Association of preoperative anemia and perioperative allogenic red blood cell transfusion with oncologic outcomes in patients with nonmetastatic colorectal cancer

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ABSTRACT

Background We investigated whether preoperative anemia and perioperative blood transfusion (pbt) are associated with overall survival and recurrence-free survival in patients with nonmetastatic colorectal cancer.

Methods From 1 January 2009 to 31 December 2014, 1003 patients with primary colorectal cancer were enrolled in the study. Perioperative clinical and oncologic outcomes were analyzed based on the presence of preoperative anemia and pbt.

Results Preoperative anemia was found in 468 patients (46.7%). In the anemia and no-anemia groups, pbt was performed in 44% and 15% of patients respectively. Independent predictors for pbt were preoperative anemia, higher American Society of Anesthesiologists score, laparotomy, lengthy operative time, advanced TNM stage, T4 stage, and 30-day morbidity. The use of pbt, but not preoperative anemia, was found to be an independent adverse prognostic factor for overall survival. In terms of recurrence-free survival, the presence of preoperative anemia was similarly not a significant prognostic factor, but the use of pbt was an independent factor for an unfavourable prognosis.

Conclusions The use of pbt, but not preoperative anemia, was independently associated with worse overall and recurrence-free survival in nonmetastatic colorectal cancer. For better oncologic outcomes, our findings indicate a need to reduce the use of blood transfusion during the perioperative period.

Key Words Colonic neoplasms, rectal neoplasms, anemia, blood transfusions, survival

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INTRODUCTION

Colorectal cancer (CRC) is the 3rd most common cancer in men and the 2nd most common cancer in women. Furthermore, CRC is the 4th most common cause of cancer-related death worldwide. Anemia is a common condition in patients with CRC, with an incidence of 38%–59% in patients with colon cancer and of 18%–50% in those with rectal cancer. The World Health Organization defines anemia as a hemoglobin level less than 13 g/dL in men and less than 12 g/dL in women. The main cause of anemia in patients with CRC is iron deficiency resulting from occult bleeding from tumours; another cause is impairment of iron homeostasis related to chronic systemic inflammation, which leads to anemia of chronic disease. Studies of whether anemia in patients with CRC is a negative prognostic factor have produced conflicting results.

Allogenic red blood cell (RBC) transfusion is a treatment for anemia that is frequently used in patients with CRC. However, concerns have been raised about the negative effect of blood transfusion on oncologic outcomes. Immuno-modulation and systemic inflammatory responses related to blood transfusion are thought to be related to adverse oncologic outcomes. Indeed, a number of studies have shown an adverse effect of blood transfusion on postoperative outcomes in CRC patients, including infection-related
complications and survival. Some investigators have suggested that perioperative blood transfusions do not influence overall or recurrence-free survival after resection for CRC. The association of preoperative anemia and perioperative blood transfusion with oncologic outcomes is still disputed. In clinical practice, the influence of preoperative anemia on outcomes is often confounded by perioperative blood transfusion. To date, studies investigating the influence on CRC outcomes of preoperative anemia with perioperative blood transfusion are lacking. The aim of the present study was to investigate whether preoperative anemia and perioperative blood transfusion are associated with overall survival (OS) and RFS in patients undergoing curative resection for nonmetastatic CRC.

METHODS

Patients
Our study enrolled 1003 patients with histology-confirmed primary CRC who underwent elective CRC surgery from 1 January 2009 to 31 December 2014. This retrospective observational study, performed at a tertiary university hospital, was approved by the institutional review board (WVMR-15-5-050). All clinical data were gathered in accordance with the principles of the Helsinki Declaration. All the work complied with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Eligibility criteria included histology-confirmed CRC, elective surgery, curative surgery for CRC, and age older than 20 years. Patients with distant organ metastases or recurrent cancer, or those undergoing emergency surgery or palliative non-resection surgery were excluded from the study cohort.

Clinical, laboratory, and pathology data, including age, sex, American Society of Anesthesiologists (ASA) classification, TNM stage as defined by the 8th edition of the American Joint Committee on Cancer staging manual, tumor location, preoperative laboratory data, and use of perioperative transfusion were obtained from electronic medical records and a dedicated institutional CRC database.

Variables and Outcome Measures

Preoperative Anemia
Based on the World Health Organization classification, anemia was defined as a hemoglobin level less than 13 g/dL in male patients and less than 12 g/dL in female patients on preoperative complete blood counts.

Perioperative Allogenic RBC Transfusion
Use of perioperative allogenic RBC transfusion was defined as receipt at least 1 unit of packed RBCs during a patient’s in-hospital admission (from the time of primary surgery to hospital discharge).

