Association Among Blood Transfusion, Sepsis, and Decreased Long-term Survival After Colon Cancer Resection

Christopher T. Aquina, MD, MPH, Neil Blumberg, MD,† Adan Z. Becerra, BA,* Francis P. Boscoe, PhD,‡ Maria J. Schymura, PhD,‡ Katia Noyes, PhD, MPH,* John R. T. Monson, MD,*§ and Fergal J. Fleming, MD**

Objective: To investigate the potential additive effects of blood transfusion and sepsis on colon cancer disease-specific survival, cardiovascular disease-specific survival, and overall survival after colon cancer surgery.

Background: Perioperative blood transfusions are associated with infectious complications and increased risk of cancer recurrence through systemic inflammatory effects. Furthermore, recent studies have suggested an association among sepsis, subsequent systemic inflammation, and adverse cardiovascular outcomes. However, no study has investigated the association among transfusion, sepsis, and disease-specific survival in postoperative patients.

Methods: The New York State Cancer Registry and Statewide Planning and Research Cooperative System were queried for stage I to III colon cancer resections from 2004 to 2011. Propensity-adjusted survival analyses assessed the association of perioperative allogeneic blood transfusion, sepsis, and 5-year colon cancer disease-specific survival, cardiovascular disease-specific survival, and overall survival.

Results: Among 24,230 patients, 29% received a transfusion and 4% developed sepsis. After risk adjustment, transfusion and sepsis were associated with worse colon cancer disease-specific survival [(+)transfusion: hazard ratio (HR) 1.19, 95% confidence interval (CI) 1.09–1.30; (+)sepsis: HR 1.84, 95% CI 1.44–2.35; (+)transfusion/(+)sepsis: HR 2.27, 95% CI 1.87–2.76], cardiovascular disease-specific survival [(+)transfusion: HR 1.18, 95% CI 1.04–1.33; (+)sepsis: HR 1.63, 95% CI 1.14–2.31; (+)transfusion/(+)sepsis: HR 2.04, 95% CI 1.58–2.63], and overall survival [(+)transfusion: HR 1.21, 95% CI 1.14–1.29; (+)sepsis: HR 1.76, 95% CI 1.48–2.09; (+)transfusion/(+)sepsis: HR 2.36, 95% CI 2.07–2.68] relative to (−)transfusion/(−)sepsis. Additional analyses suggested an additive effect with those who both received a blood transfusion and developed sepsis having even worse survival.

Conclusions: Perioperative blood transfusions are associated with shorter survival, independent of sepsis, after colon cancer resection. However, receiving a transfusion and developing sepsis has an additive effect and is associated with even worse survival. Restrictive perioperative transfusion practices are a possible strategy to reduce sepsis rates and improve survival after colon cancer surgery.

From the *Surgical Health Outcomes and Research Enterprise (SHORE), Department of Surgery, University of Rochester Medical Center, Rochester, NY; †Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY; ‡New York State Cancer Registry, New York State Department of Health, Albany, NY; and §Center for Colon and Rectal Surgery, Florida Hospital Medical Group, University of Central Florida College of Medicine, Orlando, FL.

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Reprints: Christopher T. Aquina, MD, MPH, University of Rochester Medical Center, 601 Elmwood Ave, Box SURG, Rochester, NY 14642.
E-mail: christopher_aquina@urmc.rochester.edu.

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Colorectal cancer is the second-leading cause of cancer-related mortality in both the United States and Europe.[1] With respect to prognosis, increasing evidence has suggested that systemic inflammation is a key predictor of disease progression and survival for colorectal cancer patients undergoing surgery.[2,3] Furthermore, whereas red blood cell (RBC) transfusions may be life-saving in some circumstances, there has been growing evidence that transfusions are associated with adverse postoperative outcomes, including infectious complications and cancer recurrence.[4,5]

These detrimental effects are thought to be related to systemic inflammation and transfusion-related immunomodulation (TRIM). Whereas the exact mechanisms remain unknown, TRIM seems to be related to various immunologic changes, including decreased interleukin (IL)-2 production, monocyte and cytotoxic cell activity inhibition, increased suppressor T-cell activity, and immunosuppressive prostaglandin release.[5] Although the causality between transfusion and infection has been established, the association between TRIM and cancer recurrence remains uncertain.[6] Findings from meta-analyses have supported the association between perioperative transfusions and colorectal cancer recurrence.[4,7] However, these findings may have been confounded by other pro-inflammatory factors, such as sepsis, which may not only independently promote a pro-tumor environment but also may be influenced by transfusions.

