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Albumin Use After Cardiac Surgery

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Objectives: To investigate the effect of albumin exposure in ICU after cardiac surgery on hospital mortality, complications, and costs.

Design: A retrospective, single-center cohort study with economic evaluation.

Setting: Cardiothoracic ICU in Australia.

Patients: Adult patients admitted to the ICU after cardiac surgery.

Interventions: None.

Measurements and Main Results: Comparison of outcomes and costs in ICU after cardiac surgery based on 4% human albumin exposure. During the study period, 3,656 patients underwent cardiac surgery. After exclusions, 2,594 patients were suitable for analysis. One-thousand two-hundred sixty-four (48.7%) were exposed to albumin and 19 (1.4%) of those died. The adjusted hospital mortality of albumin exposure compared with no albumin was not significant (odds ratio, 1.24; 95% CI, 0.56–2.79; $p = 0.6$). More patients exposed to albumin returned to the operating theater for bleeding and/or tamponade (6.1% vs 2.1%; odds ratio, 2.84; 95% CI, 1.81–4.45; $p < 0.01$) and received packed red cell transfusions ($p < 0.001$). ICU and hospital lengths of stay were prolonged in those exposed to albumin (mean difference, 18 hr; 95% CI, 10.3–25.6; $p < 0.001$ and 87.5 hr; 95% CI, 40.5–134.6; $p < 0.001$). Costs (U.S. dollar) were higher in patients exposed to albumin, compared with those with no albumin exposure (mean difference in ICU costs, $2,728; 95% CI, $1,566–3,890 and mean difference in hospital costs, $5,427; 95% CI, $3,294–7,560).

Conclusions: There is no increased mortality in patients who are exposed to albumin after cardiac surgery. The patients exposed to albumin had higher illness severity, suffered more complications, and incurred higher healthcare costs. A randomized controlled trial is required to determine whether albumin use is effective and safe in this setting.

Key Words: albumin; cardiac surgery; crystalloids; economic evaluation; fluid resuscitation; intensive care

Hypotension following cardiac surgery is common and often multifactorial in etiology (1). It is often treated with an IV fluid bolus, although the rationale, type, and amount of resuscitation fluid to be administered in post cardiac surgical patients remain controversial with wide practice variations (2–8). Hillman et al (9) reported that "much of our current post-operative fluid practice remains overenthusiastic and based on inflexible recipes, rather than on clinical assessment and need." A prospective multicenter observational study of IV fluid use post-operatively after cardiac surgery in Australia and New Zealand showed that fluid boluses are responsible for a large proportion of the positive fluid balance seen in these patients (10).

In trials involving the general ICU patient population, administration of albumin has not been shown to offer any significant clinical benefit when compared with administration of crystalloids (11, 12) with the notable exception of the subpopulation of ICU patients suffering from a traumatic brain injury in whom albumin was independently shown to increase mortality (13). Colloids have been favored by some due to the theoretical advantage that they will persist longer in the intravascular space and provide a higher increment in cardiac output with less volume administered (14–16).

When compared with general ICU patients, elective cardiac surgical patients have a much lower postoperative mortality (17–20); however, there is a paucity of data to guide fluid resuscitation practices for these patients after cardiac surgery.

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Crit Care Expl 2020; 2:e0164

DOI: 10.1097/CCE.0000000000000164

A large pragmatic survey across many countries showed that colloids were more frequently administered to resuscitate critically ill patients than crystalloids (21). Multiple studies and systematic reviews have shown that hydroxyethyl starches are associated with increased mortality, bleeding and acute renal injury in the critically ill with sepsis (22–26). Another recent study has shown that albumin restriction in the cardiac intensive care was feasible and safe without changes in morbidity and mortality (27).

Given that fluid boluses are commonly used after cardiac surgery and that a positive fluid balance has been associated with increased mortality, the use of albumin solutions might result in lesser volumes of fluid being used, and lower all-cause hospital mortality compared with no albumin exposure. The aim of this study was to compare the effect of 4% albumin exposure in cardiac surgical patients on hospital mortality, morbidity, and healthcare costs.

