


Significant Variation in Blood Transfusion Practice Persists following Upper GI Cancer Resection

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Abstract

Purpose Perioperative blood transfusions are costly and linked to adverse clinical outcomes. We investigated the factors associated with variation in blood transfusion utilization following upper gastrointestinal cancer resection and its association with infectious complications.

Methods The Statewide Planning and Research Cooperative System was queried for elective esophagectomy, gastrectomy, and pancreatectomy for malignancy in NY State from 2001 to 2013. Bivariate and hierarchical logistic regression analyses were performed to assess the factors associated with receiving a perioperative allogeneic red blood cell transfusion. Additional multivariable analysis examined the relationship between transfusion and infectious complications.

Results Among 14,875 patients who underwent upper GI cancer resection, 32 % of patients received a perioperative blood transfusion. After controlling for patient, surgeon, and hospital-level factors, significant variation in transfusion rates was present across both surgeons ($p < 0.0001$) and hospitals ($p < 0.0001$). Receipt of a blood transfusion was also independently associated with wound infection (OR=1.68, 95% CI=1.47 and 1.91), pneumonia (OR=1.98, 95% CI=1.74 and 2.26), and sepsis (OR=2.49, 95% CI=2.11 and 2.94).

Conclusion Significant variation in perioperative blood transfusion utilization is present at both the surgeon and hospital level. These findings are unexplained by patient-level factors and other known hospital characteristics, suggesting that variation is due to provider preferences and/or lack of standardized transfusion protocols. Implementing institutional transfusion guidelines is necessary to limit unwarranted variation and reduce infectious complication rates.

Keywords Blood transfusion · Upper gastrointestinal tract · Neoplasms · Health services research

Introduction

Nearly 14 million units of allogeneic red blood cells (RBCs) are transfused each year in the USA, and at least 20 % of these transfusions are administered perioperatively to surgical patients.¹ While blood transfusions may be vital in improving oxygen delivery to tissues in some circumstances, there has been increasing evidence that there may be adverse postoperative outcomes associated with their use.² Many of these complications have been attributed to transfusion-related immunomodulation (TRIM) resulting in a higher risk of postoperative infectious complications and cancer recurrence following oncologic resection.^{3–8} Because of this growing

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concern for post-transfusion adverse outcomes, a lack of benefit for using liberal transfusion strategies, and a goal of reducing consumption of a scarce resource, blood transfusion guidelines favoring restrictive transfusion triggers with a hemoglobin threshold between 7 and 8 g/dL for most patients have been developed to limit unnecessary utilization.^{2, 8, 9}

Despite the existence of general practice guidelines for the use of RBC transfusions over the past few decades, numerous studies have demonstrated wide variation in blood transfusion utilization following surgical procedures. Over 20 years ago, Goodnough et al. demonstrated large variation in the rate of perioperative transfusion of RBCs (range=17–100 %), plasma (range=0–97 %), and platelets (range=0–80 %) between hospitals for coronary artery bypass graft surgery despite controlling for patient and surgical practice factors.¹⁰ Since then, additional studies have further confirmed those results for cardiac surgery.^{11, 12} Similar hospital variability has been shown for orthopedic surgery with significant differences in RBC transfusion practices between hospitals following total hip and knee replacement.^{13–15} However, there is a paucity of data examining contemporary blood transfusion utilization for procedures outside of cardiac and orthopedic surgery.

Given these limitations in the literature, the aim of this study was to investigate patient, surgeon, and hospital-level factors associated with perioperative allogeneic RBC transfusion in patients undergoing elective upper gastrointestinal cancer resection using a large, population-based database. Furthermore, the study analyzes the variation in blood transfusion utilization at both the surgeon and hospital level and assesses the association between perioperative RBC transfusion and the postoperative infectious complications of deep wound infection, pneumonia, and sepsis.

Materials and Methods

Study Population

The Statewide Planning and Research Cooperative System (SPARCS), a hospital discharge database established by the New York Department of Health, was utilized for this study. SPARCS includes patient-level data for all hospital admissions, ambulatory surgery procedures, and emergency department visits within New York State and has been used extensively for research purposes, both on their own and as part of the Healthcare Cost and Utilization Project (HCUP) databases.^{16, 17} These data are abstracted from medical records by trained medical records personnel, verified for accuracy by the Department of Health, and include a unique patient identifier, patient demographics, up to 25 diagnostic codes with present-on-admission indicators, up to 15 procedures codes, and unique hospital and surgeon identifiers. The data are also

linked to New York State Vital Records to obtain mortality information.