Recent evidence has suggested that sepsis-mediated systemic inflammation also may be associated with adverse cardiovascular events.[3,8,9] Large matched-cohort studies have demonstrated an independent association between sepsis survival and increased risk of myocardial infarction, sudden cardiac death, and stroke.[8,9] However, no study has investigated the association among transfusion, sepsis, and cardiovascular disease-specific survival (DSS) in postoperative patients.

Given the continued debate regarding perioperative transfusions, infection, and survival, the aim of this study was to investigate the association among transfusion, sepsis, and survival after potentially curative colon cancer surgery, using a large, population-based dataset. The hypothesis was that a perioperative blood transfusion and sepsis would be independently associated with worse colon cancer DSS, cardiovascular DSS, and overall survival, with an additive detrimental effect observed for those who both received a transfusion and developed sepsis due to a potentially amplified inflammatory response.

METHODS

NYSCR and SPARCS

Patient-level linked data from the New York State Cancer Registry (NYSCR) and Statewide Planning and Research

Cooperative System (SPARCS) were used for this study. The NYSCR has consistently achieved the highest certification from the North American Association of Central Cancer Registries.[10] SPARCS is an all-payer, population-based hospital discharge database that includes all non-Veteran Affairs emergency department visits, hospital admissions, and ambulatory surgery procedures in the New York State. The database previously has been described in detail and used extensively for research purposes.[11–18] The NYSCR is also linked to Vital Records, which provides the cause and date of death for patients.

Study Cohort

Patients with stage I to III colon cancer, diagnosed between 2004 and 2011, were identified (site international classification of diseases (ICD)-O-3 = C180, C182-C189, C199, or surveillance, epidemiology, and end results site recode = 21041–21051) within the NYSCR. The study cohort was then restricted to those with adenocarcinoma (histology = 8140, 8210–8221, 8260–8263, or 8470–8490) and who underwent colectomy (ICD-9 = 17.31–17.39, 45.71–45.79, or 45.8–45.83) between 2004 and 2011. Exclusion criteria are presented in Fig. 1.

Outcomes

The study endpoints were colon cancer DSS, cardiovascular DSS, and overall survival within 5 years of surgery. Death due to colon cancer or metastatic disease (ICD-10 = C18–C19, C78.0–C80, C80.9, C26.0, C26.9, D37.4) was characterized as a colon cancer disease-specific death. Death due to cardiovascular disease (ICD-10 = I00–I99.9) was characterized as a cardiovascular disease-specific death. Death from any cause was used as the endpoint for overall survival. Patients who did not die during the follow-up period were censored at 5 years or December 31, 2012, whichever time point occurred first.

Transfusion and Sepsis

Receipt of a preoperative (transfusion date before the surgery date), intraoperative (transfusion date same as the surgery date), or postoperative (transfusion date after the surgery date) allogeneic RBC transfusion during the index hospital admission was identified within SPARCS.[14,18] Because the number of units transfused is not recorded in SPARCS, receipt of a transfusion was treated as a dichotomous factor (yes/no). Sepsis (ICD-9 = 003.1, 036.2, 038.x, 054.5, 449, 785.52, 790.7, or 995.91) was captured during the index admission or upon readmission within 30 days of surgery.

To evaluate the relative effects of receiving a transfusion and/or developing sepsis on survival, patients were characterized as nonreceipt of a transfusion and nondevelopment of sepsis [(−)transfusion/(−)sepsis], receipt of a transfusion, but nondevelopment of sepsis [(+)transfusion], nonreceipt of a transfusion, but development of sepsis [(+)sepsis], and both receipt of a transfusion and development of sepsis [(+)transfusion/(+)sepsis]. To investigate whether an additive effect of both receiving a transfusion and developing sepsis was present for survival, additional survival analyses were performed setting (+)transfusion as the reference. As a secondary analysis, the effect of transfusion timing on survival while adjusting for sepsis was also analyzed.

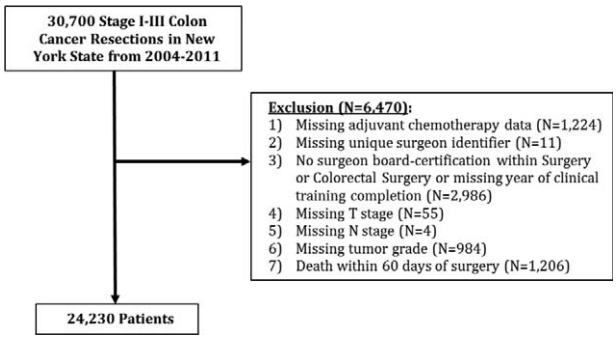

FIGURE 1. Flow chart of exclusion criteria process to determine study cohort.

