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Intraoperative Use of Albumin in Major Noncardiac Surgery: Incidence, Variability, and Association With Outcomes

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Background: The impact of albumin use during major surgery is unknown, and a dearth of evidence governing its use in major noncardiac surgery has long precluded its standardization in clinical guidelines.

Objective: In this study, we investigate institutional variation in albumin use among medical centers in the United States during major noncardiac surgery and explore the association of intraoperative albumin administration with important postoperative outcomes.

Methods: The study is an observational retrospective cohort analysis performed among 54 U.S. hospitals in the Multicenter Perioperative Outcomes Group and includes adult patients who underwent major noncardiac surgery under general anesthesia between January 2014 and June 2020. The primary endpoint was the incidence of albumin administration. Secondary endpoints are acute kidney injury (AKI), net-positive fluid balance, pulmonary complications, and 30-day mortality. Albumin-exposed and albumin-unexposed cases were compared within a propensity score-matched cohort to evaluate associations of albumin use with outcomes.

Results: Among 614,215 major surgeries, predominantly iso-oncotic albumin was administered in 15.3% of cases and featured significant inter-institutional variability in use patterns. Cases receiving intraoperative albumin involved patients of higher American Society of Anesthesiologists physical status and featured larger infused crystalloid volumes, greater blood loss, and vasopressor use. Overall, albumin was most often administered at high-volume surgery centers with academic affiliation, and within a propensity score-matched cohort (n = 153,218), the use of albumin was associated with AKI (aOR 1.24, 95% CI 1.20–1.28, $P < 0.001$), severe AKI (aOR 1.45, 95% CI 1.34–1.56, $P < 0.001$), net-positive fluid balance (aOR 1.18, 95% CI 1.16–1.20, $P < 0.001$), pulmonary complications (aOR 1.56, 95% CI 1.30–1.86, $P < 0.001$), and 30-day all-cause mortality (aOR 1.37, 95% CI 1.26–1.49, $P < 0.001$).

Conclusions: Intravenous albumin is commonly administered among noncardiac surgeries with significant inter-institutional variability in use in the United States. Albumin administration was associated with an increased risk of postoperative complications.

Key Words: acute kidney injury, intravenous fluids, surgery, mortality, centers, practice

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The choice of intravenous fluid during major surgery has long been a subject of debate. Previous studies have investigated the use of electrolyte-balanced crystalloids versus normal saline as well as isotonic crystalloids compared with starch-based artificial colloid solutions.[1–10] A recent multicenter randomized controlled trial failed to demonstrate the benefit of artificial

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colloid use in preventing postoperative events and suggested potential harm involving an increased risk of acute kidney injury (AKI).[3]

Volume overload following large-volume infusion of intravenous crystalloids is associated with organ failure, delayed gastrointestinal function, and poor outcomes in high-risk surgical and ICU patients.[4–6,9] Small observational pharmacokinetic studies have described albumin's longer duration of plasma expansion compared with crystalloids during surgery, and the use of albumin is therefore thought to be "crystalloid-sparing," minimizing the risk of large-volume crystalloid infusion and preventing fluid overload and its adverse sequelae.[11–16]

While previous studies have explored the effects of albumin-based resuscitation strategies in critically ill septic patients, the incidence of noncardiac intraoperative albumin administration and its effect on important clinical outcomes remain unexplored.[11,14,17–28] A conspicuous lack of evidence demonstrating neither risk nor benefit of albumin use in major noncardiac surgery has long precluded its standardization in clinical guidelines and further study of its perioperative use and association with important postoperative outcomes is urgently needed. This study is based on observational data from the Multicenter Perioperative Outcomes Group (MPOG), a largescale database offering granular perioperative data from 54 academic, public, and private hospitals across the United States, and explores the use of albumin in patients undergoing major noncardiac surgery and its association with important clinical outcomes.

METHODS

Design

Study approval was granted by the institutional review board of the University of California, San Francisco, to perform a multicenter, retrospective observational analysis in cooperation with the MPOG consortium (IRB# 19-269641, San Francisco, California, USA). The study does not involve any intervention or direct patient interaction, and all data was compiled from electronic health records at participating MPOG institutions in the course of routine clinical care and was subsequently de-identified. Individual consent was therefore waived, as the study met the criteria for minimal patient risk. Study outcomes, data collection, and statistical methods were established a priori and were presented and approved at a multicenter peer-review forum on June 8, 2020 before analysis.[29] The study adheres to the RECORD extension of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines in the conduct and reporting of analyses.[30,31]

This study utilized clinical data from the MPOG database, a consortium of 54 hospitals across the United States. Within this research consortium, data from enterprise and departmental electronic health record systems are routinely uploaded to a secure, centralized database. Methods used for data input, storage, quality assurance, and extraction within the MPOG consortium have been described elsewhere and utilized in prior studies. Each center uses a standardized set of data diagnostics to evaluate and address data quality on a monthly basis. Random subsets of cases are manually audited by a clinician at each center to assess and attest to the accuracy of data extraction and source data. MPOG data quality is ensured by means of publicly available, curated, precomputed electronic health record phenotypes.[32]

Study Population

The study included adult patients undergoing major noncardiac surgery under general anesthesia between January 2014 and June 2020. Major surgery was defined by general anesthetic duration of at least 2 hours and anesthesia CPT base units of 5 or greater. We excluded patients with a preoperative diagnosis of End Stage Renal Disease defined by a preoperative estimated glomerular filtration rate less than 15 mL/min/1.73 m^2; American Society of Anesthesiology (ASA) physical status 6 (deceased patients pending organ retrieval for the transplant); or repeat surgery within 30 days of the initial procedure. Cardiac surgery, obstetric, neurosurgical, and liver transplant (living donor and recipient) cases were also excluded. All inclusion and exclusion criteria are reported in detail in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

Covariates

Covariates included in the propensity score matching procedure included important patient-related, clinical, and surgical variables.

