25–p75)	47.0 (24.0–67.0)	61.0 (35.0–74.0)	45.0 (24.0–66.0)	
APS quartiles, *n* (%)				
< p25	679 (23.9)	37 (15.1)	642 (24.7)	
[p25, p50]	737 (25.9)	38 (15.5)	699 (26.9)	
[p50, p75]	735 (25.8)	73 (29.8)	662 (25.5)	
> p75	694 (24.4)	97 (39.6)	597 (23.0)	
CCI, mean (SD)	7.6 (3.5)	7.5 (3.5)	7.7 (3.5)	0.075
Median (p25–p75)	8.0 (5.0–10.0)	7.0 (5.0–10.0)	8.0 (5.0–10.0)	
CCI quartiles, *n* (%)				
< p25	544 (19.1)	54 (22.0)	490 (18.9)	
[p25, p50]	856 (30.1)	72 (29.4)	784 (30.2)	
[p50, p75]	870 (30.6)	73 (29.8)	797 (30.7)	
> p75	575 (20.2)	46 (18.8)	529 (20.4)	
Baseline SCr, mg/dL, mean (SD)	1.8 (2.4)	2.9 (3.6)	1.7 (2.2)	0.35
Median	1.0 (0.7–1.8)	1.3 (0.8–3.5)	1.0 (0.7–1.7)	
SCr quartiles, *n* (%)				
< p25	696 (24.5)	46 (18.8)	650 (25.0)	
[p25, p50]	720 (25.3)	49 (20.0)	671 (25.8)	
[p50, p75]	718 (25.2)	53 (21.6)	665 (25.6)	
> p75	711 (25.0)	97 (39.6)	614 (23.6)	
Medical interventions, *n* (%)				
Crystalloid volume (L/d)				0.132
< 1.5	2,288 (80.4)	209 (85.3)	2,079 (80.0)	
1.5–3.5	439 (15.4)	29 (11.8)	410 (15.8)	
> 3.5	118 (4.2)	7 (2.9)	111 (4.3)	
Mechanical ventilation	1,568 (55.1)	114 (46.5)	1,454 (55.9)	−0.114
RBC transfusions	642 (22.6)	50 (20.4)	592 (22.8)	−0.135
Vasopressor use[c]	1,750 (61.5)	147 (60.0)	1,603 (61.7)	−0.114
Albumin, g/d, median (p25–p75)	19.8 (10.1–28.2)	23.3 (10.4–30.7)	19.5 (10.1–27.2)	

APS = Acute Physiology Score, CCI = Charlson comorbidity index, p25 = 25th percentile, p75 = 75th percentile, SCr = serum creatinine.
[a]Includes Native American, Biracial, and Mid-eastern Indian.
[b]Includes visits where race information was not specified/available.
[c]Includes dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin.

TABLE 2.
Cause-Specific Hazard Model for Time to Discharge With Clinical Stability (*n* = 2,845)

Variables	Hazard Ratio (95% CI)	*p*
Early vs nonearly albumin	1.832 (1.564–2.146)	< 0.001[a]
Cirrhosis	0.681 (0.580–0.800)	< 0.001[a]
RBC transfusions	0.718 (0.621–0.829)	< 0.001[a]
Mechanical ventilation	0.436 (0.386–0.491)	< 0.001[a]
Vasopressors	0.697 (0.620–0.783)	< 0.001[a]
Baseline serum creatinine		
< p25	Reference	NA
[p25, p50]	0.963 (0.825–1.123)	0.628
[p50, p75]	0.907 (0.771–1.068)	0.243
> p75	0.763 (0.646–0.901)	0.001[a]
Charlson Comorbidity Index		
< p25	Reference	NA
[p25, p50]	0.918 (0.778–1.084)	0.315
[p50, p75]	0.849 (0.704–1.023)	0.085
> p75	0.812 (0.654–1.010)	0.061
Acute Physiology Score		
< p25	Reference	NA
[p25, p50]	0.986 (0.839–1.158)	0.859
[p50, p75]	1.208 (1.007–1.449)	0.042[a]
>p75	1.147 (0.947–1.389)	0.16
Crystalloid resuscitation volume, L/d		
1.5–3.5	Reference	NA
< 1.5	0.492 (0.418–0.577)	< 0.001
> 3.5	1.535 (1.087–2.168)	0.015