MATERIALS AND METHODS

A retrospective single-center cohort study was performed. Ethical approval was obtained from The Prince Charles Hospital Human Research Ethics Committee (LNR/2018/QPCH/48174). Patient data were obtained from Computer Information Systems (CIS) and linked to the ICU and cardiothoracic surgery reporting databases. The three sources of data were linked deterministically using the patient's unique hospital medical record number, which was then deleted after linkage to ensure patient privacy.

Patients were included if they were older than 16 years old and had undergone cardiac surgery with cardiopulmonary bypass (CPB) between January 2016 and December 2018. Patients were excluded if they had undergone transplantation surgery or thoracic surgery, or if they required mechanical cardiac support devices (**Fig. 1**). The study cohort was divided into two groups based on exposure to 4% albumin. Patients who received any amount of 4% albumin were assigned to the albumin exposure group. All other patients, who were exposed only to crystalloids (0.9% saline, Plasma-Lyte 148 [Baxter Healthcare Corporation, Deerfield, IL] Hartmann's solution, or dextrose containing solutions), were assigned to the no albumin exposure group. The study center does not use hydroxyethyl starches. Exposure was ascertained by interrogation of the CIS. Four percent albumin is always administered as a bolus in the study institution and nursing staff are strictly discouraged from administering any medications, including fluids without specific written medical orders on the CIS. Hence for study purposes, it was assumed that the absence of a prescription on CIS for albumin amounted to lack of exposure. The priming solution for cardiopulmonary circuits at the study institution is universally Plasma-Lyte 148; hence, both cohorts had intraoperative crystalloid exposure.

Outcomes

The primary outcome was hospital mortality. The secondary outcomes were return to operating theater for bleeding or tamponade, requirement for packed red cell transfusion, total fluid volume administered, ICU and hospital length of stay (LOS), and costs of ICU and hospital stay.

Statistical Methods

Continuous variables were summarized as mean and SD or median and interquartile range as appropriate. Categorical variables were summarized as proportions. The cohort was divided into two groups based on albumin exposure in the ICU. Between group comparisons of baseline characteristics were performed using the Mann-Whitney *U* test and chi-square test for continuous and categorical variables, respectively.

The primary outcome, hospital mortality, was compared between the two groups using an odds ratio (OR) with 95% CI. Multivariate logistic regression was conducted using the following variables known to be strongly predictive of mortality in this patient population—Australia and New Zealand Risk of Death (ANZROD) score (28), European System for Cardiac Operative Risk Evaluation-1 (EuroSCORE-1) (29), and CPB time (30). The same variables were used for covariate adjustment for the secondary outcomes. For return to operating theater and red cell transfusion, body mass index was also included in the multivariate model as it has been shown to be associated with bleeding after cardiac surgery (31).

Costs of ICU were calculated using costings from the Australian Institute of Health and Welfare (AIHW). All costs are reported in U.S. dollars with Australian $1.00 equivalent to U.S. $0.76 on June 30, 2017 (the midpoint of the inclusion period). ICU costs were calculated on an hourly basis using the AIHW reported ICU hourly cost equivalent to $154.00 per hour. Generalized linear regression was used to adjust costs in accordance with previous adjustments made. Costs are presented as adjusted means with comparisons made using *t* tests reported as mean difference with 95% CIs.

All analyses were carried out in Stata 13.0 (StataCorp, College Station, TX).

RESULTS

Within the study period (January 2016 to December 2018), 3,656 patients underwent cardiac surgery with CPB. After exclusion of duplicate records (849 patients) and missing data (213 patients), a total of 2,594 patients were included in the final study analysis (**Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A230; legend: flow chart of patient included in the study who had cardiac surgery with CPB). Of the 2,594 patients included in the study, 1,264 (48.7%) were exposed to albumin, whereas 1,330 (51.3%) were not exposed. The two groups were similar in some baseline characteristics (**Table 1**), but the albumin group were older, had higher illness severity scores (ANZROD, EuroSCORE-1, more patients with history of congestive cardiac failure, left ventricular ejection fraction less than 50%, and less patients with body mass index greater than or equal to 30).

