Association between albumin administration and survival in cardiac surgery: a retrospective cohort study

Association entre l'administration d'albumine et la survie en chirurgie cardiaque : une étude de cohorte rétrospective

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Abstract

Purpose Albumin is widely used during and after on-pump cardiac surgery, although it is unclear whether this therapy improves clinical outcomes.

Methods This observational study utilized the Cerner Health Facts® database (a large HIPAA-compliant clinical-administrative database maintained by Cerner Inc., USA) to identify a cohort of 6,188 adults that underwent on-pump cardiac surgery for valve and/or coronary artery procedures between January 2001 and March 2013. Of these, 1,095 patients who received 5% albumin with crystalloid solutions and 1,095 patients who received crystalloids alone on the day of or the day following cardiac surgery were selected by propensity-

score matching. The primary outcome was all-cause in-hospital mortality. Three secondary outcomes analyzed include acute kidney injury severity, major morbidity composite, and all-cause 30-day readmissions.

Results In the propensity-score matched cohort, receipt of perioperative 5% albumin was associated with decreased risk of in-hospital mortality (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.3 to 0.9; $P = 0.02$) and lower all-cause 30-day readmission rates (OR, 0.7; 98.3% CI, 0.5 to 0.9; $P < 0.01$). Albumin therapy was not associated with differences in overall major morbidity (OR, 0.9; 98.3% CI, 0.7 to 1.2; $P = 0.39$; composite) or acute kidney injury severity (OR, 0.9; 98.3% CI, 0.6 to 1.4; $P = 0.53$) compared with therapy with crystalloid solutions.

Conclusions In this large retrospective study, use of 5% albumin solution was associated with significantly decreased odds of in-hospital mortality and all-cause 30-day readmission rate compared with administration of crystalloids alone in adult patients undergoing on-pump cardiac surgery. These results warrant further studies to examine fluid receipt, including 5% albumin, in surgical populations via randomized-controlled trials.

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Résumé

Objectif L'albumine est largement utilisée au cours de la chirurgie cardiaque pendant et après la circulation extra-corporelle (CEC), bien qu'on ne sache pas si ce traitement améliore l'évolution clinique.

Méthodes Cette étude observationnelle a utilisé la base de données Cerner Health Facts® (une grande base de données clinico-administrative conforme à la réglementation HIPAA et tenue par Cerner Inc., aux États-Unis) pour identifier une cohorte de 6188 adultes ayant bénéficié d'une chirurgie cardiaque sous CEC pour

des procédures valvulaires et/ou coronariennes entre janvier 2001 et mars 2013. Parmi eux, 1095 patients ayant reçu de l'albumine à 5% et des solutions de cristalloïdes, d'une part, et 1095 patients ayant reçu des cristalloïdes seuls le jour même ou le jour suivant la chirurgie, d'autre part, ont été sélectionnés par appariement de score de propension. Le principal critère d'évaluation était la mortalité toutes causes confondues durant l'hospitalisation. Trois critères d'évaluation secondaires ont été analysés: la sévérité des lésions rénales aiguës, un critère composite de morbidité majeure et le nombre de réhospitalisations dans les 30 jours indépendamment de la cause.

Résultats Dans la cohorte appariée selon le score de propension, l'administration périopératoire d'albumine à 5% a été associée à une baisse du risque de mortalité à l'hôpital (rapport de cotes [OR], 0,5; intervalle de confiance [IC] à 95%: 0,3 à 0,9; $P = 0,02$) et à un plus faible taux de réhospitalisation toutes causes confondues (OR, 0,7; IC à 98,3%, 0,5 à 0,9; $P < 0,01$). Le traitement avec l'albumine n'a pas été associé à des différences de morbidité majeure globale (OR, 0,9; IC à 98,3%, 0,7 à 1,2; $P = 0,39$; composite) ou de sévérité des lésions rénales aiguës (OR, 0,9; IC à 98,3%, 0,6 à 1,4; $P = 0,53$) comparativement au traitement avec des solutions de cristalloïdes.

Conclusions Dans cette grande étude rétrospective, l'utilisation d'une solution d'albumine à 5% a significativement diminué les risques de mortalité hospitalière et de réhospitalisation dans les 30 jours comparativement aux cristalloïdes seuls chez des patients subissant une chirurgie cardiaque sous CEC. Ces résultats justifient des études supplémentaires sous forme d'essais contrôlés randomisés pour analyser l'administration des fluides, dont l'albumine à 5% dans les populations chirurgicales.

