

## Benefit of Albumin Infusion in Hospitalized Patients With Cirrhosis and Hyponatremia: A Retrospective Cohort Study

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**Conflict-of-interest statement:** The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: July 4, 2017

Revised: October 9, 2017

Accepted: October 11, 2017

Published online: October 21, 2017

### ABSTRACT

**AIM:** To investigate the optimal intravenous fluid for resuscitation of hospitalized patients with cirrhosis and hyponatremia and analyze their outcomes.

**MATERIALS AND METHODS:** In this retrospective cohort study, consecutive patients with hyponatremia and cirrhosis, portal hypertension, ascites, or hepatic encephalopathy receiving resuscitative fluids and hospitalized between 1/2011 and 12/2014

were analyzed. Patient characteristics, quantity and type of fluid administered, change in serum sodium, and 6-month mortality were recorded.

**RESULTS:** A total of 146 eligible patients were identified, of which 62% (91/146) received primarily crystalloid and 38% (55/146) primarily albumin resuscitative fluid. Those within the albumin cohort were more likely to receive diuretics (82% vs 56%,  $p = 0.001$ ), have a history of refractory ascites (56% vs 21%,  $p < 0.001$ ), ascites on admission (96% vs 60%,  $p < 0.001$ ), higher admission body mass (81.6 kg vs 75.5 kg,  $p = 0.04$ ), higher creatinine (152.9  $\mu\text{mol/L}$  vs 130.8  $\mu\text{mol/L}$ ,  $p = 0.03$ ), and higher model for end-stage liver disease (MELD) score (23.0 vs 18.9,  $p = 0.002$ ) compared to those in the crystalloid cohort. Fluid selection did not impact sodium correction ( $p = 0.67$ ). In multivariate analysis, receiving albumin and having higher baseline serum albumin were both associated with reduced 6-month mortality, odds ratio of 0.06 ( $p = 0.013$ ) and 0.13 ( $p = 0.035$ ), respectively.

**CONCLUSIONS:** Fluid selection in patients with cirrhosis and hyponatremia insignificantly impacted sodium correction. Albumin infusion was associated with reduced 6-month mortality. Larger prospective trials are required to investigate this relationship.

**Key words:** Hyponatremia; Cirrhosis; Albumin; Crystalloid; Public Policy; Hepatorenal Syndromes

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Shen NT, Barraza LH, Anam AK, Patel P, Schneider Y, Jesudian A. Benefit of Albumin Infusion in Hospitalized Patients With Cirrhosis and Hyponatremia: A Retrospective Cohort Study. *Journal of Gastroenterology and Hepatology Research* 2017; **6(5)**: 2441-2445 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2106>

### INTRODUCTION

Abnormally low serum sodium is the most common electrolyte disturbance in cirrhosis, occurring in approximately 30% of this patient population<sup>[1]</sup>. Hyponatremia, defined as serum sodium below 130 mmol/L, usually occurs in those with advanced cirrhosis<sup>[1,2]</sup>.

The development of hyponatremia portends poor prognosis and is associated with increased mortality from liver disease, hepatic decompensation, and decreased quality of life<sup>[2-5]</sup>. Therefore, determining an effective and efficient means of correcting hyponatremia in the hospitalized patient with cirrhosis is of paramount importance.

Hyponatremia in advanced cirrhosis results from the hemodynamic complications associated with worsening portal hypertension, primarily intravascular hypovolemia and renal hypoperfusion in the setting of total body volume overload<sup>[6]</sup>. Furthermore, the hepatic synthetic dysfunction associated with cirrhosis leads to abnormally low serum levels of albumin, a negatively charged protein that helps maintain adequate plasma oncotic pressure<sup>[7]</sup>. Albumin therapy for intravascular volume expansion in cirrhosis was introduced as early as the 1950s, and has been shown in small studies to be superior to normal saline or fluid restriction for correcting serum sodium in cirrhotics<sup>[7-9]</sup>.