Variables
The right-side colon was considered to extend from the cecum to the transverse colon. The left-side colon considered to include the splenic flexure to the sigmoid colon. Postoperative morbidity was defined as the need for additional treatment within 30 days after surgery. The Clavien–Dindo classification system was used to determine the severity of surgical complications. A condition requiring medical treatment was defined as a grade 2 complication. If surgical, endoscopic, or radiologic intervention was required, the complication was defined as a grade 3 complication (Clavien–Dindo classification system). Tumor recurrence was defined as any radiologic or histologic evidence of tumor growth in the previous surgical field or distant organs.

Study Objectives
The primary objective of the study was to investigate whether preoperative anemia or perioperative allogenic RBC transfusion is associated with oncologic outcomes (OS and RFS) after curative surgery in patients with nonmetastatic CRC.

Preoperative Chemoradiation, Surgery, Adjuvant Therapy, and Follow-up
Patients with clinical stage T3 and T4 or node-positive (or both) mid- or low rectal cancer received preoperative chemoradiation. A total dose of 50.4 Gy was delivered over 5 weeks. All surgeries for CRC were performed by colorectal surgery specialists. The type of surgical approach (laparotomy, laparoscopy, or robot-assisted) was discussed preoperatively with patients and their families. Complete mesocolic excision and central vascular ligation were performed for colon cancer; high ligation of the inferior mesenteric artery and total mesorectal excision were performed for rectal cancer. Adjuvant chemotherapy after recovery from surgery was recommended for patients with pathologic stage II or III CRC based on guidelines from the U.S. National Comprehensive Cancer Network. Patients in the study cohort were followed until death or 30 June 2015. The median follow-up period was 41 months (interquartile range: 23.8–70.8 months).

Statistical Analysis
All statistical analyses were performed using the IBM SPSS Statistics (version 23.0; IBM, Armonk, NY, U.S.A.) and MedCalc (version 17.4: MedCalc Software, Ostend, Belgium) software applications. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher exact test. Continuous variables are presented as means with standard deviation and were analyzed using the Student t-test.

To determine the predictors of perioperative blood transfusion, univariate logistic regression analyses were performed for all variables. Variables with a p value less than 0.05 (preoperative anemia, age, ASA score, surgical approach, operative time, TNM stage, depth of tumor invasion, and 30-day postoperative morbidity) were then used in multivariable analyses. Multivariable logistic regression analyses were performed using forward stepwise selection of variables.

Survival curves were constructed according to the Kaplan–Meier method and were compared using the log-rank test. The definition of OS was the number of months from surgery to death, and the definition of RFS was the number of months from surgery to recurrence.
We used a Cox proportional hazards model to investigate factors prognostic for OS. The univariate Cox proportional hazards model analysis used all variables, and variables with a p value less than 0.05 (preoperative anemia, perioperative transfusion, age, ASA score, surgical approach, TNM stage, 30-day postoperative morbidity, and adjuvant chemotherapy) were entered into the multivariable analysis. Likewise, Cox proportional hazards models were used to investigate factors prognostic for RFS. After the univariate analysis, variables with a p value less than 0.05 (preoperative anemia, perioperative transfusion, age, surgical approach, TNM stage, histology, and 30-day postoperative morbidity) were used in the multivariable analysis. The multivariable Cox proportional hazards model analyses used forward stepwise selection of variables.

RESULTS

Patient Characteristics by Presence of Preoperative Anemia
Of the 1003 study patients, 468 (46.7%) presented with anemia. Of the patients in the anemia and no-anemia groups, 44% and 15% respectively received a perioperative allogenic RBC transfusion (p < 0.001). Compared with patients in the no-anemia group, patients in the anemia group were older (11 years vs. 65.6 ± 11 years, p < 0.001), had a lower body mass index (22.6 ± 3 vs. 24.1 ± 3, p < 0.001), had higher ASA scores (3 or 4: 20% vs. 14%, p = 0.029), more frequently had right-side colon cancer (31% vs. 18%, p < 0.001), had higher levels of serum carcinoembryonic antigen (8.7 ± 25 ng/mL vs. 5.1 ± 11 ng/mL, p = 0.005), had a more advanced TNM stage (stage III: 47% vs. 39%, p < 0.001), had tumors larger in size (5.4 ± 2 cm vs. 3.9 ± 2 cm, p < 0.001). More women (41% vs. 33%, p = 0.013) were included in the anemia group than in the no-anemia group. In the anemia group, laparotomy was more frequent than minimally invasive surgeries such as laparoscopy and robot-assisted surgery (46% vs. 30%, p < 0.001, Table I).