Propensity Score Analysis

To account for selection bias related to which patients received a transfusion, a propensity score was estimated for each patient and entered as a covariate in the survival analyses as previously described.[13,14,18–20]

Additional Covariates

Patient-level factors considered for the analyses were age, sex, race, insurance type, unscheduled admission, a minimally invasive approach (ICD-9 = 17.31–17.39, 17.42, 45.81, 48.42, 48.51, 54.21, 54.51, or V64.41), procedure type, year of surgery, TNM staging, tumor grade, and receipt of adjuvant chemotherapy. Elixhauser comorbidities previously validated for mortality prediction by Quan et al[21] were identified as diagnoses present-on-admission for the index admission, and also any inpatient admission in the previous year.

Surgeon-level characteristics included annual colon cancer resection volume, type of board certification (surgery or colorectal surgery), and years of experience. Board certification and years of experience were identified by linking the unique surgeon identifier with the physician medical license number within the American medical association/American board of medical specialties database. Years of experience was calculated as the number of years between residency/fellowship completion and the surgical procedure.

Hospital-level characteristics included annual colon cancer resection volume, academic status, and location. Major academic status based upon the Council of Teaching Hospitals (COTHs) designation was identified using the American Hospital Association Annual Survey. Hospital location was characterized as urban or rural as defined by the United States Office of Management and Budget.[22]

Statistical Analysis

Patient, surgeon, and hospital-level factors were compared by outcome using Mann-Whitney *U* test, chi-square test, Cochrane-Armitage test for trend, or Kaplan-Meier analysis, as appropriate to the data. To account for clustering of outcomes among surgeons and hospitals, a 3-level mixed-effects Bayesian logistic regression analysis was utilized to identify factors associated with receipt of a transfusion and estimate the propensity score. To account for the competing risk of death from other causes, mixed-effects competing-risks analyses, as described by Katsahian et al,[23] were used for the DSS analyses. For the overall survival analysis, mixed-effects Cox proportional-hazards analyses were utilized. The R packages ''MCMCglmm'' (logistic regression), ''frailtyPack'' (competing-risks), and ''coxme'' (Cox proportional-hazards) were used for multivariable analyses (R version 3.1.2, R Foundation for Statistical Computing). SAS, Version 9.2 (SAS Institute, Cary, NC) was utilized for all other analyses. The study was approved by the University of Rochester (IRB #00054886) and NY State Department of Health institutional review boards (DPRB #1412–05).

RESULTS

Overall, 30,700 patients underwent colectomy for stage I to III colon cancer. Figure 1 depicts the reasons for exclusion, and 24,230

patients met inclusion criteria. The median follow-up for the study cohort was 3.84 years (interquartile range 2.12–5 years), with a total of 84,115 person-years of follow-up. Of the study cohort, 7.2% (n = 1754) underwent fecal diversion with an ileostomy or colostomy at the time of colectomy.

Transfusion and Sepsis

Overall, 29% (n = 6927) received a transfusion (38% preoperative, 28% intraoperative, 34% postoperative) and 4.0% (n = 963) developed sepsis. Of those who developed sepsis, 74% were diagnosed during the index admission and 26% upon readmission. Factors associated with receipt of a transfusion and sepsis are presented in Tables 1 and 2, respectively. Receipt of a transfusion was associated with sepsis (8.2% vs 2.3%; $P < 0.0001$). Using a test for trend, there was no significant change in the transfusion rate from 2004 to 2011 ($P = 0.27$).

Propensity Score Analysis

Significant variables ($P < 0.05$) in Table 1 were included in the propensity score analysis (Supplemental Digital Table 1, http://links.lww.com/SLA/B98). The c-statistic was 0.76, indicating good predictive ability.

Colon Cancer Disease-specific Survival

Colon cancer was the leading cause of death (n = 2703; 48.5% of deaths) (Supplemental Digital Table 1, http://links.lww.com/SLA/B98). After risk adjustment, (+)sepsis group [hazard ratio (HR) 1.84, 95% confidence interval (CI) 1.44–2.35] was associated with worse survival than (+)transfusion (HR 1.19, 95% CI 1.09–1.30), and (+)transfusion/(+)sepsis (HR 2.27, 95% CI 1.87–2.76) had the worst survival among the 4 groups (Fig. 2; Table 3). Furthermore, an additive effect was observed for the (+)transfusion/(+)sepsis group [(+)transfusion: reference; (+)transfusion/(+)sepsis: HR 1.92, 95% CI 1.59–2.33].

