Evaluating variability in use of intravenous albumin in patients undergoing surgery for cancer

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Presented at the Canadian Society for Transfusion Medicine conference, May 25 to 28, 2023, Montréal, Que., and at the Quality, Utilization, Efficacy, and Safety in Transfusion Symposium, Aug. 10, 2023, Toronto, Ont.

Accepted Feb. 6, 2025

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Cite as: *Can J Surg* 2025 October 17; 68(5). doi: 10.1503/cjs.013823

Background: Despite numerous randomized controlled trials finding that albumin is not associated with improved patient outcomes, transfusion practice is highly variable. We examined the variability and impact of albumin transfusion on outcomes in cancer surgery.

Methods: We included consecutive adults undergoing cancer surgery between 2018 and 2021 in Ontario, Canada. The primary exposure was the proportion of patients who received perioperative albumin. The secondary outcomes were hospital length of stay and the incidence of infection, anemia, venous thromboembolism, and mortality in albumin-treated versus non-albumin-treated patients in a case–control analysis.

Results: Of 155 166 cancer surgeries (66.8% female patients, median age 62.9 yr), 2.5% received perioperative albumin. The cancer surgery types with the highest proportion of patients receiving albumin were hepato-pancreato-biliary (24.8%) and colorectal (18.6%). Of 104 facilities, 12.5% had nonrandom outliers for albumin use in at least 1 cancer type (p = 0.0004). Patient outcomes were different in case–control matched cohorts for colorectal and hepato-pancreato-biliary surgeries, including a higher rate of infection, venous thromboembolism, and mortality in patients treated with albumin (cases) than those who were not (controls).

Conclusion: Albumin transfusion rates were highly variable among hospitals for the same cancer type. Quality improvement initiatives are warranted to curtail unnecessary albumin transfusions in the perioperative period.

Contexte : Bien que de nombreux essais randomisés et contrôlés aient révélé que l'albumine n'était pas associée à une amélioration des résultats cliniques, les pratiques en matière de transfusion sont très variables. Nous avons évalué la variabilité et l'influence de la transfusion d'albumine sur l'issue d'interventions chirurgicales en oncologie.

Méthodes : Nous avons inclus des adultes ayant subi une chirurgie oncologique en Ontario, au Canada, consécutivement entre 2018 et 2021. Le paramètre principal d'exposition correspondait à la proportion de cette patientèle ayant reçu de l'albumine en période périopératoire. Les paramètres secondaires étaient la durée du séjour à l'hôpital et l'incidence d'infection, d'anémie, de thromboembolie veineuse et de mortalité chez la patientèle traitée par l'albumine comparativement à celle non traitée par l'albumine dans une analyse cas–témoins.

Résultats : Des 155 166 personnes ayant subi une chirurgie en oncologie (66,8 % de femmes, âge médian 62,9 ans), 2,5 % ont reçu de l'albumine en période périopératoire. Les types de chirurgies oncologiques où la proportion de la patientèle recevant de l'albumine était la plus élevée étaient les chirurgies hépatopancréatobiliaires (24,8 %) et les chirurgies colorectales (18,6 %). Sur 104 établissements, 12,5 % présentaient des valeurs aberrantes non aléatoires pour la transfusion d'albumine dans le traitement d'au moins 1 type de cancer (p = 0,0004). On observait un écart entre les résultats cliniques dans les cohortes cas–témoins appariées sur le plan des chirurgies colorectales et hépatopancréatobiliaires, notamment des taux d'infection, de thromboembolie veineuse et de mortalité plus élevés chez la patientèle traitée par l'albumine (cas) que chez celle qui ne l'était pas (témoins).

Conclusion : Les taux de transfusion d'albumine étaient très variables entre hôpitaux pour un même type de cancer. Il y aurait lieu de mettre en œuvre des initiatives d'amélioration de la qualité visant à réduire les transfusions d'albumine inutiles en période périopératoire.

Albumin is the most abundant protein in human plasma, constituting half of the total intravascular protein content in healthy humans.[1] The important physiologic roles of albumin include maintaining plasma oncotic pressure and transporting substances such as drugs and bilirubin.[1] Intravenous albumin is a fractionated blood product that is administered as an intravenous infusion of either 4% to 5% or 20% to 25% albumin.[2]

Large randomized controlled trials (RCTs) encompassing more than 10 000 patients have shown the limited efficacy of albumin in improving patient outcomes in different clinical settings.[3–5] Specifically, the Albumin in Cardiac Surgery (ALBICS) trial,[3] the Saline Versus Albumin Fluid Evaluation (SAFE) study,[4] and the Albumin Italian Outcome Sepsis (ALBIOS) study[5] reported that, compared with alternative intravenous fluids, there was no significant patient-important benefit to using albumin over crystalloid. The utility of albumin transfusion in surgical oncology is not as well understood, although the results of 3 smaller RCTs, totalling 329 patients in the cancer surgery population, also suggest that albumin does not improve patient outcomes compared with crystalloid.[6–8] Albumin transfusion is also associated with the risk of adverse transfusion reactions, including hypotension, peripheral gangrene, increased bleeding, fluid overload, infections, and anaphylaxis.[8–12] The Ontario Regional Blood Coordinating Network recommends albumin for only a limited number of indications, including patients with cirrhosis, hypotension during dialysis, and plasma exchange procedures.[13] International agencies, such as the International Collaboration for Transfusion Medicine Guidelines and the Surviving Sepsis Campaign, also recommend a very limited, if any, role for albumin transfusion in noncardiac surgery.[14,15]

In addition to being associated with no improvements in patient outcomes, albumin is an expensive and scarce blood plasma product.[16,17] During the COVID-19 pandemic it became increasingly difficult to obtain albumin because of an additional need for plasma to investigate COVID-19 therapies.[17] From an ethical point of view, Canadian legislature restricts paid plasma donation in most jurisdictions, resulting in the majority of plasma products used in Canada being derived from paid donors from the United States.[17] There are concerns with the ethics of paid plasma donation as it is possible that donors are compromising their health for the monetary compensation, with US donors alone comprising 71% of the global plasma supply in 2017.[17]

The lack of evidence for the efficacy and safety of albumin transfusion in cancer surgery is reflected in the exclusion of intravenous albumin use for cancer surgery from Ontario and worldwide guidelines.[13–15] Concerns regarding cost and resource intensity were highlighted by Ontario Health's 2009 provincial plan, which indicated the need for more efficient use of resources, including albumin. More recently, in 2022, the Surgical Oncology Program at Ontario Health added use of albumin during admission for cancer surgery as a quality metric for all hospitals in Ontario because of its associated adverse effects, high cost, scarcity, and unexplained variability across hospitals.