Predictors for Perioperative Allogenic RBC Transfusion
In the univariate analysis, preoperative anemia, age 80 years or older, higher ASA score (3 or 4), laparotomy rather than minimally invasive surgery, longer operative time (≥300 minutes), more advanced TNM stage, greater tumor invasion depth (T4), and 30-day postoperative morbidity were associated with perioperative blood transfusion. In the multivariate analysis, preoperative anemia [hazard ratio (HR): 5.06; 95% confidence interval (CI): 3.42 to 7.48; p < 0.001], higher ASA score [3 or 4 (HR: 1.88; 95% CI: 1.19 to 2.98; p = 0.007)], laparotomy (HR: 1.78; 95% CI: 1.20 to 2.63; p = 0.004), lengthy operative time (HR: 3.74; 95% CI: 2.20 to 6.35; p < 0.001), advanced TNM stage (p = 0.036), T4 stage (HR: 1.67; 95% CI: 1.01 to 2.76; p = 0.048), and 30-day postoperative morbidity (HR: 2.86; 95% CI: 1.96 to 4.19; p < 0.001) were independent predictors of perioperative blood transfusion (Table II).

Cox Proportional Model of Factors Prognostic for OS
The presence of preoperative anemia was a significant factor in univariate analysis (HR: 1.58; 95% CI: 1.17 to 2.12; p = 0.002), but not in multivariate analysis (HR: 1.06; 95% CI: 0.77 to 1.45; p = 0.729). The use of perioperative allogenic RBC transfusion was an independent adverse prognostic factor (HR: 1.55; 95% CI: 1.21 to 2.13; p = 0.008). Other adverse prognostic factors for OS (Table III) were laparotomy rather than minimally invasive surgery (HR: 1.75; 95% CI: 1.26 to 2.41; p = 0.001), advanced TNM stage, including stage III (HR: 2.99; 95% CI: 1.71 to 5.21; p < 0.001) and stage III (HR: 6.12; 95% CI: 3.62 to 10.32; p < 0.001), 30-day postoperative morbidity (HR: 1.51; 95% CI: 1.11 to 2.05; p = 0.009); and no adjuvant chemotherapy (HR: 3.85; 95% CI: 2.66 to 5.59; p < 0.001).

Cox Proportional Hazards Model of Factors Prognostic for RFS
The presence of preoperative anemia was not a significant prognostic factor in either the univariate (p = 0.06) or the multivariate analysis (p = 0.902). However, the use of perioperative allogenic RBC transfusion (HR: 1.65; 95% CI: 1.24 to 2.20; p = 0.001), TNM stage III (HR: 3.2; 95% CI: 2.12 to 4.83; p < 0.001), and histologic grade 3 (HR: 1.8; 95% CI: 1.02 to 3.17; p = 0.041) were independent unfavourable prognostic factors for RFS (Table IV).

Kaplan–Meier Survival Analysis for Three-Year Rates of OS and RFS
The 3-year OS rate was significantly worse in the anemia group than in the no-anemia group [81.5% vs. 87.5%, p = 0.002, Figure 1(A)]. Compared with patients who did not receive perioperative allogenic RBC transfusions, those who received such transfusions had a worse 3-year OS rate [76.9% vs. 88.2%, p < 0.001, Figure 1(B)]. When preoperative anemia and perioperative transfusions were both taken into consideration, the 3-year OS rates were 76.1%, 78.4%, 86.2%, and 89.4% in the anemia and transfusion, the anemia and no-transfusion, the no-anemia and transfusion, and the no-anemia and no-transfusion groups respectively [p < 0.001, Figure 1(C)].

The presence of preoperative anemia was not associated with a significantly worse RFS rate [75.0% vs. 80.6%, p = 0.059, Figure 2(A)]. However, receiving a perioperative allogenic RBC transfusion was associated with a significantly worse RFS rate [70.9% vs. 80.9%, p < 0.001, Figure 2(B)]. Overall, the 3-year RFS rates were 71.3%, 76.7%, 78.6%, and 82.4% in the no-anemia and transfusion, the anemia and transfusion, the anemia and no-transfusion, and the no-anemia and no-transfusion groups respectively [p < 0.001, Figure 2(C)].