Cardiovascular Disease-specific Survival

Cardiovascular disease was the second-leading cause of death for the study cohort (n = 1318; 23.6% of deaths) (Supplemental Digital Table 2, http://links.lww.com/SLA/B98). After risk adjustment, the (+)sepsis group (HR 1.63, 95% CI 1.14–2.31) was associated with worse survival than (+)transfusion (HR 1.18, 95% CI 1.04–1.33), and (+)transfusion/(+)sepsis (HR 2.04, 95% CI 1.58–2.63) had the worst survival among the 4 groups (Fig. 3; Table 3). Again, an additive effect was observed for the (+)transfusion/(+)sepsis group [(+)transfusion: reference; (+)transfusion/(+)sep-)sepsis: HR 1.70, 95% CI 1.33–2.19].

Overall Survival

Overall, 5575 (23%) patients died from any cause. The causes of death for the study cohort are presented in Supplemental Digital Table 2 (http://links.lww.com/SLA/B98). After risk adjustment, the (+)sepsis group (HR 1.76, 95% CI 1.48–2.09) had worse survival than (+)transfusion (HR 1.21, 95% CI 1.14–1.29), and (+)trans-)transfusion/(+)sepsis (HR 2.36, 95% CI 2.07–2.68) had the worst survival among the 4 groups (Fig. 4; Table 3). Finally, an additive effect was observed for the (+)transfusion/(+)sepsis group [(+)transfusion: reference; (+)transfusion/(+)sepsis: HR 1.96, 95% CI 1.72–2.22].

Transfusion Timing

After risk adjustment and controlling for sepsis, there was no difference in colon cancer DSS or overall survival between those who received a preoperative transfusion (colon cancer DSS: HR 0.91, 95% CI 0.80–1.03; overall survival: HR 1.04, 95% CI 0.95–1.13) and those who did not receive a transfusion (reference). However, receipt of an intraoperative (colon cancer DSS: HR 1.25, 95% CI 1.10–1.42; overall survival: HR 1.28, 95% CI 1.17–1.40) or postoperative (colon cancer DSS: HR 1.32, 95% CI 1.17–1.50; overall survival: HR 1.34, 95% CI 1.23–1.46) transfusion was independently associated with worse colon cancer DSS and overall survival compared with nonreceipt of a transfusion. There were no differences in cardiovascular DSS with respect to transfusion timing (preoperative: HR 1.16, 95% CI 0.99–1.35; intraoperative: HR 1.15, 95% CI 0.96–1.38; postoperative: HR 1.12, 95% CI 0.94–1.33).

DISCUSSION

This study found that preoperative and postoperative blood transfusions are independently associated with worse colon cancer DSS, cardiovascular DSS, and overall survival after potentially curative colon cancer resection. This finding was independent of sepsis, and an additive detrimental effect of both receipt of a transfusion and development of sepsis on survival was observed. However, no difference in colon cancer DSS or overall survival was observed between those who received a preoperative transfusion and those who did not receive a transfusion. For cardiovascular DSS, the timing of the transfusion did not have an effect, because preoperative, intraoperative, and postoperative transfusions were each associated with worse survival. As transfusions have an independent, and also a synergistic effect with sepsis on survival after colon cancer surgery, these findings strongly support restrictive transfusion practices to reduce the risk of sepsis and improve survival.

Relation to Other Studies

The current study is the first to examine the effects of blood transfusion and sepsis on cardiovascular DSS, the largest to investigate its impact on colon cancer survival, and only the second to analyze the relative effects of transfusion and infection on survival. In the only other study to investigate the impact of both transfusion and postoperative infection on survival, Mynster et al[24] performed an ad hoc analysis of data from a randomized controlled trial that included 20 Danish hospitals in the RANX05 Colorectal Cancer Study Group. Among 532 patients who underwent colorectal cancer resection, the authors observed a similar synergistic effect in which the (+)transfusion/(+)infection group had a higher risk of cancer recurrence (HR 1.79, 95% CI 1.13–2.82) than the (−)transfusion/(−)infection group. In contrast to the current study, no significant differences in recurrence-free survival were observed among the (−)transfusion/(−)infection (reference), (+)transfusion/(−)infec-)infection (HR 1.16, 95% CI 0.80–1.68), and (−)transfusion/(+)infection (HR 1.21, 95% CI 0.70–2.09) groups. However, the study by Mynster et al was underpowered, had a more heterogeneous cohort that included both colon and rectal cancer patients, and did not include patients who underwent adjuvant therapy, which limits the study's external validity. In addition, the authors included superficial wound infections in the definition of infection, which may be too minor to augment systemic inflammation. Furthermore, evidence from meta-analyses supports the association between transfusions and cancer recurrence after colorectal cancer resection.[4,7]