Patient-related variables included age, gender, African-American race, ASA physical status, and history of outpatient renin-angiotensin axis blockers (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) as manually identified from outpatient medication lists. We identified preexisting comorbidities, including a history of hypertension, diabetes, non–end-stage chronic kidney disease, peripheral vascular disease, anemia, chronic obstructive pulmonary disease, congestive heart failure, cardiac arrhythmia, cardiac valvulopathy, liver disease, malignancy, neuromuscular disorder, bleeding disorder, hypothyroidism, and obesity as phenotyped by the Elixhauser comorbidity index according to relevant ICD-9/10 diagnostic codes.[32,33]

Clinical covariates included baseline values of the following laboratory studies: estimated glomerular filtration rate, serum creatinine, hematocrit, hemoglobin, platelets, serum sodium, and the urgency of surgery (elective vs. emergent). Intraoperative covariates included total crystalloid volume, the use of starch-based artificial colloid, the presence of hypotension (as defined by ≥ 1 episode of mean arterial pressure <65 mm Hg lasting ≥ 15 min), the overall duration of hypotension (minutes with mean arterial pressure <65 mm Hg), the use of 1 or more continuous vasopressor infusions, the use of specific vasopressor infusions (including phenylephrine, norepinephrine, dopamine, vasopressin, and epinephrine), cumulative vasopressor dose in norepinephrine equivalents (defined in Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/E381), the incidence of blood transfusion, estimated blood loss, the combined volume of transfused blood products, individual blood product component volumes (red blood cells, plasma, and platelets), the rate of urine output, and the use of nephrotoxic drugs (including vancomycin, aminoglycosides, and/or non–steroidal anti-inflammatory drugs).

Finally, surgical variables included case duration, the involvement of abdominal surgery (based on anesthetic CPT code), and surgical or proceduralist subspecialty as defined in the MPOG database, classified as general surgery, surgical oncology, thoracic surgery, urologic surgery, gynecologic surgery, orthopedic surgery, trauma surgery, transplant surgery, neurosurgery, vascular surgery, head and neck surgery, plastic surgery, gastroenterology, ophthalmology, radiology, nephrology, or medical oncology. Covariate definitions are reported in

Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

Outcomes

This study's primary aim was to describe the incidence of intravenous albumin administered in major noncardiac surgery performed in MPOG-affiliated medical centers. Secondary aims explored the association between intraoperative use of albumin and clinical outcomes, including acute kidney injury (AKI), severe AKI, pulmonary complications, net-positive fluid balance, and 30-day all-cause mortality. AKI was defined by the Kidney Disease-improving Global Outcomes definition (binary at any severity stage) based on elevated plasma creatinine values, whereas severe AKI was defined by Kidney Disease-improving Global Outcomes Stages 2-3. Pulmonary complications included acute respiratory failure, pneumonia, pulmonary edema, and transfusion-related acute lung injury as phenotyped according to ICD-9/10 codes. Fluid balance was reported in net liters after tabulating all recorded intraoperative inputs and outputs, including crystalloid, colloid, blood product transfusion, surgical blood loss, and urine volumes (preoperative oral intake and insensible losses were not included in this calculation). Secondary outcomes and their definitions are reported in detail in Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

Statistical Approach

Patient, clinical, and surgical characteristics were compared across albumin-exposed and albumin-unexposed cases in both the overall and propensity score (PS)-matched cohorts. Categorical variables were described using counts and percentages, while continuous variables were described using means with SD alongside medians with interquartile ranges (IQR). The actual mean or percentage differences between albumin-exposed and albumin-unexposed cases were reported with 95% confidence intervals.

We assigned institutions into quartiles according to the proportion of cases at each center featuring documented albumin administration of any nonzero volume, thereby grouping cases by location at minimal-use, low-use, medium-use, or high-use centers. We described key institutional and perioperative metrics stratified by institutional quartile of albumin use. The average proportion of surgeries involving intraoperative use of albumin among the centers included in that quartile was plotted over time.