DISCUSSION

The major finding of the present study is that the perioperative use of blood transfusion is independently associated with worse OS and RFS after curative surgery in patients with nonmetastatic CRC, but that preoperative anemia is not. Compared with patients not having anemia, those with anemia had distinctive patient factors (older age, female sex, lower body mass index, higher likelihood of an ASA score of 3, more predominant right-sided colon cancer, more advanced TNM stage, higher level of carcinoembryonic antigen, and larger tumour size) and treatment-related factors (laparotomy). In our study, the use of perioperative blood transfusion was independently associated with...
worse os and rfs, and the independent predictors for perioperative blood transfusion were inherent patient factors (including preoperative anemia, greater ASA score, advanced TNM stage, and T4 disease) and treatment-related factors (including laparotomy, lengthy operative time, and 30-day postoperative morbidity).

Although we could not identify a direct causative relationship between perioperative transfusion and adverse oncologic outcomes, we tried to show the actual effect of preoperative anemia and perioperative transfusion by controlling for possible confounding variables in a multivariate analysis. Our findings showed that perioperative blood

| TABLE I Patient characteristics according to the presence of preoperative anemia |
|---------------------------------|-----------------|-----------------|---------|
| Characteristic                  | Overall (n=1003) | Anemia (n=468)  | No anemia (n=535) |
| Perioperative allogenic RBC transfusion [n (%) yes] | 295 (29) | 207 (44) | 88 (16) |
| Mean age (years)                | 67.3±11 | 69.4±11 | 65.6±11 |
| Sex [n (%) men]                 | 630 (63) | 275 (59) | 355 (66) |
| Mean BMI (kg/m²)                | 23.4±3 | 22.6±3 | 24.1±3 |
| ASA score [n (%)]               | 1 | 195 (19) | 79 (17) | 116 (22) | 0.029 |
| 2                              | 635 (63) | 294 (63) | 341 (64) |
| 3                              | 168 (167) | 91 (19) | 77 (14) |
| 4                              | 5 (0) | 4 (1) | 1 (0) |
| Preoperative chemoradiation [n (%)] | 113 (11) | 43 (9) | 70 (13) | 0.052 |
| Tumour location [n (%)]         | 239 (24) | 144 (31) | 95 (18) | <0.001 |
| Right-side colon                | 270 (27) | 121 (26) | 149 (28) |
| Rectum                          | 469 (47) | 186 (40) | 283 (53) |
| Multiple sites                  | 25 (2) | 17 (4) | 8 (1) |
| Mean serum CEA (ng/mL)          | 6.7±19 | 8.7±25 | 5.1±11 | 0.005 |
| Surgical approach [n (%)]       | 378 (38) | 215 (46) | 163 (30) | <0.001 |
| Laparotomy                      | 625 (62) | 253 (54) | 372 (70) |
| Mean operative time (minutes)   | 212±94 | 206±105 | 217±83 | 0.118 |
| TNM stage [n (%)]               | 0, I   | 253 (25) | 79 (17) | 174 (33) | < 0.001 |
| II                              | 318 (32) | 168 (36) | 150 (28) |
| III                             | 432 (43) | 221 (47) | 211 (39) |
| Histologic grade [n (%)]        | 1, 2   | 898 (90) | 432 (92) | 466 (87) | 0.007 |
| 3, Other                        | 105 (10) | 36 (8) | 69 (13) |
| Retrieved lymph nodes (n)       | 21.8±12 | 24.1±12 | 19.8±11 | <0.001 |
| Mean tumour size (cm)           | 4.6±2 | 5.4±2 | 3.9±2 | <0.001 |
| 30-Day postoperative ...         | Morbidity [n (%)] | 309 (31) | 146 (31) | 163 (30) | 0.803 |
| Infectious morbidity [n (%)]    | 177 (18) | 90 (19) | 87 (16) | 0.218 |
| Mortality [n (%)]               | 11 (1) | 4 (1) | 7 (1) | 0.491 |
| Clavien–Dindo classification [n (%)] | 1, 2   | 173 (56) | 76 (52) | 97 (59) | 0.233 |
| 3–5                             | 138 (44) | 70 (48) | 68 (41) |
| Adjuvant chemotherapy [n (%)]    | 607 (61) | 296 (63) | 311 (58) | 0.098 |

RBC = red blood cell; BMI = body mass index; ASA = American Society of Anesthesiologists; CEA = carcinoembryonic antigen.
transfusion was an independent prognostic factor for os and rrs, but that preoperative anemia was not. Compared with findings in other studies, those results are unique.