Inclusion/Exclusion Criteria

The SPARCS inpatient file was queried for all elective admissions for esophagectomy, gastrectomy, or pancreatectomy for malignancy using *International Classification of Diseases, Ninth Revision* (ICD-9) codes. From these claims, patients at least 18 years old with a primary or secondary diagnosis of esophageal cancer (ICD-9=150.0–151.0) who underwent esophagectomy (ICD-9=42.40–42.42), gastric cancer (ICD-9=151.0–151.9) who underwent partial gastrectomy (ICD-9=43.5–43.7, 43.81–43.89) or total gastrectomy (ICD-9=43.91–43.99), or hepatobiliary cancer (ICD-9=152.0, 156.1–156.8, 157.0–157.9) who underwent distal pancreatectomy (ICD-9=52.52) or pancreaticoduodenectomy (ICD-9=52.7) between January 1, 2001 and December 31, 2013 were selected. Patients who had non-elective admission to the hospital or who had a missing unique surgeon identifier were excluded. In addition, because the date of blood transfusion is not captured for many patients in SPARCS, patients who were admitted prior to the date of surgery were necessarily excluded to ensure that blood transfusions were not administered preoperatively (Fig. 1).

Outcome Measures

The primary outcome was the receipt of a perioperative (intraoperative or postoperative) allogeneic red blood cell transfusion. The receipt of a blood transfusion was captured either through ICD-9 procedural coding (ICD-9=99.03, 99.04) or ancillary revenue codes for red blood cell products (code=0381, 0382) and transfusion (code=0391). Because the number of units of blood product is not captured in SPARCS, the receipt of a blood transfusion was only characterized as a dichotomous outcome.

Secondary outcome measures included the postoperative infectious complications of deep wound infection, pneumonia, and sepsis. These adverse outcomes were captured using secondary diagnosis codes categorized as “not present-on-admission.” The inclusion and exclusion criteria and corresponding ICD-9 coding for these complications were previously described and validated by Silber et al.¹⁸

Patient-Level Factors

Patient factors considered for the analyses were age, sex, race, insurance type, active tobacco use, and the 30 comorbidities included in the Elixhauser Comorbidity Index, including several factors that would influence the likelihood of receiving a blood transfusion, such as anemia, congestive heart failure, end-stage renal disease, and coagulation disorders. These

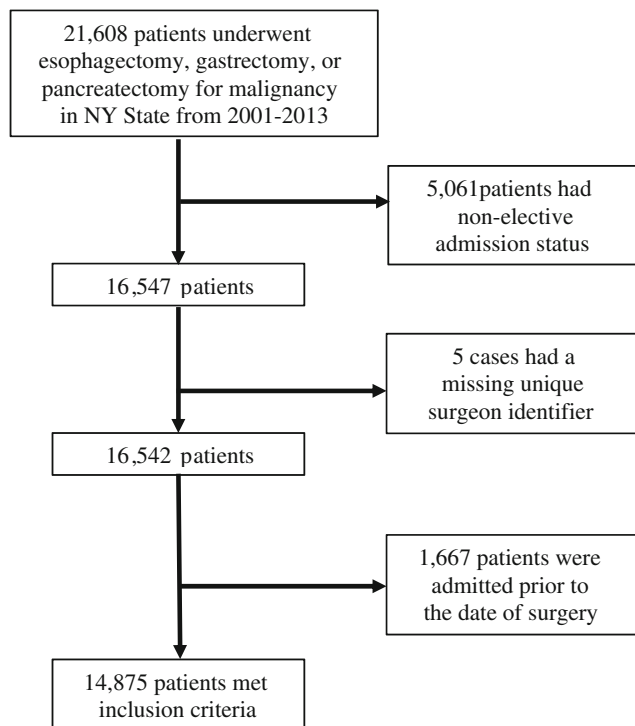


Fig. 1 Flow chart of exclusion criteria process to determine initial patient cohort

patient comorbidities were extracted from the current claim as well as all claims up to 1 year prior to the index operation based upon ICD-9 diagnostic codes using the Elixhauser Comorbidity Index method.¹⁹

Surgeon-Level Factors

Procedure-specific individual surgeon procedure volumes were calculated as the total number of esophagectomies, gastrectomies, or pancreatectomies for cancer performed during that calendar year by that individual surgeon using the unique surgeon identifier. Because individual surgeon volumes fluctuated over the years, surgeon volumes were calculated for each individual calendar year. Volume was then categorized into procedure-specific tertiles. The volume categories for esophagectomy were low (1–3 cases/year), medium (4–9 cases/year), and high (≥ 10 cases/year). The volume categories for gastrectomy were low (1–2 cases/year), medium (3–5 cases/year), and high (≥ 6 cases/year). The volume categories for pancreatectomy were low (1–4 cases/year), medium (5–19 cases/year), and high (≥ 20 cases/year).