The impact of albumin on secondary outcomes was estimated using a PS matching estimator. The PS was estimated using a logistic regression model with binary albumin administration as the dependent outcome. Covariates included in the model—including patient-related, surgical, and hemodynamic variables—were selected a priori based on their plausible association with intraoperative albumin use and with the outcomes of interest. The estimated PS was then used to pair albumin-exposed and albumin-unexposed cases using a nearest neighbor approach, 1:1 matching without replacement and with calipers set to 0.2 of the SD of the logit of the PS, as per convention (MatchIt statistical package for R).[34] The balance in covariate distribution between the albumin-exposed and albumin-unexposed cases after matching was assessed using the standardized mean difference, with a cutoff threshold of less than |0.1|. A comprehensive list of all covariates included in the model across both overall and PS-matched cohorts with their standardized mean differences are reported in Supplemental Table 3 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381), while matched and unmatched cases are compared in Supplemental Table 4 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381). Supplemental Tables 3-4 (Supplemental Digital Content 1, http://links.lww.com/SLA/E381) also compare incidences of all measured outcomes across these groups.

This PS-matched cohort was used to evaluate the average treatment effect in the treated (ATT) through mixed-effects logistic and linear regression adjusting for the institution as a random effect for binary and continuous outcomes, respectively. 95% confidence intervals were derived using a cluster-robust variance estimator (lmtest and sandwich statistical packages for R).[35–37] As sensitivity analyses, secondary clinical outcomes were also evaluated in the overall cohort using univariate and multivariate logistic and linear regression models for binary and continuous outcomes, respectively, to compare outcome associations with albumin to those of the PS-matched cohort (Supplemental Table 5, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). As an additional sensitivity analysis, directed acyclic graphs were employed to delineate potential confounders from effect modifiers in the albumin-outcome relationships (example of albumin-AKI relationship in Supplemental Fig 1 Supplemental Digital Content 1, http://links.lww.com/SLA/E381), and the PS-matched model was subsequently re-run on a more conservative, parsimonious set of covariates, excluding those intraoperative variables that may lie downstream on the causal pathway: crystalloid volume, urine output, intraoperative hypotension, vasopressor administration, blood loss, blood product transfusion, and surgical duration (Supplemental Table 6, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). Finally, a causal inference model was employed by means of an Instrumental Variable Estimator (IVE)-based approach using the parsimonious covariates as an additional sensitivity analysis intended to minimize residual confounding (ivtools statistical package for R).[38]

No imputation was used for missing data. Observations with missing data involving albumin administration or AKI outcome were excluded from the analysis.

To further explore the impact of albumin on AKI, predefined subgroups were evaluated within the PS-matched cohort, including patients 65 years of age or older, patients undergoing abdominal surgery (as defined by anesthetic CPT code), patients requiring continuous vasopressor infusions, patients with a history of chronic kidney disease, congestive heart failure, or liver failure, patients receiving massive blood transfusion ($\geq$1 L) or high-volume crystalloid resuscitation ($\geq$30 mL/kg), patients of ASA status 4 or 5, patients undergoing emergent (ie, nonelective) procedures, patients undergoing surgery with a total intravenous anesthetic (TIVA) (defined by $\leq$5 min of cumulative volatile anesthetic use during case), and cases at centers in the highest quartile of institutional albumin use.

Sensitivity analyses exploring AKI specifically included ordered logistic regression to evaluate AKI by stage and logistic regressions evaluating iso-oncotic (5%) and hyper-oncotic (25%) albumin solutions separately.

RESULTS

Overview of Intraoperative Albumin Use

Among the 614,215 cases meeting the inclusion criteria for the study, 93,954 (15.3%) featured documented use of intraoperative albumin. Key demographic, clinical, and surgical covariates are reported in Table 1. The overwhelming majority (96.8%) involved the use of iso-oncotic (5%) solution.

TABLE 1. Patient, Clinical, and Perioperative Characteristics compared between Albumin-exposed and -Unexposed Cases in Overall and Propensity Score (PS)-matched Cohorts

Characteristic n (%), μm (SD), median	Albumin-unexposed (n = 520,261), n (%)	Albumin-exposed (n = 93,954), n (%)	Difference in μm, OR % (95% CI)
Patient demographics			
Age (y)	57.98 (15.92), 60	59.37 (14.77), 61	−1.39 (−1.5 to −1.28)
Male	248,387 (47.74)	48,606 (51.73)	−3.99% (−4.34 to −3.64)
Black	56,904 (10.94)	8,622 (9.18)	1.76% (1.56 to 1.96)
White	394,283 (75.79)	72,128 (76.77)	−0.98% (−1.28 to −0.69)
ASA 1-2	172,157 (33.09)	18,702 (19.91)	13.18% (12.90 to 13.47)
ASA 3	301,779 (58.01)	63,278 (67.35)	−9.34% (−9.67 to −9.02)
ASA 4-5	46,325 (8.9)	11,974 (12.74)	−3.84% (−4.07 to −3.61)
Pre-existing comorbidities			
Obesity	110,843 (21.31)	15,925 (16.95)	4.36% (4.20 to 4.73)
Hypertension	249,067 (47.87)	48,806 (51.95)	−4.08% (−4.22 to −3.52)
Diabetes mellitus	73,239 (14.08)	14,150 (15.06)	−0.98% (−1.17 to −0.67)
Chronic kidney disease	70,401 (13.53)	14,013 (14.91)	−1.38% (−1.63 to −1.14)
Chronic obstructive pulmonary disease	94,456 (18.16)	17,046 (18.14)	0.02% (−0.26 to −0.28)
Congestive heart failure	31,266 (6.01)	5,788 (6.16)	−0.15% (−0.32 to −0.02)
Peripheral vascular disease	46,967 (9.03)	10,624 (11.31)	−2.28% (−2.50 to −2.06)
Malignancy	171,744 (33.01)	52,615 (56)	−22.99% (−23.26 to −22.58)
Liver disease	35,573 (6.84)	9,482 (10.09)	−3.25% (−3.46 to −3.05)
Preoperative lab values			
eGFR (mL/min/1.72 m^2)	88.48 (25.12), 88.32	86.59 (24.32), 87.17	1.89 (1.71 to 2.06)
Serum creatinine (mg/dL)	0.88 (0.29), 0.83	0.89 (0.31), 0.84	−0.02 (−0.02 to −0.01)
Hemoglobin (g/dL)	12.74 (2.17), 13	12.4 (2.2), 12.6	0.34 (0.32 to 0.35)
Surgical characteristics			
Emergent case	44,349 (8.52)	8,038 (8.56)	−0.04% (−0.22 to 0.17)
Case duration (min)	236.44 (106.88), 209	372.8 (175.17), 335	−136.36 (−137.2 to −135.53)
Abdominal surgery	261,306 (50.23)	56,407 (60.04)	−9.81% (−10.15 to −9.47)