NA = not applicable.
[a]Statistically significant at alpha level of 0.05 between early and nonearly group.
The model includes a random effect for hospitals to account for the center effects.

of 0.46, indicating a small difference between the two groups. The early albumin group had a lower proportion of cases requiring mechanical ventilation, RBC transfusions, and vasopressor use, with standardized difference scores indicating a small difference.

Of the 2,845 hospital encounters included in this analysis, 1,424 (50.1%) resulted in death or discharge to hospice, of which 33 (2.3%) involved early albumin administration. Of the remaining 1,421 encounters in which patients were discharged alive, 212 (14.9%) received early albumin. The median hospital LOS in the early albumin group was 12.0 days (range, 2.1–25.0 d) compared with 10.7 in the nonearly group (range, 2.0–25.1 d).

Figure 2 depicts the daily distribution of cases reaching hospital discharge with clinical stability, while censoring for death and discharge to hospice. A Log-rank test showed that the median time to discharge in the early albumin group was 13.2 days (95% CI, 11.9–14.0 d) compared with 17.0 days (95% CI, 16.2–17.5 d) in the nonearly group (Log-rank $p < 0.0001$).

The multivariable cause-specific proportional hazards model **(Table 2)** showed that the rate of hospital discharge with clinical stability increased by 83% in the early albumin group compared with the nonearly group (HR = 1.832; 95% CI, 1.564–2.146; $p < 0.001$). The adjusted rate of hospital discharge decreased by 31.9% for cases with comorbid cirrhosis (HR = 0.681; 95% CI, 0.580–0.800; $p <$