Intravenous fluid therapy employing solutions containing human-derived albumin is widely used in intensive care units (ICUs)¹ and during cardiac surgery.^{2,3} Significant debate exists as to whether colloid use provides clinical benefit compared with use of crystalloid solutions alone.^{4,5} Some studies suggest that colloids afford augmentation of circulating volume with smaller fluid volumes compared with crystalloids, which may more effectively maintain plasma oncotic pressure.⁶ In cardiac surgery specifically, colloids such as albumin may have additional benefits of decreasing inflammation and platelet activation as well as potential antioxidant effects. Albumin's antioxidant properties stem in part from its effects as a nitric oxide

scavenger,^{7,8} which may potentially decrease nitric oxide-mediated vasodilation during cardiac surgery. Moreover, albumin may mitigate adverse effects of cardiopulmonary bypass (CPB) surgery because of its effect on the endothelial glycocalyx degradation pathway.⁹⁻¹² Nevertheless, potential risks of albumin use include anaphylactic reactions,¹³⁻¹⁵ transmission of prion disease, and a possible increase in acute kidney injury (AKI) among patients with underlying kidney dysfunction.² In contrast to colloids, crystalloids are inexpensive and readily available, and randomized-controlled trials (RCTs) comparing colloids with crystalloids in acute settings suggest that the "volume potency" of colloids compared with crystalloids may be limited.¹⁶⁻¹⁸ Given the lack of consensus on fluid therapy benefits, albumin might best be restricted to specific settings and subgroups (e.g., patients considered at risk for crystalloid overdose).

Research evaluating albumin use in on-pump cardiac surgery has reported superiority over crystalloids when used as a "pump-priming" solution.¹⁹ Recent data using a 20% albumin preparation suggest a benefit in off-pump surgery,²⁰ and albumin has been shown to reduce bleeding compared with hydroxyethyl starch solutions.²¹ Among patients undergoing coronary artery bypass graft (CABG) procedures,²² albumin has been associated with AKI²; hence, the question of albumin superiority and safety vs crystalloid remains. Therefore, we sought to investigate the associations between receipt of 5% albumin solution given as part of a patient's fluid resuscitation and mortality, composite morbidity, AKI, and 30-day readmissions in cardiac surgical patients undergoing CPB. It was hypothesized that use of a 5% albumin solution is associated with improved outcomes in adult patients undergoing on-pump cardiac surgery compared with patients who received crystalloid alone. Since effects of albumin can depend on the albumin concentration utilized (e.g., 5% vs 20%) and state of inflammation,²³ we limited our investigation to the effects of 5% albumin in on-pump cardiac surgery.

Methods

Study design and data source

Following study plan development, and prior to data extraction, the study was approved (25 November 2013) by the Duke University Medical Center institutional review board. This retrospective study utilized HIPAA-compliant data extracted from the U.S. Cerner Health Facts® (Cerner Corp., Kansas City, MO, USA) electronic health records database. In addition to hospital characteristics (bed size, teaching status, location) and encounter-level patient data

(demographics, admission type, payer), comprehensive time-stamped medication orders, pharmacy records, laboratory results, vital signs, admission and discharge diagnoses (International Classification of Diseases Ninth Revision Clinical Modification, ICD-9-CM codes), and procedures were available. The Health Facts® database incorporates multiple checks for data quality before record release and shows good agreement with patient charts.^{24,25} This manuscript adheres to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

Study population

Patients ≥ 18 yr old who underwent cardiac surgery utilizing CPB between January 2001 and March 2013 from 59 U.S. institutions were included. Patients who underwent isolated valve, isolated CABG, or two or more procedures utilizing CPB and who survived for at least 24 hr were eligible (except when CABG was performed emergently following a percutaneous coronary intervention). Procedures were identified using ICD-9-CM codes (39.61 = extracorporeal circulation auxiliary to open heart surgery) or current procedural terminology (CPT) codes indicating “on-pump” surgery (Electronic Supplementary Material [ESM] Table 1). Patients with missing or incomplete information about the admission, procedure, and/or discharge dates, gender, and age were excluded. Discrete encounters less than four hours apart within the same hospital system were considered contiguous. Patients undergoing heart transplantation or with any of the following Elixhauser comorbidities were excluded: acquired immunodeficiency syndrome, lymphoma, metastatic cancer, or solid tumours without metastases.²⁶ The first of multiple qualifying visits in the database for each patient was considered the index visit. No single institution contributed $> 13\%$ of patients (the largest contributing hospital had > 500 beds).