ASA indicates American Society of Anesthesiologists physical status; eGFR = estimated glomerular filtration rate

Hyper-oncotic (25%) albumin solutions were used in a minority of cases—3,586 total procedures over the 6-year survey period. In cases using albumin, the average amount administered was ~310 mL (SD 290) with a median volume of 250 mL (IQR 250-250), mode 250 mL, and range of 1 mL–37.6 L.

Cases receiving albumin were more likely to involve higher complexity patients as defined by ASA status 4 or 5 (12.7% vs. 8.9%), including histories of diabetes, hypertension, and/or chronic kidney disease (Table 1). Albumin-exposed cases were significantly longer in duration (mean 370 min vs. 240 min) and averaged greater total crystalloid volume (mean 1.6 L vs.

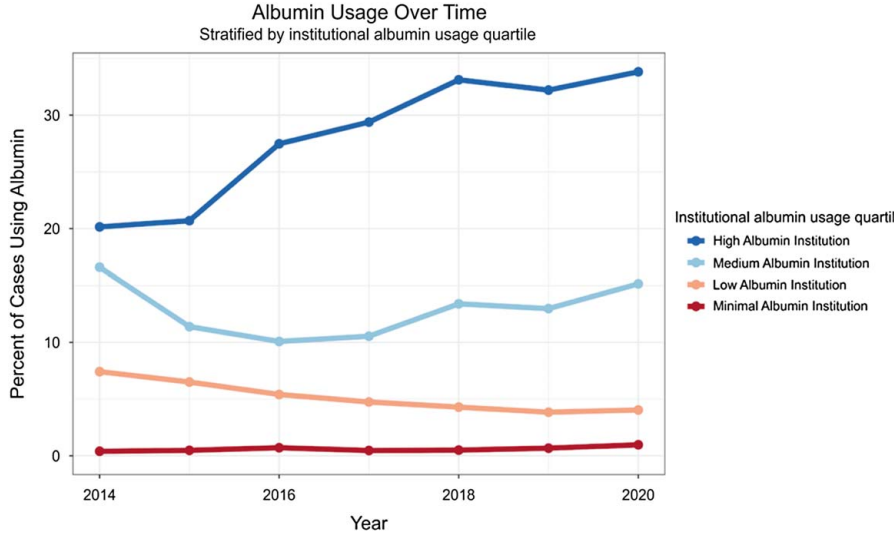

FIGURE 1. Albumin use over time. This graph depicts albumin use over the course of the 6-year retrospective period plotted by institutional use quartile. Cases were stratified by institution, with surgery centers divided into albumin use quartiles according to the proportion of cases at each center using any amount of albumin, thereby grouping cases by location at minimal-use, low-use, medium-use, or high-use centers.

TABLE 2. Cases Stratified by Institutional Albumin use, With Surgery Centers Divided Into Albumin-use Quartiles According to the Proportion of Cases at Each Center Using Any Amount of Albumin, Thereby Grouping Cases by Location at Minimal-use, Low-use, Medium-use, or High-use Centers