Hospital-Level Factors

Procedure-specific individual hospital procedure volumes were calculated as the total number of esophagectomies, gastrectomies, or pancreatectomies for cancer performed during

that calendar year by that individual hospital using the unique hospital identifier. Because individual hospital volumes fluctuated over the years, hospital volumes were calculated for each individual calendar year. Volume was then categorized into procedure-specific tertiles. The volume categories for esophagectomy were low (1–9 cases/year), medium (10–29 cases/year), and high (≥ 30 cases/year). The volume categories for gastrectomy were low (1–7 cases/year), medium (8–24 cases/year), and high (≥ 25 cases/year). The volume categories for pancreatectomy were low (1–14 cases/year), medium (15–39 cases/year), and high (≥ 40 cases/year).

In addition to facility volume, hospital characteristics included major academic status based upon Council of Teaching Hospitals (COTH) designation and facility location (urban or rural). The American Hospital Association Annual Survey was used to identify facilities considered to be major academic centers.

Propensity Score Analysis

Because of the observational nature of the data and potential for selection bias with respect to which patients received a blood transfusion for the secondary analysis involving infectious complications, a propensity score for each patient was estimated to determine the probability of receiving a perioperative blood transfusion. The propensity score was estimated using the same multivariable model used to assess the factors associated with the primary outcome of receipt of a blood transfusion. In order to avoid reduction in study size, the propensity score was used as a continuous variable and entered as a covariate in the multivariable models as has been previously described.^{20–24}

Statistical Analysis

Patient, operative, surgeon, and hospital characteristics were assessed using Pearson's chi-square test, Mann–Whitney *U* test, and Cochran-Armitage test for trend as appropriate to the data. Clinically appropriate variables with a *p* value of less than 0.1 were manually entered in multivariable analysis. To account for clustering of outcomes among surgeons and hospitals, a three-level mixed-effects logistic regression model was used for the primary outcome of perioperative blood transfusion, as well as the secondary outcomes of deep wound infection, pneumonia, and sepsis. The models estimated random effects for each individual surgeon and hospital identifier.

To identify individual surgeons and hospitals who were significant outliers with regard to blood transfusion utilization, exact Poisson 95 % confidence intervals (CI) were calculated for the risk-adjusted observed/expected (O/E) ratios for each surgeon and hospital. The observed represents the total number of patients who received a blood transfusion, and the expected was calculated by summing the probability of

receiving a blood transfusion across all patients. Only surgeons and hospitals that performed at least 10 cases over the 2001 to 2013 study period were included in this analysis. Low outliers (low blood transfusion utilization) were defined as surgeons or hospitals with an O/E ratio significantly less than one, and high outliers (high blood transfusion utilization) were those with an O/E ratio significantly greater than one.

For the mixed-effects models, the glmer function in the lme4 package was used in R version 3.1.0 (R Foundation for Statistical Computing). All other analyses were performed using SAS, Version 9.3 (SAS Institute, Cary, NY, USA). The study was approved by both the University of Rochester (IRB #00054886) and the New York State Department of Health institutional review boards.

Results

Population Characteristics

Out of 21,608 patients who underwent esophagectomy, gastrectomy, or pancreatectomy for malignancy between 2001 and 2013 in New York State, 14,875 patients met inclusion criteria. Of the 6733 patients who were excluded, 5061 patients had a non-elective admission for the index hospital stay, 5 had a missing unique surgeon identifier, and 1667 were admitted to the hospital prior to the date of surgery (Fig. 1). Patient, surgeon, and facility characteristics are presented in Table 1. For the procedure type, 14 % of the cohort underwent esophagectomy, 49 % underwent partial or total gastrectomy, and 37 % underwent distal pancreatectomy or pancreaticoduodenectomy.

Blood Transfusion

The overall rate of perioperative red blood cell transfusion was 32 %. The unadjusted blood transfusion rate varied according to procedure type from 22 % for esophagectomy to as high as 41 % for total gastrectomy. Among individual surgeons and hospitals that performed at least 10 cases during the study period, large variation in transfusion utilization was seen across both surgeons and hospitals. Unadjusted blood transfusion rates ranged from 0 to 82 % for individual surgeons and 0 to 64 % for individual hospitals. Using a test for trend, there was no significant change in the overall rate of transfusion observed over the 2001 to 2013 study period ($p=0.57$).