Possible Explanations for the Study Findings

The mechanism by which transfusions increase the risk of cancer recurrence appears to be through TRIM. It is now well-established that blood transfusions augment the immune system and increase the risk of infectious complications.[6] This phenomenon was first reported in 1978 when Opelz and Terasaki[25] observed a reduction in renal allograft rejection with increasing numbers of transfusions. Since then, large observational studies have

TABLE 1. Bivariate Analysis of Factors Associated with Perioperative Blood Transfusion

	(−) Transfusion (n = 17,303) (71.4%)	(+) Transfusion (n = 6927) (28.6%)	*P*
Patient-level factors			
Age (median) (IQR)	69 (59–79)	77 (68–84)	<0.0001
Sex			<0.0001
Male	8249 (47.7)	2858 (41.3)	
Female	9054 (52.3)	4069 (58.7)	
Race			<0.0001
White	12,663 (73.2)	5216 (75.3)	
Black	2092 (12.1)	884 (12.8)	
Other	1985 (11.5)	661 (9.5)	
Unknown	563 (3.2)	166 (2.4)	
Medicaid insurance	4756 (27.5)	2501 (36.1)	<0.0001
Comorbidities			
HTN	9874 (57.1)	4539 (65.5)	<0.0001
CHF	1110 (6.4)	1126 (16.3)	<0.0001
Diabetes mellitus	3428 (19.8)	1817 (26.2)	<0.0001
COPD	2602 (15.0)	1462 (21.1)	<0.0001
Peripheral vascular disease	690 (4.0)	470 (6.8)	<0.0001
Renal failure	647 (3.7)	676 (9.8)	<0.0001
Liver disease	500 (2.9)	255 (3.7)	0.001
Preoperative anemia	433 (2.5)	769 (11.1)	<0.0001
Coagulation disorder	170 (1.0)	206 (3.0)	<0.0001
Unscheduled admission	4087 (23.6)	3879 (56.0)	<0.0001
T classification*			<0.0001
1	3045 (17.6)	549 (7.9)	
2	3113 (18.0)	1002 (14.5)	
3	9667 (55.9)	4434 (64.0)	
4	1478 (8.5)	942 (13.6)	
N classification*			0.0007
0	11,463 (66.2)	4411 (63.7)	
1	3928 (22.7)	1694 (24.5)	
2	1912 (11.0)	822 (11.9)	
Operative approach			<0.0001
Minimally invasive approach	5017 (29.0)	1398 (20.2)	
Open	12,286 (71.0)	5529 (79.8)	
Procedure			<0.0001
Right colectomy	6416 (37.1)	1872 (27.0)	
Left colectomy	10,031 (58.0)	4689 (67.7)	
Partial colectomy	616 (3.5)	248 (3.6)	
Total colectomy	240 (1.4)	118 (1.7)	
Year of surgery			0.99
2004–2005	4566 (26.4)	1836 (26.5)	
2006–2007	4494 (26.0)	1792 (25.9)	
2008–2009	4273 (24.7)	1712 (24.7)	
2010–2011	3970 (22.9)	1587 (22.9)	
Surgeon-level factors			
Board certification			<0.0001
General surgery	13,428 (77.6)	5616 (81.1)	
Colorectal surgery	3875 (22.4)	1311 (18.9)	
Years in practice			<0.0001
<5	1682 (9.7)	782 (11.3)	
5–9	2850 (16.5)	1090 (15.7)	
10–19	5952 (34.4)	2089 (30.2)	
≥20	6819 (39.4)	2966 (42.8)	
Annual colon cancer resection volume			<0.0001
Low	4723 (27.3)	2387 (34.5)	
Medium	4754 (27.5)	1972 (28.5)	
High	7826 (45.2)	2568 (37.1)	
Hospital-level factors			
Academic status			<0.0001
Major Academic	7818 (45.2)	2732 (39.4)	
Nonacademic	9485 (54.8)	4195 (60.6)	
Location			0.01
Urban	16,164 (93.4)	6408 (92.5)	
Rural	1139 (6.6)	519 (7.5)	
Annual colon cancer resection volume			<0.0001
Low	5175 (29.9)	2311 (33.4)	
Medium	5172 (29.9)	2050 (29.6)	
High	6956 (40.2)	2566 (37.0)	
Sepsis	397 (2.3)	566 (8.2)	<0.0001
5-Year mortality outcomes			
Death from colon cancer	1599 (9.2)	1104 (15.9)	<0.0001
Death from cardiovascular disease	695 (4.0)	623 (9.0)	<0.0001
Death from any cause	3170 (18.3)	2405 (34.7)	<0.0001

*From TNM staging.

demonstrated an association, and also a dose-response relationship between transfusions and the risk of infection even after controlling for a large number of potential confounders.[26–29]

