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Research Article

Impact of Perioperative Transfusion Practice on Postoperative Morbidity in Patients with Colorectal Cancer

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Abstract

Background: Colorectal Cancer (CRC) has currently one of the highest incidence and mortality rates, both in Portugal and worldwide. CRC staging is known to be the major determinant of the prognosis and morbidity of these patients, but increased morbidity has been suggested in patients with CRC when they undergo blood transfusions, especially in the perioperative context.

Aim of the Study: To analyze the impact of perioperative transfusion practice on the postoperative morbidity of patients undergoing elective surgery with curative intention for CRC, at the Hospital de Braga (HB) between 2016 and 2017.

Materials and Methods: We performed a retrospective analysis of patients undergoing curative surgery on HB between 2016 and 2017 by CRC, including 183 patients. Variables related to patient characterization, tumor characterization, surgery characterization and postoperative morbidity were collected, and the respective statistical analysis of the collected data was performed to identify predictors of increased postoperative morbidity of the included patients.

Results: Inferential analysis distinguished a total of 110 (61.1%) patients with postoperative morbidity grade I and 73 (39.9%) with postoperative morbidity grade II or higher, and there were statistically significant differences between these groups regarding, surgical approach ($p = 0.013$), tumor differentiation ($p = 0.034$) and number of perioperative blood transfusions ($p < 0.001$). Logistic regression showed that an increase in the number of perioperative blood transfusions increases 100 times (95% CI 14.8 - 846) the patient's propensity to have a higher degree of postoperative morbidity, i.e. grade II or higher.

Conclusion: Perioperative blood transfusions proved to be a statistically significant predictor of the degree of postoperative morbidity of patients with CRC undergoing curative surgery in HB.

Keywords: *Colorectal Cancer; Colorectal Surgery; Postoperative Morbidity; Perioperative Blood Transfusions*

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; CRC: Colorectal Cancer; IQR: Interquartile Range; Mdn: Median; N: Number of Lymph Nodes Involved; OR: Odds Ratio; p: p-Value; Phi: Phi Coefficient; r: Approximate Effect Size Calculated for Mann-Whitney Statistic; SD: Standard Deviation; T: Depth of Tumor Invasion; X^2: Chi-Square; Z: Standardized Test Statistics

Introduction

Colorectal Cancer (CRC) is currently one of the neoplasms with the highest incidence and mortality in the world. According to the latest data from Globocan - International Agency for Research on Cancer, for 2018, CCR is the third most common type of cancer, with about 1.8 million cases worldwide, corresponding to 10.2% of the total cancer incidence [1]. Therefore, given the high incidence and mortality of CRC, it is important to invest in the search for knowledge about this type of cancer, particularly in the study of predisposing factors to greater morbidity and mortality, to improve the prognosis and quality of life of these patients.

In fact, the prognosis of patients with CRC is highly variable and depends on several factors, such as the stage of the disease, which can be measured through the malignant tumor classification system, TMN, with the T corresponding to the depth of tumor invasion, the N corresponding to the number of invaded lymph nodes and the M to the absence or presence of distant metastases [2].

The performance of blood transfusions has been associated with a worse prognosis in patients with CRC, especially in patients undergoing tumor recession surgery [3-5]. Although this association is not yet completely understood, it has been demonstrated that patients who undergo a greater number of blood transfusions in the perioperative period have a higher rate of cancer recurrence and shorter survival time [3,6-8]. In Gunka., *et al.* [9], patients with CRC with a higher number of units of blood transfused (3 or more) perioperatively had greater postoperative morbidity, less disease-free time, and worse survival rate compared to patients who did not had been transfused or had received fewer units of blood [9]. The evidence of this knowledge makes it essential to monitor more closely patients with CRC during the perioperative period. Furthermore, approaches to minimize blood loss are of paramount importance [8,9].

Transfusion practice in oncology patients

Transfusion therapy is fundamental and often life-saving, particularly in patients with acute hemorrhagic bleeding, but we know today that it can also bring disadvantages to the transfused patient [10].

Regarding the long-term effect of hemotherapy, there have been numerous studies focusing on different pathologies, such as oncological disease. A relationship between blood transfusions and a worse prognosis in these patients has already been described [10]. It is believed that a complex immunomodulatory effect that culminates in immunosuppression may be involved in this relationship, interfering with postoperative morbidity of patients with cancer [4,5]. This immunomodulatory effect associated with blood transfusion was first suggested in 1978 by Opelz., *et al.* [11], describing that patients who had received allogeneic blood transfusions had greater survival after undergoing renal transplantation, due to immunosuppression.