Bivariate results of factors associated with blood transfusion are presented in Table 2. In addition to patient-level factors, several surgeon and hospital-level factors, including low surgeon procedure volume, low hospital procedure volume, non-academic hospital status, and rural hospital location, were significantly associated with higher blood transfusion utilization. After controlling for relevant covariates in a hierarchical

Table 1 Patient, operative, surgeon, and hospital characteristics

Characteristic	Value (N=14,875)
Patient-level characteristics	
Age (median) (interquartile range)	66 (17)
Sex, n (%)	
Male	9170 (61.6)
Female	5705 (38.4)
Race, n (%)	
White	10,923 (73.4)
Black	1287 (8.7)
Other	2236 (15.0)
Unknown	429 (2.9)
Medicaid insurance, n (%)	2161 (14.5)
Comorbidities, n (%)	
Anemia	824 (5.5)
Congestive heart failure	684 (4.6)
End-stage renal disease	516 (3.5)
Coagulation disorder	391 (2.6)
Active tobacco use, n (%)	1083 (7.3)
Blood transfusion within previous year, n (%)	1258 (8.5)
Metastasis, n (%)	
Lymph node	5224 (35.1)
Distant	3084 (20.7)
Procedure type, n (%)	
Esophagectomy	2007 (13.5)
Partial gastrectomy	5121 (34.4)
Total gastrectomy	2185 (14.7)
Distal pancreatectomy	1232 (8.3)
Pancreaticoduodenectomy	4330 (29.1)
Operative approach, n (%)	
Open	12,394 (83.3)
Minimally invasive	2481 (16.7)
Surgeon-level characteristics	
Procedure volume, n (%)	
Low	3943 (26.5)
Medium	4314 (29.0)
High	6618 (44.5)
Hospital-level characteristics	
Procedure volume, n (%)	
Low	3277 (22.0)
Medium	4719 (31.7)
High	6879 (46.3)
Academic status, n (%)	
Major academic	11,880 (79.9)
Non-academic	2995 (20.1)
Hospital location, n (%)	
Urban	14,700 (98.8)
Rural	175 (1.2)

Table 2 Bivariate analysis assessing factors associated with perioperative blood transfusion

	No transfusion (<i>n</i> =10,158; 68.3 %)	Transfusion (<i>n</i> =4,717; 31.7 %)	<i>p</i> value
Patient factors			
Age (years)			<0.0001
<65	4998 (49.2)	1759 (37.3)	
65–79	4191 (41.3)	2301 (48.8)	
≥80	969 (9.5)	657 (13.9)	
Sex			0.05
Male	6317 (62.2)	2853 (60.5)	
Female	3841 (37.8)	1864 (39.5)	
Race			0.14
White	7402 (72.9)	3521 (74.6)	
Black	891 (8.8)	396 (8.4)	
Other	1563 (15.4)	673 (14.3)	
Unknown	302 (2.9)	127 (2.7)	
Medicaid insurance	1533 (15.1)	628 (13.3)	0.004
Comorbidities			
Anemia	466 (4.6)	358 (7.6)	<0.0001
Congestive heart failure	351 (3.5)	333 (7.1)	<0.0001
End-stage renal disease	255 (2.5)	261 (5.5)	<0.0001
Coagulation disorder	204 (2.0)	187 (4.0)	<0.0001
Active tobacco use	779 (7.7)	304 (6.4)	0.007
Blood transfusion within previous year	619 (6.1)	639 (13.5)	<0.0001
Procedure type			
Esophagectomy	1178 (11.6)	829 (17.6)	<0.0001
Partial gastrectomy	3963 (39.0)	1158 (24.5)	
Total gastrectomy	1437 (14.2)	748 (15.9)	
Distal pancreatectomy	915 (9.0)	317 (6.7)	
Pancreaticoduodenectomy	2665 (26.2)	1665 (35.3)	
Operative approach			
Open	8249 (81.2)	4145 (87.9)	<0.0001
Minimally invasive	1909 (18.8)	572 (12.1)	
Surgeon factors			
Procedure volume			
Low	2558 (25.2)	1385 (29.4)	<0.0001
Medium	2859 (28.1)	1455 (30.8)	
High	4741 (46.7)	1877 (39.8)	
Hospital factors			
Procedure volume			
Low	2137 (21.0)	1140 (24.2)	<0.0001
Medium	3197 (31.5)	1522 (32.3)	
High	4824 (47.5)	2055 (43.6)	
Academic status			
Major academic	8174 (80.5)	3706 (78.6)	0.007
Non-academic	1984 (19.5)	1011 (21.4)	
Hospital location			
Urban	10,051 (98.9)	4649 (98.6)	0.04
Rural	107 (1.1)	68 (1.4)	

mixed-effects multivariable analysis, the hospital-level factors of procedure volume, academic status, and location were no longer significant (Table 3). Low-volume surgeons were