Nevertheless, it remains unclear whether volume resuscitation with colloid albumin infusion is more effective than crystalloid in the correction of hyponatremia in hospitalized patients with decompensated cirrhosis. To address this question, we conducted a retrospective cohort study comparing clinical outcomes in patients admitted to our center with decompensated cirrhosis and hyponatremia who were administered primarily albumin-containing fluid vs primarily crystalloid-containing fluid for volume resuscitation.

## MATERIALS AND METHODS

We conducted a single center, retrospective cohort study of adult subjects aged  $\geq 18$  years admitted to New York-Presbyterian Hospital/Weill Cornell Medical Center between January 2011 and December 2014 with serum sodium  $\leq 130$  mmol/L and concomitant ICD-9 diagnosis codes for portal hypertension (572.3), ascites (789.5x), hepatic encephalopathy (572.2), or cirrhosis (571.x). Eligible subjects were identified by utilizing AMALGA software. This study was approved by the Institutional Review Board.

For subjects with multiple hospitalizations, only the index hospitalization was analyzed. Individual charts were reviewed and subjects with clinical, radiographic, or pathologic confirmation of cirrhosis were selected for further investigation. Subjects not receiving intravenous fluids within the first 24 hours of admission or who were fluid restricted, treated with intravenous vasopressors, or diagnosed with end-stage renal disease requiring dialysis were excluded from analysis. Subjects were assigned to one of two cohorts based on the predominant type of resuscitative fluid they received. Those who were given albumin alone or primarily albumin with  $\leq 1$  liter of crystalloid were assigned to the albumin cohort. Those who received either crystalloid alone or primarily crystalloid with  $\leq 500$  cc of albumin were assigned to the crystalloid cohort.

Baseline characteristics including age, sex, body mass, serum sodium, creatinine, albumin, presence of ascites, model for end-stage liver disease (MELD) score, history of variceal hemorrhage (VH), refractory ascites (defined as ascites recurring within 48 hours of large volume paracentesis), hepatorenal syndrome (HRS), hepatocellular carcinoma (HCC), liver transplant, transjugular intrahepatic portosystemic shunt (TIPS), and daily diuretic use were recorded. The quantity and type of fluid administered, diuretics prescribed, changes in serum sodium (up to 7 values excluding the admission and discharge values), daily body mass, and MELD scores during hospitalization were collected. Complications of cirrhosis

diagnosed during the hospital stay, including spontaneous bacterial peritonitis (SBP), HRS, and VH were documented. The hospital length of stay (LOS) and 6-month mortality was recorded. The primary outcomes were change in sodium and 6-month mortality. Secondary outcomes included in-hospital complications of cirrhosis, changes in MELD, changes in body mass, and LOS.

## Statistical plan for analysis

Baseline characteristics and outcomes were analyzed and compared between the two cohorts to test for significance ( $p < 0.05$ , two-tailed). Continuous variables were analyzed with the Student *t* test or Wilcoxon rank sum test (the latter was preferred if the data was not thought to follow a normal distribution). Categorical data were analyzed by the chi-square test or Fisher's exact test. Additional sub-analyses were performed on the primary endpoint (6-month mortality) by controlling for SBP and HRS diagnosed during hospitalization. Time-to-event (mortality) and Kaplan-Meier survival curve for the adjusted mortality were created. The statistical methods were reviewed by Dr. Yechezkel Schneider of New York Presbyterian Hospital/Weill-Cornell Medical Center. Calculations and analyses were performed using the statistical software R and RStudio.

## RESULTS

Study flow is summarized in Figure 1. Initial screen yielded 785 hospitalizations, of which 639 were excluded: 455 lacked evidence of cirrhosis, 151 were readmissions, 25 were fluid restricted instead of volume resuscitated, and 8 were end stage renal disease on dialysis. A total of 146 eligible subjects were included in the study, of which 62% (91/146) received primarily crystalloid solution and 38% (55/146) received primarily albumin.