Thus, as mentioned above, it is essential to study the correlation between transfusion practice and postoperative morbidity of patients with CRC undergoing surgery for curative purposes. This way, it will be possible to adjust the transfusion practice to the reality of these patients and develop strategies that can reduce or even avoid the need of transfusion in the perioperative period.

Aim of the Study

The main objective of this study is to retrospectively analyze the impact of perioperative transfusion practice on postoperative morbidity of patients undergoing elective surgery with curative intent for colorectal cancer, at Hospital de Braga between 2016 and 2017.

Materials and Methods

Study oversight and patients inclusion

This is a retrospective study that included all patients with CRC undergoing elective surgical recession with curative intent, in the Department of General Surgery of Hospital de Braga, between February 2016 and December 2017.

The patients who presented the following criteria were excluded: patients with distant metastases; patients with a previous malignant tumor in the last 5 years; patients who have undergone urgent surgical recession.

All the procedures had been performed by the surgical team at the Department of General Surgery, Hospital de Braga.

Data collection

The sample was characterized by analysis and collection of information, according to the inclusion criteria, from an existing database of patients who had undergone elective surgery for CRC at Braga Hospital, between February 2016 and December 2017.

A survey and analysis of the respective clinical files were then performed, and the clinical records were consulted through the Glintt® informatic software.

The variables collected from this database refers to a set of information:

- Patient's data: Age, gender, weight, height, body mass index (BMI), blood type and the search for irregular antibodies.
- Tumor's data: Location, depth of tumor invasion (T), number of lymph nodes involved (N) and degree of tumor differentiation.
- Surgical reporting: Bleeding during surgery (ml), duration of surgery (in minutes, from surgical incision to closure of the skin), type of surgical intervention and approach, pre- and postoperative hemoglobin value (to calculate the drop of hemoglobin level between pre- and post-operative periods) and the number of blood transfusions the patient underwent in the peri-operative period. The perioperative period was defined as the time between the 4 weeks prior to the surgery and the 4 consecutive weeks.
- Postoperative morbidity: Postoperative complications were classified according to Clavien-Dindo classification (30-day complication grade I, II, IIIa, IIIb, IVa, IVb and V) [12].

Statistical analysis

The statistical analysis was performed using SPSS - Statistical Package for the Social Science Program, version 25 (IBM Corporation, 2017).

The variables duration of surgery and drop of hemoglobin level between the pre- and postoperative period were treated as continuous variables, and all the others were categorized. For characterize the sample, a descriptive analysis of all collected variables was performed, describing the absolute and relative frequencies for all categorical variables. On the other hand, for continuous variables, normality was verified using the Shapiro-Wilk normality test, histogram symmetry analysis and kurtosis value. In cases where normality was verified, the mean and standard deviation (SD) were used as measures of central tendency, while in cases where normality was not verified, the median (Mdn) and the interquartile range (IQR) were used.

For the inferential statistics, the following variables were dichotomized: postoperative morbidity was dichotomized into Grade I and Grade II or higher; the variable blood transfusions was dichotomized into 0 transfused units or 1 or more transfused units; the variable BMI was dichotomized into < 25 kg/m^2 and BMI ≥ 25 kg/m^2; the variable tumor differentiation was dichotomized into well-differentiated tumors and moderately or poorly differentiated tumors.

A p-value of < 0.05 was considered significant and the Confidence Interval (CI) used was 95%.

The correlation between postoperative morbidity and continuous variables was determined by comparing medians using the *Mann Whitney test*. The magnitude of the differences found was evaluated by calculating the effect size, given by the value of *r*[1], considering small, medium, or large effect for absolute values of 0.20, 0.50 and 0.80 respectively [13,14].

In order to determine the correlation between postoperative morbidity and the remaining variables, crosstabs were performed, and the interdependence between the variables was analyzed using the Fisher's exact test whenever the number of cells with a value less than 5 was greater than 20% of the total number of cells and the Chi-square (X^2), when the number of cells with a value less than 5 was less than 20%. As a measure of effect size, we used the Phi coefficient for 2 x 2 tables and Cramer's V for larger tables. For both coefficients, a small, medium, or large effect was considered for absolute values close to 0.10, 0.30 and 0.50 [15], respectively. In cases where the existence of statistically significant differences between the groups was verified, the adjusted residuals were analyzed in order to identify the differences.