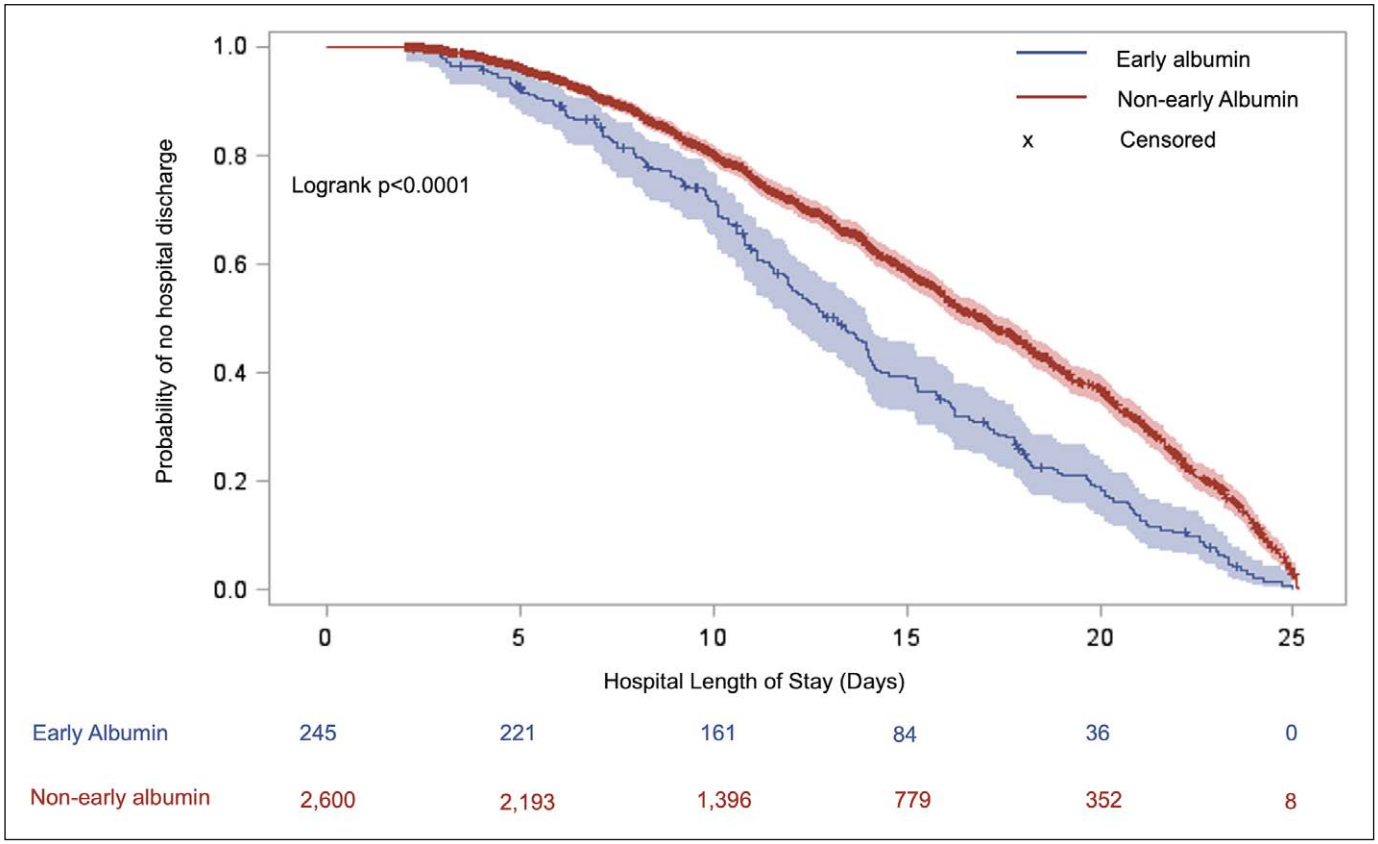

Figure 2. Kaplan-Meier plot showing time to hospital discharge with clinical stability. Daily distribution of cases reaching hospital discharge with clinical stability, while censoring death and discharge to hospice.

0.001), by 56.4% for cases where mechanical ventilation was used (HR = 0.436; 95% CI, 0.386–0.491; $p < 0.001$), by 30.3% when vasopressors were used (HR = 0.697; 95% CI, 0.620–0.783; $p < 0.001$), and by 28.2% when RBCs were transfused (HR = 0.718; 95% CI, 0.621–0.829; $p < 0.001$).

Volume of crystalloid resuscitation and baseline SCr also seemed to affect time to hospital discharge. Compared with 1.5–3.5 L/d, a crystalloid resuscitation volume of greater than 3.5 L/d increased the rate of discharge by 53.5% (HR = 1.535; 95% CI, 1.087–2.168; $p = 0.015$), whereas a volume of less than 1.5 L/d decreased the rate of discharge by 50.8% (HR = 0.492; 95% CI, 0.418–0.577; $p < 0.001$). A baseline SCr above the 75th percentile decreased the rate of discharge by 23.7% (HR = 0.763; 95% CI, 0.646–0.901; $p = 0.001$), compared with a referent SCr below the 25th percentile.

DISCUSSION

In the case of critically ill patients who require specialized care, such as those with sepsis/septic shock and AKI, the time between admission and hospital discharge is an important metric in understanding healthcare resource utilization, as it produces estimates relevant to real-world service planning. Our analysis found that patients who were hospitalized with a diagnosis of sepsis/septic shock and developed stage 3 AKI had an increased rate of hospital discharge (with clinical stability) when treated with albumin within 24 hours of hospital admission. AKI is common in patients with sepsis and septic shock (9), and sepsis is associated with higher ICU and in-hospital mortality, as well as longer LOS. Longer hospital stays lead to significant healthcare costs and avoidable nosocomial risks (23). Therefore, a reduction in time to discharge and an increase in the rate of discharge with clinical stability are meaningful clinical and patient-centered outcomes.

We assessed baseline comorbidity and the acuity of illness at presentation using detailed data from EHRs. We observed that in cases where patients received albumin early, despite having higher APS scores at baseline than those in the "nonearly" group, had shorter time to discharge when censoring death and hospice discharge and had a higher rate of discharge with clinical stability.

