

ORIGINAL ARTICLE

The Effect of Preoperative Anemia on the Odds of Allogeneic Blood Transfusion and Patient Outcomes in Colorectal Neoplasm Patients

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SUMMARY

Background: The optimal preoperative hemoglobin (Hb) value of colorectal neoplasm patients is still being debated. This study aimed at determining the effect of preoperative anemia on patient outcomes and allogeneic blood transfusion (ABT).

Methods: This retrospective cohort study enrolled colorectal neoplasm patients, that underwent surgery, from January 1, 2012, to December 31, 2021. The primary outcomes were the association between anemia and average length of stay (ALOS) and the odds of ABT. The secondary outcomes were the risk factors of the primary outcomes. Univariate and multivariate logistic regression analyses were applied to identify the association and risk factors.

Results: A total of 14,352 inpatients were included in the study, of whom 3,035 experienced (21.15%) mild anemia, 1,500 (10.45%) moderate anemia, and 104 (0.72%) severe anemia. Overall, 1,418 (9.88%) patients received ABT during the hospitalization, and 546 (3.80%) patients received perioperative ABT. In the multivariate logistic regression analysis, compared with the no anemic group, the odds ratio [OR] of ABT during the hospitalization for patients with mild/moderate/severe anemia were 5.915, 95% confidence interval [CI]: 4.717 - 7.418; 104.777, 95% CI: 84.345 - 130.160; and 13,361.442, 95% CI: 816.004 - 218,783.511, respectively, and the OR of perioperative ABT were 4.332, 95% CI: 3.245 - 5.785; 27.492, 95% CI: 20.974 - 36.037; and 20.912, 95% CI: 11.832 - 36.959, respectively. Besides, the ALOS was longer, β were 0.619, 95% CI: 0.346 - 0.892; 1.188, 95% CI: 0.821 - 1.554; and 1.395, 95% CI: 0.107 - 2.684, respectively.

Conclusions: Anemia is a common phenomenon in colorectal neoplasm surgical patients, and even mild anemia could be a deleterious predictor on the outcomes of colorectal neoplasm patients that underwent surgery.

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KEYWORDS

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INTRODUCTION

For decades, one of the most popular ideas in literature has been that preoperative anemia is related to adverse outcomes, such as an increased postoperative morbidity and an average length of stay (ALOS) [1,2]. A common strategy used to manage preoperative anemia is allogeneic blood transfusion (ABT), although previous works [3,4] state that ABT is associated with a higher risk of

complication and higher medical costs for hospitalized patients. For patients with anemia, colorectal neoplasm patient outcomes have always been a main concern, due to its high incidence and mortality [5], and these patients frequently manifest anemia at the time of diagnosis [6,7]. Therefore, these patients are more likely to require ABT during hospitalization.

Previous studies indicate that anemia is independently associated with an increased mortality and ALOS, while transfusion to improve anemia is an additional independent risk factor [1,8]. Various studies [9,10] investigated the effect of anemia on patient outcomes for adjusting RBC transfusion; few studies investigated how the exact degree of preoperative anemia interacts with the odds of ABT in colorectal neoplasm patients that underwent surgery. Furthermore, how the exact degree of anemia contributes to its recovery has not been extensively investigated. A challenging problem, which arises in this domain, is the balance of anemia and transfusion.

To study the association between preoperative hemoglobin (Hb) level and ABT and ALOS in more detail, we chose colorectal neoplasm patients that underwent surgery as study subjects to investigate how preoperative Hb levels interact with the odds of ABT and ALOS, and to identify the risk factors of ABT and ALOS in colorectal neoplasm patients. Our research aimed at providing evidence for clinicians to better manage the preoperative anemia of colorectal neoplasm patients, minimizing the avoidable, inappropriate exposure to ABT, saving the blood, and meanwhile improving the patient outcome.

MATERIALS AND METHODS

Study design and participants

This study was approved by the Institutional Review Board and Medical Ethics Committee of the West China Hospital of Sichuan University (no. 2021/516). The requirement for written informed consent was waived, because of the retrospective design of the study.

This retrospective observational cohort study included all admissions to the West China Hospital of Sichuan University between January 2012 and December 2022. Admissions were sourced from the hospital information system. The inclusion criteria were patients that underwent surgery for colorectal neoplasms, and patients with preoperative anemia. The exclusion criteria were recurrent patients, patients with temporary stoma, age below 18 years, short-stay admissions (defined as admissions less than 2 days), admissions receiving a massive transfusion (defined as those receiving 10 u ABTs within 24 hours), missing preoperative hemoglobin values, missing surgical date, and irrelevant surgery. The preoperative Hb value was defined as the last Hb value three days before the surgery.