Exposure

The study cohort consisted of patients that had either received at least 500 mL of crystalloid solution (0.9% saline, buffered salt solutions such as Plasma-LyteTM or NormosolTM, or lactated Ringers), the “crystalloid” cohort, or any volume of 5% albumin with crystalloid solutions, the “albumin” cohort. All intravenous fluids documented on the day of or the day following surgery were considered to determine eligibility for inclusion, and fluid volumes from the day of surgery through two days following surgery were monitored. Crystalloids with volumes ≤ 250 mL were excluded as these were most likely utilized for medication admixture rather than resuscitation in this adult

population. Volume thresholds were not imposed for colloids in the albumin cohort. Patients were excluded if they received hypertonic saline or a colloid other than 5% albumin or plasma protein fraction (PPF).

Outcomes

The primary outcome was designated a priori as all-cause in-hospital mortality during the index admission in which cardiac surgery was performed. Secondary outcomes comprised acute kidney injury severity (Acute Kidney Injury Network [AKIN] classification; AKI/AKIN severity), major morbidity (composite), and all-cause 30-day readmissions. The major morbidity composite included complications for all major organ systems defined via medical codes (ESM Table 2) and/or via laboratory/microbiology results and medications (ESM Table 3). The AKIN classification was utilized to score AKI severity (staged as 1, 2, or 3) during the postoperative period (through day 10) based upon serum creatinine (SCr) readings. AKI was evaluated only for patients who had both preoperative baseline as well as postoperative SCr readings (limited to matched pairs). Acute kidney injury stage was calculated based on a combination of absolute SCr levels and relative SCr increases compared with baseline.²⁷ Baseline SCr was set as the most recent reading within a 30-day period prior to surgery. Acute Kidney Injury Network scores are presented without respect to administration/non-administration of preoperative diuretics. Thirty-day hospital readmissions include hospital admissions within 30 days of index visit discharge (similar for 60 and 90 days examined within exploratory outcomes). Additional exploratory outcomes examined were length of stay (procedure to discharge); 30-, 60-, and 90-day hospital mortality (mortality during hospital stays within the specified time frame from index visit discharge); 60- and 90-day all-cause readmissions; abnormal SOFA (sequential organ failure assessment) scores (cardiovascular, pulmonary, liver); and electrolyte imbalances (calcium, potassium, magnesium, and sodium) (ESM Tables 2, 3). Volumes of total intravenous and resuscitation fluids (volumes received only of 5% albumin, PPF, dextran, 0.9% saline, lactated Ringer’s, calcium-free balanced solutions [without dextrose] and Ringer’s solution [no 0.45% saline]) were analyzed from the day of through two days following cardiac surgery (ESM Table 4).

Statistical analysis

We controlled for potential confounders using 1:1 propensity score matching. Propensity scores were calculated using logistic regression with all patient and hospital variables described in Table 1 (results of the