To assess the existence of predictors of postoperative morbidity, a binary logistic regression was performed, and all those that presented significant results (p-value < 0.050) in the bivariate analysis were included in the analysis as independent variables. To assess multicollinearity, a matrix of correlations between the independent variables was performed.

Results

A total of 183 patients with CRC who underwent elective surgical recession at the Hospital de Braga, with curative intent, between February 2016 and December 2017, met the inclusion criteria of the present study.

Characterization of patients

The sample showed a predominance of male patients with 118 (32.5%) patients, and 65 (64.5%) female patients. Of these patients, only 6 (3.28%) were equal or less than 45 years old, while 177 (96.7%) were aged over 45 years. The search for irregular antibodies was negative in 175 (95.6%) patients and positive in only 8 (4.37%) patients (Table 1).

Regarding BMI, 86 (47.0%) patients had a normal variation, while only 19 (10.4%), 4 (2.19%) and 2 (1.09%) patients had grade I, grade II and grade III obesity, respectively.

Tumor characterization

In a perspective of characterization of the primary tumor of the patients included in the study, data were collected regarding the location of the tumor, the degree of tumor invasion, the degree of lymph node invasion and the differentiation of the tumor. The absolute and relative frequencies of the distribution of these variables across the sample are shown in table 2.

[1] $r = Z/(\sqrt{n})$, corresponding z to the standardized test statistic value, r to the effect size and n to the size of the sample.

Variable	Frequency, n (%)
Gender	
Female	65 (64.5%)
Male	118 (32.5%)
Age (years)	
≤ 45	6 (3.28%)
> 45	177 (96.7%)
BMI (kg/m^2)	
< 18.5	5 (2.70%)
18.5 - 24.9	86 (47.0%)
25.0 - 29.9	67 (36.6%)
30.0 - 34.9	19 (10.4%)
35.0 - 39.9	4 (2.19%)
≥ 40.0	2 (1.09%)

Table 1: *Characterization of patients.*

Variable	Frequency, n (%)
Location of the tumor	
Right colon	58 (31.7%)
Transverse colon	11 (6.01%)
Left colon	61 (33.3%)
Rectum	53 (29.0%)
Degree of tumor invasion	
T1	50 (27.3%)
T2	33 (18.0%)
T3	94 (51.4%)
T4	6 (3.28%)
Lymph node invasion	
N0	127 (69.4%)
N1	47 (25.7%)
N2	9 (4.92%)
Tumor differentiation	
Well differentiated	116 (63.4%)
Moderately differentiated	62 (33.9%)
Poorly differentiated	5 (2.70%)

Table 2: *Tumor characterization.*

61 (33.3%) patients had tumor in the left colon, 58 (31.7%) in the right colon, 53 (29.0%) in the rectum and only 11 (6.01%) in the transverse colon.

Surgery characterization

In order to characterize the surgery, data were collected regarding the type of surgical intervention, the surgical approach, the duration of the surgery, the bleeding (in ml) during the surgery and the drop of hemoglobin between the preoperative and postoperative periods.

The measures of central tendency of the variables duration of surgery and drop of hemoglobin between the pre- and postoperative period are shown in table 3. The absolute and relative frequencies of the distribution of the remaining variables are shown in table 4.

Variable	Mdn, IQR
Duration of the surgery (minutes)	140, 85
Drop of hemoglobin between the preoperative and postoperative periods (g/dl)	1.60, 1.50

Table 3: *Surgery characterization: Continuous variables.*

Variable	Frequency, n (%)
Type of surgical intervention	
Right colectomy	64 (35.0%)
Anterior resection of the rectum	51 (27.9%)
Sigmoidectomy	43 (23.5%)
Left colectomy	16 (8.74%)
Total colectomy	4 (2.19%)
Abdominoperineal resection	3 (1.64%)
Segmental resection of the transverse colon	2 (1.09%)
Surgical approach	
Laparotomy	96 (52.5%)
Laparoscopy	87 (47.5%)
Bleeding (ml)	
≤ 500	181 (98.9%)
> 500	2 (1.09%)
Perioperative Blood Transfusions	
0 unit of blood	145 (79.2%)
1 unit of blood	15 (8.20%)
2 units of blood	10 (5.46%)
≥ 3 units of blood	13 (7.10%)

Table 4: *Surgery characterization.*

With the application of the Shapiro-Wilk normality test ($p < 0.001$), the evaluation of histogram symmetry and kurtosis value (0.40), it was concluded that the duration of surgery in minutes does not follow a normal distribution. The surgery duration Mdn was 140 minutes, with an IQR of 85 minutes, with a minimum duration of 60 minutes and a maximum of 360 minutes.

