Joint effect of pre-operative anemia and perioperative blood transfusion on outcomes of colon-cancer patients undergoing colectomy

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Abstract

Background: Both pre-operative anemia and perioperative (intra- and/or post-operative) blood transfusion have been reported to increase post-operative complications in patients with colon cancer undergoing colectomy. However, their joint effect has not been investigated. The purpose of this study was to evaluate the joint effect of pre-operative anemia and perioperative blood transfusion on the post-operative outcome of colon-cancer patients after colectomy.

Methods: We identified patients from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database 2006–2016 who underwent colectomy for colon cancer. Multivariate logistic regression analysis was employed to assess the independent and joint effects of anemia and blood transfusion on patient outcomes.

Results: A total of 35,863 patients—18,936 (52.8%) with left-side colon cancer (LCC) and 16,927 (47.2%) with right-side colon cancer (RCC)—were identified. RCC patients were more likely to have mild anemia (62.7%) and severe anemia (2.9%) than LCC patients (40.2% mild anemia and 1.4% severe anemia). A total of 2,661 (7.4%) of all patients (1,079 [5.7%] with LCC and 1,582 [9.3%] with RCC) received a perioperative blood transfusion. Overall, the occurrence rates of complications were comparable between LCC and RCC patients (odds ratio [OR] = 1.01; 95% confidence interval [CI] = 0.95–1.07; P = 0.750). There were significant joint effects of anemia and transfusion on complications and the 30-day death rate (P for interaction: 0.010). Patients without anemia who received a transfusion had a higher risk of any complications (LCC, OR = 3.51; 95% CI = 2.55–4.85; P < 0.001; RCC, OR = 3.74; 95% CI = 2.50–5.59; P < 0.001), minor complications (LCC, OR = 2.54; 95% CI = 1.63–3.97; P < 0.001; RCC, OR = 2.27; 95% CI = 1.24–4.15; P = 0.008), and major complications (LCC, OR = 5.31; 95% CI = 3.68–7.64; P < 0.001; RCC, OR = 5.64; 95% CI = 3.61–8.79; P < 0.001), and had an increased 30-day death rate (LCC, OR = 6.97;...
Colon cancer is one of the most common malignancies worldwide [1]. In the USA, it was estimated that 97,220 new colon-cancer cases would be diagnosed in 2018 [2]. Surgical resection is the only curative treatment modality for colon cancer; mortality should be kept low with adequate assessment of comorbidities [3]. A large number of colon-cancer patients have anemia [4, 5] and pre-operative anemia has been reported to be associated with poor post-operative outcomes in patients undergoing colectomy [6].

Perioperative (intra- and/or post-operative) blood transfusion is sometimes necessary for colon-cancer patients with anemia who underwent surgery [7, 8]. However, the relationship between blood transfusion and post-operative outcomes is unclear, as published studies report conflicting results [9–12]. Although there are some suggestions that transfusions and pre-operative anemia are both independent predictors of a poor outcome [6, 13], no studies have investigated the joint effect of anemia and transfusion on surgical outcomes among colon-cancer patients who have undergone colectomy. Transfusions are commonly perioperatively given to patients with anemia during surgery [14]. Due to the strong association between anemia and transfusion, the joint effect of anemia and transfusions should be considered. Additionally, there is growing evidence that demonstrates that right colon cancer (RCC) and left colon cancer (LCC) might be different malignancies [15–18]. It is not clear whether anemia and transfusions have differential effects on RCC or LCC outcomes. Furthermore, stratification by tumor location provides an opportunity to identify patients who may benefit from a transfusion treatment. This study aimed to evaluate the combined effect of anemia and transfusion on surgical outcomes stratified by tumor location.