Out of the 30 patients who died, 19 (1.4%) were exposed to albumin and 11 (0.8%) patients had no albumin exposure. The unadjusted in-hospital mortality in those exposed to albumin was not statistically significant (OR, 2.01; 95% CI, 0.93–4.35; $p < 0.07$). The OR for readmission to ICU was not statistically significant (OR, 1.51; 95% CI, 0.92–2.50; $p = 0.11$). The median total volume of albumin administered during the ICU stay was 500 mL

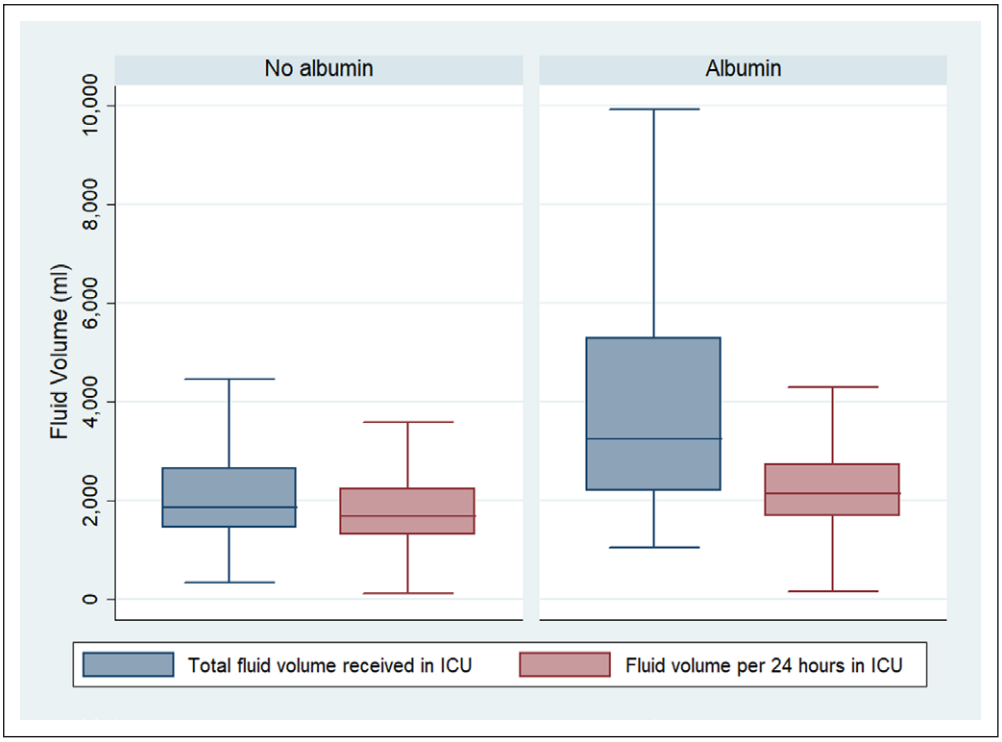

Figure 1. *Box plot* comparing the total fluids received by patients who received albumin compared with those who did not receive albumin during the first 24 hr of ICU and also during the total ICU stay. The volumes are shown as median with interquartile ranges.

(interquartile range [IQR], 500–1,020 mL). The median total fluid volume administered to those exposed to albumin during the ICU stay was 3,245 mL (IQR, 2,194–5,288 mL) compared with 1,852 mL (IQR, 1,438–2,649 mL) in those who did not receive albumin (Fig. 1).

After covariate adjustments in multivariate logistic regression models for ANZROD, EuroSCORE-1, and CPB time, there was no statistically significant association between albumin exposure and hospital mortality (OR, 1.24; 95% CI, 0.56–2.79; $p = 0.6$) (**Table 2**; and **Supplementary Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCX/A231). Albumin exposure was independently associated with a statistically significant increase in return to operating theater (OR, 2.84; 95% CI, 1.81–4.45; $p < 0.001$). There was a significant interaction between ANZROD and EuroSCORE-1 in the red cell transfusion model; hence, the OR's for albumin exposure are presented in EuroSCORE-1 strata in Table 2. In all EuroSCORE-1 strata, albumin exposure resulted in significantly higher risk of red cell transfusion. The interaction between ANZROD and EuroSCORE-1 was not significant in the other multivariate models.