Table 1 Patient demographics and Elixhauser comorbidities

Demographic	Group Statistics				Standardized Differences	
	Unmatched		Matched		Unmatched	Matched
	Crystalloid% (n)	Albumin % (n)	Crystalloid % (n)	Albumin % (n)		
Age, mean (SD)	63.8 (12.5)	64.9 (12.6)	63.7 (12.5)	63.8 (12.7)	0.09	0.01
Gender						
Female	31.5 (377)	34.4 (1,716)	31.3 (343)	35.4 (388)	− 0.13	0.03
Male	68.5 (820)	65.6 (3,275)	68.7 (752)	64.6 (707)		
Race						
Black	15.0 (179)	10.6 (529)	14.9 (163)	15.8 (173)	0.27	0.08
Other	12.4 (148)	6.3 (312)	9.3 (102)	11.6 (127)		
White	72.7 (870)	83.2 (4,150)	75.8 (830)	72.6 (795)		
Year of admission						
2001	7.4 (88)	0.9 (47)	7.3 (80)	3.3 (36)	0.77	0.31
2002	7.1 (85)	1.8 (90)	7.3 (80)	4.4 (48)		
2003	9.6 (115)	2.4 (120)	8.1 (89)	2.9 (32)		
2004	6.4 (77)	1.7 (85)	5.4 (59)	2.4 (26)		
2005	4.7 (56)	1.2 (60)	4.8 (53)	0.8 (9)		
2006	2.8 (33)	5.2 (261)	2.7 (29)	5.3 (58)		
2007	7.4 (89)	13.1 (654)	7.7 (84)	11.3 (124)		
2008	9.9 (118)	17.0 (847)	10.0 (109)	15.0 (164)		
2009	7.4 (89)	13.6 (680)	7.1 (78)	14.5 (159)		
2010	9.8 (117)	11.7 (585)	9.7 (106)	10.1 (110)		
2011	17.0 (204)	15.1 (751)	18.5 (202)	11.8 (129)		
2012	10.0 (120)	13.3 (662)	11.0 (120)	14.6 (160)		
2013	0.5 (6)	3.0 (149)	0.6 (6)	3.7 (40)		
Procedure group (surgical type)						
CABG	62.2 (745)	50.3 (2,509)	59.1 (647)	55.3 (606)	0.25	0.08
Valve	28.9 (364)	36.1 (1,803)	31.4 (344)	33.9 (371)		
Multi-procedure	8.9 (106)	13.6 (679)	9.5 (104)	10.8 (118)		
Admission type						
Elective	55.6 (666)	58.6 (2,926)	57.4 (629)	54.3 (595)	0.08	0.11
Emergency	11.1 (133)	11.9 (594)	12.0 (131)	10.1 (111)		
Unknown/ other	33.3 (398)	29.5 (1,471)	30.6 (335)	35.5 (389)		
Urban/rural hospital						
Urban	100.0 (1,197)	100.0 (4,990)	100.0 (1,095)	99.9 (1,094)	− 0.02	− 0.04
Rural	0.0 (0)	0.02 (1)	0.0 (0)	0.1 (1)		
Acute/non-acute hospital						
Acute	99.9 (1,196)	100.0 (4,990)	99.9 (1,094)	100.0 (1,095)	0.03	0.04
Non-acute	0.1 (1)	0.02 (1)	0.1 (1)	0.0 (0)		
Hospital teaching status						
Teaching	76.9 (921)	83.1 (4,145)	79.0 (865)	78.5 (860)	0.15	− 0.01
Non-teaching	23.1 (276)	17.0 (846)	21.0 (230)	21.5 (235)		
Hospital bed-size range						
< 199	4.1 (49)	14.7 (734)	4.5 (49)	3.7 (40)	0.41	0.05
200-499	62.3 (746)	47.6 (2,373)	59.0 (646)	58.3 (638)		
500+	33.6 (402)	37.8 (1,884)	36.5 (400)	38.1 (417)		