Table 3 Hierarchical mixed-effects model assessing factors associated with perioperative blood transfusion

	Odds ratio (95 % CI)	<i>p</i> value
Patient-level factors		
Age (years)		
<65	Reference	
65–79	1.58 (1.45, 1.71)	<0.0001
≥80	2.08 (1.83, 2.37)	<0.0001
Sex		
Male	Reference	
Female	1.14 (1.05, 1.24)	0.001
Comorbidities		
Anemia	1.34 (1.12, 1.59)	0.0009
Congestive heart failure	1.60 (1.34, 1.91)	<0.0001
End-stage renal disease	1.74 (1.42, 2.13)	<0.0001
Coagulation disorder	1.55 (1.23, 1.94)	0.0002
Active tobacco use	0.87 (0.75, 1.02)	0.08
Blood transfusion within previous year	2.15 (1.86, 2.48)	<0.0001
Procedure type		
Partial gastrectomy	Reference	<0.0001
Total gastrectomy	2.01 (1.77, 2.28)	<0.0001
Esophagectomy	1.90 (1.64, 2.19)	<0.0001
Distal pancreatectomy	1.56 (1.31, 1.86)	<0.0001
Pancreaticoduodenectomy	2.87 (2.53, 3.26)	<0.0001
Operative approach		
Minimally invasive	Reference	
Open	1.23 (1.09, 1.40)	0.0007
Surgeon-level factors		
Procedure volume*		
High	Reference	
Medium	1.08 (0.95, 1.23)	0.22
Low	1.16 (1.00, 1.35)	0.04
Hospital-level factors		
Procedure volume*		
High	Reference	
Medium	0.92 (0.80, 1.07)	0.28
Low	1.16 (0.95, 1.42)	0.15
Academic status		
Major academic	Reference	
Non-academic	1.04 (0.78, 1.38)	0.81
Hospital location		
Urban	Reference	
Rural	1.13 (0.61, 2.09)	0.69

*Due to a high degree of collinearity ($R=0.625$) between surgeon and hospital procedure volume, separate multivariable analyses were performed including either surgeon or hospital volume in the model. The model had good predictive ability with a c-statistic of 0.74

associated with 16 % higher odds of blood transfusion compared to high-volume surgeons.

After adjusting for these patient, surgeon, and hospital-level factors in the multivariable analysis, significant variation was still present among individual surgeons ($p<0.0001$) and hospitals ($p<0.0001$). Only 2 % of the surgeon-level variation was explained by surgeon procedure volume, and only 11 % of the hospital-level variation was explained by the hospital characteristics of hospital procedure volume, academic status, and hospital location. Of the remaining variation not explained by the multivariable model, 42 % was due to surgeon-level factors and 58 % due to hospital-level factors. After excluding 939 surgeons and 72 hospitals that performed less than 10 cases over the study period to reduce random statistical variation, 223 surgeons and 99 hospitals were evaluated for status as outliers using risk-adjusted observed/expected ratios. Among surgeons, 28 % were low outliers, 59 % were non-outliers, and 13 % were high outliers (Fig. 2). Among hospitals, 24 % were low outliers, 61 % were non-outliers, and 15 % were high outliers (Fig. 3).

Propensity Analysis

The propensity score for receipt of a blood transfusion had good predictive ability with a c-statistic of 0.74 (area under the receiver operating characteristic curve). All of the variables included in the propensity score model are listed in Table 3.