It was also concluded that the drop of hemoglobin between the pre- and postoperative period did not follow a normal distribution. The Mdn of was 1.60 g/dl, with an IQR of 1.50 g/dl, with the maximum drop of hemoglobin being 6.00 g/dl and the minimum drop of 0.00 g/dl.

181 (98.9%) patients bled equal or less than 500 ml, and only 2 (1.09%) patients bled more than 500 ml. Regarding blood transfusions, 145 (79.2%) patients were not transfused perioperatively, 15 (8.20%) patients received 1 unit of blood, 10 patients (5.46%) received 2 units of blood and 13 (7.10%) patients received 3 or more units of blood in this period (Table 4).

Postoperative morbidity

Regarding postoperative morbidity, grade I morbidity was observed in 110 (60.1%) patients, grade II morbidity in 45 (24.6%) patients, grade IIIa morbidity in 7 (3.83%) patients, grade IIIb morbidity in 14 (7.65%) patients, grade IVa morbidity in 1 (0.55%) patient, grade IVb morbidity in 1 (0.55%) patient and grade V morbidity in 5 (2.73%) patients. The absolute and relative frequencies regarding the distribution of the variable postoperative morbidity are shown in table 5.

Variable	Frequency, n (%)
Postoperative Morbidity	
Grade I	110 (60.1%)
Grade II	45 (24.6%)
Grade IIIa	7 (3.83%)
Grade IIIb	14 (7.65%)
Grade IVa	1 (0.55%)
Grade IVb	1 (0.55%)
Grade V	5 (2.73%)

Table 5: *Postoperative morbidity.*

Inferential statistics

The sample included 110 patients belonging to grade I morbidity, with only 1 person belonging to grade IVa morbidity and 1 person to IVb morbidity. Thus, for the purposes of inferential analysis, the morbidity variable was dichotomized into: Grade I morbidity and Grade II morbidity or higher. Therefore, we obtained a group of 110 patients, in whom a grade I postoperative morbidity was verified - they did not have the need for surgical, endoscopic, and radiological interventions or pharmacological treatment, in addition to antiemetics, antipyretics, analgesics, diuretics and electrolytes. On the other hand, another group of 73 patients with grade II or higher morbidity was obtained - these are all cases in which, postoperatively, any additional treatment to that contemplated in grade I morbidity was needed, or when there were fatal complications or potentially fatal.

In what concerns to blood transfusions performed in the perioperative period, 145 patients did not receive any blood transfusions, while only 15 had 1 transfusion, 10 had 2 transfusions and 13 had 3 or more transfusions. Thus, this variable was also dichotomized into: 0 blood transfusions performed in the perioperative period, and 1 or more transfusions performed during this period. Thus, a group of 145 non-transfused patients and a group of 38 patients transfused in the perioperative period were obtained.

Regarding the BMI, it was also possible to verify in the descriptive statistics that only 2 patients were morbidly obese (BMI ≥ 40 kg/m^2) and 4 patients with grade II obesity (BMI 35.0 - 39.9 kg/m^2), while the majority of sample had normal weight (18.5 - 24.9 kg/m^2), 86 patients, or overweight (25.0 - 29.9 kg/m^2), 67 patients. Thus, given this heterogeneity of the sample, this variable was dichotomized into BMI less than 25 kg/m^2, with 91 patients belonging to this group, and BMI equal to or greater than 25 kg/m^2, with 92 patients [16].

Finally, the tumor differentiation variable also showed great heterogeneity in the sample distribution, with only 5 patients presenting poorly differentiated tumors. Thus, it was dichotomized into a well-differentiated tumor and a moderately or poorly differentiated tumor. The first group made up a total of 116 patients and the second group a total of 67 patients.

The evaluation of the interdependence between postoperative morbidity and the different variables collected is shown in table 6. The results of Fisher's exact test were reported, in cases where the assumptions for using the Chi-square test were not verified.