Table 1 continued

Demographic	Group Statistics				Standardized Differences	
	Unmatched		Matched		Unmatched	Matched
	Crystalloid % (n)	Albumin % (n)	Crystalloid % (n)	Albumin % (n)		
Census region						
West	10.3 (123)	10.7 (535)	11.2 (123)	14.3 (156)	0.86	0.10
Midwest	42.4 (508)	19.5 (972)	37.2 (407)	36.4 (399)		
Northeast	6.9 (82)	38.3 (1,909)	7.5 (82)	8.0 (87)		
South	40.4 (484)	31.6 (1,575)	44.1 (483)	41.4 (453)		
Payer						
Commercial	19.8 (237)	14.8 (739)	19.4 (212)	22.4 (245)	0.15	0.08
Government	27.7 (332)	32.8 (1,638)	29.9 (327)	29.9 (327)		
Other	52.5 (628)	52.4 (2,614)	50.8 (556)	47.8 (523)		
Congestive heart failure	1.6 (19)	1.2 (60)	1.7 (19)	0.9 (10)	− 0.03	− 0.07
Valvular disease*	6.9 (83)	8.4 (417)	7.5 (82)	8.9 (97)		
Pulmonary circulation disease	2.5 (30)	1.8 (91)	2.3 (25)	2.9 (32)	− 0.05	0.04
Peripheral vascular disease	9.3 (111)	11.5 (572)	10.0 (109)	9.7 (106)	0.07	− 0.01
Paralysis	1.2 (14)	1.5 (76)	1.2 (13)	1.6 (18)	0.03	0.04
Other neurologic disorders	2.3 (27)	2.9 (146)	2.2 (24)	3.1 (34)	0.04	0.06
Chronic pulmonary disease (COPD)	20.6 (246)	18.6 (926)	20.8 (228)	20.0 (219)	− 0.05	− 0.02
Renal failure (CKD III, IV, V, ESRD, dialysis) [†]	9.8 (117)	8.9 (442)	10.3 (113)	8.7 (95)	− 0.03	− 0.06
Diabetes without chronic complications	27.2 (326)	27.3 (1,362)	27.7 (303)	27.1 (297)	0.00	− 0.01
Diabetes with chronic complications	4.3 (52)	4.0 (197)	4.4 (48)	3.7 (41)	− 0.02	− 0.03
Hypothyroidism	6.7 (80)	7.2 (359)	6.8 (74)	6.2 (68)	0.02	− 0.02
Liver disease	1.2 (14)	0.9 (43)	1.3 (14)	1.2 (13)	− 0.03	− 0.01
Peptic ulcer disease excluding bleeding	0.08 (1)	0.04 (2)	0.09 (1)	0.09 (1)	− 0.02	0.00
Rheumatoid arthritis/collagen vascular disease	1.3 (16)	2.3 (114)	1.5 (16)	2.4 (26)	0.07	0.07
Coagulopathy	10.9 (131)	13.7 (682)	11.2 (123)	13.9 (152)	0.08	0.08
Obesity	12.8 (153)	12.3 (613)	13.4 (147)	11.3 (124)	− 0.02	− 0.06
Weight loss	2.8 (34)	2.8 (140)	3.0 (33)	3.5 (38)	0.00	0.03
Chronic blood loss anemia	1.5 (18)	1.4 (71)	1.6 (17)	0.8 (9)	− 0.01	− 0.07
Deficiency anemias	15.5 (186)	12.3 (612)	16.0 (175)	14.4 (158)	− 0.09	− 0.04
Alcohol abuse	2.8 (34)	1.7 (83)	2.7 (30)	2.8 (31)	− 0.08	0.01
Drug abuse	1.8 (22)	1.4 (72)	1.8 (20)	2.6 (28)	− 0.03	0.05
Psychoses	1.3 (16)	1.5 (75)	1.3 (14)	2.0 (22)	0.01	0.06
Depression	3.9 (47)	4.9 (244)	4.1 (45)	3.7 (41)	0.05	− 0.02
Hypertension	57.6 (690)	61.8 (3,082)	58.6 (642)	58.6 (642)	0.08	0.00

Elixhauser comorbidities excluded the following ICD-9 codes from comorbidity definitions: 557.9 (peripheral vascular disease), 586 (unspecified renal failure), and all codes for valvular heart diseases and electrolyte abnormalities, as these were used to define postoperative complications.^{26,28}

Unmatched cohort: $n = 1,197$ crystalloid; $n = 4,991$ albumin; matched cohort: $n = 1,095$ per arm

*Comorbidity of valvular disease was not used as an outcome

[†] Excludes ICD-9-CM code “586” (used in outcomes); CABG = coronary artery bypass graft; CKD = chronic kidney disease; ESRD = end-stage renal disease; SD = standard deviation

propensity score logistic regression model are found in ESM Table 5). Matching on propensity score was performed using the Greedy 8- to 1-digit matching algorithm²⁸ to establish two treatment groups (not pairs). The Greedy algorithm attempts to match each albumin

patient to a crystalloid patient first with the highest propensity score precision (eight digits) and, if unsuccessful, sequentially decreases precision by one decimal, ending at the lowest precision of one digit. We assessed match quality by comparing standardized

differences of the variables between the cohorts before and after matching, with a difference > 0.1 considered to be unbalanced (Table 1).²⁹ Admission year was identified as a confounder for albumin use in our preliminary analysis by the Cochran-Mantel-Haenszel test, which revealed a linear trend of increasing albumin use over time ($P < 0.0001$), suggesting a potential linear relationship. We therefore included year in the propensity score model as a numeric variable. Nevertheless, as outlined below, admission year was not treated as a numeric variable in the multiple logistic regression analysis.