The adjusted increase in ICU LOS was 18 hours (95% CI, 10.3–25.6; $p < 0.001$) and hospital LOS was 87.5 hours (95% CI, 40.7–134.6; $p < 0.001$). The increased length of time (both in ICU and in hospital) in the albumin group can visualized from the Kaplan-Meier curves of time (**Figs. 2** and **3**).

After adjusting for the prespecified covariates, ICU and hospital costs were higher for patients exposed to albumin, compared with those who did not receive albumin (ICU: $9,266 ± $827 vs $6,538 ± $806; mean difference, $2,728; 95% CI, $1,566–3,890) (hospital: $21,437 ± $1,518 vs $16,010 ± $1,479; mean difference, $5,427; 95% CI, $3,294–7,560).

DISCUSSION

The key findings of our study are that 4% albumin exposure after cardiac surgery was not significantly associated with hospital mortality but was associated with significant morbidity (bleeding, tamponade, return to theater, and increased ICU and hospital LOS) and higher adjusted ICU and hospital costs. The patients who received albumin had greater illness severity (as measures by ANZROD and EuroSCORE-1) which was accounted for in the multivariate modeling.

The use of albumin, blood products, reoperations, and consequent longer ICU and hospital stay translated to significantly higher hospital costs. Previous studies that compared healthcare costs pre and post restriction of albumin use have shown a significant reduction in overall costs by more than U.S. 45,000/mo (32). In this setting, the preferential albumin use in the sicker cohort is intriguing, especially given that there is currently no evidence to suggest that albumin is superior to crystalloids in this patient population. This may be simply put down to human behavior where a relatively expensive fluid with unproven plasma expansion benefit is chosen over another based on clinical held beliefs. Well-designed, placebo-controlled, blinded randomized trials will be required to confirm whether albumin use after cardiac surgery is safe and effective. Large, multicenter randomized trials that failed to establish any mortality benefit from albumin use in general critical care populations, specifically excluded cardiac surgical patients (11).

The results from previous studies on cardiac surgical patients regarding mortality associated with type of fluid used are inconclusive. A retrospective study of 2,190 propensity matched cohort of cardiothoracic surgical patients demonstrated a lower in-hospital mortality and all-cause 30-day readmission with albumin use when compared with crystalloids (33). Another retrospective study that utilized a large database of 19,578 patients who underwent coronary artery bypass grafting surgery indicated lower all-cause mortality with albumin use (OR, 0.80; 95% CI, 0.67–0.96) (34). These findings contrast with ours. It is possible that the lack of survival benefit with albumin in our study may be due to the rigorous risk adjustment, we performed through the use of the ANZROD score, which is known to have high discriminative capacity and calibration in the Australia and New Zealand ICU population, and through adjustment for other variables known to be associated with mortality such as the EuroSCORE-1 and CPB time. It is also possible that the study populations between these studies and ours