Characteristic N = Institution, n = cases [N, n (%) vs. mean (SD), median (IQR)]	Minimal-use Institutions (N = 14, n = 76,043), n (%)	Low-use Institutions (N = 13, n = 145,808), n (%)	Medium-use Institutions (N = 13, n = 161,889), n (%)	High-use Institutions (N = 13, n = 229,156), n (%)	*P*
Surgical (n)Ta					
ASA 4-5	8,870 (11.7)	11,653 (8)	16,472 (10.2)	21,273 (9.3)	< 0.001
Emergent case	10,231 (13.5)	14,111 (9.7)	14,925 (9.2)	13,000 (5.7)	< 0.001
Case duration (min)	234 (122), 195 (150-274)	246 (119), 213 (162-246)	250 (124), 216 (163-296)	278 (139), 242 (180-331)	< 0.001
Medical school affiliation (N)	3 (21.4)	8 (61.5)	12 (92.3)	13 (100)	< 0.001
Geographic Region (N)					< 0.001
Midwest	12 (85.7)	9 (69.2)	3 (23.1)	2 (15.4)	
West	2 (14.3)	0 (0)	2 (15.4)	2 (15.4)	
Northeast	0 (0)	4 (30.8)	4 (30.8)	2 (15.4)	
Southeast	0 (0)	0 (0)	4 (30.8)	2 (15.4)	
South	0 (0)	0 (0)	0 (0)	5 (38.5)	
Annual case volume (n)	17,100 (12,900), 12,500 (7,250-25,100)	38,200 (32,300), 27,200 (11,300-63,800)	39,400 (20,200), 39,800 (32,900-51,500)	40,000 (23,300), 38,200 (28,900-41,700)	0.01
Fluids					
Total crystalloid (mL)	1,160 (819), 1,000 (700-1,400)	1,020 (853), 1,000 (600-1,083)	1,040 (910), 1,000 (550-1,075)	1,350 (921), 1,000 (940-1,689)	< 0.001
Averaged crystalloid rate (mL/hr)	340 (255), 292 (184-429)	280 (253), 234 (154-344)	275 (245), 230 (148-337)	317 (195), 286 (197-396)	< 0.001
Total albumin (mL)	1.41 (26.2), 0 (0-0)	16.0 (142), 0 (0-0)	41.2 (140), 0 (0-0)	86.2 (196), 0 (0-250)	< 0.001
Albumin as % of total IV fluids	0.1 (1.4), 0 (0-0)	1.0 (5.4), 0 (0-0)	3.2 (9.9), 0 (0-0)	6.2 (13.0), 0 (0-9.8)	< 0.001
Total artificial colloids (mL)]	0.60 (19), 0 (0-0)	0.77 (20), 0 (0-0)	0.12 (8.2), 0 (0-0)	6.53 (57.2), 0 (0-0)	< 0.001
Urine output (mL/kg/hr)	1.28 (1.82), 0.77 (0.18-1.64)	1.21 (1.90), 0.68 (0-1.56)	1.66 (3.56), 0.67 (0-1.74)	1.52 (3.05), 0.69 (0-1.58)	< 0.001
Estimated blood loss (mL)	195 (502), 75 (15-200)	178 (432), 50 (3-200)	214 (511), 75 (10-250)	226 (557), 100 (15-250)	< 0.001
Blood product transfusion (mL)	63 (503), 0 (0-0)	37 (310), 0 (0-0)	555 (476), 0 (0-0)	64 (459), 0 (0-0)	< 0.001
Hemodynamics					
Intraoperative hypotension^{+}	35,420 (46.6)	55,487 (38.1)	54,478 (33.7)	87,713 (38.3)	< 0.001
Hypotension duration (min)	26.9 (38.9), 14 (3-35)	20.9 (33.2), 10 (2-26)	19.7 (33.8), 8 (1-23)	21.5 (35.5), 10 (2-26)	< 0.001
≥ 1 Continuous vasopressor(s)	19,289 (25.4)	41,663 (28.6)	57,901 (35.8%)	39,775 (17.4)	< 0.001
Vasopressor dose (total NEE$^{\perp}$)	6.67 (325), 0 (0-0)	2.27 (18.2), 0 (0-0)	3.92 (58.7), 0 (0-1.0)	1.86 (43.2), 0 (0-0)	< 0.001
Clinical Outcomes (n)					
Any AKI$^{\pm}$	7,355 (9.7)	12,596 (8.6)	15,769 (9.7)	24,681 (10.8)	< 0.001
Severe AKI (Stage 2-3)	1,289 (1.7)	2,320 (1.6)	2,735 (1.7)	3,682 (1.6)	0.05
Fluid Balance (net L)	+0.644 (0.988), +0.59 (+0.19 to +0.98)	+0.50 (1.03), +0.49 (+0.15 to +0.82)	+0.39 (1.23), +0.47 (+0.03 to +0.85)	+0.78 (1.23), +0.80 (+0.35 to +34.21)	< 0.001
Pulmonary complications$^{\Diamond}$	453 (0.6)	477 (0.3)	398 (0.2)	623 (0.3)	< 0.001

The sole institution without any documented albumin use is not included in this table.* = Geographic region: West: California, Washington, Oregon, Utah, Midwest: Illinois, Wisconsin, Michigan, Ohio, South: Colorado, Oklahoma, Texas, Arkansas, Missouri, Southeast: Florida, Tennessee, North Carolina, Virginia, Northeast: Pennsylvania, New York, Massachusetts, New Hampshire, Vermont; + = Intraoperative hypotension: Incidence, as defined by ≥1 episode of mean arterial pressure <65 mmHg lasting ≥15 minutes; ⊥ = NEE, Norepinephrine Equivalents: [norepinephrine (mcg/kg)] + [epinephrine (mcg/kg)] + [dopamine (mcg/kg)]/150 + [phenylephrine (mcg/kg)]/10 + [vasopressin (U)]/[0.4*weight (kg)]; ± = Acute Kidney Injury (AKI): defined by KDIGO criteria;◊Pulmonary complications: Inclusive of acute respiratory failure, pneumonia, pulmonary edema, and pulmonary insufficiency by ICD-9/10 code (Supplemental Table 2).