Outcomes were modelled via multiple logistic regression (or ordinal logistic regression for AKI/AKIN severity analysis of a nested matched cohort defined by the availability of baseline and postoperative SCr readings). We included covariates that were unbalanced after matching (census region, admission type, and admission year, as determined by standardized difference ≥ 0.1) in addition to the acute physiology score (APS) from the Acute Physiology and Chronic Health Evaluation II (APACHE II) to account for surgical case severity.³⁰ Admission year was included as one of a three-year group (2001–2007, 2008–2010, 2011–2013) to allow for a nonlinear relationship between the admission year and various outcomes (standardized difference for matched cohort by year group = 0.31). The APS score³⁰ was calculated using parameters from the day of to the day following surgery. APS scores were compared between matched treatment groups using the Wilcoxon rank-sum test.

For the secondary outcome of AKI/AKIN severity, we additionally adjusted for pre-existing renal impairment by assessing the estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, 2009) method in the 30-day preoperative time period.³¹ The CKD-EPI requires an SCr laboratory value, gender, age, and race. eGFR values were subsequently mapped to GFR categories per the National Kidney Foundation Kidney Disease: Improving Global Outcomes (2012) numeric ranges (all $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) and placed into two groups: G1–G2 ≥ 60 and G3A–5 < 60 .³²

Robust sandwich variance was used to account for potential hospital effects for all outcomes.³³ Adjusted odds ratios (ORs) and confidence intervals (CIs) were calculated. For the primary outcome of mortality, $P < 0.05$ was considered significant. Bonferroni correction was applied to correct the CIs for multiple testing ($= 0.0167$) for each of three secondary outcomes ($P < 0.0167$ is considered significant). For the exploratory outcomes, we used $\alpha = 0.01$ to adjust the CIs for multi-testing ($P < 0.01$ is considered significant). Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the patient population

Prior to matching, 6,188 patients met the study criteria: $n = 1,197$ for the crystalloid cohort and 4,991 for the albumin cohort. Propensity score calculation and performance of a 1:1 match yielded a study population of 2,190 patients, with 1,095 patients per arm who either received or did not receive 5% albumin solution with crystalloid therapy (Fig. 1). Standardized differences calculated before and after the match for all baseline variables are shown in Table 1 (See ESM Table 6 for Elixhauser comorbidity frequencies). Patients were well matched for all patient and hospital variables except census region (standardized difference, 0.10), admission type (standardized difference, 0.11), and admission year (standardized difference, 0.31). Patients were well matched for surgical type (standardized difference, 0.08), which is the main determinant of surgical duration, cross clamp time, and bypass time. In addition to the covariates that were unbalanced after matching (standardized difference, ≥ 0.1), APS (not used to match patients) was used to adjust for surgical case severity when assessing the association between albumin administration and study outcomes. The mean (standard deviation) APS scores for the matched population were 9.6 (7.7) in the albumin cohort and 8.1 (6.1) in the crystalloid cohort ($P < 0.01$ by Wilcoxon rank-sum test). Intravenous fluid volumes for the cohort arms are shown in ESM Table 4.

Outcomes

On-pump cardiac surgical patients who received perioperative 5% albumin with crystalloids were found to have a significant survival benefit over patients who received only crystalloid solutions (OR, 0.5; 95% CI, 0.3 to 0.9; $P = 0.02$; Table 2; Fig. 2). Observed all-cause mortality rates were 2.3% for the albumin cohort ($n = 25$) and 3.3% ($n = 36$) for patients who received solely crystalloid solutions. There was no association between fluid types with respect to AKI/AKIN severity (OR, 0.9; 98.3% CI, 0.6 to 1.4; $P = 0.53$) or composite major morbidity (OR, 0.9; 98.3% CI, 0.7 to 1.2; $P = 0.39$; Fig. 2). All-cause 30-day readmission rates were in favour of the albumin cohort (OR, 0.7; 98.3% CI, 0.5 to 0.9; $P < 0.01$), with rates of 10.0% for the albumin group vs 14.0% for the crystalloid group (Fig. 2). Results of the primary and secondary outcomes logistic regression models are in ESM Table 7.

The major morbidity composite comprised the exploratory outcomes shown in ESM Fig. 1. Exploratory outcomes are shown in ESM Figs. 1 and 2; ESM Tables 4 and 8 include patient mortality and hospital readmission rates through 90 days, among others listed in the Methods.