**Preoperative Anemia**

In the present study, 46.7% of the patients presented with anemia. Anemia is more common in patients who are elderly and female. Hemoglobin levels are affected by physiologic changes associated with aging, such as declining production of rbc and a shortened rbc lifespan. Anemia occurs more frequently in right-side colon cancer, in which the development of obstructive symptoms is frequently delayed. Intraluminal bleeding from friable cancer mucosa might persist until tumour progression in patients without symptoms. Considering that the anemia in crc is explained by intraluminal tumour bleeding, anemia is more likely to be a feature of advanced tumours, which are likely to be larger in size, associated with higher levels of carcinoembryonic antigen, and classified into a more advanced T stage. Anemia of chronic disease is caused by a systemic inflammatory response to crc and is frequently associated with sarcopenia, decreased body

| Variable | Comparator | Univariate | Multivariate |
|----------|------------|------------|--------------|
| Preoperative anemia (yes) | No | 4.03 | 3.01 to 5.40 | <0.001 | 5.06 | 3.42 to 7.48 | <0.001 |
| Age ≥80 years | <80 Years | 1.72 | 1.17 to 2.54 | 0.006 | 1.48 | 0.91 to 2.39 | 0.111 |
| Male sex | Female sex | 0.90 | 0.68 to 1.19 | 0.448 | 1.88 | 1.19 to 2.98 | 0.007 |
| ASA score 3 or 4 | ASA score 1 or 2 | 1.88 | 1.34 to 2.64 | <0.001 | 1.88 | 1.19 to 2.98 | 0.007 |
| Tumour location (rectum) | Colon | 1.11 | 0.84 to 1.46 | 0.443 | 1.78 | 1.20 to 2.63 | 0.004 |
| Surgical approach (laparotomy) | Laparoscopy or robot | 2.27 | 1.72 to 3.00 | <0.001 | 3.74 | 2.20 to 6.35 | <0.001 |
| Operative time ≥300 minutes | <300 Minutes | 2.64 | 1.71 to 4.10 | <0.001 | 3.74 | 2.20 to 6.35 | <0.001 |
| TNM stage | | | |
| 0, 1 | | 2.04 | 1.40 to 2.97 | <0.001 | 1.56 | 0.95 to 2.56 | 0.082 |
| II | | 1.47 | 1.02 to 2.11 | 0.039 | 0.93 | 0.56 to 1.54 | 0.772 |
| III | | 1.62 | 1.15 to 2.29 | 0.006 | 1.67 | 1.01 to 2.76 | 0.048 |
| Depth of tumour invasion (T4) | T1–3 | 1.62 | 1.15 to 2.29 | 0.006 | 1.67 | 1.01 to 2.76 | 0.048 |
| 30-Day postoperative morbidity (yes) | No | 2.59 | 1.95 to 3.45 | <0.001 | 2.86 | 1.96 to 4.19 | <0.001 |

**Cox proportional hazards model for prognostic factors of overall survival**

| Variable | Comparator | Univariate | Multivariate |
|----------|------------|------------|--------------|
| Preoperative anemia (yes) | No | 1.58 | 1.17 to 2.12 | 0.002 | 1.06 | 0.77 to 1.45 | 0.729 |
| Perioperative transfusion (yes) | No | 1.91 | 1.42 to 2.57 | <0.001 | 1.55 | 1.12 to 2.13 | 0.008 |
| Age ≥80 years | <80 Years | 2.35 | 1.62 to 3.41 | <0.001 | 1.36 | 0.90 to 2.05 | 0.148 |
| Male sex | Female sex | 0.87 | 0.64 to 1.18 | 0.368 | 1.16 | 0.81 to 1.67 | 0.422 |
| ASA score 3 or 4 | ASA score 1 or 2 | 1.96 | 1.39 to 2.77 | <0.001 | 1.16 | 0.81 to 1.67 | 0.422 |
| Tumour location (right-side colon) | | 0.187 | | |
| Left-side colon | | 0.97 | 0.62 to 1.52 | 0.885 | |
| Rectum | | 1.36 | 0.93 to 1.99 | 0.113 | |
| Multiple sites | | 1.45 | 0.57 to 3.69 | 0.441 | |
| Surgical approach (laparotomy) | Laparoscopy or robot | 2.22 | 1.64 to 3.02 | <0.001 | 1.75 | 1.26 to 2.41 | 0.001 |
| TNM stage | | | |
| 0, 1 | | 1.46 | 0.88 to 2.42 | 0.141 | 2.99 | 1.71 to 5.21 | <0.001 |
| II | | 2.71 | 1.73 to 4.24 | <0.001 | 6.12 | 3.62 to 10.32 | <0.001 |
| III | | 0.60 | 0.32 to 1.11 | 0.104 | 0.60 | 0.32 to 1.11 | 0.104 |
| Histologic grade 3 or other | Grade 1 or 2 | 1.98 | 1.48 to 2.65 | <0.001 | 1.51 | 1.11 to 2.05 | 0.009 |
| 30-Day postoperative morbidity (yes) | No | 1.89 | 1.41 to 2.53 | <0.001 | 3.85 | 2.66 to 5.59 | <0.001 |

**HR = hazard ratio; CI = confidence interval; ASA = American Society of Anesthesiologists.**
mass index, and the presence of severe comorbidities\(^{37}\), as confirmed in our study.