1.1 L), blood loss (mean 530 mL vs. 150 mL), and volume of transfused blood products (mean 180 mL vs. 30 mL). Finally, cases involving albumin use featured a greater rate and average duration of hypotension (56%, 37 min vs. 35%, 19 min), more frequent use of 1 or more continuous vasopressor infusions (34% vs. 24%), and greater overall dosing of vasopressors (5.8 NEE vs. 2.7 NEE).

The breakdown of procedure by surgical service was similar between albumin-exposed and albumin-unexposed cases. Among all cases using albumin, the most common surgical service was general surgery (31.8%), followed by orthopedic surgery (11.7%), urology (19.3%), and nonobstetric gynecology (8.2%) (Supplemental Fig 2, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). The most common procedures using albumin were hepatectomies, rectum-sparing bowel resections, and Whipple-type pancreatectomies.

Among the 54 institutions surveyed in the MPOG consortium, 53 featured one or more cases with documented use of intraoperative albumin during the 6-year timeline. 70.6% of all consortium-wide cases receiving albumin were performed in centers within the highest quartile of institutional use. 29% of all cases performed at the 13 centers in this high-use quartile featured documented use of intraoperative albumin, averaging 6.2% of total intravenous fluids by volume per case. Only 3.8% of all albumin-exposed cases in the entire cohort involved the use of hyper-oncotic (25%) albumin solution. Over the 6-year retrospective period, the proportion of cases using albumin at a given institution grew only within the highest-use institutional quartile, while other quartiles showed static or decreased use over time (Fig. 1). Institutions in the highest quartile of albumin use had the lowest qualitative and quantitative use of vasopressors by the incidence of continuous vasopressor infusions and cumulative vasopressor dose, respectively (Table 2). These cases also had greater crystalloid volume, blood loss, and transfusion volume compared with cases performed at centers in lower-use quartiles. Interestingly, centers in the highest quartile of use were

academically oriented by virtue of medical school affiliation, were more likely to be located in the geographic South of the United States, and were high-volume surgical centers, averaging ~40,000 major cases per year. Only 1 institution reported no use of albumin at all—a Midwestern, lower-volume, nonacademic center—uniquely featuring healthier patients overall by ASA status (2.4% ASA ≥ 4 vs. 8% among institutions in the low-use quartile, $P < 0.001$) as well as a net-negative average fluid balance. By contrast, all 4 quartiles of institutional albumin use featured net-positive average fluid balances.

Association between Albumin Use and Perioperative Outcomes

Sixty-eight thousand three hundred sixty-two cases involving missing covariate data were excluded from the PS matching cohort used for ATT analysis (Supplemental Fig 3, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). Ten thousand eight hundred ninety-eight albumin-exposed cases remained unmatched. Compared with the unmatched cases, matched cases were more likely to involve abdominal surgery, higher ASA status, intraoperative blood transfusion, continuous vasopressor use, and intraoperative hypotension (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

The mixed-effects model in the PS-matched cohort demonstrated significant associations of albumin use with all measured outcomes, including AKI (aOR 1.24, 95% CI 1.20–1.28, $P < 0.001$), severe AKI (aOR 1.45, 95% CI 1.34–1.56, $P < 0.001$), net-positive fluid balance (aOR 1.18, 95% CI 1.16–1.20, $P < 0.001$), pulmonary complications (aOR 1.56, 95% CI 1.30–1.86, $P < 0.001$), and 30-day all-cause mortality (aOR 1.37, 95% CI 1.26–1.49, $P < 0.001$) (Fig. 2). The rate of AKI observed in albumin-exposed cases was nearly double that of albumin-unexposed cases (15.8% vs. 8.8%, Fig. 3). Sensitivity analysis using a parsimonious set of covariates in a separate PS-matched, institution-clustered model revealed similar trends, albeit with exaggerated aOR values for all outcomes except 30-day mortality, which was comparable with that of the primary PS-matched analysis (aOR 1.27 vs. 1.37, respectively) (Supplemental Table 6, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). By contrast, the IVE-based model demonstrated consistent but attenuated signals across all measured outcomes

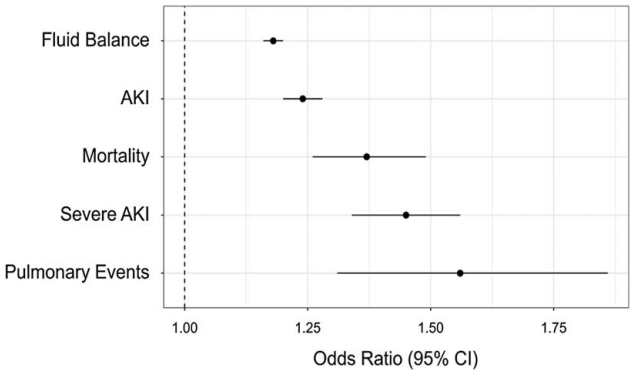

FIGURE 2. Secondary clinical endpoints in propensity score-matched cohort based on albumin exposure. These include AKI, severe AKI, net-positive fluid balance, pulmonary complications, and 30-day all-cause mortality, graphically depicted in odds ratios and 95% confidence intervals (CI). AKI indicates acute kidney injury.