Infectious Complications

The overall rates of deep wound infection, pneumonia, and sepsis were 7.7, 8.2, and 4.5 %, respectively, for the entire study cohort. Receipt of a perioperative blood transfusion was associated with significantly higher unadjusted rates of each of the infectious complications, including deep wound infection (10.7 vs. 6.4 %), pneumonia (12.2 vs. 6.4 %), and sepsis (7.8 vs. 3.0 %). After adjusting for patient, operative, surgeon, and hospital factors as well as the propensity score during multivariable analysis, perioperative blood transfusion

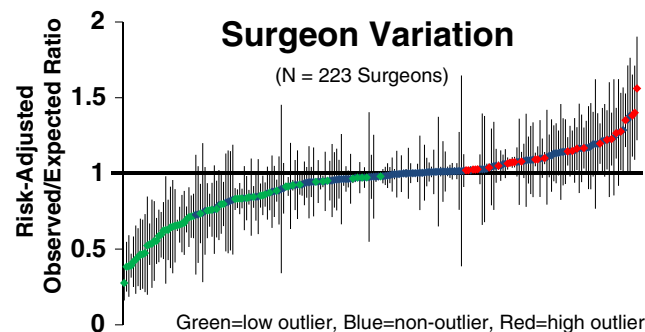


Fig. 2 Graph demonstrating surgeon-level variation and low and high outliers related to RBC transfusion utilization

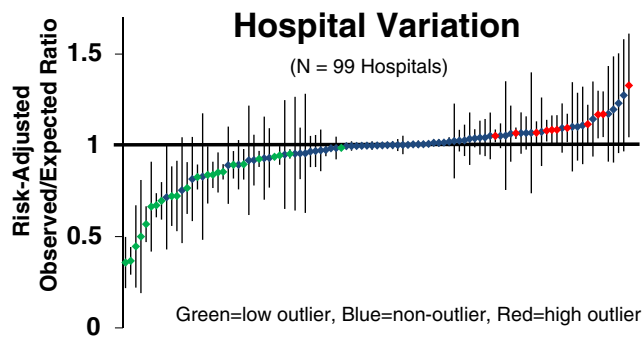


Fig. 3 Graph demonstrating hospital-level variation and low and high outliers related to RBC transfusion utilization

was independently associated with increased odds of deep wound infection (odds ratio [OR]=1.64, 95 % CI=1.43, 1.89), pneumonia (OR=1.93, 95 % CI=1.69, 2.22), and sepsis (OR=2.34, 95 % CI=1.96, 2.78) (Table 4).

Discussion

This study demonstrated that marked variation in perioperative RBC transfusion utilization persists across both surgeons and hospitals following elective upper gastrointestinal cancer resection. Thirteen percent of surgeons and 15 % of hospitals were considered high outliers for blood transfusion utilization. Furthermore, surgeon volume accounted for only 2 % of the variation between surgeons, and known hospital characteristics explained only 11 % of the variation between hospitals. In addition, no change in the overall rate of transfusion was observed over the 2001 to 2013 study period. These findings suggest that the wide variation in transfusion practices is most likely due to provider preferences or lack of standardized transfusion protocols. Unfortunately, this surgeon and hospital variation were not without major consequences to patients as blood transfusions were independently associated with postoperative deep wound infection, pneumonia, and sepsis.

Despite the creation of general practice guidelines by various healthcare organizations for the use of RBC transfusions several decades ago, several recent large studies investigating perioperative transfusion rates continue to show marked variation across hospitals in the USA.²⁵ In fact, in a study by Bennett-Guerrero et al. including over 80,000 cases at 408 different institutions, a 7.7-fold difference in perioperative RBC transfusion usage between hospitals in 2008 was observed for coronary artery bypass graft surgery patients even after adjusting for patient risk factors.²⁶ Similarly, Qian et al. demonstrated dramatic variation in RBC, fresh frozen plasma, and platelet transfusion utilization between 77 academic hospitals following approximately 80,000 cases of total hip replacement, colectomy, or pancreaticoduodenectomy performed between 2006 and 2010.²⁷

Aside from the study by Qian et al., the current study is one of the first to investigate the variation in blood transfusion usage for surgical procedures outside of cardiac and orthopedic surgery. Furthermore, it is one of the first studies to analyze both surgeon and hospital-level variation. While most previous studies have focused solely on hospital-level variability, the current study found that 42 % of the unexplained variation in blood transfusion utilization resided at the surgeon level. To date, only small, single-hospital studies have specifically investigated surgeon variation in blood transfusion usage in the USA. Several studies by Ejaz et al. using an institutional prospective database have demonstrated variability between surgeons regarding perioperative blood transfusion utilization, indication for transfusion (“trigger”), and transfusion goal (“target”) in patients undergoing major gastrointestinal surgery.^{28–30} Using data from 2010 to 2013, the authors found that one in four patients who received an intraoperative blood transfusion had a hemoglobin level of 10 g/dL or more.²⁸ Furthermore, they found significant differences in the mean hemoglobin level trigger and target across surgical services and individual surgeons for perioperative transfusion usage.²⁹