Despite the lack of guideline recommendations and supportive evidence from RCTs, albumin transfusion rates in cancer surgery remain highly variable. We aimed to assess the Ontario-wide variability in albumin transfusion for cancer surgery and the association between albumin transfusion and patient outcomes in cancer surgery.

Methods

Study design and data sources

This retrospective population-based cohort study included adults who underwent surgery for cancer and were discharged between Apr. 1, 2018, and Mar. 31, 2021, in Ontario, Canada. Ontario has a universally accessible, single-payer health care system that allows for the capture of every health care encounter for the province's 14.6 million residents. We used the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) checklist to report the results of our analyses for an accurate and clear description of our methods and results (www.record-statement.org).[18] We analyzed routinely collected administrative data in the Canadian Institute for Health Information (CIHI) Discharge Abstracts Database (DAD) and National Ambulatory Care Reporting System (NACRS) to identify cancer surgeries and health outcomes. The DAD and NACRS are accurate, valid, and reliable sources of information for routinely collected health care data.[19,20] We used the Registered Persons Database and Ontario Cancer Registry to identify patient demographics and dates of death, respectively.

Study cohort

We identified adults aged 18 years and older who underwent surgery for cancer (breast, colorectal, gastric, genitourinary, gynecologic, head and neck, hepato-pancreato-biliary, neurosurgery, prostate, bone, skin, thoracic, and thyroid) using the DAD and NACRS. We selected patients into the cohort based on quality-based procedure (QBP) methodology for discharge dates between Apr. 1, 2018, and Mar. 31, 2021. Quality-based procedures are specific groups of patient services that allow health care providers to share best practices with the aim of enhancing system quality and efficiency. Cancer surgery QBP methodology inclusion criteria were an in-scope Canadian Classification of Health Interventions coded as the primary intervention on DAD or NACRS record, and an in-scope *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, Canada (ICD-10-CA) coded as the main diagnosis on DAD/NACRS records.

We then applied QBP exclusions to the total population. The QBP exclusions were patients without a unique Ontario Health Insurance Plan (OHIP) number; patients younger than 18 years at the time of operation; patients for whom the main intervention was not recorded; non-Ontario records (non-Ontario health card number); patients not covered under OHIP; and interventions that were cancelled, abandoned, or performed out of hospital.

Exposure

The primary exposure measure was albumin transfusion. If the patient was transfused during their hospital stay, they were coded as having a transfusion. If patients received erythrocytes, autologous or autotransfusion, plasma, platelets and other blood products without albumin, they were identified as having no albumin transfusion. The coding for albumin transfusion does not report formulation (5% v. 25%), volume transfused, timing of the infusion, or location of patient at the time of transfusion (operating room, postanesthesia care unit, intensive care unit, or ward).

Outcomes

The patient outcomes of interest were identified in the DAD, NACRS, and Ontario Cancer Registry, and included 30-day all-cause mortality, perioperative infection, perioperative anemia, postoperative anemia, perioperative venous thromboembolism, and mean hospital length of stay. Mortality was defined as death from any cause within 30 days of surgery, as indicated in the Ontario Cancer Registry and Registered Persons Database. We defined perioperative infection, perioperative anemia, postoperative anemia, and perioperative venous thromboembolism using CIHI's Hospital Harm Framework. Perioperative infection included urinary tract infections, postprocedural infections, viral gastroenteritis, pneumonia, and sepsis, and infections due to *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococcus.[21] We defined perioperative anemia as anemia secondary to hemorrhage or hemorrhagic disorders that require(s) blood transfusion, identified during a hospital stay, related to the health care delivered or therapeutic use of anticoagulants.[21] We defined postoperative anemia as hemorrhage or anemia secondary to hemorrhage, associated with a medical or surgical procedure.[21] We defined venous thromboembolism as embolism, thrombosis, phlebitis, or thrombophlebitis of the pulmonary vein or other veins (excluding superficial veins) identified during a hospital stay.[21]

Covariates

Patient characteristics included sex, age at time of surgery, and Charlson Comorbidity Index score.[22] Disease and treatment characteristics included cancer type, year of surgery, and resection approach (minimally invasive or open). Hospital characteristics included hospital type — large community, small, or teaching — and annual resection volumes.

Statistical analysis

We measured the albumin transfusion rates for all cancer surgeries at each hospital. To visualize the variability in albumin transfusion between hospitals, we plotted each hospital's crude albumin transfusion rate against its total number of cancer surgeries in a funnel plot. The funnel plot included 95% confidence limits to identify whether a hospital's rate of albumin transfusion was outside or within the expected variation. We conducted further analyses to assess albumin transfusion rates across all hospitals by cancer type. For each cancer type, we determined the mean albumin transfusion rate across all hospitals, the minimum and maximum albumin transfusion rate across all hospitals, and the number of hospitals with outliers. We defined outliers as hospitals with albumin transfusion rates above the 95th percentile for a particular cancer type. To visualize the variability in albumin transfusion at all hospitals by cancer type, we plotted the mean albumin transfusion rates for each cancer type across all hospitals against the total number of surgeries performed during the study period in a funnel plot. The funnel plot included 95% confidence limits to identify whether a cancer type's rate of albumin transfusion was outside or within the expected variation.

We subsequently performed a bootstrap analysis to confirm the results of our conditional probability calculations of the likelihood that there are outliers. For each bootstrap sample, we used unrestricted random sampling; that is, selection with equal probability and replacement. The bootstrap is a data simulation method that is used for sample size estimates and data analysis.[23] It repeatedly samples the original data to provide an estimate of the parameter of interest; in this study, this was the number of hospitals with outliers for albumin transfusion based on random chance alone.[23]

Finally, we evaluated clinical outcomes for patients who underwent surgery for colorectal and hepato-pancreato-biliary (HPB) cancer. For colorectal cancer, perioperative albumin transfusion recipients (cases) were matched to patients who did not receive albumin transfusion (controls) based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status (yes or no erythrocyte transfusion), surgical approach, and extent of excision in a 1:3 manner. For HPB cancer, cases were matched to controls based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status, surgical approach, extent of excision, and extent of liver disease (none or mild liver disease)[24] in a 1:2 manner. We chose a 1:3 matching ratio for colorectal surgeries after assessing matching ratios from

1:1 to 1:5 to optimize statistical power while balancing bias and variance.