Studies of whether preoperative anemia leads to worse outcomes have produced conflicting results. Several reasons for those findings could be considered. First, the systemic inflammatory response linked to anemia is associated with tumour progression\(^{18}\). Anemia is associated with increased systemic inflammation, including a higher modified Glasgow prognostic score and higher levels of C-reactive protein and interleukin 8\(^{7}\). Second, anemia is associated with an increased occurrence of postoperative complications, which are adversely associated with oncologic outcomes\(^{36}\). Third, increased use of blood transfusions is associated with worse oncologic outcomes because of transfusion-induced immunomodulation and systemic inflammatory responses\(^{9,20}\). Fourth, tumour hypoxia induced by anemia worsens oncologic outcomes by increasing proliferative and metastatic potentials\(^{46}\). However, the theoretical detrimental effect of anemia has not always translated into poorer oncologic outcomes in previous studies\(^{8,10,14,38}\).

### Perioperative Blood Transfusion

In crc, the perioperative transfusion rate has been reported to be between 21.6% and 65.1%\(^{9,22–24,39–43}\); the rate in the present study was 29.4%. The detrimental effect of blood transfusion is thought to be attributable to transfusion-related immunomodulation and the systemic inflammatory response. The immunologic changes induced by transfusion include decreased production of interleukin 2, inhibition of cytotoxic T cell activity, and increased immunosuppressive prostaglandin release\(^{20}\). Those theoretical disadvantages have not always translated into worse oncologic outcomes in previous studies. Indeed, the use of transfusion was related to worse os in several studies\(^{40–42}\), with several other studies showing the opposite result\(^{8,24,44}\).

Several factors could account for those conflicting results. First, diverse definitions of "perioperative" have been used in the studies\(^{9,24,40,44–47}\); estimating the exact association between the use of blood transfusion and worse oncologic outcomes is therefore difficult. Second, complex clinical circumstances necessitating blood transfusion have been considered. It has been suggested that, not the transfusion itself, but the situation that necessitates the blood transfusion is the real determinant of prognosis\(^{23,24}\). But our study did not support that hypothesis. Our results suggest that the use of perioperative transfusion is independently associated with worse oncologic outcomes regardless of the clinical circumstances. Third, there is a possibility that selection bias because of small study samples or variation in study cohorts might have led to the conflicting results. One study conducted in a single centre that used propensity score matching (\(n = 401\)) showed that blood transfusion was not associated with worse oncologic outcomes\(^{22}\). Another study based on population-based data from a large number of cases (\(n = 24,330\)) showed that blood transfusion was related to worse outcomes\(^{45}\). Finally, not all studies performed a multivariate analysis to control for confounding factors\(^{39}\). We therefore reviewed earlier studies that investigated the effect of preoperative anemia and perioperative blood transfusion in nonmetastatic crc with multivariate analyses (details summarized in supplementary Table 1).

Tang et al.\(^{45}\) and Jagoditsch et al.\(^{44}\) investigated prognostic factors in crc by conducting multivariate analyses. In both studies, preoperative anemia and perioperative transfusion were used as variables in the univariate analysis; however, preoperative anemia was not included into the multivariate analysis because it was nonsignificant in the univariate analysis. Moreover, those two studies failed to demonstrate any prognostic significance of preoperative

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**TABLE IV** Prognostic factors for recurrence-free survival using Cox proportional hazards model