	Postoperative Morbidity Grade I (n = 110)	**Postoperative Morbidity Grade II or higher (n = 73)**	**Test statistics**
Gender			
Male	72 (65.5%)	46 (63.0%)	X^2 = 0.032, p = 0.86, Phi = 0.025
Female	38 (34.5%)	27 (37.0%)	
Age (years)			
≤ 45	4 (3.60%)	2 (2.70%)	** p = 1.00, Phi = 0.025
> 45	106 (96.4%)	71 (97.3%)	
BMI (kg/m^2)			
< 25.0	53 (48.2%)	38 (52.1%)	X^2 = 0.13, p = 0.72, Phi = - 0.038
≥ 25.0	57 (51.8%)	35 (47.9%)	
Blood type			
A positive	48 (43.6%)	22 (30.1%)	** p = 0.34, V = 0.21
A negative	8 (7.30%)	5 (6.80%)	
B positive	8 (7.30%)	5 (6.80%)	
B negative	4 (3.60%)	1 (1.40%)	
AB positive	4 (3.60%)	2 (2.70%)	
AB negative	0 (0.00%)	1 (1.40%)	
O positive	33 (30.0%)	34 (46.6%)	
O negative	5 (4.60%)	3 (4.20%)	
Search for irregular antibodies			
Negative	104 (94.5%)	71 (97.3%)	** p = 0.48, Phi = - 0.065
Positive	6 (5.50%)	2 (2.70%)	
Tumor Location			
Right colon	32 (29.1%)	26 (35.6%)	X^2 = 4.02, p = 0.27, V = 0.15
Transverse colon	9 (8.20%)	2 (2.70%)	
Left colon	34 (30.9%)	27 (37.0%)	
Rectum	35 (31.8%)	18 (24.7%)	

Degree of tumor invasion			
T1	36 (32.7%)	14 (19.2%)	** p = 0.13, V = 0.18
T2	20 (18.2%)	13 (17.8%)	
T3	52 (47.3%)	42 (57.5%)	
T4	2 (1.80%)	4 (5.50%)	
Lymph node invasion			
N0	80 (72.7%)	47 (64.4%)	X^2 = 1.81, p = 0.38, V = 0.099
N1	26 (23.6%)	21 (28.8%)	
N2	4 (3.70%)	5 (6.80%)	
Tumor differentiation			
Well differentiated	77 (70.0%)	39 (53.4%)	X^2 = 4.51, p = 0.034*, Phi = - 0.17
Moderately or Poorly Differentiated	33 (30.0%)	34 (46.6%)	
Type of surgical intervention			
Right colectomy	38 (34.5%)	26 (35.6%)	** p = 0.052, V = 0.26
Anterior resection of the rectum	34 (30.9%)	17 (23.3%)	
Sigmoidectomy	28 (25.5%)	15 (20.5%)	
Left colectomy	6 (5.50%)	10 (13.7%)	
Total colectomy	0 (0.00%)	4 (5.50%)	
Abdominoperineal resection	2 (1.80%)	1 (1.40%)	
Segmental resection of the transverse colon	2 (1.80%)	0 (0.00%)	
Surgical approach			
Laparotomy	49 (44.5%)	47 (64.4%)	X^2 = 6.15, p = 0.013*, Phi = - 0.20
Laparoscopy	61 (55.5%)	26 (35.6%)	
Bleeding (ml)			
≤ 500	110 (100.0%)	71 (97.3%)	** p = 0.16, Phi = 0.13
> 500	0 (0.00%)	2 (2.70%)	
Perioperative Blood Transfusions			
0 unit	109 (99.1%)	36 (49.3%)	X^2 = 63.1, p < 0.001*, Phi = 0.60
≥ 1 unit	1 (0.90%)	37 (50.7%)	
Duration of Surgery	Mdn = 140.00, IQR = 71	Mdn = 140.0, IQR = 92	U = 3828, z = - 0.53, p = 0.59, r = - 0.039
Hemoglobin drop between the preoperative and the postoperative period	Mdn = 1.700, IQR = 1.25	Mdn = 1.600, IQR = 2.000	U = 3738, z = - 0.79, p = 0.43, r = - 0.058

Table 6: *Inferential statistics.*

**: Statistically significant.*

***: Fisher's exact test performed*

IQR (Interquartile Range); BMI (Body Mass Index); Mdn (Median); p (p-value); Phi (Coefficient Phi); r (Approximate effect size calculated for Mann-Whitney statistic [1]); U (U of Mann-Whitney); V (V of Cramer); X^2 (chi square); z (standardized test statistics).