Variables and definitions of anemia

Preoperative Hb value was chosen as the main exposure variable. Anemia is graded based on its hemoglobin value, according to the currently available criteria of China [11], with a normal value defined as male ≥ 120 g/L and female ≥ 110 g/L. The grading system based on Hb value was classified into four levels: normal (Hb ≥ 120 g/L in male and 110 g/L in female), mild (90 g/L \leq Hb < 120 g/L in male, 90 g/L \leq Hb < 110 g/L in female), moderate (60 g/L \leq Hb < 90 g/L), and severe (Hb < 60 g/L).

Outcomes

Perioperative ABT [12] was defined as intraoperative and postoperative in-hospital transfusion. The primary outcomes were ALOS and the odds of ABT during hospitalization and perioperative ABT. The secondary outcomes of interest were the risk factors associated with ALOS and ABT. Potential confounders, such as patient age, gender, body mass index (BMI), smoking, previous histories (surgical history and blood transfusion history), comorbidities (hypertension, diabetes, pulmonary infection, hyperlipidemia, and coronary heart disease), tumor location (right half colon, transverse colon, left half colon, sigmoid colon, and rectum), and operation method (laparoscopy or not), were included in the analysis.

Blood transfusion strategy

The trigger for intraoperative RBC transfusion was totally at the discretion of the attending anesthesiologist or surgeons. After surgery, RBC transfusion was at the discretion of the attending ICU physicians and surgeons. The blood components were provided by the department of transfusion medicine, with 1 unit RBCs derived from 200 mL of whole blood, and the volume was approximately 150 mL.

Statistical analysis

Patients were classified into four subgroups: normal, mild anemia, moderate anemia, and severe anemia. Continuous variables were described as mean and standard deviations (SDs) or median and interquartile range, as appropriate, and the comparison between the subgroups were done with Student's *t*-test or analysis of variance. Categorical variables are presented as frequencies and percentages and were compared by using the chi-squared test or Fisher's exact test, where appropriate.

Univariate analyses were followed by multivariable models, adjusting for age, gender, body mass index (BMI), smoking, previous histories (surgical history and blood transfusion history), comorbidities (hypertension, diabetes, pulmonary infection, hyperlipidemia, and coronary heart disease), tumor location (right half colon, transverse colon, left half colon, sigmoid colon, and rectum), and operation method (laparoscopy or not), to identify the difference of the primary outcomes between the subgroups and to explore the risk factors of the pri-

Table 1. Multivariable analysis of the baseline characteristics and ABT.

Variables		ABT during the hospitalization			Perioperative ABT		
		OR (95% CI)	Wald χ^2	P	OR (95% CI)	Wald χ^2	P
Age, years	< 60	0.947 (0.783, 1.145)	0.318	0.573	0.940 (0.743, 1.190)	0.264	0.607
	≥ 70	1.467 (1.215, 1.770)	15.936	< 0.001	1.272 (1.015, 1.596)	4.346	0.037
Smoking					0.738 (0.583, 0.935)	6.319	0.012
Mild anemia		5.915 (4.717, 7.418)	236.888	< 0.001	4.332 (3.243, 5.785)	98.628	< 0.001
Moderate anemia		104.777 (84.345, 130.160)	1,766.585	< 0.001	27.492 (20.974, 36.037)	576.007	< 0.001
Severe anemia		13,361.442 (816.004, 218,783.511)	44.36	< 0.001	20.912 (11.832, 36.959)	109.489	< 0.001
Hypertension		1.293 (1.073, 1.557)	7.31	0.007	1.283 (1.029, 1.600)	4.91	0.027
Pulmonary infection		1.937 (1.526, 2.459)	29.516	< 0.001	2.347 (1.819, 3.028)	43.086	< 0.001
Right half colon		1.790 (1.510, 2.122)	45.032	< 0.001	1.710 (1.309, 2.234)	15.464	< 0.001
Left half colon		1.340 (1.033, 1.738)	4.854	0.028			
Rectum					1.502 (1.141, 1.978)	8.402	0.004
Non-laparoscopy surgery		1.338 (1.134, 1.579)	11.887	0.001	1.450 (1.175, 1.790)	11.979	0.001

OR - odds ratio, ABT - allogeneic blood transfusion.

mary outcomes. Variables with a p-value less than 0.05 in the univariate analysis were included in the multivariate analysis, and the stepwise method was used to screen the variables.

Statistical analyses were performed by using SAS 9.4. p-values are two-sided, with significance set at the 5% level.