Introduction

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Material and methods

Data source and study population

The American College of Surgeons National Surgical Outcome Improvement Program (ACS NSQIP) database is a nationally validated, risk-adjusted, outcomes-based program used to measure and improve the quality of surgical care. A total of 39,729 patients who underwent elective laparoscopic or open colectomy for RCC or LCC were identified from the NSQIP 2006–2016 database. RCC colectomy was defined as a partial colectomy with ileocolic anastomosis (current procedural terminology [CPT] codes: 44160 or 44205) for a malignant neoplasm of the colon (the International Classification of Diseases, Ninth Revision [ICD-9] or Tenth Revision [ICD-10]), cecum (153.4 or C18.0), ascending colon (153.6 or C18.2), or hepatic flexure (153.0 or C18.3). LCC colectomy was defined as a partial colectomy (CPT codes: 44140, 44204, 44145, or 44207) for malignant neoplasm of the descending colon (153.2 or C18.6) or sigmoid colon (153.3 or C18.7).

Patients admitted as urgent or emergency cases; patients with missing information on hematocrit analysis or blood-transfusion details; patients with sepsis, open wounds, or wound infections; and patients dependent on a ventilator were excluded from consideration. This study was designed to compare outcomes between LCC and RCC, so the patients undergoing total colectomy were excluded.

Variable definition

Using the pre-operative hematocrit levels, anemia was categorized as severe (hematocrit <26%), moderate (26% to <30%), mild (30% to <38%), and no anemia (≥38%) according to the criteria established in a previous study [6]. We combined the moderate and mild anemia categories into the ‘mild anemia’ group according to a previous study [19]. Perioperative blood transfusion was defined as patients who received a transfusion any time from the start of surgery to 72 hours after surgery (intra-and/or post-operative). Minor complications included superficial surgical-site infection (SSI), urinary-tract infection (UTI), deep venous thrombosis (DVT), and thrombophlebitis. Major complications included deep SSI, organ-space SSI, wound disruption, pneumonia, re-intubation, pulmonary embolism, greater than 48-hour post-operative ventilator-assisted respiration, progressive renal insufficiency, acute renal failure (ARF), cardiovascular accident (CVA), cardiac arrest requiring cardio-pulmonary resuscitation, myocardial infarction (MI), sepsis, and septic shock. Patients experiencing any complication were defined as having at least one minor or major complication.

Statistical analysis

The baseline characteristics between RCC and LCC patients were compared using Pearson’s chi-square tests for categorical variables and Student’s t-test for continuous variables. Multivariate logistic regression models were employed to examine the associations of surgical outcomes with anemia and transfusion while adjusting for potential confounding variables. The significance of the anemia–transfusion interaction was assessed by adding an interaction term in the logistic regression models. All statistical tests were two-sided. A P < 0.05 was considered statistically significant. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC, USA).

Results

Demographics and comorbidities

After applying the exclusion criteria, 35,863 patients (18,936 LCC and 16,927 RCC) were analysed. Compared with RCC patients, LCC patients were more likely to be younger, male, non-white, and current smokers (Table 1), and were also more likely to be functionally independent and have an American Society of Anesthesiologists (ASA) classification of <3 and a body mass index (BMI) of >30 kg/m². RCC patients experienced less weight loss and comorbidities of diabetes mellitus, MI, congestive heart failure (CHF), previous cardiac surgery, previous percutaneous coronary intervention (PCI), transient ischemic attack (TIA),
Table 1. Distribution of 35,863 patients with colon cancer from the American College of Surgeons National Surgical Outcome Improvement Program (ACS NSQIP) database