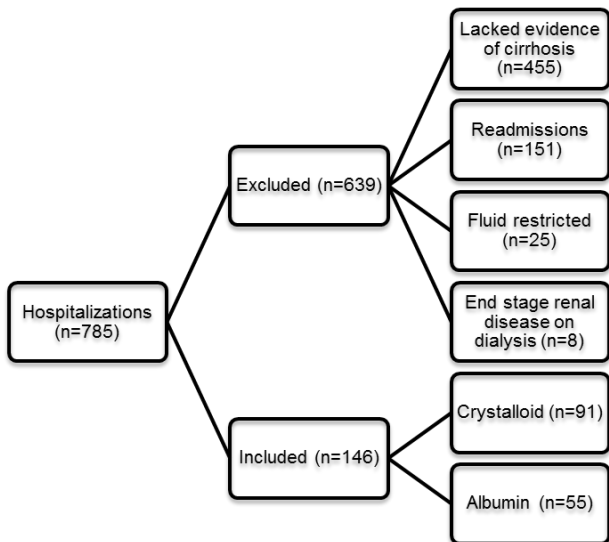
Baseline characteristics (Table 1) were notable for younger age (58 years vs 63 years,  $p = 0.01$ ) and larger proportion of male subjects (78% vs 59%,  $p = 0.02$ ) in the albumin cohort compared to the crystalloid cohort respectively. The albumin cohort had significantly more home diuretic use compared to the crystalloid cohort (82% vs 56%,  $p = 0.001$ ), history of refractory ascites (56% vs 21%,  $p < 0.001$ ), ascites present on admission (96% vs 60%,  $p < 0.001$ ), higher admission body mass (81.6 kg vs 75.5 kg,  $p = 0.04$ ), higher admission creatinine (152.9  $\mu\text{mol/L}$  vs 130.8  $\mu\text{mol/L}$ ,  $p = 0.03$ ), lower admission albumin (2.3 g/L vs 2.5 g/L,  $p = 0.03$ ), and higher admission MELD (23.0 vs 18.9,  $p = 0.002$ ). Serum sodium values at admission were similar ( $p = 0.42$ ) between the cohorts with average sodium of  $126 \pm 4$  mmol/L.

The MELD score, on average, decreased by 0.92 in the albumin cohort compared to an increase of 0.89 in the crystalloid cohort ( $p = 0.04$ ), but changes in body mass, sodium, and creatinine between admission and discharge were not significantly different between the two groups. Hospital length of stay also did not differ significantly between those receiving primarily albumin and primarily crystalloid (Table 2). Individuals were more likely to receive albumin than crystalloid if they were diagnosed with HRS (34% vs 10%,  $p < 0.001$ ) and SBP (22% vs 4%,  $p = 0.001$ ) during the hospitalization.

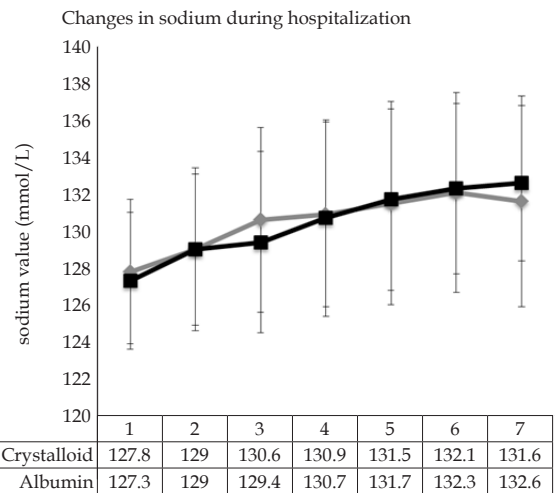
The mean serum sodium at discharge was 132.6 mmol/L and 131.6 mmol/L for the albumin and crystalloid cohorts, respectively ( $p = 0.67$ ) (Figure 2). Six-month mortality was 22% in both the albumin and crystalloid cohorts. In sensitivity analysis correcting for the mortality associated with HRS and SBP in the albumin cohort compared to the crystalloid cohort, the difference in the respective 6-month mortality, was 7% vs 19%,  $p = 0.13$ , trending toward statistical significance to favor albumin (Figure 3). A multivariate