In our study, among the 118 cases where crystalloids were administered at a volume greater than 3.5 L/d,

the adjusted HR showed a 53% higher rate of hospital discharge with clinical stability when compared with 1.5–3.5 L/d. It is possible that: 1) the higher volume of crystalloids showed a benefit in the rate of discharge (24) or 2) these cases also received albumin at some point (after 24 hr of admission) during their hospital encounter; as Ge et al (25) recently indicated, most patients with septic shock receive mixed liquid resuscitation rather than single liquid resuscitation. It was interesting to see that crystalloid administration at a volume less than 1.5 L/d showed a 51% decrease in the rate of discharge with clinical stability. This could be explained by a failure to restore intravascular volume. The timing of crystalloid resuscitation in regard to hospital admission would give better insight to this finding, however, our analysis did not consider this factor. In general, crystalloids are effective and inexpensive (26), but the use of albumin may be better in select patient populations (25, 27–31). Our findings suggest among all the covariates analyzed in the multivariable cause-specific hazard model, the use of early albumin showed the greatest benefit in increasing the rate of hospital discharge with clinical stability.

Investigators of the Investigators of the Albumin Italian Outcome Sepsis study evaluated the effects of the administration of albumin and crystalloids, as compared with crystalloids alone, in patients with severe sepsis/septic shock, and reported that mortality rates were comparable, and hospital and ICU LOS were also similar (median of 20 and 9 d, respectively, in both groups). However, the time to suspension of vasopressors was significantly shorter in the albumin group (a median of 3 rather than 4 d, $p = 0.007$) suggesting that albumin administration may also have hemodynamic benefits (32). It is therefore plausible that early administration was associated with shorter LOS because of faster discontinuation of vasopressors.

Although our study shows that early albumin infusion is associated with only a modest reduction in time to hospital discharge (13.7 vs 17.0 d), it is possible that cost savings from albumin may accrue over time (33, 34), particularly when critically ill patients with AKI who fail to recover renal function can reach end-stage kidney disease with dialysis dependence accompanied by a 5-year cost of ~$38,000 (35).

There are several limitations associated with our study. Due to the retrospective nature of our analysis, causal inferences cannot be made as unmeasured confounders may exist. Second, we were primarily interested in reporting the effects of early albumin only, given that early management in patients with sepsis is paramount, and were not able to assess three groups of albumin infusion (early, late, and none) due to small sample sizes between groups and should be considered in future studies evaluating resuscitation strategies in septic AKI. Third, we considered sepsis/septic shock and the development of stage 3 AKI concurrently and did not fully account for bias introduced by the timing of potential confounders of the "early albumin and time to hospital discharge" relationship (including when RBC transfusions, mechanical ventilation, and vasopressors were used). Thus, it is possible that early albumin use is merely a surrogate for more aggressive care soon after presentation. Providers with a preference for early albumin use may also deliver care that is associated with improved survival independent of albumin use. Last, due to database limitations, the effects of mixed resuscitation (i.e., albumin and crystalloid), total crystalloid volume, and crystalloid infusion timing were not analyzed in this study, and we were unable to discern whether crystalloids were balanced or unbalanced.

CONCLUSIONS

In this study, approximately one of every 10 patients who were admitted with sepsis/septic shock and developed stage 3 AKI received albumin early. Despite presenting with higher disease severity at baseline, this group had a shorter time to discharge and a higher rate of discharge with clinical stability when compared with those not receiving early albumin. These observational findings may serve as the basis for a more comprehensive evaluation of the potential clinical and economic benefits of early albumin administration in this patient population, such as a prospective, randomized control trial assessing time to discharge, LOS, and additional cost-related outcomes.

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1 Department of Anesthesiology, Duke University, Durham, NC.

2 Department of Medicine, Emory University, Atlanta, GA.

3 Grifols Shared Services North America (SSNA), Research Triangle Park, Durham, NC.

4 Boston Strategic Partners, Inc, Boston, MA.

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