Fig. 1 Patient selection and flow diagram

Table 2 Statistics for primary and secondary outcomes in the matched cohort ($n = 1,095$ per arm)

Primary outcome	Frequencies		Unadjusted Odds Ratios		Adjusted Odds Ratios	
	Crystalloid % (n)	Albumin% (n)	OR (CI)	P value	OR (CI)	P value
In-hospital mortality	3.3 (36)	2.3 (25)	0.7 (0.4-1.2)	0.21	0.5 (0.3 to 0.9)	0.02
Secondary outcomes	Crystalloid% (n)	Albumin% (n)	OR (Bonferroni Corrected CI)	P value	OR (Bonferroni Corrected CI)	P value
AKI / AKIN severity (stage 1,2,3) *	44.7 (231)	51.8 (268)	1.2 (0.7-2.2)	0.27	0.9 (0.6 to 1.4)	0.53
Major morbidity composite	57.4 (628)	56.1 (614)	0.9 (0.7-1.3)	0.59	0.9 (0.7 to 1.2)	0.39
All-cause 30-day readmission	14.0 (153)	10.1 (110)	0.7 (0.5-1.0)	< 0.01	0.7 (0.5 to 0.9)	< 0.001

Unadjusted odds ratios were only corrected by the Bonferroni correction; the adjusted odds ratios were adjusted for both covariates and the Bonferroni correction. For secondary outcomes, $P < 0.0167$ is considered significant

Refer to ESM Table 7 for effects of all covariates

AKIN = Acute Kidney Injury (AKI) Network Classification; CI = confidence interval; OR = odds ratio

*AKI/AKIN severity has 517 evaluable subjects in each group

Discussion

In this retrospective study, we report an association between 5% albumin therapy and improved in-hospital mortality (primary outcome) and all-cause 30-day

readmissions in adult patients undergoing on-pump cardiac surgery and no differences between 5% albumin with crystalloid vs. crystalloid alone with respect to AKI/severity or overall major morbidity. The mechanism behind the favourable effects of 5% albumin on in-hospital

Fig. 2 Primary and secondary outcomes associated with 5% albumin use. In-hospital mortality (primary outcome), severity of acute kidney injury (AKI), major morbidity composite, and all-cause 30-day

readmission rates (secondary outcomes) in adult subjects undergoing cardiac surgery administered either 5% albumin solution or crystalloids alone. AKIN = Acute Kidney Injury Network

mortality and all-cause 30-day readmissions within patients undergoing on-pump cardiac surgery are unclear, but a possibility includes favourable SOFA (sequential organ failure assessment) pulmonary scores (albumin 44.9%; crystalloid 67.0%; $P < 0.01$; ESM Table 6; ESM Fig. 2). Patients exposed to 5% albumin had significantly reduced rates of large hemoglobin drops (maximum drop in hemoglobin >2 g·dL⁻¹; ESM Fig. 1) than those administered crystalloids alone. Nevertheless, there were no differences between the groups in transfusion rates. Since the outcome of hemoglobin drop was based on laboratory data (and not ICD-9 codes), it is likely less subject to measurement errors.³⁴ The observed reduced odds of pulmonary dysfunction with 5% albumin are consistent with previous reports of decreased extravascular lung water with albumin utilization.³⁵ In general, the mechanistic pathways underlying the favourable effect associated with 5% albumin on mortality and all-cause 30-day readmission warrants further investigation.

This study, which analyzed AKI severity (via AKIN scores) limited to matched pairs from each treatment arm possessing both recorded baseline and postoperative SCr readings and outcomes adjusted on preoperative CKD, revealed no significant association between fluid utilization and AKI. The extent of the lack of baseline and postoperative SCr values (approximately half of the study population) underscores the need to consistently evaluate SCr levels in cardiac surgery. The results of this study are different from those of a recent observational study within a cardiac surgical population in which a greater risk of postoperative dialysis was associated with albumin compared with crystalloid utilization.²³ Nevertheless, the albumin group included patients who received volumes of 20% and/or 5% albumin, and the type received by each patient was not known with certainty, while the current study restricted analysis to patients who received solely 5%

albumin. While Ryhammer *et al.*²³ found that patients administered 20% albumin had nearly a three-fold increased risk of postoperative dialysis compared with those thought to receive 5% albumin, there was no propensity-matched analysis of patients who received crystalloids vs 5% albumin performed, making it difficult to draw conclusions.²³