| Characteristic                  | No. of patients (%) | P-value |
|--------------------------------|---------------------|---------|
|                                | LCC (n = 18,936)    | RCC (n = 16,927) |
| Age, years                     |                     |         |
| ≤49                            | 2,541 (13.4)        | 971 (5.7)  <0.001 |
| 50–64                          | 7,303 (38.6)        | 4,100 (24.2)   |
| 65–79                          | 6,627 (35.0)        | 7,233 (42.7)   |
| ≥80                            | 2,465 (13.0)        | 4,623 (27.3)   |
| Sex                            |                     |         |
| Female                         | 8,841 (46.7)        | 9,291 (54.9)  <0.001 |
| Male                           | 10,095 (53.3)       | 7,636 (45.1)   |
| Race                           |                     |         |
| White                          | 12,178 (64.3)       | 11,822 (69.8)  <0.001 |
| Black                          | 1,680 (8.9)         | 1,596 (9.4)    |
| Others                         | 5,078 (26.8)        | 3,509 (20.7)   |
| Current smoker                 |                     |         |
| No                             | 16,508 (87.2)       | 14,948 (88.3)  0.001 |
| Yes                            | 2,428 (12.8)        | 1,979 (11.7)   |
| Functional status              |                     |         |
| Independent                    | 18,503 (97.7)       | 16,266 (96.1)  <0.001 |
| Partially or fully dependent   | 433 (2.3)           | 661 (3.9)      <0.001 |
| ASA classification             |                     |         |
| <3                             | 9,050 (47.8)        | 6,074 (35.9)   <0.001 |
| ≥3                             | 9,886 (52.2)        | 10,853 (64.1)  |
| BMI, kg/m²                     |                     |         |
| <18.5                          | 340 (1.8)           | 393 (2.3)      <0.001 |
| 18.5–24.9                      | 4,659 (24.6)        | 4,511 (26.7)   |
| 25–29.9                        | 6,454 (34.1)        | 5,784 (34.2)   |
| ≥30                            | 7,483 (39.5)        | 6,239 (36.9)   |
| Weight loss >10%               |                     |         |
| No                             | 18,168 (95.9)       | 16,000 (94.5)  <0.001 |
| Yes                            | 768 (4.1)           | 927 (5.5)      |
| Surgery procedure              |                     |         |
| Laparoscopic                   | 11,330 (59.8)       | 10,005 (59.1)  0.19 |
| Open                           | 7,606 (40.2)        | 6,922 (40.9)   |
| Comorbidities                  |                     |         |
| Diabetes mellitus              | 3,499 (18.5)        | 3,474 (20.5)   <0.001 |
| MI                             | 35 (0.2)            | 61 (0.4)       0.001 |
| CHF                            | 154 (0.8)           | 238 (1.4)      <0.001 |
| Revascularization or amputation| 78 (0.4)            | 68 (0.4)       0.88 |
| Previous cardiac surgery       | 335 (1.8)           | 410 (2.4)      <0.001 |
| Previous PCI                   | 378 (2.0)           | 403 (2.4)      0.01 |
| TIA                            | 150 (0.8)           | 197 (1.2)      <0.001 |
| Hypertension                   | 10,025 (52.9)       | 10,276 (60.7)  <0.001 |
| Pneumonia                      | 1 (0)               | 13 (0.1)       <0.001 |
| COPD                           | 847 (4.5)           | 1,112 (6.6)    <0.001 |
| Renal failure                  | 66 (0.4)            | 66 (0.4)       0.52 |
| Dialysis                       | 100 (0.5)           | 98 (0.6)       0.52 |
| CVA                            | 110 (0.6)           | 147 (0.9)      0.001 |
| Impaired sensorium             | 5 (0)               | 5 (0)          0.86 |
| Hemiplegia                     | 38 (0.2)            | 64 (0.4)       0.002 |
| Quadriplegia                   | 4 (0)               | 2 (0)          0.5  |
| Operation approach             |                     |         |
| Open                           | 7,606 (40.2)        | 6,922 (40.9)   0.1619 |
| Laparoscopic                   | 11,330 (59.8)       | 10,005 (59.1)  |
| Anemia                         | 11,073 (58.5)       | 5,829 (34.4)   |
| No                             | 7,602 (40.2)        | 10,606 (62.7)  <0.001 |
| Mild                           | 261 (1.4)           | 492 (2.9)      <0.001 |
| Severe                         | (continued)         |         |

Table 1. (continued)

| Characteristic                  | No. of patients (%) | P-value |
|                                | LCC (n = 18,936)    | RCC (n = 16,927) |
| Blood transfusion              |                     |         |
| No                             | 17,867 (94.4)       | 15,345 (90.7)  <0.001 |
| Yes                            | 1,069 (5.7)         | 1,582 (9.4)    |