logistic regression was performed (Table 3). All variables that were significant on univariate analysis were included in the model, and it adjusted for HRS and SBP (as these have an increased risk of mortality, and these diagnoses mandate albumin administration as standard of care). The model revealed that after controlling for age, sex, diuretic use pre-admission, history of refractory ascites, presence of ascites on admission, baseline creatinine, baseline body mass, and baseline MELD, administration of albumin fluids

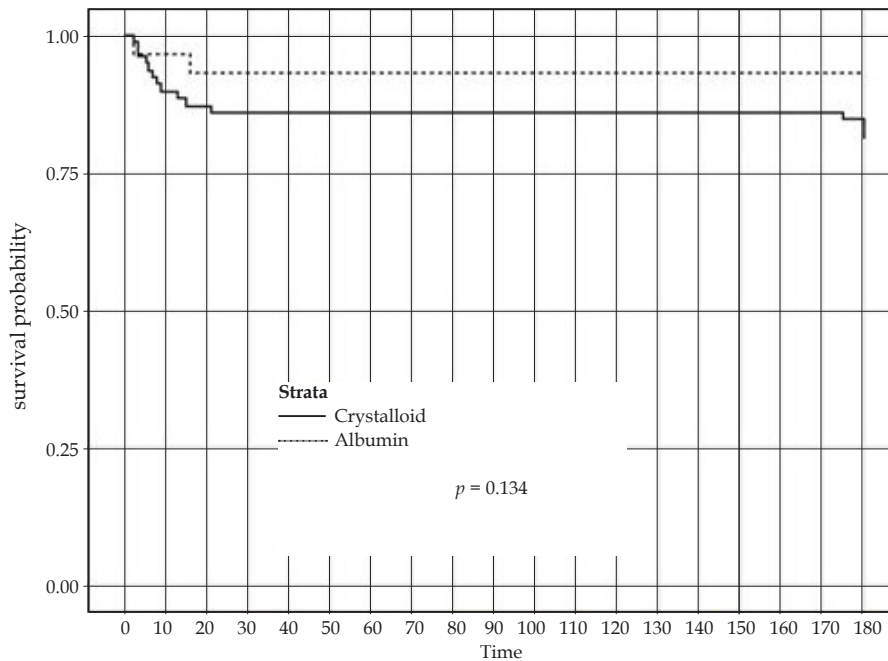
(compared to crystalloid fluids) was associated with reduced 6-month mortality with an OR of 0.06 (confidence intervals 0.005-0.4,  $p = 0.013$ ). In addition, the baseline serum albumin level on admission was also associated with reduced 6-month mortality with an OR of 0.13 (confidence intervals 0.02-0.73,  $p = 0.035$ ). A higher baseline creatinine on admission had a trend towards predicting increased 6-month mortality but did not reach significance (OR 3.6, confidence intervals 0.98-17,  $p = 0.074$ ).



**Figure 1** Flow chart depicting the screening and selection process, highlighting rationale for exclusion, and grouping subjects into either crystalloid or albumin cohorts.



**Figure 2** Line graph comparing the changes in serum sodium between the two cohorts, crystalloid and albumin, from the initial value to the seventh value.



	Number (patients) at risk											
	Day 0	Day 2	Day 3	Day 5	Day 10	Day 15	Day 20	Day 30	Day 60	Day 90	Day 180	
Crystalloid	78	78	77	75	70	69	69	67	67	67	63	
Albumin	29	29	28	28	28	28	27	27	27	27	27	

**Figure 3** Kaplan Meier curve of survival for crystalloid and albumin cohorts adjusted for hepatorenal syndrome and spontaneous bacterial peritonitis.