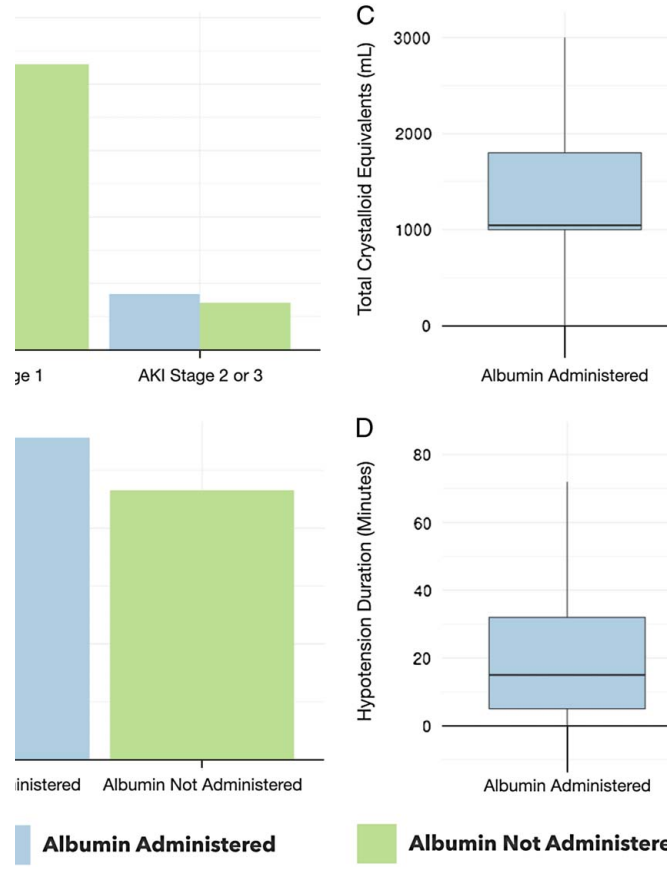

FIGURE 3. Incidences of secondary endpoints. Incidence of acute kidney injury (A), respiratory complications (B), volume of crystalloids received (C), and duration of hypotension (D) in the propensity score-matched cohort stratified by albumin exposure.

(Supplemental Table 6, Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

Albumin's association with AKI persisted across all predefined subgroups, except in the large-volume transfusion (aOR 1.01, 95% CI 0.86–1.18) and large-volume crystalloid subgroups (aOR 1.04, 95% CI 0.92–1.18) (Supplemental Table 7, Supplemental Digital Content 1, http://links.lww.com/SLA/E381). All sensitivity analyses were consistent with the primary analysis, demonstrating an association between albumin and postoperative AKI (Supplemental Tables 6-9, Supplemental Digital Content 1, http://links.lww.com/SLA/E381).

DISCUSSION

In this retrospective cohort analysis, among the 614,215 major noncardiac surgeries performed at 54 US. medical centers, 15% featured the use of intraoperative albumin. The proportion of cases involving albumin varied widely between institutions, ranging from 0% to 47% of all surgical procedures performed at a given center. The overall median volume of albumin administered was 250 mL, and the breakdown of solution tonicity was overwhelmingly iso-oncotic, with 96.8% of all albumin-exposed cases involving the use of 5% albumin solution. When stratified by institutional albumin use, cases in the highest-use quartile

used the least amount of vasopressor despite patient populations of comparable medical complexity according to ASA status and estimated blood loss. Moreover, the top 2 quartiles were overwhelmingly academic (92% and 100% in the third and fourth quartiles, respectively), which may reflect the cultural focus on the theoretical justifications for albumin use over crystalloids despite a lack of clear consensus guidelines governing its use. It should be noted that the sole institution that did not use any albumin was the only case group with a net-negative average fluid balance, although this finding is caveated by a markedly less complex patient population according to ASA status. Finally, within a PS-matched cohort clustered by institution, the use of albumin was associated with greater net-positive fluid balance and increased risk of postoperative complications, including AKI, severe AKI, acute pulmonary events, and all-cause mortality at 30 days. Taken together, it appears that the decision to administer intraoperative albumin is greatly influenced by provider preference and institutional practice. These findings were consistent across all sensitivity analyses in which intraoperative covariates were conservatively excluded from the model, as evidenced by separate parsimonious PS-matched and IVE-based analyses.

This study describes current practices of albumin administration in major noncardiac surgeries performed at US medical centers. The wide variation in albumin administration suggests that the decision to administer albumin is heavily influenced by provider preference and institutional policy. This practice variation is not unexpected given the lack of evidence-based guidelines for perioperative albumin and a paucity of data exploring important clinical outcomes associated with its use.