After evaluating the balance of patient characteristics and the consistency of findings across ratios, we observed diminishing returns beyond the 1:3 ratio, which offered the best balance for this data set. For HPB surgeries, we selected a 1:2 ratio based on the data characteristics and analysis needs. To assess balance after matching, we used absolute standardized difference, where a difference of 0.1 was considered statistically significant. We performed hierarchical multivariable logistic regression models with a binary distribution and logit linkage to assess the correlation between perioperative albumin transfusion and 30-day all-cause mortality, perioperative infection, perioperative anemia, venous thromboembolism, and postoperative anemia. We also performed hierarchical multivariable linear regression with negative binomial distribution to assess how perioperative albumin transfusion correlated with mean hospital length of stay. We performed analyses using Statistical Analysis System software version 9.4, with significance at $p < 0.05$.

Ethics approval

Ontario Health (Cancer Care Ontario) is designated a "prescribed entity" for the purposes of section 45(1) of the *Personal Health Information Protection Act* of 2004. As a prescribed entity, Ontario Health (Cancer Care Ontario) is authorized to collect personal health information from health information custodians without the consent of the patient, and to use such personal health information for the purpose of analysis or compiling statistical information with respect to the management, evaluation, or monitoring of the allocation of resources to or planning for all or part of the health system, including the delivery of services. Because this study is in compliance with privacy regulations, ethics review was not required.

Results

Description of study cohort

We included 155 166 cancer surgeries, which encompassed 104 hospitals and 13 cancer types. The 13 cancer types were breast, colorectal, gastric, genitourinary, gynecologic, head and neck, HPB, neurosurgical, prostate, sarcoma, skin, thoracic, and thyroid. All procedures were completed in a main operating room (excludes surgical procedures in endoscopy, diagnostic imaging, cardiac catheterization suite, and obstetric operating room). Patient, procedural, and hospital characteristics are detailed in Table 1. Overall, the median patient age was 62.9 years (interquartile range [IQR] 52.2 to 71.9) and 66.8% were female. The most common surgeries were breast (31.1%), colorectal (12.1%), and gynecologic (11.9%) cancer surgeries. A roughly equal proportion of patients underwent surgery during each year of the study, and 58.1% of surgeries were performed at large community hospitals.

Table 1. Baseline characteristics of study cohort

Characteristic	No. (%)* of patients overall *n* = 141 343	No. (%)* of patients who had albumin transfusion *n* = 3890
No. of cancer surgeries	155 166	3922
Sex		
Female	94 354 (66.8)	1725 (44.3)
Male	46 989 (33.2)	2165 (55.7)
Surgery age, yr, continuous, median (IQR)	62.9 (52.2–71.9)	67.5 (58.6–75.0)
Age group, yr		
1: < 50	32 369 (20.9)	435 (11.1)
2: 51–60	33 434 (21.5)	674 (17.2)
3: 61–70	42 689 (27.5)	1140 (29.1)
4: 71–80	32 922 (21.2)	1190 (30.3)
5: > 80	13 752 (8.9)	483 (12.3)
Charlson Comorbidity Index group		
0: No comorbidity	66 023 (42.5)	167 (4.3)
1: 1 comorbidity	52 060 (33.6)	1310 (33.4)
2: 2 comorbidities	26 604 (17.1)	1558 (39.7)
3: 3 comorbidities	7234 (4.7)	578 (14.7)
4: > 3 comorbidities	3245 (2.1)	309 (7.9)
Cancer type		
Breast	48 237 (31.1)	47 (1.2)
Colorectal	18 833 (12.1)	730 (18.6)
Gastric	982 (0.6)	95 (2.4)
Genitourinary	9774 (6.3)	447 (11.4)
Gynecological	18 521 (11.9)	331 (8.4)
Head and neck	14 528 (9.4)	281 (7.2)
Hepato-pancreato-biliary	4130 (2.7)	971 (24.8)
Neurosurgical	9388 (6.1)	348 (8.9)
Prostate	6818 (4.4)	55 (1.4)
Sarcoma	246 (1.6)	20 (0.5)
Skin	2448 (1.6)	Low volume
Thoracic	9602 (6.2)	591 (15.1)
Thyroid	11 659 (7.5)	Low volume
Fiscal year		
2018–2019	53 889 (34.7)	1410 (36.0)
2019–2020	53 627 (34.6)	1236 (31.5)
2020–2021	47 650 (30.7)	1276 (32.5)
Facility type*		
Large community hospital	90 113 (58.1)	864 (22.0)
Small hospital	2084 (1.3)	7 (0.2)
Teaching hospital	62 969 (40.6)	3051 (77.8)
Resection approach†		
Minimally invasive	13 815 (53.9)	179 (22.8)
Open	11 836 (46.1)	606 (77.2)

*Facility type is a classification for Health System Funding Reform, which is developed and maintained by the Ministry of Health and the Ministry of Long-Term Care, based on the total number of weighted cases at each hospital. There are thresholds for classifying facilities in the Teaching, Community, and Small categories. The groups classified in this report are based on the most recent listings available to Cancer Care Ontario and may not correspond to current Ministry classifications.
†Resection approach is applicable only to colorectal and prostate cancer surgeries.

After exclusions, we determined that 3922 (2.5%) patients undergoing cancer surgeries received albumin. Overall, the average albumin transfusion rates for all cancer surgeries ranged between 0% and 23.5% (Figure 1). In the albumin-treated group, the median patient age was 67.5 years (IQR 58.6 to 75.0) and 55.7% were male. Most patients treated with albumin underwent surgery for colorectal (18.6%), genitourinary (11.4%), HPB (24.8%), or thoracic cancer (15.1%). The proportion of patients who underwent surgery in the albumin-treated group was roughly comparable in each study year and 77.8% of albumin-treated cancer surgeries occurred at academic hospitals. The majority (77.2%) of surgeries were open procedures.

Variability in the use of intravenous albumin for cancer surgery

Of 104 hospitals, 7 had albumin transfusion rates above the 95th percentile for cancer surgery during the study period (Figure 1). Figure 1 shows the variability in rates of albumin transfusion across all hospitals for cancer surgery. The cancer types with the highest variability in albumin transfusion rates across all hospitals were (3-yr mean transfusion rate, range) HPB (23.5%, 0% to 100%), thoracic (6.2%, 0% to 100%), gastric (9.7%, 0% to 50%), and genitourinary (4.6%, 0% to 25.2%) (Table 2). Table 2 describes the mean albumin transfusion rate across all hospitals, minimum and maximum albumin transfusion rates across all hospitals, and number of hospitals with outliers for each cancer type. Figure 2 shows the variability in albumin transfusion rates across all hospitals by cancer type.