## DISCUSSION

The burden of decompensated cirrhosis is rising in the United States and is responsible for an increasing number of emergency department visits where the majority of patients require hospital admission<sup>[1]</sup>. Approximately 30% of these patients have hyponatremia, which is associated with increased complications and has been shown to be an independent predictor of short-term mortality<sup>[4]</sup>. Efficient correction and management of hyponatremia could significantly impact mortality and cost during and after these hospitalizations.

Volume expansion with resuscitative fluid infusion is often required for hospitalized cirrhotic patients<sup>[10]</sup>. Evidence supports human serum albumin infusion in the treatment of certain specific complications of cirrhosis including HRS and prevention of both acute kidney injury in SBP and post-paracentesis circulatory dysfunction following large volume paracentesis<sup>[11]</sup>. However, given the significantly higher cost associated with albumin compared to crystalloid, limiting administration to appropriate clinical indications is essential<sup>[12]</sup>.

Our study revealed in a multivariate model that albumin infusion compared to crystalloid fluids was associated with reduced 6-month mortality in hospitalized cirrhotic patients with hyponatremia who required volume resuscitation. There was no significant difference in degree of sodium correction, suggesting that this protective effect may be independent of sodium levels. Albumin infusion is postulated to confer many benefits to cirrhotic patients beyond volume expansion, including immunomodulation, antioxidant effects, endothelial stabilization, and hemostatic effects, any and all of which might contribute to increased survival<sup>[7]</sup>.

The study has several limitations. Given its retrospective nature, patients were not required to be administered exclusively albumin or crystalloid fluid. We designed the cohorts in order to represent primarily albumin or primarily crystalloid infusion. Also, the baseline characteristics of the albumin cohort suggested that this group of patients had more advanced cirrhosis (history of refractory ascites, higher diuretic use, more ascites on presentation) compared to the crystalloid cohort. Notably, despite this, albumin infusion was still shown to be associated with reduced 6-month mortality on multivariate regression – an odds ratio less than one indicating lower odds of mortality with the use of albumin infusion, further confirmed given that the confidence interval did not span the null value of 1. Although we attempted to control for the differences in the baseline characteristics, there may be unobservable differences between the two groups, which may have influenced patient outcomes. A larger sample size may help strengthen the association between albumin infusion and baseline serum albumin with reduced 6-month mortality, and our current sample size was appropriately powered to avoid type II error. Larger prospective randomized controlled trials are required to validate the potential mortality benefit of albumin. Finally, the indication for volume resuscitation was not always clearly documented and we relied on provider clinical decision-making in choosing to administer fluids and which type was selected. Though this reflects the realities of inpatient care of decompensated cirrhotics, it may have confounded our results.

Study strengths include the clinical and economic relevance of effective and efficient treatment of hyponatremia in hospitalized patients with decompensated cirrhosis. To date, no prior large-scale study has been conducted comparing crystalloid infusion to albumin in cirrhotic patients with hyponatremia. This study identifies a provider-dependent practice that is currently not evidence based and is costly. The cost of albumin has been shown to be as high as \$21,600,000 in a single country over a 9-month period in 2008, with

**Table 1** Baseline and admission cohort characteristics.

	Crystalloid (n = 91)	Albumin (n = 55)	P value
Age (SD)	63 (12)	58 (9)	0.01
Male (%)	54 (59)	43 (78)	0.02
Diuretic use (%)	51 (56)	45 (82)	0.001
Plasma expander (%)	2 (2)	2 (4)	0.63
Variceal bleed (%)	24 (26)	16 (29)	0.75
Refractory ascites (%) <sup>a</sup>	19 (21)	31 (56)	< 0.001
Hepatorenal syndrome (%)	2 (2)	5 (9)	0.11
Hepatocellular carcinoma (%)	20 (22)	10 (18)	0.56
Liver transplant (%)	7 (8)	3 (5)	0.74
TIPS (%)	4 (4)	6 (11)	0.18
Body Mass in kg (SD)	75.5 (22.3)	81.6 (19.1)	0.04
Sodium in mmol/L (SD)	126.5 (4)	126.1 (4)	0.42
Creatinine in $\mu$ mol/L (SD)	130.8 (97.2)	152.9 (88.4)	0.03
Albumin in g/L (SD)	25 (6)	23 (6)	0.03
Ascites (%)	55 (60)	53 (96)	< 0.001
MELD (SD)	18.9 (9)	23.0 (8)	0.002