Fluid resuscitation strategies are thought to have an important effect on postoperative outcomes, and the implications of intravenous fluid choice have undergone renewed scrutiny in recent decades, with studies exploring crystalloid volume during abdominal surgery and the sequelae of artificial colloid use. A multicenter randomized controlled trial demonstrated an increased risk of AKI when using hydroxyethyl starch in major abdominal surgery.[1,3,39] While smaller trials were inconclusive and likely statistically underpowered, these findings on balance have led to a dramatic decrease in the use of artificial colloids. Interestingly, the institutions using hydroxyethyl starch in this study commonly used albumin as well, and while the use of hydroxyethyl starch decreased over time, its use may have been partially replaced by albumin, which trended upwards within high-use centers. These institutions appeared to average greater crystalloid infusion volumes and fewer vasopressors, both qualitatively and quantitatively.

Potential benefits of the use of intravenous albumin include relative endothelial protection, antioxidant properties, and general anti-inflammatory effects[40]. Many providers choose to administer albumin for the colloid's unique intravascular kinetics, which allows for rapid restoration of preload and stroke volume in settings of acute hypovolemia while potentially limiting total intravenous fluid to prevent volume overload.[16,41–44] While pharmacokinetic studies have indeed suggested that albumin features faster and prolonged plasma expansion compared with crystalloids, there is no evidence that the use of albumin decreases the volume of infused crystalloids or the complications of volume overload in surgical patients. In this cohort, albumin use was associated with greater volumes of infused crystalloid (1.6 L vs. 1.1 L) and net-positive fluid balance (+0.9 L vs. +0.6 L). Although residual confounding likely remains, these findings challenge the conventionally held belief that albumin use conveys a crystalloid-sparing effect to limit positive fluid balance and corroborate randomized controlled trials in critically ill patients demonstrating the minimal impact of albumin administration on overall fluid balance. The ALBIOS study, for example, enrolled patients with sepsis or septic shock, and 20% albumin solution was administered daily to maintain serum albumin levels greater than or equal to 30 g/L.[20,45] The albumin group received slightly less crystalloid over the first week (14.2 L [7.4-27.6 L] vs. 16.2 L [8.6-28 L], $P = 0.07$), but ultimately the total daily amount of administered fluids did not differ significantly between albumin and nonalbumin groups ($P = 0.10$).

We observed several associations between albumin exposure and postoperative outcomes, including AKI, severe AKI, net-positive fluid balance, pulmonary complications, and 30-day all-cause mortality. There are several possible explanations for albumin's association with these outcomes. First and foremost, albumin was more commonly administered to sicker, more complicated patients—which itself poses a higher risk of postoperative complications—and given the constraints of a nonprospective, nonrandomized design, it is likely that residual confounding remains. Alternatively, albumin may indirectly affect renal function by means of the oncotic pressure it exerts on transcapillary glomerular filtration, which is driven by pressure gradients across the capillary endothelium as determined by opposing hydrostatic and oncotic forces between the capillary lumina and Bowman's space. Increasing intracapillary oncotic pressure with protein-rich albumin solution can decrease the hydrostatic-oncotic pressure gradient and, in turn, decrease glomerular filtration. Osmotic nephropathy has been described following exposure to hydroxyethyl starches, and an analogous mechanism of injury is possible with albumin solutions.[46,47] However, the overwhelming predominance of iso-oncotic (5%) albumin argues against osmotic drivers of renal toxicity, especially given the similar risk of AKI associated with albumin when stratified by concentration.[18,26] Venous congestion in the kidney from the albumin's increased hydrostatic venous pressure may also adversely affect renal perfusion. Finally, albumin was more likely to be administered in cases complicated by hypotension, itself a known driver of renal injury.[48]

This retrospective analysis has several strengths, including large sample size, granular data collection, and limited missing data among key covariates. To date, there are no large population studies exploring intraoperative albumin use and postoperative outcomes, and the MPOG population is uniquely generalizable given its inclusion of academic, private, and public hospitals involving a wide array of surgical subspecialties across the United States. Furthermore, MPOG's on-site extraction protocols and well-documented auditing methods strengthen the internal validity of the data.[32] On the other hand, the study also suffers from limitations stemming from its observational design, and with unbalanced confounding likely at play, associations between albumin and postoperative outcomes should be interpreted cautiously and considered exploratory pending prospective randomized controlled investigations.[49]

The instrumental variable (IV)-based estimator has been proposed as an alternative to other causal estimators to overcome the risk of bias associated with unmeasured confounders. Indeed, when a perfect IV is identified—one demonstrating variation in the exposure without direct impact on the outcome—the remaining unmeasured confounders have minimal impact on the bias. However, in practice, perfect IVs are rarely observed, and when the IV is weakly correlated with the exposure or any requisite assumptions are even slightly violated, the IV estimator will be imprecise and subsequently biased.[50]

Ultimately, randomized controlled trials are needed to prospectively explore albumin resuscitation strategies in the perioperative setting.

CONCLUSION

Albumin is commonly administered during major noncardiac surgery and features significant inter-institutional variation in patterns of use among the US medical centers. After adjusting for measured confounders using a PS-matched design, its use is associated with an increased risk of postoperative complications, including AKI, acute pulmonary events, and death. Given the high cost of albumin compared with crystalloid solutions and the former's association with adverse clinical outcomes, the indications and use of albumin resuscitation strategies in the perioperative setting merit renewed scrutiny with randomized controlled trials.

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