Nonrandom variability in the use of intravenous albumin for cancer surgery

Of the 104 hospitals included in the study, 4 (3.85%) had outliers in 1 cancer type, 9 (8.65%) had outliers in 2 or more cancer types, and the remaining 91 (87.5%) had no outliers (Table 3). We determined that the outliers were not randomly distributed.

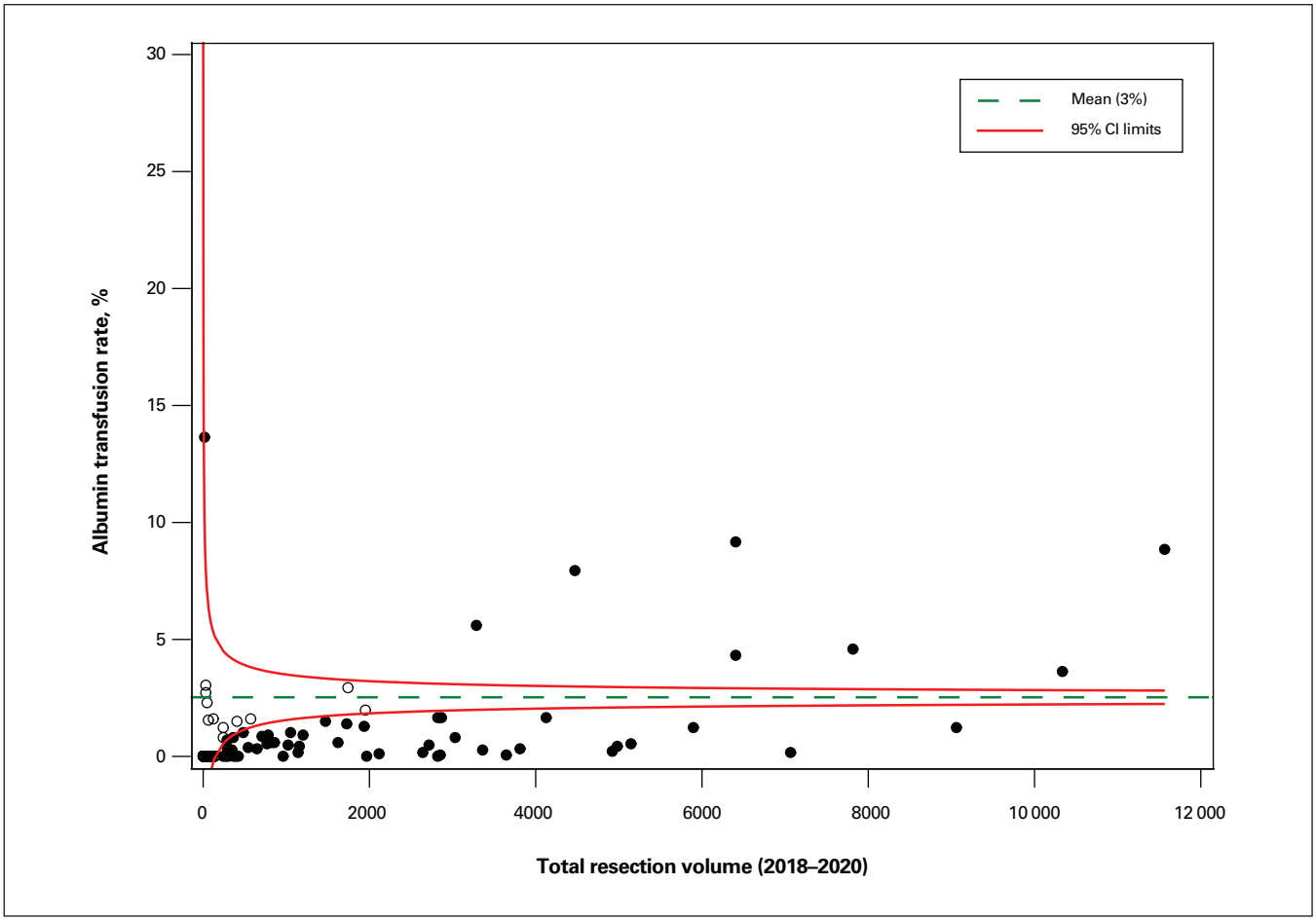

Fig. 1. Average albumin transfusion rate by hospital for cancer surgery in Ontario between 2018 and 2020. The total resection volumes (number of surgical procedures) across all hospitals for cancer surgery (X axis) are plotted against the total albumin transfusion rates (Y axis) for the period between 2018 and 2020. Solid red lines represent upper and lower 95% confidence intervals (CI) of the average albumin transfusion rate across all hospitals in Ontario for cancer surgery. The dashed green line represents the average albumin transfusion rate across all hospitals for cancer surgery. Each black dot represents a different hospital in Ontario; white dots are within 95th percentile.

Table 2. Averages and ranges of albumin transfusion for cancer surgery in 104 Ontario hospitals between 2018 and 2020

Cancer type	3-year mean transfusion rate, %*	Range, %†	No. of hospitals with outliers‡
Breast	0.1	0–1.5	5
Colorectal	3.9	0–18.8	8
Gastric	9.7	0–50.0	6
Genitourinary	4.6	0–25.2	6
Gynecological	1.8	0–10.5	4
Head and neck	1.9	0–7.9	4
Hepato-pancreato-biliary	23.5	0–100.0	5
Neurosurgical	3.7	0–22.5	4
Prostate	0.8	0–9.6	3
Sarcoma	8.1	0–12.0	0
Skin	0.0	0–1.1	1
Thoracic	6.2	0–100.0	4
Thyroid	0.0	0–0.9	2

*The 3-year mean transfusion rate refers to the average rate of albumin transfusion over the 3 years for each cancer type, defined as the total number of cases with albumin transfusion for each cancer type over the total number of cases (with or without albumin transfusion) for each cancer type.

†The range outlines the minimum and maximum albumin transfusion rates at all hospitals for each cancer type over the 3-year study period.

‡Outliers are defined as hospitals with an albumin transfusion rate above the 95th percentile for a particular cancer type.