For surgical oncology, current evidence suggests that systemic inflammation in the perioperative period likely plays a major role in the fate of residual disease.[2,3,30–32] Intraoperative tumor manipulation appears to increase the number of circulating tumor cells with a subsequent increased risk of distant metastatic establishment, and the outcome of residual disease is likely determined within days of surgery.[30,33,34] Additionally, surgery, transfusions, and the presence of bacterial antigens all induce proangiogenic factors which promote tumor cell extravasation and growth.[34,35] Furthermore, several small studies have demonstrated that postoperative sepsis is associated with excessive and sustained levels of proinflammatory cytokines.[36,37]

In a study by Miki et al that analyzed levels of early postoperative systemic responses of tumor growth factors in blood samples of patients undergoing colorectal cancer resection, exaggerated systemic induction of IL-6 and IL-6-triggered tumor growth factors, which can promote the survival of circulating metastatic seeds, was observed in patients who received a transfusion for intraoperative blood loss.[5,32,38] Interestingly, patients who received a preoperative transfusion for anemia did not exhibit this response and had lower rates of disease recurrence. These findings are similar to that of the current study in which only intraoperative and postoperative transfusions were associated with worse cancer-specific survival. The combination of surgery, receipt of an intraoperative or postoperative transfusion, and sepsis likely have a synergistic effect during the perioperative period that creates a protumor environment for microscopic residual disease, thus increasing the risk of disease recurrence.

This synergistic inflammatory effect may also explain the increased risk of cardiovascular-related death. Several recent large matched cohort studies investigating sepsis survivorship have demonstrated an association between sepsis and increased risk of long-term adverse cardiovascular events.[8,9] Possible explanations for this association include chronic organ dysfunction, such as subsequent chronic kidney disease after acute kidney injury, and persistent

TABLE 2. Bivariate Analysis of Factors Associated With Perioperative Sepsis

	(−) Sepsis (n = 23,267) (96%)	(+) Sepsis (n = 963) (4%)	*P*
Patient-level factors			
Age (median) (IQR)	72 (61–80)	76 (65–83)	
Sex			<0.0001
Male	10,593 (45.5)	514 (53.4)	
Female	12,674 (54.5)	449 (46.6)	
Race			0.01
White	17,170 (73.8)	709 (73.6)	
Black	2835 (12.2)	141 (14.6)	
Other	2550 (10.9)	96 (10.0)	
Unknown	712 (3.1)	17 (1.8)	
Medicaid insurance	6864 (29.5)	393 (40.8)	<0.0001
Comorbidities			
HTN	13,856 (59.5)	557 (57.8)	0.29
CHF	2048 (8.8)	188 (19.5)	<0.0001
Diabetes mellitus	5012 (21.5)	233 (24.2)	0.05
COPD	3859 (16.6)	205 (21.3)	0.0001
Peripheral vasculardisease	1092 (4.7)	68 (7.1)	0.0007
Renal failure	1209 (5.2)	114 (11.8)	<0.0001
Liver disease	718 (3.1)	37 (3.8)	0.19
Preoperative anemia	1064 (4.6)	138 (14.3)	<0.0001
Coagulation disorder	326 (1.4)	50 (5.2)	<0.0001
Unscheduled admission	7349 (31.6)	617 (64.1)	<0.0001
T classification*			<0.0001
1	3478 (14.9)	116 (12.0)	
2	3991 (17.2)	124 (12.9)	
3	13,530 (58.2)	571 (59.3)	
4	2268 (9.7)	152 (15.8)	
N classification*			0.97
0	15,244 (65.5)	630 (65.4)	
1	5396 (23.2)	226 (23.5)	
2	2627 (11.3)	107 (11.1)	
Operative approach			<0.0001
Minimally invasive approach	6267 (26.9)	148 (15.4)	
Open	17,000 (73.1)	815 (84.6)	
Procedure			<0.0001
Right colectomy	7947 (34.2)	341 (35.4)	
Left colectomy	14,191 (61.0)	529 (54.9)	
Partial colectomy	802 (3.4)	62 (6.5)	
Total colectomy	327 (1.4)	31 (3.2)	
Year of surgery			0.0005
2004–2005	6193 (26.6)	208 (21.7)	
2006–2007	6038 (26.0)	245 (25.8)	
2008–2009	5744 (24.7)	239 (25.0)	
2010–2011	5292 (22.7)	260 (27.5)	
Surgeon-level factors			
Board certification			<0.0001
General surgery	18,235 (78.4)	809 (84.0)	
Colorectal surgery	5032 (21.6)	154 (16.0)	
Years in practice			<0.0001
<5	2359 (10.1)	105 (10.9)	
5–9	3810 (16.4)	130 (13.5)	
10–19	7765 (33.4)	276 (28.7)	
≥20	9333 (40.1)	452 (46.9)	
Annual colon cancer resection volume			<0.0001
Low	6725 (28.9)	385 (40.0)	
Medium	6464 (27.8)	262 (27.3)	
High	10,078 (43.3)	313 (32.8)	
Hospital-level factors			
Academic status			0.83
Major academic	10,134 (43.6)	416 (43.2)	
Nonacademic	13,133 (56.4)	547 (56.8)	
Location			0.003
Urban	21,652 (93.1)	920 (95.5)	
Rural	1615 (6.9)	43 (4.5)	
Annual colon cancer resection volume			0.05
Low	7174 (30.8)	312 (32.4)	
Medium	6914 (29.7)	308 (32.0)	
High	9179 (39.5)	343 (35.6)	
Blood transfusion	6361 (27.3)	566 (58.8)	<0.0001
5-Year mortality outcomes			
Death from colon cancer	2512 (10.8)	191 (19.8)	<0.0001
Death from cardiovascular disease	1211 (5.2)	107 (11.1)	<0.0001
Death from any cause	5144 (22.1)	431 (44.8)	<0.0001