RESULTS

Baseline characteristics of colorectal neoplasm patients

Over the 10-year study period, a total of 29,327 patients, that underwent surgery for colorectal neoplasms, were identified. After applying the exclusion criteria, 14,352 patients were eligible for analysis (Figure 1). Baseline characteristics of colorectal neoplasm patients with and without anemia are summarized in Table S1. The mean (SD) age of patients was 60.62 (12.55) years, and the male gender was predominant (58.32%). Nearly half of the patients had comorbidities. Based on the preoperative Hb value, a total of 4,639 (32.32%) patients had preoperative anemia, with 3,035 (21.15%) experiencing mild anemia, 1,500 (10.45%) moderate anemia, and 104 (0.72%) severe anemia.

Risk factors of allogeneic blood transfusion (ABT)

When evaluating factors associated with ABT, univariate analyses were followed by multivariable models. The univariate analysis of the baseline characteristics and ABT showed that age, sex, BMI, smoking, anemia, transfusion history, comorbidities (except hyperlipidemia), tumor location (except left colon), and non-laparoscopy surgery were related to perioperative ABT (Table S2). When it came to ABT during the hospitalization, only the factor of hyperlipidemia was not correlated (Table S2). Furthermore, the multivariable analysis showed that old age (age ≥ 70 years), smoking, anemia, comorbidities (hypertension and pulmonary infection), tumor location (right colon and rectum), and non-laparoscopy surgery were related to perioperative ABT (Table 1). There was an additional factor of left colon, when considering the use of ABT during the hospitalization (Table 1).

Risk factors of ALOS

The univariate analysis of the baseline characteristics and ALOS showed that age, smoking, anemia, surgery history, transfusion history, comorbidities (except hyperlipidemia), and tumor location of right half colon were related to ALOS (Table S3). In the multivariable analysis of the baseline characteristics and ALOS, old

Table 2. Multivariable analysis of the baseline characteristics and ALOS.

Variables		ALOS		
		β (95% CI)	<i>t</i>	<i>p</i>
Demographic variables				
Age, years	< 60	0.047 (-0.212, 0.305)	0.355	0.722
	\geq 70	0.944 (0.658, 1.230)	6.475	< 0.001
Smoking		1.253 (1.004, 1.502)	9.858	< 0.001
Anemia (ref. normal)				
Mild anemia		0.619 (0.346, 0.892)	4.444	< 0.001
Moderate anemia		1.188 (0.821, 1.554)	6.347	< 0.001
Severe anemia		1.395 (0.107, 2.684)	2.122	0.034
Previous history				
Surgery history		0.769 (0.540, 0.998)	6.587	< 0.001
Transfusion history		0.693 (0.080, 1.305)	2.216	0.027
Comorbidity				
Hypertension		0.655 (0.374, 0.935)	4.572	< 0.001

age (age \geq 70 years), smoking, anemia, surgery history, transfusion history, and comorbidity (hypertension and pulmonary infection) were associated with longer ALOS (Table 2).

Anemia and allogeneic blood transfusion (ABT)

Among all participants, 1,418 (9.88) patients received ABT during the hospitalization, and 546 (3.80) patients received perioperative ABT (Table S2). After adjustment for baseline characteristics, multivariable analysis of the anemia subgroup and ABT showed that anemia was independently associated with ABT, and a dose-response relationship was observed in ABT during hospitalization, compared with the no anemia group (Table 1). The odds of ABT increased, even in the mild anemia group, respectively 5.915-fold (95% CI 4.717 - 7.418, $p < 0.001$) for ABT during the hospitalization and 4.332-fold (95% CI 3.243 - 5.785, $p < 0.001$) for perioperative ABT (Table 1). Meanwhile, the odds of ABT in the severe anemia group was 13,361.442-fold (95% CI 816.004 - 218,783.511, $p < 0.001$) for ABT during the hospitalization and 20.912-fold (95% CI 11.832 - 36.959, $p < 0.001$) for perioperative ABT (Table 1).

Anemia and ALOS

After adjustment for baseline characteristics, the multivariable analysis showed ALOS was extended in mild and moderate to severe anemia, but to a greater extent

in severe anemia patients, when compared to patients without anemia (Table 2). Compared to patients without anemia, the ALOS were 0.619 (95% CI 0.346 - 0.892, $p < 0.001$) days longer for patients with mild anemia, 1.188 (95% CI 0.821 - 1.554, $p < 0.001$) days longer for moderate anemia, and 1.395 (95% CI 0.107 - 2.684, $p < 0.001$) days longer for severe anemia.