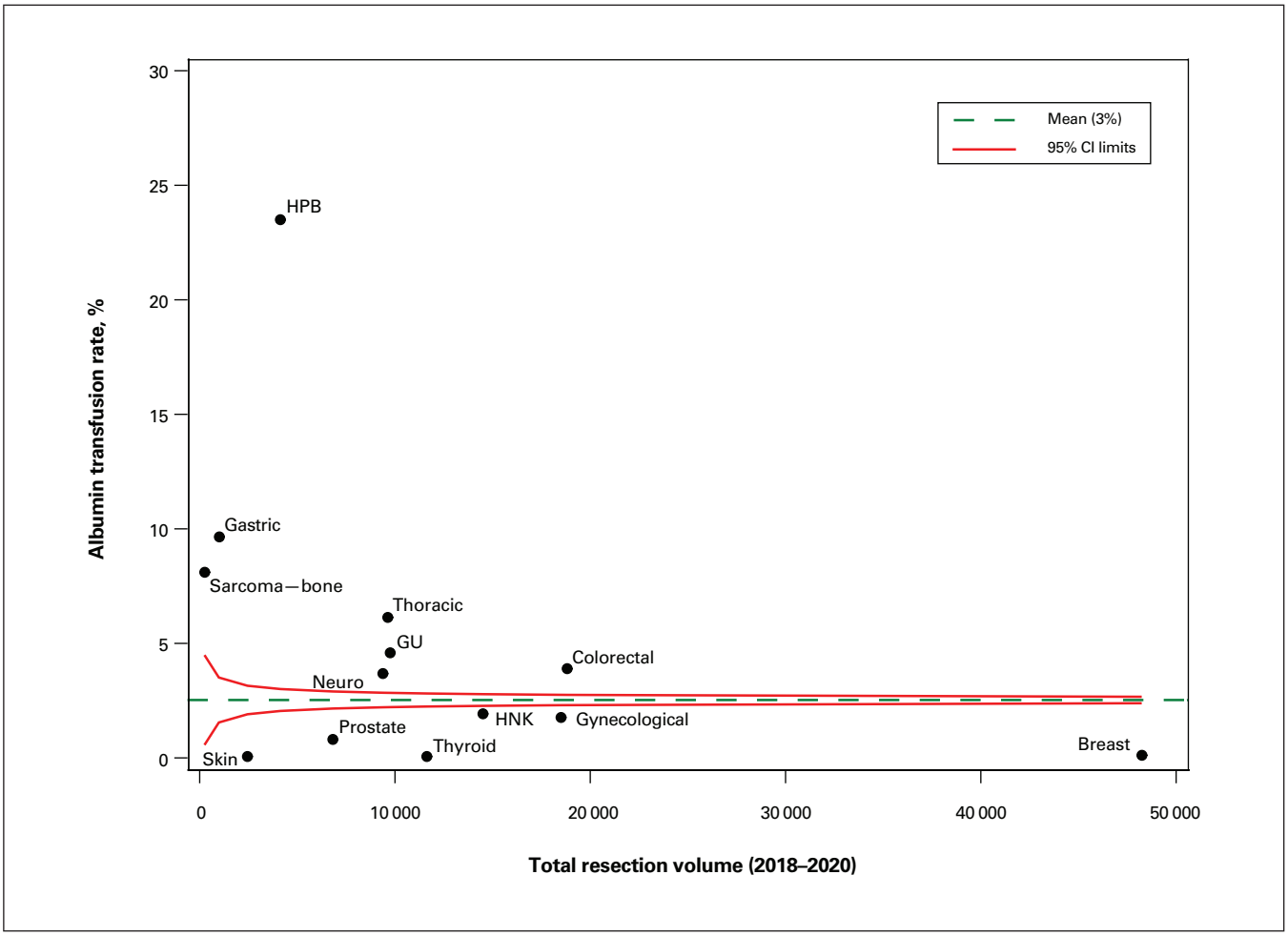

Fig. 2. Average albumin transfusion rate by cancer type for all hospitals in Ontario between 2018 and 2020. The total resection volumes (number of surgical procedures) for all hospitals and cancer types (X axis) are plotted against the total albumin transfusion rates (Y axis) for the period between 2018 and 2020. The solid red lines represent the upper and lower 95% confidence intervals (CI) for the average cancer surgery albumin transfusion rate in Ontario. The dashed green line represents the average albumin transfusion rate for all cancer surgery types in Ontario hospitals. Each black dot represents a different cancer type. GU = genitourinary; HNK = head and neck; HPB = hepato-pancreato-biliary.

Table 3. Number of hospitals with outliers for patients undergoing cancer surgery in Ontario

No. of outliers*	No. (%) of hospitals
0	91 (87.5)
1	4 (3.9)
2	3 (2.9)
3	1 (1.0)
5	2 (1.9)
7	1 (1.0)
10	1 (1.0)
12	1 (1.0)

*Outliers were defined as a cancer type with albumin transfusion rates above the 95th percentile.

Based on conditional probability calculations of the number of outliers during the study, we determined that there was a 69.2% chance that a hospital had a second outlier if the hospital already had 1 outlier. This finding was confirmed by bootstrap sampling, which showed that with 1000 estimates of probabilities of a hospital having a second outlier when it already has 1 outlier, the mean (standard deviation [SD]) was 69.18% (13.83) and the median with 95% confidence interval (CI) was 69.23% (68.75% to 70.00%). Further χ^2 hypothesis testing showed that the 13 hospitals with outliers in at least 1 cancer type were not randomly distributed (χ^2 12.32, $p < 0.05$).