*From TNM staging.

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; HTN, hypertension.

inflammation after the episode of sepsis.[8,39,40] Unstable atherosclerotic plaques may form or a procoagulant response may occur as a result of vascular inflammation during the recovery period, increasing the risk of cardiovascular events.[41,42] Furthermore, in the current study, given that 83% of the deaths in the study cohort were due to colon cancer, cardiovascular disease, or another cancer type, these inflammatory effects also likely explain the differences in overall survival across the (−)transfusion/(−)sepsis, (+)transfusion, (+)sep-)sepsis, and (+)transfusion/(+)sepsis groups.

Strategies to Reduce Perioperative Transfusions

The most effective strategy in reducing the number of transfusions and improving survival is the promotion and implementation of restrictive transfusion policies. Unexplained variation in perioperative transfusion practices seems to be a major

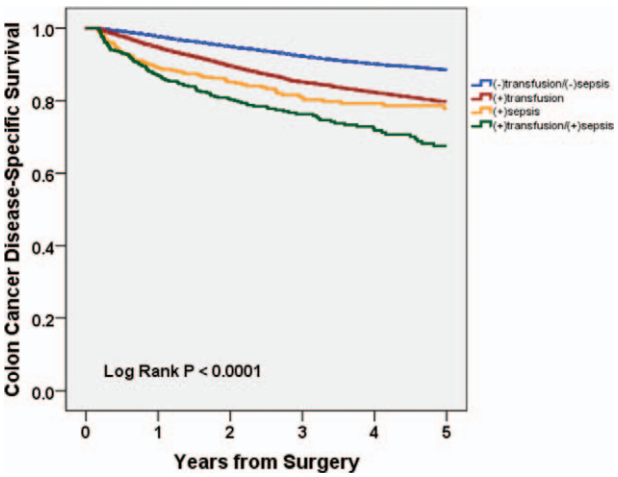

FIGURE 2. Kaplan-Meier graph of time to death from colon cancer within 5 years of surgery stratified by blood transfusion and sepsis status (n = 24,230).

TABLE 3. Multivariable Analyses of 5-year Disease-specific and Overall Survival

	Death From Colon Cancer* [HR (95% CI)]	Death from Cardiovascular Disease† [HR (95% CI)]	Death from Any Cause‡ [HR (95% CI)]
Propensity score	1.43 (1.02, 2.00)	1.65 (1.04, 2.62)	1.51 (1.20, 1.90)
Blood transfusion/sepsis			
(−) Transfusion/(−) Sepsis	Reference	Reference	Reference
(+) Transfusion	1.19 (1.09, 1.30)	1.18 (1.04, 1.33)	1.21 (1.14, 1.29)
(+) Sepsis	1.84 (1.44, 2.35)	1.63 (1.14, 2.31)	1.76 (1.48, 2.09)
(+) Transfusion/(+) Sepsis	2.27 (1.87, 2.76)	2.04 (1.58, 2.63)	2.36 (2.07, 2.68)

*Model also controls for patient age, sex, race, Medicaid insurance, comorbidities, unscheduled admission, tumor grade, AJCC stage, operative approach, procedure type, adjuvant chemotherapy, year of surgery, surgeon board-certification, surgeon volume, hospital academic status, and hospital volume.

†Model also controls for patient age, race, Medicaid insurance, comorbidities, unscheduled admission, AJCC stage, operative approach, procedure type, adjuvant chemotherapy, year of surgery, surgeon board-certification, surgeon volume, and hospital academic status.