TABLE 1. Baseline Characteristics of Patients in Albumin and No Albumin Groups

Patient Characteristics	Albumin Group, *n* = 1,264	No Albumin Group, *n* = 1,330	*p*
Died, *n* (%)	19 (1.4)	11 (0.8)	0.1
Survived, *n* (%)	1,245 (98.6)	1,319 (99.2)	
Sex, male, *n* (%)	943 (75)	951 (72)	0.08
Age, yr, median (IQR)	68 (60–75)	65.9 (55.8–72.8)	< 0.001
Valve surgery only, *n* (%)	330 (26)	431 (32)	< 0.001
Valve and CABG surgery, *n* (%)	215 (17)	103 (8)	
CABG surgery only, *n* (%)	626 (50)	680 (51)	
Aortic surgery, *n* (%)	33 (3)	25 (2)	
Other surgeries, *n* (%)	60 (5)	91 (7)	
BMI ≤ 20, *n* (%)	10 (0.8)	10 (0.8)	0.007
BMI 20–24.9, *n* (%)	322 (26)	265 (20)	
BMI 25–29.9, *n* (%)	476 (38)	495 (37)	
BMI 30–34.5, *n* (%)	290 (23)	340 (26)	
BMI 35–39.9, *n* (%)	105 (8)	141 (11)	
BMI > 40, *n* (%)	59 (5)	77 (6)	
Smoking, *n* (%)	802 (63)	838 (63)	0.8
Chronic kidney disease, *n* (%)	11 (1)	14 (1)	0.6
Chronic cardiovascular disease, *n* (%)	69 (5)	56 (4)	0.1
Congestive cardiac failure, *n* (%)	185 (15)	124 (9)	< 0.001
Chronic respiratory disease, *n* (%)	34 (3)	30 (2)	0.5
Diabetes, *n* (%)	343 (27)	379 (28)	0.4
Hypertension, *n* (%)	882 (70)	905 (68)	0.3
Cirrhosis, *n* (%)	5 (0.4)	4 (0.3)	0.7
Elective surgery, *n* (%)	706 (56)	864 (65)	< 0.001
Nonelective surgery, *n* (%)	558 (44)	466 (35)	
Acute Physiology and Chronic Health Evaluation III, median (IQR)	52 (43–62)	47 (39–56)	< 0.001
Australia and New Zealand Risk of Death, median (IQR)	0.8 (0.2–1.7)	0.5 (0.2–1)	< 0.001
European System for Cardiac Operative Risk Evaluation-1, median (IQR)	4.3 (2.4–8.0)	3.5 (2.1–6.2)	< 0.001
Left ventricular function > 50%, *n* (%)	933 (74)	1,044 (78)	0.001
Left ventricular function 30–49%, *n* (%)	258 (20)	236 (18)	
Left ventricular function < 30%, *n* (%)	60 (5)	32 (2)	

BMI = body mass index, CABG = coronary artery bypass graft, IQR = interquartile range.

may be systematically different—our center is a quaternary cardiorespiratory referral center with a special interest in high-risk cardiac surgery. Missing data may explain some of the differences. In the study by Sedrakyan et al (34), although the authors were aware that the nonprotein colloid group included starches or dextran, they could not separate these categories. Hydroxyethyl starches are associated with increased mortality and complications and are currently not in use in our institution. Also, given the same limitation, unmeasured clinical characteristics (New York Heart Association class, CPB time, systolic ejection fraction, etc.) by the study by Sedrakyan et al (34) may still confound their results. One of the previous studies also excluded patients with missing data (33) but do not report this proportion of patients, and the other (34) does not mention missing data at all. Further, the

TABLE 2. Adjusted Outcomes in Albumin and No Albumin Groups

Adjusted Outcomes	Albumin, *n* = 1,264	No Albumin, *n* = 1,330	Adjusted OR (95% CI)	*p*
Hospital mortality, *n* (%)	**19 (1.5)**	**11 (0.8)**	**1.24 (0.56–2.79)**	**0.6**
Return to operating theater (bleeding/tamponade), *n* (%)	77 (6)	28 (2)	2.84 (1.81–4.45)	< 0.001
Red cell transfusion, *n* (%)	471 (37)	240 (18)		
EuroSCORE-1 mortality risk < 4.99%	190 (15)	103 (8)	2.5 (1.9–3.22)	< 0.001
EuroSCORE-1 mortality risk 5–9.99%	146 (12)	78 (6)	2.17 (1.54–3.07)	< 0.001
EuroSCORE-1 mortality risk 10–24.99%	103 (8)	49 (4)	1.67 (1.02–2.74)	0.04
EuroSCORE-1 mortality risk ≥ 25%	32 (3)	10 (1)	6.92 (1.8–26.62)	0.01
			Adjusted Coefficient (95% CI)	p
ICU LOS, hr, median (IQR)	27 (23–69)	24 (21–39)	17.95 (10.31–25.58)	< 0.001
Hospital LOS, hr, median (IQR)	267 (193–407)	217 (168–314)	87.53 (40.47–134.59)	< 0.001

EuroSCORE-1 = European System for Cardiac Operative Risk Evaluation-1, IQR = interquartile range, LOS = length of stay, OR = odds ratio.