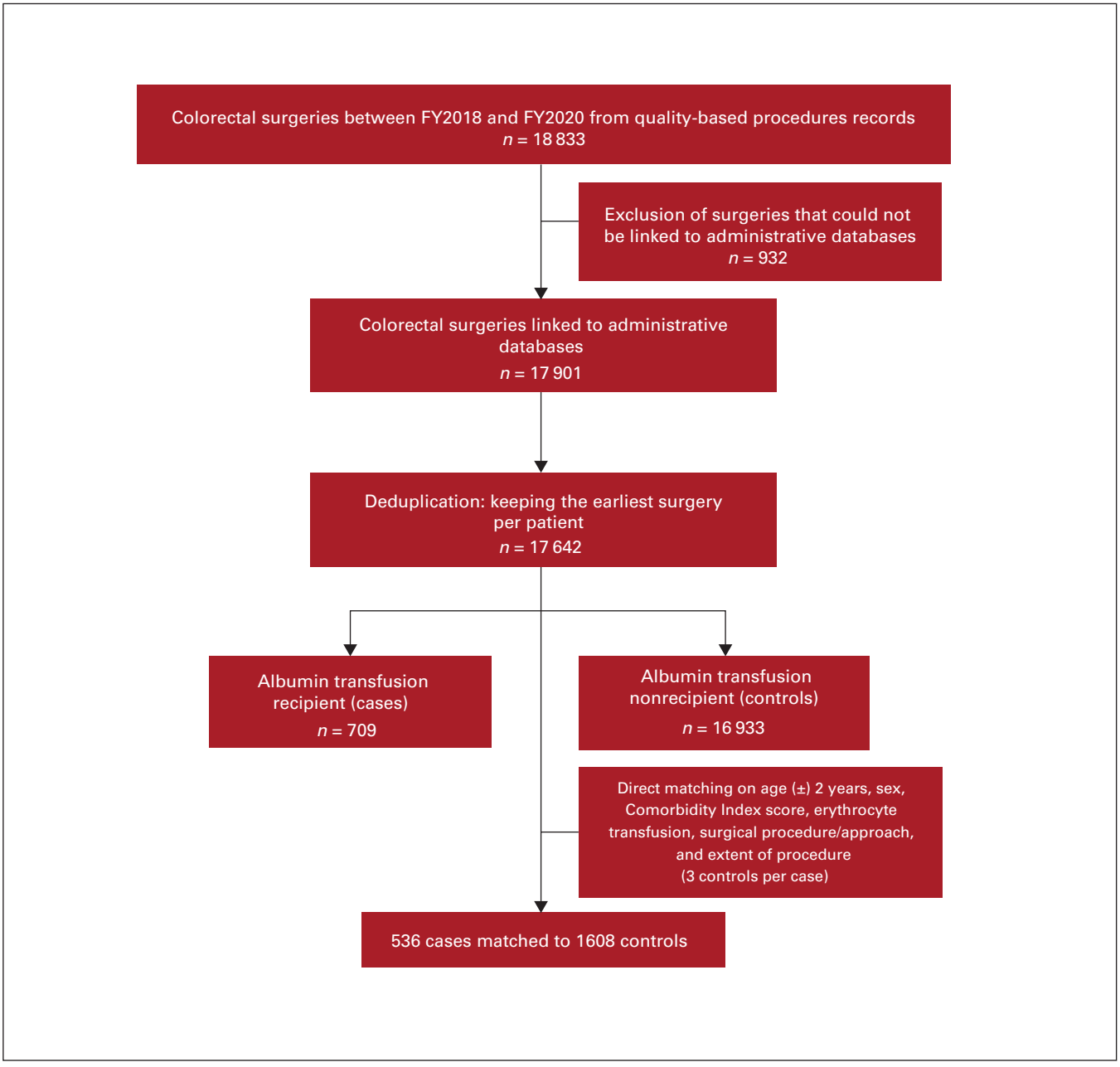

Fig. 3. Matching scheme for patients undergoing surgery for colorectal cancer. FY = fiscal year.

Outcomes for colorectal cancer surgery patients

A total of 536 colorectal cancer surgery patients who received albumin transfusion (cases) were matched with 1608 colorectal cancer surgery patients who did not receive albumin transfusion (controls) (Figure 4). Cases were matched to controls based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status, surgical approach, and extent of excision. Albumin transfusion was positively correlated with 30-day all-cause mortality ($p < 0.05$), perioperative infection (OR 3.87, 95% CI 3.07 to 4.87, $p < 0.05$), and perioperative venous thromboembolism (OR 2.66, 95% CI 1.55 to 4.59, $p < 0.05$) (Table 4). Mean length of hospital stay (days ± SD) was longer for cases than for controls, with an average stay of 21.5 ± 25.6 days for cases and an average stay of 11.1 ± 14.9 days for controls ($p < 0.0001$) (Table 4). We found no significant differences between cases and controls for perioperative anemia (OR 2.59, 95% CI 0.87 to 7.75) and postoperative anemia (OR 1.00, 95% CI 0.69 to 1.46) (Table 4).

Outcomes for HPB cancer surgery patients

A total of 431 HPB cancer surgery cases were matched with 862 controls (Figure 5). Cases were matched to controls based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status, surgical approach, extent of excision, and extent of liver disease. Albumin transfusion was positively correlated with 30-day all-cause mortality (OR 3.42, 95% CI 1.48 to 7.88, $p < 0.05$), perioperative infection (OR 1.59, 95% CI 1.16 to 2.19, $p < 0.05$), and perioperative venous thromboembolism