LCC, left colon cancer; RCC, right colon cancer; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MI, myocardial infarction; CHF, congestive heart failure; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

Association between outcomes and locations

After adjusting for patient demographics and comorbidities, there was no significant difference in complications between RCC and LCC patients (Table 2). When specific complications were considered, RCC patients had higher risk of pneumonia (odds ratio [OR] = 1.23; 95% confidence interval [CI] = 1.04–1.45; P = 0.016), re-intubation (OR = 1.04; 95% CI = 1.04–1.04; P < 0.001), and DVT (OR = 1.28; 95% CI = 1.02–1.60; P = 0.033) than LCC patients. RCC patients had lower risk of wound disruption (OR = 0.66; 95% CI = 0.54–0.89; P = 0.003), ventilator dependence (OR = 0.89; 95% CI = 0.89–0.89; P < 0.001), and ARF (OR = 0.94; 95% CI = 0.94–0.95; P < 0.001) than LCC patients. Lastly, the operation time of colectomy for RCC was shorter than that for LCC patients (OR = 0.38; 95% CI = 0.36–0.39; P < 0.001); however, RCC patients stayed in the hospital longer (OR = 1.10; 95% CI = 1.05–1.15; P < 0.001) than LCC patients.

Association between outcomes and locations according to anemia and blood transfusion

Both anemia and transfusion were independently associated with an increased risk of post-operative complications and death based on multivariate analyses (Table 3). The observed increased risks of complications seemed greater among LCC than RCC patients. We also found significant joint effects of anemia and transfusion on complications and 30-day mortality. Among LCC patients without anemia, patients receiving transfusions had higher risk of any complications (OR = 3.51; 95% CI = 2.55–4.85; P < 0.001), minor complications (OR = 2.54; 95% CI = 1.63–3.97; P < 0.001), and major complications (OR = 5.31; 95% CI = 3.68–7.64; P < 0.001) than those receiving transfusions (Table 3). The high risks of any complications, minor complications, and major complications were also observed in patients with mild and severe anemia who underwent a transfusion. Similar patterns were observed for RCC patients (OR = 3.74; 95%
Table 2. Association between surgical outcomes and colon-cancer locations