‡Model also controls for patient age, race, Medicaid insurance, comorbidities, unscheduled admission, tumor grade, AJCC stage, operative approach, procedure type, adjuvant chemotherapy, year of surgery, surgeon board certification, surgeon volume, hospital academic status, hospital location, and hospital volume.

problem as recent studies have demonstrated wide variation in transfusion practices at both the surgeon and hospital-level after gastrointestinal surgery.[14,18,43,44] In addition, restrictive transfusion policies seem to be effective. Recent meta-analyses of randomized trials have demonstrated that restrictive strategies are associated with a reduction in the number of RBC units transfused, the number of patients transfused, and the risk of serious infection compared with a liberal transfusion strategy.[45,46] For patients with anemia below the recommended hemoglobin trigger of 7 to 8 g/dL or life-threatening hemorrhage, other strategies that may help avoid perioperative transfusions or reduce the risk of infection include preoperative iron supplementation, reducing the storage time of blood, and leukoreduction of blood products.[5,47–50]

Study Weaknesses and Strengths

Although this study has important findings, it has several limitations. First, the data derived from SPARCS are administrative in nature. Whereas the data are extracted by trained medical records personnel, there is a risk of miscoding. The date of chemotherapy initiation is also not reliably captured in the NYSCR. In addition, the study only includes the population within New York State and may not be generalizable to populations in other states within the United States or other countries. Furthermore, the number of RBC units transfused is not captured within SPARCS. As a result, a dose-response relationship between the number of units transfused and survival could not be assessed. Finally, there may be underlying selection bias and other confounding factors related to receipt of a transfusion that may influence disease-specific and overall survival. However, the study utilized a propensity score that included several important patient and oncologic factors that may influence the need for a transfusion to reduce the impact of selection bias on the study results.

Notwithstanding these limitations, this is the largest study to investigate the impact of transfusion and sepsis on long-term survival after colon cancer surgery. The study also excluded patients who died within 60 days of surgery to reduce the influence of death from sepsis complications on long-term survival. Finally, whereas future large randomized controlled trials would be ideal, it would be unethical to randomize patients to receipt or nonreceipt of an allogeneic blood transfusion. Therefore, large population-based analyses such as the current study are the best alternatives in evaluating the effect of transfusions on long-term survival after oncologic resection in the general population.

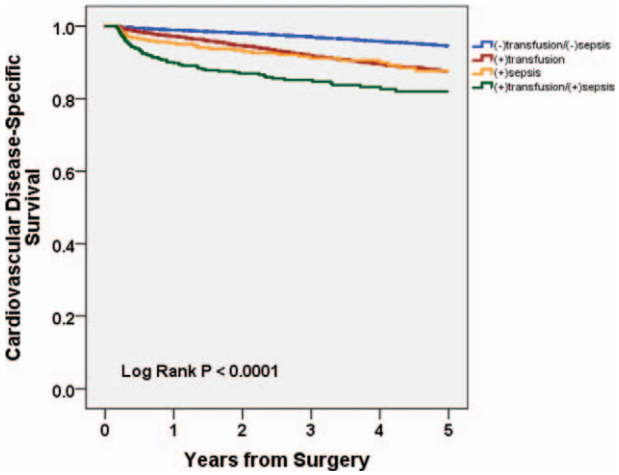

FIGURE 3. Kaplan-Meier graph of time to death from cardiovascular disease within 5 years of surgery stratified by blood transfusion and sepsis status (n = 24,230).

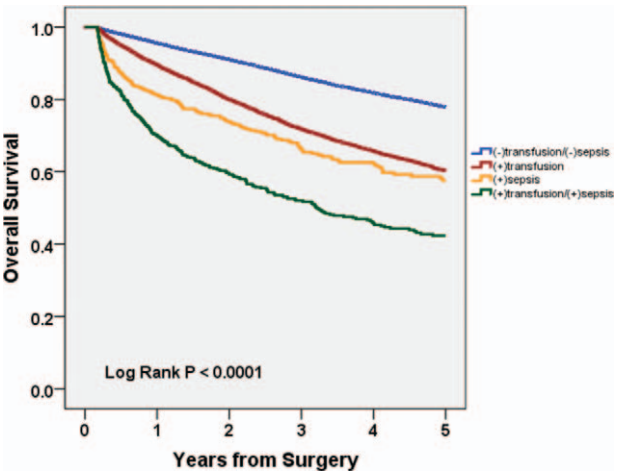

FIGURE 4. Kaplan-Meier graph of time to death from any cause within 5 years of surgery stratified by blood transfusion and sepsis status (n = 24,230).

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