DISCUSSION

Our 10-year cohort study identified anemia as common in colorectal neoplasm patients that underwent surgery. Out of the 14,352 study patients, 9.88% of the patients received ABT during the hospitalization, and that is why this population is particularly worthy of our attention. This is consistent with the review, which found that the highest prevalence of preoperative anemia is in patients that underwent a colorectal cancer resection [13]. The mean age was 60.62 (12.55) years, and the male gender was predominant. Nearly half the patients had comorbidities, and the most prevalent was hypertension. These basic characteristics were similar to the research of the network-based study of Hang Qiu [14], whose study objects were also from southwest China. Based on the preoperative Hb value, a total of 4,639 (32.32%) patients had preoperative anemia, similar to the proportion reported by other studies [15,16], but

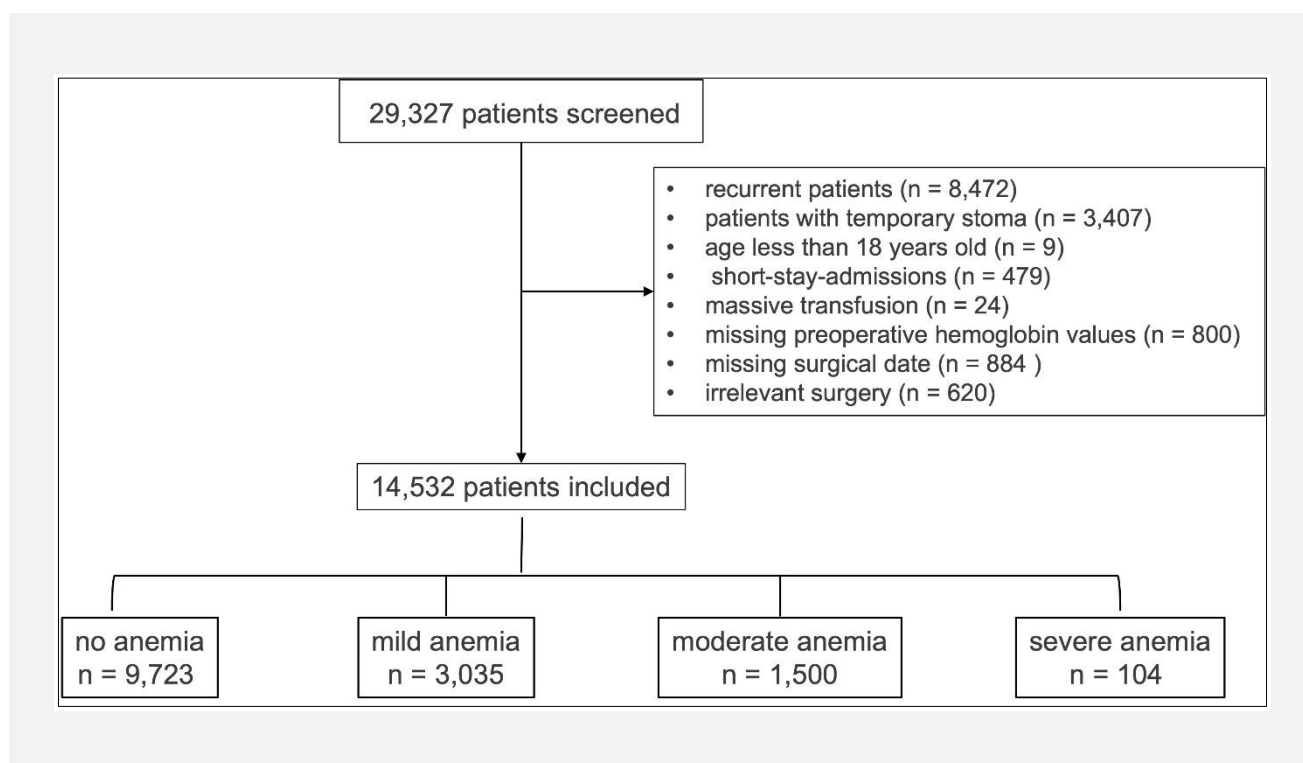


Figure 1. Flow chart of study population eligible for analysis.

more than what was reported (23.5%) in the study of another center in China [12]. One possible reason could be that the patients' condition was worse. Our research mainly shows that the preoperative anemia is strongly associated with worse outcomes, such as longer ALOS and higher odds to receive ABT, even in mild anemia. Compared with the no anemia group, the odds to receive ABT during the hospitalization increased 13,361-fold in the severe anemic group, and the odds of perioperative ABT increased 21-fold. While, in the mild anemic group, the odds to receive ABT during the hospitalization increased 6-fold in the severe anemic group, compared with the no anemia group, and the odds of perioperative ABT increased 4-fold. Our findings matched the recent study [12], which suggests that preoperative anemia is an independent risk factor for long-term adverse outcomes in this population. Rotem Gvirtzman's study [17] even thought, when anemia is present, the risk for highly advanced CRC increases.