The models for hospital mortality, ICU LOS, and hospital LOS were adjusted for Australia and New Zealand Risk of Death (ANZROD), EuroSCORE-1, and cardiopulmonary bypass time.

The model for return to operating theater was adjusted for ANZROD, EuroSCORE-1, cardiopulmonary bypass time, and body mass index.

The model for red cell transfusion was adjusted for ANZROD, cardiopulmonary bypass time, and body mass index. The ORs are presented in EuroSCORE-1 strata as there was significant interaction between ANZROD and EuroSCORE-1 for this outcome.

Boldface values indicate primary outcome.

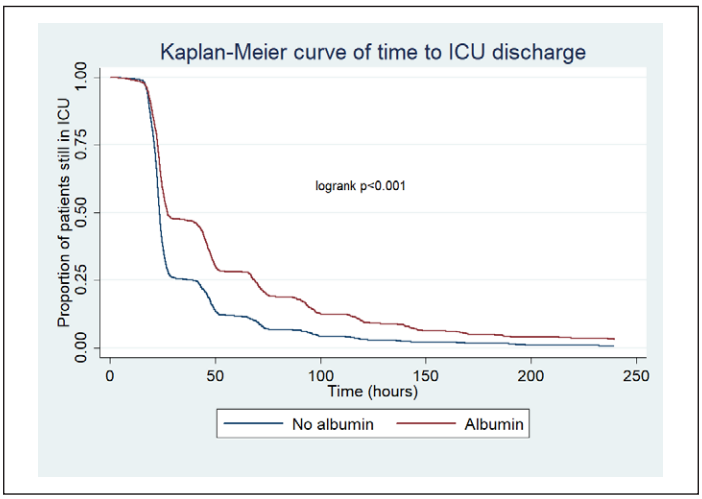

Figure 2. Kaplan-Meier curve of ICU length of stay.

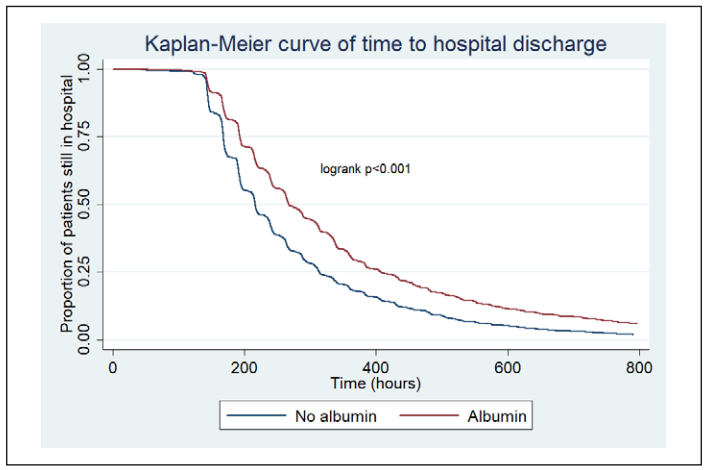

Figure 3. Kaplan- Meier curve of hospital length of stay.

exact indications (e.g., hypotension, low urine output, low central venous pressure, and high lactate) for albumin use could not be determined due to the retrospective nature of our study. It is possible that for some indications, albumin may be associated with benefit, and harm when used for other indications.