| Outcome                      | No. of patients (%) | OR* (95% CI) | P-value |
|------------------------------|---------------------|--------------|---------|
|                              | LCC (n = 18,936)    | RCC (n = 16,927) |         |
| No complication              | 16,315 (86.2)       | 14,238 (84.1) | 1 [Reference] |
| Any complicationb             | 2,621 (13.8)        | 2,689 (15.9) | 1.01 (0.95–1.07) | 0.750 |
| Minor complicationsc          | 1,434 (7.5)         | 1,503 (8.9)  | 1.00 (0.92–1.08) | 1.000 |
| Major complicationsd          | 3,189 (16.7)        | 3,129 (18.5) | 1.00 (0.93–1.07) | 0.790 |
| Superficial SSI               | 994 (5.3)           | 848 (5.0)    | 0.95 (0.86–1.05) | 0.312 |
| Deep SSI                     | 132 (0.7)           | 119 (0.7)    | 0.96 (0.74–1.24) | 0.759 |
| Organ-specific SSI           | 498 (2.6)           | 479 (2.8)    | 1.08 (0.94–1.23) | 0.277 |
| Wound disruption              | 165 (0.9)           | 116 (0.7)    | 0.69 (0.54–0.89) | 0.003 |
| Pneumonia                    | 273 (1.4)           | 390 (2.3)    | 1.23 (1.04–1.45) | 0.016 |
| Re-intubation                 | 246 (1.3)           | 321 (1.9)    | 1.04 (1.04–1.04) | <0.001 |
| Pulmonary embolism            | 97 (0.5)            | 135 (0.8)    | 1.25 (0.95–1.65) | 0.111 |
| Ventilator dependence         | 213 (1.1)           | 216 (1.3)    | 0.89 (0.89–0.89) | <0.001 |
| Renal progressive insufficiency| 102 (0.5)          | 100 (0.6)    | 0.91 (0.68–1.22) | 0.526 |
| ARF                          | 66 (0.4)            | 66 (0.4)     | 0.94 (0.94–0.95) | <0.001 |
| CVA                          | 45 (0.2)            | 70 (0.4)     | 1.14 (0.77–1.69) | 0.513 |
| Coma                         | 5 (0)               | 0 (0)        | NA       |
| Cardiac arrest                | 76 (0.4)            | 94 (0.6)     | 1.04 (0.76–1.43) | 0.806 |
| MI                           | 115 (0.6)           | 141 (0.8)    | 0.94 (0.73–1.22) | 0.631 |
| Sepsis                       | 405 (2.1)           | 406 (2.4)    | 1.06 (0.91–1.23) | 0.454 |
| Septic shock                 | 212 (1.1)           | 222 (1.3)    | 0.95 (0.78–1.16) | 0.610 |
| UTI                          | 359 (1.9)           | 393 (2.3)    | 0.91 (0.78–1.06) | 0.230 |
| DVT                          | 150 (0.8)           | 209 (1.2)    | 1.28 (1.02–1.60) | 0.033 |
| Re-operation                 | 56 (0.3)            | 41 (0.2)     | 0.77 (0.50–1.18) | 0.235 |
| 30-day mortality             | 175 (0.9)           | 251 (1.5)    | 1.04 (0.85–1.27) | 0.703 |
| Operation time of colectomy*, min |                   |              |         |
| <160                         | 8,955 (47.3)        | 12,107 (71.5) | 1 [Reference] |
| ≥160                         | 9,981 (52.7)        | 4,820 (28.5) | 0.38 (0.36–0.39) | <0.001 |
| Length of hospital stayb, days |                   |              |         |
| <5                           | 8,740 (46.2)        | 6,945 (41.0) | 1 [Reference] |
| ≥5                           | 10,196 (53.8)       | 9,982 (59.0) | 1.10 (1.05–1.15) | <0.001 |

LCC, left colon cancer; RCC, right colon cancer; OR, odds ratio; CI, confidence interval; SSI, surgical-site infection; ARF, acute renal failure, CVA, cerebrovascular accident; MI, myocardial infarction; UTI, urinary-tract infection; DVT, deep vein thrombosis; NA, not applicable.

aAdjusted for age, sex, race, smoking, functional status, American Society of Anesthesiologists classification, body mass index, weight loss >10%, diabetes, congestive heart failure, previous cardiac surgery, previous percutaneous coronary intervention, myocardial infarction, transient ischemic attack, hypertension, pneumonia, chronic obstructive pulmonary disease, cerebrovascular accident, and hemiplegia.
bIncluding one or more of the complications listed in Table 2.
cIncluding superficial SSI, organ-space SSI, wound disruption, pneumonia, re-intubation, pulmonary embolism, greater than 48-hour post-operative ventilator-assisted respiration, progressive renal insufficiency, ARF, CVA, cardiac arrest requiring cardiopulmonary resuscitation, MI, sepsis, and septic shock.
dMedian value was based on the distribution of patients with LCC colectomy.

Cl = 2.50–5.59; P < 0.001 for any complication; OR = 2.27; 95% CI = 1.24–4.15; P = 0.008 for minor complications; OR = 5.64; 95% CI = 3.61–8.79; P < 0.001 for major complications) (Table 3). The risk of 30-day mortality was the highest among LCC patients without anemia but who had a transfusion (OR = 6.97; 95% CI = 3.07–15.80; P < 0.001), followed by patients with mild anemia and transfusion (OR = 4.48; 95% CI = 2.75–7.27; P < 0.001). Similarly, in RCC patients, the risk of 30-day mortality was the highest among patients without anemia but with transfusion (OR = 4.91; 95% CI = 1.88–12.85; P = 0.001), followed by patients with severe anemia but no transfusion (OR = 3.18; 95% CI = 1.54–6.57; P = 0.002) and patients with mild anemia and transfusion (OR = 3.18; 95% CI = 2.00–4.81; P < 0.001). Similar associations between anemia/transfusion and overall outcomes were found between open and laparoscopic groups (Supplementary Table 1) and between patients who had longer and shorter operation times (Supplementary Table 2), and all models fit well (Supplementary Table 3).