| Variable                              | Comparator        | Univariate                | Multivariate              |
|---------------------------------------|-------------------|---------------------------|---------------------------|
|                                      |                   | HR | 95% CI       | \(p\) Value | HR | 95% CI       | \(p\) Value |
| Preoperative anemia (yes)             | No                | 1.28 | 0.99 to 1.66 | 0.06        | 0.98 | 0.74 to 1.30 | 0.902        |
| Perioperative transfusion (yes)       | No                | 1.77 | 1.36 to 2.30 | <0.001      | 1.65 | 1.24 to 2.20 | 0.001        |
| Age ≥80 years                         | <80 Years         | 1.48 | 1.02 to 2.13 | 0.037       | 1.45 | 1.00 to 2.09 | 0.05         |
| Male sex                              | Female sex        | 0.87 | 0.64 to 1.18 | 0.368       |      |              |              |
| ASA score 3 or 4                      | ASA score 1 or 2  | 1.32 | 0.95 to 1.83 | 0.104       |      |              |              |
| Tumour location (right-side colon)   | Left-side colon   | 1 | 0.67 to 1.49 | 0.998       |      |              |              |
|                                      | Rectum            | 1.39 | 0.99 to 1.95 | 0.058       |      |              |              |
|                                      | Multiple sites    | 2.07 | 1.01 to 4.23 | 0.046       |      |              |              |
| Surgical approach (laparotomy)       | Laparoscopy or robot | 1.54 | 1.19 to 2.00 | 0.001       | 1.3 | 0.99 to 1.70 | 0.057        |
| TNM stage 0, I                        |                   |    | <0.001       | <0.001      |      |              |              |
| II                                    |                   | 1.61 | 1.02 to 2.53 | 0.041       | 1.51 | 0.95 to 2.39 | 0.082        |
| III                                   |                   | 3.31 | 2.21 to 4.96 | <0.001      | 3.2  | 2.12 to 4.83 | <0.001       |
| Histologic grade 3 or other           | Grade 1 or 2      | 1.92 | 1.1 to 3.36  | 0.023       | 1.8  | 1.02 to 3.17 | 0.041        |
| 30-Day postoperative morbidity (yes)  | No                | 1.46 | 1.12 to 1.91 | 0.005       | 1.24 | 0.94 to 1.62 | 0.123        |
| Adjuvant chemotherapy (yes)           | No                | 1.06 | 0.81 to 1.39 | 0.659       |      |              |              |

\(HR = \text{hazard ratio}; \ CI = \text{confidence interval}; \ ASA = \text{American Society of Anesthesiologists}.\)
FIGURE 1 Overall survival by the Kaplan–Meier method. (A) The 3-year overall survival rate was significantly worse in the anemia group than in the no-anemia group (81.5% vs. 87.5%, \( p = 0.002 \)). (B) The 3-year overall survival rate was worse for patients who received a perioperative allogenic red blood cell transfusion than for those who did not (76.9% vs. 88.2%, \( p < 0.001 \)). (C) Taking preoperative anemia and perioperative transfusion into consideration, the 3-year overall survival rates were 76.1%, 78.4%, 86.2%, and 89.4% in the anemia and transfusion, the anemia and no-transfusion, the no-anemia and transfusion, and the no-anemia and no-transfusion groups respectively (\( p < 0.001 \)).

FIGURE 2 Recurrence-free survival by the Kaplan–Meier method. (A) The presence of preoperative anemia did not lead to a significantly worse recurrence-free survival rate (75.0% vs. 80.6%, \( p = 0.059 \)). (B) Receiving a perioperative allogenic red blood cell transfusion resulted in significantly worse recurrence-free survival (70.9% vs. 80.9%, \( p < 0.001 \)). (C) The overall 3-year recurrence-free survival rates were 71.3%, 76.7%, 78.6%, and 82.4% in the no-anemia and transfusion, the anemia and transfusion, the anemia and no-transfusion, and the no-anemia and no-transfusion groups respectively (\( p < 0.001 \)).
anemia or perioperative transfusion. In the study by Tang et al., performed in 1993, the included patients had a mean age that was quite young compared with the age of the patients in other studies (no-transfusion group: 54.4 ± 12.5 years; transfusion group: 55.2 ± 12.2 years), and only 14% had anemia, the lowest value in the reports that we reviewed. The presence of anemia and the detrimental effect of transfusion might be less in young patients. The study by Jagoditsch et al., performed in 2006, included only patients with rectal cancer. In that study, preoperative anemia was defined as a hemoglobin level of 14 g/dL or less, the highest value in the reports we reviewed. The percentage of patients with anemia was as high as 51.5%.