MELD, Model for end-stage liver disease; TIPS, Transjugular intrahepatic portosystemic shunt. <sup>a</sup>Refractory ascites was defined as ascites that recurs within 48 hours of large volume paracentesis.

**Table 2** Parameter changes, complications and outcomes during hospitalization.

	Crystalloid	Albumin	P value
Change in			
Body Mass (kg) (SD)	0.195 (14.1)	-1.064 (6.4)	0.09
Sodium (mmol/L) (SD)	6.244 (5.2)	5.043 (19.0)	0.22
Creatinine ( $\mu$ mol/L) (SD)	10.4 (88.4)	-4.7 (114.9)	0.98
Albumin (g/L) (SD)	-1.33 (7)	6.87 (9)	< 0.001
MELD (SD)	0.889 (7.1)	-0.92 (7.8)	0.04
Complication of			
Spontaneous bacterial peritonitis (%)	4 (4)	12 (22)	0.001
Hepatorenal syndrome (%)	9 (10)	19 (34)	< 0.001
Variceal bleed (%)	7 (8)	7 (13)	0.33
Outcomes			
Days hospitalized (SD)	8.9 (7.8)	11.0 (9.3)	0.15
Mortality at 6 months (%)	20 (22)	12 (22)	0.96
Adjusted mortality at 6 months (%) <sup>a</sup>	15 (19)	2 (7)	0.13

MELD, Model for end-stage liver disease. <sup>a</sup>Mortality after adjusting for spontaneous bacterial peritonitis and hepatorenal syndrome.

**Table 3** Multivariate Logistic Regression Model – Predictors of 6-Month Mortality.

Variable	OR	95% CI	P value
Age	1.03	0.97 - 1.11	0.362
Sex (male)	0.57	0.09 - 3.27	0.53
Diuretic use pre-admission	3.06	0.68 - 17.99	0.17
History of refractory ascites	1.62	0.25 - 11.00	0.609
Presence of ascites on admission	1.29	0.22 - 7.81	0.775
Albumin infusion (versus crystalloid infusion)	0.06	0.005 - 0.445	0.013
Baseline Albumin	0.13	0.02 - 0.73	0.035
Baseline creatinine	3.6	0.98 - 17.08	0.074
Baseline Body Mass	1.01	0.99 - 1.06	0.275
Baseline MELD	1.03	0.90 - 1.17	0.699

MELD, Model for end-stage liver disease. <sup>a</sup>Model inputs performed excluding SBP and HRS in both groups.

evidence based albumin use occurring only a third of the time<sup>[13]</sup>. A single university hospital investigated rising albumin use costing over \$1,250,000 in 2002, and was able to decrease unnecessary use by 20% through educating providers about the evidence-based use of albumin<sup>[12]</sup>. Addressing the cost burden of albumin infusion

is especially important, as hospitalizations for liver disease have increased over the past 20 years. When compared to other diagnoses, hospitalized patients with liver disease generate higher aggregate costs despite less inpatient days<sup>[14]</sup>. Our study suggests an important area for resource allocation as the economic burden of liver disease grows – further defining the patient populations and clinical circumstances in which albumin infusion is superior to crystalloid infusion.

## ACKNOWLEDGEMENTS

This study was unfunded and the authors do not have any industrial links or affiliations to disclose. Thank you to the authors of this study for your time and dedication, and to our institution for supporting this research.

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Peer reviewer: Kuhu Roy