Discussion

This study investigated the joint effect of pre-operative anemia and perioperative transfusion by tumor location on post-operative outcomes in colon-cancer patients undergoing colectomy. A novel finding from the study was that patients without anemia but with transfusion experienced the highest risk of complications and mortality, followed by patients with mild or severe anemia and with blood transfusion, suggesting that a conservative transfusion practice should be considered during colectomy.

The exact mechanisms linking transfusion and adverse outcomes are not fully understood; several phenomena have been suggested [20]. For example, transfusion induces immunosuppression, which results in an increased susceptibility to infection [21, 22]. Transfusion can also increase inflammation by inducing alloimmunization [23]. As expected, this study demonstrated that perioperative transfusion was associated with

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| Variable                      | No complications | Any complication | Minor complication | Major complication | 30-day mortality |
|-------------------------------|------------------|------------------|-------------------|-------------------|------------------|
|                               | No. of cases     | No. of cases     | ORa (95% CI)      | P-value           | No. of cases     | ORa (95% CI)      | P-value           | No. of cases     | ORa (95% CI)      | P-value           |
| LCC, Anemia                   |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No                            | 9,794            | 1,279            | 1 [Reference]     | <0.001            | 608              | 1.22 (1.08-1.37) | 0.001             | 744              | 1.41 (1.24-1.59) | <0.001             |
| Mild                          | 6,318            | 1,284            | 1.26 (1.15-1.38)  | <0.001            | 26               | 1.19 (0.77-1.84) | 0.433             | 41               | 1.54 (1.06-2.24) | 0.023             |
| Severe                        | 203              | 58               | 1.27 (0.92-1.74)  | 0.146             | 113              | 1.55 (1.09-2.11) | 0.015             | 136              | 3.05 (2.05-4.51) | <0.001             |
| Transfusion                   |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No                            | 15,567           | 2,300            | 1 [Reference]     | <0.001            | 1,312            | 1.66 (1.34-2.04) | <0.001            | 1,184            | 3.22 (2.71-3.82) | <0.001             |
| Yes                           | 748              | 321              | 2.40 (2.06-2.78)  | <0.001            | 122              | 1.66 (1.34-2.04) | <0.001            | 235              | 3.22 (2.71-3.82) | <0.001             |
| Anemia/transfusion            |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No anemia, no transfusion     | 9,602            | 1,221            | 1 [Reference]     | <0.001            | 592              | 1 [Reference]    | <0.001            | 52               | 1 [Reference]    |                   |
| No anemia, transfusion        | 132              | 58               | 3.51 (2.55-4.85)  | <0.001            | 24               | 2.54 (1.63-3.97) | <0.001            | 42               | 5.31 (3.68-7.64) | <0.001             |
| Mild anemia, no transfusion   | 5,779            | 1,049            | 1.29 (1.17-1.41)  | <0.001            | 590              | 1.24 (1.09-1.40) | 0.001             | 573              | 1.46 (1.29-1.66) | <0.001             |
| Mild anemia, transfusion      | 539              | 235              | 2.89 (2.43-3.44)  | <0.001            | 90               | 1.96 (1.53-2.50) | <0.001            | 171              | 4.32 (3.52-5.29) | <0.001             |
| Severe anemia, no transfusion | 126              | 30               | 1.62 (1.07-2.44)  | 0.023             | 18               | 1.67 (1.00-2.77) | 0.050             | 19               | 2.13 (1.30-3.51) | 0.003             |
| Severe anemia, transfusion    | 77               | 28               | 2.42 (1.55-3.78)  | <0.001            | 8                | 1.20 (0.57-2.51) | 0.631             | 22               | 3.90 (2.38-6.39) | <0.001             |
| P-value for interaction       | 0.002            | 0.006            |                   |                   |                  |                   |                   |                  | 0.01             |                   |
| RCC, Anemia                   |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No                            | 5,042            | 787              | 1 [Reference]     |                   | 434              | 1 [Reference]    |                   | 415              | 1 [Reference]    | 47 [Reference]    |
| Mild                          | 8,788            | 1,181            | 1.13 (1.02-1.24)  | 0.019             | 891              | 1.04 (0.92-1.18) | 0.531             | 1,033            | 1.16 (1.02-1.32) | 0.024             |
| Severe                        | 408              | 84               | 0.87 (0.67-1.13)  | 0.296             | 44               | 0.99 (0.66-1.31) | 0.678             | 55               | 0.93 (0.68-1.29) | 0.650             |
| Transfusion                   |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No                            | 13,078           | 2,267            | 1 [Reference]     |                   | 1,192            | 1 [Reference]    |                   | 1,217            | 1 [Reference]    |                   |
| Yes                           | 1,160            | 422              | 1.97 (1.73-2.24)  | <0.001            | 177              | 1.63 (1.37-1.95) | <0.001            | 286              | 2.43 (2.08-2.82) | <0.001            |
| Anemia/transfusion            |                  |                  |                   |                   |                  |                  |                   |                  |                  |                   |
| No anemia, no transfusion     | 4,972            | 747              | 1 [Reference]     |                   | 421              | 1 [Reference]    |                   | 384              | 1 [Reference]    | 42 [Reference]    |
| No anemia, transfusion        | 70               | 40               | 3.74 (2.50-5.59)  | <0.001            | 13               | 2.27 (1.24-4.15) | 0.008             | 31               | 5.64 (3.61-8.79) | <0.001            |
| Mild anemia, no transfusion   | 7,866            | 1,477            | 1.16 (1.05-1.28)  | 0.004             | 744              | 1.04 (0.91-1.19) | 0.565             | 806              | 1.22 (1.07-1.39) | 0.003             |
| Mild anemia, transfusion      | 922              | 341              | 2.21 (1.89-2.57)  | <0.001            | 147              | 1.74 (1.42-2.14) | <0.001            | 227              | 2.79 (2.32-3.37) | <0.001            |
| Severe anemia, no transfusion | 240              | 43               | 1.09 (0.77-1.52)  | 0.627             | 27               | 1.23 (0.81-1.86) | 0.331             | 27               | 1.29 (0.85-1.96) | 0.232             |
| Severe anemia, transfusion    | 168              | 41               | 1.43 (1.00-2.04)  | 0.050             | 17               | 1.09 (0.65-1.82) | 0.744             | 28               | 1.85 (1.21-2.82) | 0.005             |
| P-value for interaction       | <0.001           | 0.03             |                   |                   |                  |                   |                   |                  | <0.001           | 0.004             |