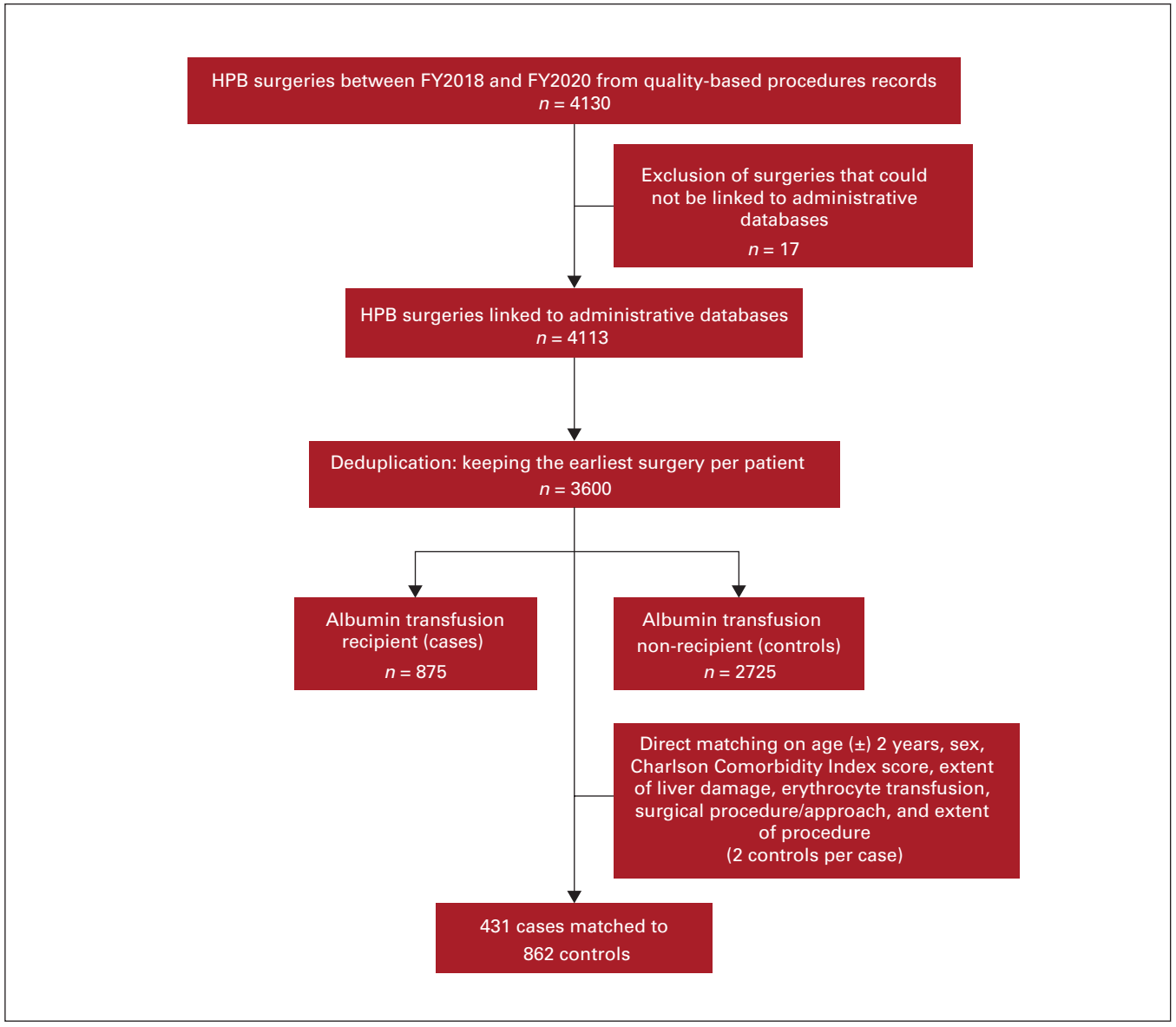

Fig. 4. Matching scheme for patients undergoing surgery for hepato-pancreato-biliary (HPB) cancer. FY = fiscal year.

(OR 2.44, 95% CI 1.04 to 5.70) (Table 5). Mean length of hospital stay was longer for cases than for controls, with an average stay of 10.7 ± 8.9 days for cases and an average of 8.8 ± 8.0 days for controls (p = 0.0001) (Table 5). We found no significant differences between cases and controls for postoperative anemia (OR 1.07, 95% CI 0.58 to 1.95) (Table 5).

Discussion

In this population-based cohort (2018 to 2021) of cancer surgery patients, we observed wide variation in albumin transfusion across the hospitals in Ontario. We observed variability across all cancer surgeries and hospitals for all subtypes of cancer surgeries, with HPB cancer surgery rates, for example, ranging between 0% and 100%. Although patient and procedural factors explained some of the variation (e.g., more patients transfused albumin during colorectal cancer surgery v. breast cancer surgery), the nonrandom clustering of albumin transfusion in certain hospitals suggests that hospital-level factors were likely a key determinant of albumin use. Furthermore, our results suggest that albumin transfusion was not only variable, but also was not associated with improved outcomes in this surgical population.

Variable transfusion practice has been well documented in cardiac and noncardiac surgery studies.[25–27] Additionally, blood transfusion variability has been found not only in Ontario, but also in other Canadian provinces and countries worldwide. A 2022 audit of erythrocyte transfusion for gastrointestinal cancer surgery patients in Ontario showed that patient-level factors alone were not responsible for the high variability in erythrocyte transfusion.[25] This study showed that there was an approximately 30% difference in the odds of transfusion between 2 similar patients who were treated by different physicians at different hospitals.[25] Similarly, a multihospital review of blood transfusion in cardiac procedures found that the main determinant of blood use was the hospital culture.[26] Additionally, a cross-sectional survey in Alberta evaluated the

Table 4. Secondary outcomes for patients undergoing surgery for colorectal cancer comparing albumin transfusion recipients (cases) matched to patients who did not receive albumin transfusion (controls) in a 1:3 manner*

Type of outcome	No. (%)† of cases n = 536	No. (%)† of controls n = 1608	Odds ratio (95% CI)	p value
Binary				
30-day all-cause mortality	80 (14.9)	82 (5.1)	3.27 (2.36–4.53)	< 0.0001
Perioperative infection	191 (35.6)	202 (12.6)	3.87 (3.07–4.87)	< 0.0001
Perioperative anemia	6 (1.1)	7 (0.4)	2.59 (0.87–7.75)	0.0773
Postoperative anemia	39 (7.3)	117 (7.3)	1.0 (0.69–1.46)	1.0000
Perioperative venous thromboembolism	25 (4.7)	29 (1.8)	2.66 (1.55–4.59)	0.0003
Continuous, d ± SD				
Mean hospital length of stay	21.5 ± 25.6	11.1 ± 14.9		< 0.0001

CI = confidence interval; SD = standard deviation.

*Controls were matched based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status, surgical approach, and extent of excision. Mortality was defined as death from any cause within 30 days of surgery. Perioperative infection, perioperative anemia, postoperative anemia, and perioperative venous thromboembolism were defined using CIHI's Hospital Harm Framework.

†Unless otherwise specified.

Table 5. Secondary outcomes for patients undergoing surgery for HPB cancer comparing albumin transfusion recipients (cases) matched to patients who did not receive albumin transfusion (controls) in a 1:2 manner*

Type of outcome	No. (%)† of cases n = 431	No. (%)† of controls n = 862	Odds ratio (95% CI)	p value
Binary‡				
30-day all-cause mortality	15 (3.5)	9 (1.0)	3.42 (1.48–7.88)	0.0022
Perioperative infection	80 (18.6)	108 (12.5)	1.59 (1.16–2.19)	0.0037
Postoperative anemia	17 (3.9)	32 (3.7)	1.07 (0.58–1.95)	0.8368
Perioperative venous thromboembolism	12 (2.8)	10 (1.2)	2.44 (1.04–5.70.)	0.0333
Continuous, d ± SD				
Mean hospital length of stay	10.7 ± 8.9	8.8 ± 8.0		0.0001

CI = confidence interval; HPB = hepato-pancreato-biliary; SD = standard deviation.

*Matching was based on age, sex, Charlson Comorbidity Index score, erythrocyte transfusion status, surgical approach, extent of excision, and extent of liver disease. Mortality was defined as death from any cause within 30 days of surgery. Perioperative infection, postoperative anemia, and perioperative venous thromboembolism were defined using the Canadian Institute for Health Information's Hospital Harm Framework.

†Unless otherwise specified.

‡Not enough events to compute perioperative anemia.

facilitators of and barriers to adopting a restrictive approach to erythrocyte transfusion practice.[27] In Alberta, 42 intensive care physicians completed a survey and the identified barriers to reducing erythrocyte use were social influences, medical knowledge or skills, and the perceived nonissue of high erythrocyte transfusion variability.[27] The identified facilitators of reducing red blood cell transfusion included a culture of acceptance and collegial support, a multidisciplinary approach to education, and the use of clinical guidelines.[27] This suggests that both environmental and social contexts are important determinants of transfusion and, thus, transfusion variability.