Unfortunately, this wide variation is present despite the existence of numerous national evidence-based blood transfusion guidelines supporting restrictive use of RBC transfusions.^{2–9–31} These guidelines are largely based on multiple randomized clinical trials that have demonstrated equivalent or superior outcomes for restrictive use of blood transfusion with a hemoglobin threshold between 7 and 8 g/dL compared to liberal use protocols that utilize higher hemoglobin level transfusion triggers.^{32–36} In fact, some have argued for clinical trials using an even lower hemoglobin threshold of 5 or 6 g/dL.³⁷ This push toward restrictive blood transfusion usage is due to a growing body of literature regarding adverse outcomes secondary to TRIM.

The immunologic effects of blood transfusions were first discovered in the late 1970s when Opelz and Terasaki described an improvement in kidney transplant graft survival in patients who received an increased number of blood transfusions.³⁸ Since then, the paradigm of “blood must be good” has been seriously called into question as studies have begun establishing a causative mechanism between blood transfusions and infectious complications as a result of TRIM.^{39–41} The current study further establishes this association between blood transfusions and postoperative infections as RBC transfusions were independently associated with deep wound infection, pneumonia, and sepsis. A large study by Bernard et al. including over 125,000 general surgery patients from the National Surgical Quality Improvement Program (NSQIP) database had similar findings.³ The authors reported that intraoperative transfusion of packed RBCs was associated with increased rates of morbidity, surgical site infection, pneumonia, sepsis, and 30-day mortality. An even larger study

Table 4 Hierarchical mixed-effects model assessing factors associated with infectious complications following upper GI cancer resection

Factor	Deep wound infection* Odds ratio (95 % CI)	Pneumonia* Odds ratio (95 % CI)	Sepsis* Odds ratio (95 % CI)
Age (years)			
<65	–	Reference	Reference
65–79	–	1.07 (0.93, 1.24)	1.32 (1.10, 1.58)
≥80	–	1.07 (0.85, 1.35)	1.46 (1.11, 1.94)
Sex			
Female	Reference	Reference	Reference
Male	1.23 (1.08, 1.40)	1.52 (1.33, 1.75)	1.53 (1.29, 1.83)
Race			
White	–	Reference	Reference
Black	–	0.69 (0.53, 0.90)	0.88 (0.65, 1.20)
Other	–	0.85 (0.69, 1.05)	0.96 (0.75, 1.22)
Unknown	–	0.99 (0.67, 1.47)	0.67 (0.37, 1.23)
Comorbidities			
CHF	1.40 (1.06, 1.83)	1.73 (1.34, 2.21)	–
Diabetes mellitus	0.85 (0.73, 1.00)	0.79 (0.67, 0.92)	–
COPD	–	1.68 (1.45, 1.95)	–
ECS≥3	–	–	0.99 (0.84, 1.17)
Metastasis			
Lymph nodes	–	0.89 (0.78, 1.01)	–
Distant	1.16 (0.99, 1.35)	–	–
Operative approach			
Minimally invasive	Reference	Reference	Reference
Open	1.23 (1.02, 1.49)	1.30 (1.06, 1.60)	1.00 (0.78, 1.29)
Procedure type			
Partial gastrectomy	Reference	Reference	Reference
Total gastrectomy	1.71 (1.38, 2.10)	1.64 (1.35, 2.01)	2.03 (1.56, 2.64)
Esophagectomy	1.84 (1.47, 2.30)	1.89 (1.54, 2.32)	2.30 (1.75, 3.02)
Distal pancreatectomy	0.68 (0.48, 0.97)	0.87 (0.64, 1.17)	0.99 (0.65, 1.51)
Pancreaticoduodenectomy	2.23 (1.82, 2.74)	0.76 (0.60, 0.96)	1.70 (1.30, 2.23)
Surgeon volume			
High	Reference	Reference	Reference
Medium	1.16 (0.96, 1.40)	1.15 (0.95, 1.39)	1.10 (0.87, 1.40)
Low	1.25 (1.01, 1.54)	1.32 (1.07, 1.62)	1.56 (1.21, 2.00)
Academic status			
Non-academic	Reference	–	–
Major academic	1.27 (1.00, 1.60)	–	–
Propensity score	1.30 (0.74, 2.29)	1.48 (0.77, 2.85)	2.77 (1.29, 5.93)
Blood transfusion	1.64 (1.43, 1.89)	1.93 (1.69, 2.22)	2.34 (1.96, 2.78)