LCC, left colon cancer; RCC, right colon cancer; OR, odds ratio; CI, confidential interval.

aAdjusted for age, sex, race, smoking, functional status, American Society of Anesthesiologists classification, body mass index, weight loss >10%, diabetes, congestive heart failure, previous cardiac surgery, previous percutaneous coronary intervention, transient ischemic attack, hypertension, pneumonia, myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular accident, and hemiplegia.

bIncluding one or more of the complications listed in Table 2.

cIncluding superficial surgical-site infection, deep vein thrombosis, urinary-tract infection, and/or thrombophlebitis.

dIncluding deep surgical-site infection, organ-space surgical-site infection, wound disruption, pneumonia, re-intubation, pulmonary embolism, greater than 48-hour post-operative ventilator-assisted respiration, progressive renal insufficiency, acute renal failure, cerebrovascular accident, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, sepsis, and septic shock.
increased risk of post-operative complications and mortality regardless of anemia status in patients who underwent colectomy. Although pre-operative anemia was reported as an independent predictor on post-operative outcomes, the combined effect appears more closely related to blood transfusion. An earlier study based on NSQIP data reported an increased risk of complications and mortality associated with pre-operative transfusion in patients who underwent colectomy [13]. To eliminate potential confounding from pre-operative transfusion, our study population excluded patients with a history of pre-operative transfusion.