More postoperative complications were observed in the patients exposed to albumin. Bleeding is a common complication following cardiac surgery with multiple known contributory factors (patient factors, extracorporeal circuit, anesthetic related, operative, and drug factors). Studies on whether albumin has coagulation effects are contradictory. One study from 1979 suggested that albumin can be an anticoagulant due to its ability to bind antithrombin III and through neutralization effects on factor Xa (35). An experimental study on dogs showed that albumin did not have an effect on coagulation profile except for activated partial thromboplastin time (36). Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9% saline on whole blood coagulation showed that albumin had a tendency to produce early hypocoagulable effects on thromboelastography (37). A retrospective study on abdominal surgery patients comparing normal saline to balanced solutions showed an increased transfusion in the saline group (38). A small randomized trial of patients undergoing major general surgery reported that the use of albumin infusions compared with Ringers lactate infusions was not associated with an increased bleeding or transfusion requirement (39). On the other hand, the higher rates of bleeding may be explained by the higher volume of fluid administered in the albumin exposure group that subsequently led to hemodilution. Hemodilution resulting in low hematocrit levels during CPB is

known to be responsible for impaired hemostasis. Retrograde autologous priming (RAP) is a technique that may reduce hemodilution and subsequently reduce transfusion requirement and possibly bleeding (40). RAP is not used at our institution and, therefore, we cannot comment on the effect of RAP on the decision to use albumin postoperatively.

Patients who were exposed to albumin had greater overall positive fluid balance during both ICU and hospital stay. The question that arises is whether the patients received more fluid due to the increased LOS or whether the LOS resulted in more fluid given. Previous studies have demonstrated that a positive fluid balance in cardiac surgical patients may result in an increased LOS (41). A recent study showed a correlation between acute degradation of the endothelial glycocalyx and microcirculatory dysfunction during CPB (42), and this may explain why the use of large volumes of colloids may result in increased third spacing much more than crystalloids (43, 44). Studies in noncardiac patients have shown increased mortality and morbidity in patients with a positive fluid balance (45–48).

This study has several strengths. It is one of the largest studies of fluid use in cardiac surgical patients. The only larger study, a retrospective study (34) of 19,578 patients who underwent coronary artery surgery, did not use robust and validated risk adjustment techniques like we did using ANZROD and EuroSCORE-1. Linking multiple databases, including the ICU and cardiac surgical reporting databases, and the CIS, gave us access to a wide range of clinical endpoints and risk adjustment variables which are often lacking from retrospective studies.

There are however several limitations. First, it is a single-center retrospective study, and therefore the results should be viewed as exploratory and hypothesis-generating. The timing of the albumin exposure during the ICU stay could not be precisely delineated. It was assumed that all 4% albumin was given as a bolus for resuscitation purposes. While it was expected that most fluid blouses would be given early in the ICU stay, or shortly after the index operation, this could not be confirmed from the data set. Furthermore, not all administered albumin may have been documented in the CIS, leading to exposure ascertainment bias. Intraoperative exposure to albumin is also possible and was not accounted for in the analysis. The substantial amount of missing data and assumptions may introduce reporting bias in our study. The confounding from preferential use of 4% albumin in the sicker patients who are then likely to have more complications and the retrospective nature of the study may not be overcome by adjustments for severity of illness at admission and perioperative risks. This is an inherent limitation of a retrospective study. This can only be corrected and answered by a well-conducted randomized controlled trial with stratification.

CONCLUSIONS

In this single-center study, 4% albumin use was not associated with increased mortality after appropriate covariate adjustment. The patients who received albumin were sicker, suffered greater postoperative complications, had increased LOS, and higher healthcare expenditure. There are conflicting results from retrospective studies regarding the safety and efficacy of albumin use after cardiac surgery. Combining this with the higher healthcare costs for patients treated with albumin, a high-quality randomized controlled trial that evaluates albumin versus crystalloid in cardiac surgical patients is indicated.

ACKNOWLEDGMENTS

We thank Dr. Denzil Gill and Dr. Elliott Worku for assistance with proofreading and revisions.

Supplemental digital content is available for this article. Direct URL citations appear in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Matebele received funding from The Prince Charles Hospital Foundations New Researchers Grant (NI2019-42). Dr. Shekar has a Clinical Research Fellowship with the Metro North Area Health Service, QLD, Australia. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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