CHF congestive heart failure, COPD chronic obstructive pulmonary disease, ECS Elixhauser comorbidity score

*Separate multivariable analyses were performed for each of the infectious complication outcomes.

by Ferraris et al. using NSQIP that included 941,496 non-cardiac surgical cases demonstrated that even intraoperative transfusion of only 1 unit of packed RBCs was associated with increased odds of postoperative wound problems, pulmonary complications, renal dysfunction, sepsis, length of stay, and mortality.⁷

Given the strong association between blood transfusions and infectious complications, numerous studies have attempted to elucidate the exact mechanism behind this immunomodulatory phenomenon. Proposed reasons include decreases in the helper/suppressor T-lymphocyte ratio, killer cell function, efficacy of antigen presentation, or delayed-type

hypersensitivity, suppression of blastogenesis, and the development of tolerance to specific antigens.^{39–42, 43} While the exact mechanism remains unknown, randomized controlled trials have shown that modification of stored red blood cells, such as leukoreduction, can improve inflammatory responses and reduce the adverse effects of RBC transfusion.⁴ These trials have demonstrated a reduction in the incidence of postoperative infection by 30–71 % with the use of white blood cell reduction prior to the transfusion of packed RBCs in surgical patients.^{44–46} However, despite this evidence, there has been strong opposition by some physicians from academic blood banks against the Food and Drug Administration's proposed plan for a universal leukocyte reduction mandate due to the high medical costs of leukoreduction.⁴⁷ As a result, policies regarding white blood cell reduction remain at the institutional level. Furthermore, there is some evidence to suggest that other non-leukocyte mechanisms may also be involved in the development of TRIM.⁴⁸

For these reasons, limiting unwarranted variation in blood transfusion usage through the adoption and implementation of institutional perioperative blood transfusion protocols remains the most effective method of reducing TRIM and subsequent risk of postoperative infection. According to the most recent National Blood Collection and Utilization Survey Report in 2011, only 27 % of reporting hospitals had institutional guidelines in place promoting restrictive use of postoperative transfusions.¹ Future work should focus on adopting new quality improvement initiatives focusing on the creation of blood conservation programs at these institutions. This strategy would not only protect a scarce, life-saving resource when used appropriately but also reduce the risk of postoperative infectious complications.

Despite its potentially impactful findings, this study is not without limitations. First, the SPARCS database is comprised of administrative data that lacks detailed clinical information related to surgical technique, a comprehensive list of medical comorbidities, provider decision-making, and patient preferences. An additional limitation is that preoperative anemia was captured using administrative coding instead of from laboratory hemoglobin or hematocrit levels. Without preoperative laboratory values available, it is not known whether the provider was utilizing appropriate transfusion triggers consistent with the current evidence-based practice guidelines. Other pathologic- or tumor-related factors that might affect the need for blood transfusions are also not available in the database. Furthermore, while the data is abstracted from medical records by trained personnel, the possibility of ICD-9 miscoding error does exist. The date of transfusion and number of units of RBCs transfused are also not captured making it difficult to know whether the blood transfusion preceded the infectious complication or whether a dose–response relationship existed between the amount of blood transfused and the rate of infectious complications. However, previous studies have already

established a causal mechanism and dose–response relationship between allogeneic blood transfusions and infectious complications.^{40–41} In addition, we utilized a propensity score to reduce potential selection bias with regard to which patients received a blood transfusion and their risk of an infectious complication.

Notwithstanding these limitations, this is one of the first studies to examine both surgeon-level and hospital variation using a large population-based database. Previous studies have either been single-institution studies or only investigated hospital-level variability in blood transfusion utilization. It is also one of the few large studies that have looked at variation in transfusion practices outside of cardiac and orthopedic surgery. Furthermore, the study is population-based which provides real world data regarding current transfusion practices at all non-Veteran Administration hospitals across New York State.

Conclusion

Significant variation in perioperative blood transfusion utilization following elective upper gastrointestinal cancer resection is present across both surgeons and hospitals. This variation is not explained by patient-level factors, surgical volume, or other known hospital characteristics, suggesting that it is largely due to provider preferences or lack of standardized transfusion protocols. The adoption and implementation of perioperative blood transfusion guidelines aimed at limiting unwarranted variation in transfusion practices are necessary to reduce the risk of infectious complications.

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