Our study found that the risk of post-operative complications associated with transfusion varied by anemia status. There are reasons for transfusion in clinical practice. For example, patients with significant blood loss during or after colectomy [24], patients with certain conditions (liver disease, etc.) affecting the production of clotting proteins [25], patients who underwent chemotherapy, and/or patients with certain heart or lung diseases [26, 27] were all transfusion candidates. It is also possible that the underlying clinical reasons for transfusion resulted in adverse outcomes rather than the transfusion itself. Due to a lack of information on the reason for blood transfusion in our patient cohort, we were unable to evaluate this association. Furthermore, as the decision to transfuse a patient depends on an individual evaluation by a physician, the decision is also influenced by regulations, fear of future litigation, and public expectations in addition to clinical evidence [28]. On the other hand, conditions that suggest a blood transfusion might further worsen blood transfusion’s adverse effect on outcomes, even after adjusting demographics and comorbidities.

Our study’s findings provide a strong argument for a more optimal and prudent transfusion practice, suggesting a restrictive rather than liberal transfusion strategy [29, 30]. Alternatives to transfusion have been long anticipated. Pre-operative ferric carboxymaltose treatment has been shown to significantly reduce transfusion requirements and hospital length of stay in colon-cancer patients with anemia and improves hemoglobin response at 12 weeks in patients who underwent gastrectomy, suggesting that it could be a viable alternative to transfusion when a rapid increase in the hemoglobin level is required [31, 32].

In addition to providing strong evidence for the joint effect of pre-operative anemia and perioperative transfusion on post-operative outcomes of colectomy, the present study also raised a concern about the transfusion criteria for patients undergoing colectomy for cancer, specifically for patients with no anemia. The most common reason for transfusion in such patients is either large amounts of blood loss during surgery or major bleeding complications after surgery. Nevertheless, this reason cannot be explained by the NSQIP, which does not collect any data on blood loss.

A common concern is that case complexity is associated with transfusion requirements. Without a reliable measurement of case complexity, the operation time could serve as a surrogate indicator. Further, laparoscopic surgery was also associated with lower transfusion requirements than an open approach [8] likely because open surgery may amplify the effect of anemia and blood transfusion. In comparison, we found that patients who experienced open surgery or longer operation time did not show different patterns. Another interesting finding was the stronger association of anemia and transfusion with complications and mortality in LCC patients than in RCC patients. To our knowledge, this result has not been described in previous studies. A previous study with a relatively small sample size (n = 4,875) reported comparable complication rates between LCC and RCC patients undergoing colectomy with the exception of superficial SSI, which was found to be less common in RCC colectomy [33]. Reasons for this difference may be associated with a delay in the diagnosis and associated advanced stage of RCC [34–36]. Additionally, the occurrence rate of mild and severe anemia was lower in LCC than in RCC patients. We suspect that LCC patients exhibited a better physical condition and earlier presentation than RCC patients.

Our study had several limitations related to its retrospective design. Although the NSQIP is a large worldwide database, the samples included in our study are likely heterogeneous and subject to selection bias because the patients were all deemed fit for surgery. We were unable to consider the specific therapy for each patient. Additionally, the NSQIP does not provide detailed data on the subtype of anemia, duration prior to surgery, volume of blood transfusion, and estimated blood loss during the operation. Sorting these factors out of such a large database would be impractical. Finally, the database does not define the transfusion criteria or rationale.

Conclusions
The study found that perioperative blood transfusion posed a greater risk of complications and mortality regardless of anemia status, suggesting that a perioperative blood transfusion should be judiciously administered, particularly in patients with mild anemia or without anemia.

Supplementary data
Supplementary data are available at Gastroenterology Report online.

Authors’ contributions
Z.L. and J.I.L. contributed to the study concept and design; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. K.Y.P., S.A.K., X.X.W., Z.X.Z., M.Y., C.H.J., X.S.W., and Y.W.Z. contributed to the study concept and design, analysis, and interpretation of the data, and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Conflicts of interest
None declared.
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