Procedure-to-discharge length of stay and all-cause 30-day readmission rate post cardiac surgery represent surrogates of cost. No difference between lengths of stay (ESM Table 6) suggests possible comparable treatment costs between patients treated with albumin and crystalloid and those treated with crystalloid alone. This finding is consequential to hospitals because of the inception of Centers of Medicare and Medicaid Services' hospital readmissions reduction program to provide financial incentives to hospitals to reduce readmissions, particularly within 30 days post-cardiac surgery. Thus, although analysis included all-cause readmissions, the significant observed reduction in all-cause 30-day readmissions may suggest decreased hospital payment penalties with albumin utilization.

Our observations are consistent with the significant body of literature showing relatively limited "volume-sparing"¹⁷ advantages with colloid compared with crystalloid fluids. The total intravenous fluid volume received in the albumin cohort probably was slightly less (11.6% relative decrease in total intravenous fluids administered; albumin: 3.8 ± 3.2 L; crystalloid: 4.3 ± 3.9 L; $P < 0.01$; ESM Table 4) than the volume received in the crystalloid only cohort. Nevertheless, the volume-sparing effect of albumin by itself may be insufficient to explain the possible benefit. Other possible mechanistic explanations include mitigation of CPB-induced inflammation^{21,36-38} with decreased loss of fluid into the interstitium.

This study has several limitations. The observational study included 2,190 matched patients admitted over a 12-year period for common cardiac surgical procedures across a large number of geographically dispersed U.S. institutions. There were no significant differences in fluid choice (albumin versus not) by region and bed size; however, patients were less likely to receive albumin in a teaching institution. Potentially important unmeasured confounding may include differences in the duration of CPB, type of CPB pump priming solution, the choices of cardiac surgeons, cardiac anesthesiologists, and earlier use of vasopressors at sites using albumin versus those using crystalloids.^{39,40} The above concerns cannot be sufficiently resolved from this historic cohort, and the potential for residual confounding remains. Nevertheless, while some unobserved confounding may bias the outcomes, no single hospital contributed more than 13% of patients to the cohort and we used robust variance to account for the clustering of patients at the hospital level. Precise timing of albumin utilization with respect to cardiac procedure is unknown on the day of the procedure as the procedure time is not recorded in the database. The fact that not all subjects had complete (baseline and postoperative) SCr values may represent an important source of bias. To assess whether SCr values were missing at random, mortality was assessed in subjects with and without baseline SCr readings via a Chi-square test for overall association, and the result was not significant ($P = 0.11$). To reduce the chance of bias, only those matched pairs with baseline and postoperative SCr readings were analyzed. In the absence of RCT-derived evidence to guide current clinical decision-making, our data—while not adequate in isolation—add to other observational evidence supporting the use of albumin in cardiac surgery when colloid use is indicated in the clinician's judgement. We do not infer a causal link between administration of 5% albumin and improved survival in patients undergoing on-pump cardiac surgery. These findings should be seen as hypothesis-generating, and an RCT trial is necessary to establish a causal link.

In conclusion, we report an association between 5% albumin administration and decreased odds of in-hospital mortality in adult patients undergoing on-pump cardiac surgery and reduced all-cause 30-day readmissions. Future RCT designs should incorporate sample size estimates based on expected differences for pulmonary dysfunction and rates of large hemoglobin drop, as lower rates were seen with 5% albumin.

Conflicts of interest Martin Bunke is an employee of Grifols, Inc. Sibyl Munson, David Hayashida, Xuan Zhang, and Sloka Iyengar are consultants of Boston Strategic Partners, Inc., which has received research funding from Grifols for the conduct of this study and assistance with manuscript preparation. Andrew Shaw has previously

been a consultant to Grifols, but is not currently. The other authors have no conflicts of interest to declare.

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Author contributions Adam J. Kingeter helped design the study and prepare the manuscript. Karthik Raghunathan and Sibyl H. Munson helped analyze the data and prepare the manuscript. David K. Hayashida and Xuan Zhang helped analyze the data. Sloka Iyengar helped prepare the manuscript. Martin Bunke helped design the study. Andrew D. Shaw helped design the study, analyze data, and prepare the manuscript.

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