The results of our study emphasize the importance to improve anemia, even mild anemia, before the surgery, in order to get a better patient outcome. Therefore, we assume that the optimization of preoperative Hb level may be favorable for the reduction in ABT and ALOS, which is consistent with the results of previous studies [13,18]. It is known to us that all anemia is caused by complex etiology, such as nutritional deficiencies, inherited disorders, infections and inflammation, blood loss, and so on, so there are multiple relevant interven-

tions to improve anemia, like iron supplementation [19], vitamin A supplementation [20], controlling infections [21], treating primary diseases [19], minimizing the blood loss by adopting minimally invasive surgery (endoscopic surgery) [22], etc. While it is generally accepted that ABT is the primary solution to improve anemia, in spite of the fact that it itself is an independent risk factor for poor clinical outcomes [23,24], we do not advise clinicians to take a rigorous restrictive transfusion strategy for colorectal neoplasm patients before surgery, in view of that fact. For decades, the gap between blood supply and demand has been prominent around the world [25], which is particularly concerning in China [26]; therefore, more and more evidence encourages the clinicians to adopt restrictive transfusion strategies, where appropriated. For one thing, restrictive transfusion strategies could save blood resources. For another, the implementation of patient blood management (PBM) has attracted considerable attention, which focuses on the implementation of transfusion guidelines, perioperative blood conservation, and anemia management [27]. The clinical practice guidelines from the AABB have also advocated the restrictive transfusion threshold [28], which is in agreement with the increasing body of literature [29-32] supporting the use of restrictive transfusion strategy, which draws the conclusion that the use of restrictive transfusion strategy is associated with a reduced number of RBCs transfused, and patient outcomes seem to be unaltered, compared

with liberal transfusion strategy. Although our previous study [33] also demonstrated that clinicians are encouraged to adopt restrictive transfusion strategies in our hospital, there is another concern raised by Mo A. [34], that arises the question whether we have left patient-centered outcomes behind. And they also doubt our confidence level on whether restrictive transfusion strategies should be the standard of care [35]. On the one hand, present study was unable to demonstrate non-inferiority of restrictive transfusion for long-term HRQoL [36,37], so whether the restrictive transfusion strategy is better is not certain. On the other hand, the research of colorectal neoplasm patients was worth it in the context of advocating of individualized treatment.

In the regression analysis, we assessed the association between basic characteristic with the main outcomes. There were some modifiable risk factors, which we can pay attention to, such as BMI and smoking, which were consistent with the previous study of a review [38]. Furthermore, the right-side tumor location appears to be the risk factor of ABT and ALOS in our study. This might be attributed to the molecular, embryological, biological, and anatomical differences that exist between right-sided (proximal) colon cancers and left-sided (distal) colon cancers [39]. We should also take notice of other risk factors such as old age (age ≥ 70 years) and comorbidities (hypertension and pulmonary infection). Considering that the phenomenon of aging was global, we may pay more attention on this population.

To our knowledge, specific recommendations or guidelines for the value of preoperative Hb, particularly for colorectal neoplasm patients, have not been proposed, yet. There are lasting discussions and controversies about perioperative anemia and ABT on the prognosis in patients with colorectal neoplasms [3]. Focused on the controversial issue, we compared the different degree of anemia groups with the no anemic group, providing a new insight of preoperative Hb value on patient outcomes. In the prevalence of restrictive transfusion strategy, we provided evidence to guide clinicians to improve even mild anemia prior to surgery in order to get a better patient outcome.

Although several limitations are inherent in this study, the results still deserve affirmation. The main advantage of this study is the relatively large sample size focused on the preoperative anemia subgroup, and that it is providing new insights into the risk factors in preoperative anemia patients with colorectal neoplasms. Clinicians can identify high-risk patients to receive ABT or have a longer ALOS, so that they could develop individualized interventions to monitor and manage the preoperative anemia to achieve a better outcome. However, one concern about the findings is that the evidence is not as strong as a retrospective study, and some missing data may weaken the strength of our conclusions. Notwithstanding these limitations, our study not only identified that anemia, even mild anemia, negatively influenced the patient outcomes, such as ABT and ALOS, but it also emphasized the importance of considering basic

risk factors of the patient outcome to provide an individualized treatment.

CONCLUSION

In summary, our findings show that anemia is common in colorectal neoplasm patients, and even mild anemia could be a deleterious predictor on the prognosis of colorectal neoplasms for subjects who underwent surgery.

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Data Availability Statement:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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