Of all the reports we reviewed, the study by Talukder et al., performed in 2014, included the largest number of patients (n = 1370). In that study, 36.5% of the patients presented with preoperative anemia (hemoglobin ≤ 12 g/dL), and 30.9% received a perioperative transfusion. The methods used by those authors had some distinct features. First, where we included 30-day postoperative morbidity in the multivariate analysis, they included variables related to the clinical circumstances requiring transfusion—for example, surgical urgency, medical complications, and reoperation. Second, they divided the perioperative period into intraoperative, preoperative, and postoperative periods. They analyzed the effect on prognosis of transfusion during each period individually or during all periods in combination. In their results, preoperative anemia was not a significant prognostic factor for OS and RFS. Only intraoperative transfusion was significantly associated with OS (HR: 1.31; p = 0.004) and RFS (HR: 1.37; p = 0.013). Perioperative transfusion was not a significant prognostic factor for OS, but it was significant for RFS (HR: 1.26; p = 0.024). They explained that the loss of significance of perioperative transfusion in the multivariate analysis for OS could be attributed to confounding factors and the circumstances that necessitated transfusion rather than to the transfusion itself. That analysis contradicts our results that perioperative transfusion is an independent prognostic factor for OS regardless of unfavourable clinical confounding factors. Their study is somewhat different from our study in that their study period was quite long (1984–2004), which suggests that patient treatments might be heterogeneous. In fact, some patients received transfusions with whole blood and not packed RBCs. Differences in the type of transfusion and the definition of “perioperative transfusion” might have contributed to their different results.

Kaneko et al. reported results similar to those in our study about perioperative allogenic blood transfusion (HR: 3.16; p = 0.031), but not preoperative hemoglobin, being an independent prognostic factor for OS. However, their study included only a small number (n = 108) of elderly patients (more than 75 years of age) and differed from other studies that analyzed preoperative hemoglobin rather than the presence of preoperative anemia. The variables used in their multivariate analysis were tumour depth, lymph node metastasis, preoperative hemoglobin, and perioperative transfusion. Given that the study included only elderly patients, we cannot compare their results with ours. In elderly patients, the adverse effect of blood transfusion might be greater.

Morner et al. also used a multivariate analysis to investigate the effects of preoperative anemia and perioperative transfusion. The purpose and design of their study seem similar to ours, but their results are the opposite of ours. In their study, preoperative anemia was an independent prognostic factor for OS (HR: 2.3; p < 0.001) and RFS (HR: 1.7; p < 0.05), but perioperative anemia was not. The Morner et al. study and our study have several differences. One is the number of patients. The Morner group acknowledged the limited statistical power in their multivariate analysis of risk factors for recurrence. The number of patients enrolled in their study was 496; our study enrolled 1003 patients. Another difference is the definition of the period of “perioperative transfusion.” We defined perioperative transfusion as receipt of a transfusion during postoperative hospitalization. Hypothetically, transfusion induces harmful immune reactions such as immunosuppression. If transfusion causes an adverse immune reaction, that reaction could last until the postoperative period in affected hosts. The healing process includes an inflammatory response in damaged tissue, secretion of growth factors, and cellular proliferation. Those reactions can occur during the postoperative period. We therefore believe that it is reasonable to use a longer period (from the operative day to the date of discharge) for the use of transfusion. In the case of the study by the Morner group, the period of perioperative transfusion was defined as 24 hours before and after the operation. Third, despite the relatively short period defined for transfusion, the transfusion rate was higher in the Morner group’s study than in our study (40.1% vs. 29.4%). Fourth, their institution used leucocyte-depleted blood components, which are presumably less immunomodulatory. Finally, the study locations were different (Europe vs. Asia). Those differences might have been responsible for the conflicting results.

As we reviewed the published studies, we found that the effects of preoperative anemia and postoperative transfusion were reported differently. The inconsistent results between the studies might be attributable to heterogeneous study designs, patient cohorts, hemoglobin levels used to define preoperative anemia, and perioperative transfusion periods, in addition to complex treatment-related factors such as the surgical approach, the amount of intraoperative bleeding, and the indications for blood transfusion.

We found that transfusion was negatively associated with oncologic outcomes. Thus, we believe that perioperative transfusion must be reduced. Well-organized treatment processes must be recommended for patients who need a perioperative blood transfusion. Even though preoperative anemia was not an independent prognostic factor for survival in nonmetastatic CRC, it was a predictive factor for perioperative transfusion. For patients with preoperative anemia, the indications for blood transfusion and preoperative iron supplementation should be standardized. During surgery, modifiable treatment-related predictive factors that might mitigate the need for blood transfusion—laparotomy, lengthy operative time, and meticulous surgical techniques that minimize blood loss—must be considered. In addition, efforts must be taken to reduce postoperative morbidity that requires blood transfusion during the perioperative period.
CONCLUSIONS

The use of perioperative blood transfusion, but not preoperative anemia, was independently associated with worse oncologic outcomes. Although our study did not demonstrate a relationship between transfusion volume and poor prognosis, it clearly demonstrated that perioperative transfusion itself is associated with a detrimental effect on oncologic outcomes.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

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