Transfusion variability is not restricted to erythrocyte transfusion, as evidenced by the results of our study and other studies that highlight highly variable albumin transfusion practice and the questionable utility of albumin across different patient populations. A 2022 cross-sectional survey of cardiovascular anesthesiologists and intensivists in Canada showed that although most anesthesiologists and intensivists (≥ 90%) did not believe that mortality, renal injury, or coagulopathy were improved by albumin usage, 62% of anesthesiologists and intensivists stated that they use albumin for cardiac surgery patients.[28] Another recent Canadian study showed that for cardiac surgery patients, albumin transfusion rates ranged between 4.8% and 97.4% across hospitals and there were no significant improvements in outcomes in albumin-treated patients.[29]

The results of our study indicate that albumin transfusion rates for cancer surgery can vary from 0% to 100%. Further, we have shown that 13 of 104 hospitals included in this study had at least 1 outlier procedure for albumin transfusion that was not randomly distributed ($p = 0.0004$). These outliers were determined to be hospital specific, with a 69.23% chance that a hospital had a second outlier procedure if it already had 1 outlier in a different cancer type. Our results specific to the cancer surgery population therefore support and add to the existing literature that suggest patient factors alone are not responsible for determining transfusion practice and for driving albumin transfusion variability.

We also found that albumin-treated patients undergoing surgery for colorectal and HPB cancer correlated with greater morbidity for clinically important patient outcomes, including infection, anemia, and venous thromboembolism. No causality should be inferred between these worse outcomes and albumin transfusion owing to the limitations of our outcomes analyses, although our findings correspond with the literature that albumin transfusion is not associated with improved patient outcomes. Previous RCTs found that albumin reduces coagulation competence and levels of immunoglobulins and natural anticoagulants, which may increase susceptibility to bleeding, infection, and thrombotic events.[8,10,30–32] Importantly, a real-world quality improvement study at a single centre showed that after marked deprescribing of albumin (800 to 450 vials per month), there was no (negative) impact on patient outcomes.[33] Similar results were produced in a surgical intensive care unit (ICU), whereby a 54% reduction in albumin use led to no differences in ICU mortality or risk of death, and no significant differences in ICU mean length of stay.[34] The consistent lack of positive impact of albumin on patient outcomes and increased cost of albumin should help with efforts to commence wider deprescribing of albumin for cancer surgery.

Despite the limitations of our study (listed below), there are also several strengths. The NACRS and DAD are accurate, valid, and reliable sources of hospital administrative data.[19,20] The population-based cohort used in this study is also advantageous because it provides a comprehensive and large sample population, which minimizes sampling bias and facilitates the extrapolation of results to different settings. Another strength to our study is that all 141 343 patients included were consecutive, constituting the largest analysis of the use of albumin in cancer surgery to date, to our knowledge. To further optimize albumin utilization in cancer surgery in our jurisdiction, annual reports are being provided to all hospitals to assist with benchmarking and changing the culture surrounding albumin prescribing. In addition, albumin use across all patient types is being evaluated in the GEMINI Medicine hospital data-sharing network,[35] which includes formulation of albumin, volumes, and number of doses for more than 35 hospitals, which may provide additional granularity to assist with continuous quality improvement.

Limitations

There are limitations to our study. Routinely collected administrative data in the NACRS and DAD lack specific transfusion characteristics; for instance, factors such as the timing, location, reason, quantity, and formulation of albumin (5% or 25% albumin) are not coded in the DAD. Furthermore, with the use of matching in our study as a retrospective review, we cannot account for all the unknown variables in the study population that can cause confounding. For instance, patients who receive albumin may be sicker than those who do not receive albumin, or the decision to transfuse albumin is hospital dependent. Without an understanding of this information, we could not provide in-depth granularity to identify the main source of albumin transfusion variability and the causality of the relationship between albumin transfusion and patient outcomes.

Conclusion

We found wide variation in albumin transfusion for patients undergoing surgery for cancer. This variation was not randomly distributed between hospitals. In addition,

our analysis suggests that albumin transfusion did not improve outcomes in this population. To determine the relationship between albumin transfusion and patient outcomes, more detailed patient data are required to allow for stringent matching and the minimization of unmeasured confounding between patients who received albumin transfusion and those who did not. Overall, our primary variability analysis suggests a need to investigate hospital-level determinants of variable albumin transfusion practice to optimize the care of this surgical population and allow for better utilization of this scarce blood product.

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Competing interests: Amber Hunter is an employee of Ontario Health. Justyna Bartoszko reports receiving grants from Octapharma, Grifols, and Canadian Blood Services, and honoraria and travel support from Octapharma. Dr. Bartoszko also reports participating on a data safety monitoring board for Octapharma. Frances Wright reports receiving funding from Cancer Care Ontario in the role of surgical oncology provincial lead (in support of the current manuscript). Dr. Wright also reports receiving travel support from AIM Melanoma (outside the submitted work). Jeannie Callum reports receiving consulting fees and speaking fees from Octapharma. Dr. Callum also reports participation on a data safety monitoring board for the FEISTY trial, and has held the role of board member of the Canadian Hematology Society. No other competing interests were declared.

Contributors: Jane Yang and Amber Hunter designed the study. Frances Wright acquired the data, which Tharsiya Martin, Victor Mak, Mohammed Rashid, Liying Zhang, Justyna Bartoszko, Jesse Zuckerman, and Julie Hallet analyzed. Jane Yang and Tharsiya Martin wrote the manuscript, which Victor Mak, Mohammed Rashid, Liying Zhang, Justyna Bartoszko, Jesse Zuckerman, Julie Hallet, Frances Wright, and Jeannie Callum revised critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Data disclaimer: Parts of this material are based on data and information provided by Ontario Health (Cancer Care Ontario) and include data received by Ontario Health (Cancer Care Ontario) from the Canadian Institute for Health Information (CIHI) and ICES. The opinions, reviews, views, and conclusions reported in this publication are those of the authors and do not necessarily reflect those of Ontario Health (Cancer Care Ontario), CIHI, and/or ICES. No endorsement by Ontario Health (Cancer Care Ontario) is intended or should be inferred.

Data accessibility statement: Ontario Health is prohibited from making the data used in this research publicly accessible if it includes potentially identifiable personal health information and/or personal information as defined in Ontario law, specifically the *Personal Health Information Protection Act* and the *Freedom of Information and Protection of Privacy Act*. Upon request, data de-identified to a level suitable for public release may be provided.

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