A Chi-square test indicated a significant strong association between the degree of postoperative morbidity and perioperative blood transfusions, $X^2 = 63.1$, $p < 0.001$, Phi = 0.60. Analysis of the adjusted residuals revealed that patients who received perioperative blood transfusions had higher morbidity, while those who were not transfused had lower postoperative morbidity.

The Chi-square test indicated a significant weak association between the degree of postoperative morbidity and the type of surgical approach, $X^2 = 6.15$, $p = 0.013$, Phi = - 0.20. The analysis of the adjusted residuals revealed that patients who underwent laparotomic surgery had greater morbidity, on the other hand, those who underwent laparoscopic surgery had lower morbidity.

The Chi-square test indicated a significant weak association between the degree of postoperative morbidity and tumor differentiation, $X^2 = 4.51$ $p = 0.034$, Phi = - 0.17. Adjusted residual analysis revealed that patients with well-differentiated tumors had less morbidity, whereas patients with moderately or poorly differentiated tumors had greater morbidity.

The remaining variables under study did not reveal any association with the degree of postoperative morbidity (p-value > 0.050).

Predictors of postoperative degree of morbidity

The variables surgical approach ($p = 0.013$), tumor differentiation ($p = 0.034$) and perioperative blood transfusions ($p < 0.001$) revealed statistically significant differences between patients with grade I morbidity and patients with grade II or higher morbidity.

A binary logistic regression was then performed, including these variables as outcome predictors. To assess multicollinearity, a matrix of correlations between the various independent variables was performed, verifying that there were no correlations between these variables.

Therefore, this outcome predictor model allowed us to estimate the occurrence of postoperative morbidity based on tumor differentiation, type of surgical approach and number of perioperative blood transfusions, through the equation:

Z = 1.11 + 4.61 × number of perioperative transfusions + 0.54 × tumor differentiation + 0.39 × surgical approach[2].

The variable blood transfusions is replaced by number 1 when the patient receives transfusion therapy in the perioperative period. The variable tumor differentiation is replaced by number 1 when the patient's tumor is moderately or poorly differentiated. The surgical approach variable is replaced by the number 1 when the patient is submitted to surgery by laparotomy.

The predictive model explained between 34.5% (Cox and Snell's R squared) and 46.7% (Nagelkerke's R squared) of the variation in postoperative morbidity. The number of blood transfusions has the greatest contribution in predicting postoperative morbidity, explained by a higher Wald value (19.9).

In table 7, it can be seen that an increase in the number of perioperative blood transfusions increases 100 times (95% CI 14.8 - 846, $p < 0.001$) the propensity of the patient to have a higher degree of postoperative morbidity. The remaining variables did not show statistically significant results.

[2]The probability of occurrence of the event (postoperative morbidity) is given by the equation $P = 1/(1 + e^{(-z(x))})$, where x is the number of perioperative blood transfusions.

	B	S.E.	Wald	df	*p*	OR	95% CI for OR	
							Inferior	Superior
Surgical Approach	0.39	0.38	1.03	1	0.31	0.68	0.32	1.43
Tumor Differentiation	0.54	0.39	1.90	1	0.17	1.71	0.80	3.69
Perioperative Blood Transfusions	4.61	1.04	19.9	1	< 0.001*	100	13.2	767
Constant	1.11	0.31	12.6	1	< 0.001	0.33		

Table 7: *Postoperative degree of morbidity predictive model.*

**: Statistically significant.*

B (coefficient); CI (confidence interval); p (p-value); S.E. (Standard Error); OR (Odds Ratio).

Discussion

Several studies have shown evidence that blood transfusions can influence the prognosis of patients with CRC, especially when performed in the perioperative period [3]. This influence is most likely caused by the immunosuppression underlying the reception of blood transfusions.

In Watering., *et al*. [17], it was observed that patients with CRC not transfused in the perioperative period had a higher 5-year survival rate and lower rates of disease recurrence, compared to transfused patients. Also, in Mynster., *et al*. [18], patients with CRC undergoing surgery with curative intent showed a worse long-term prognosis, when they presented a combination of perioperative blood transfusions and postoperative infectious complications.

It is worth remembering that all blood transfusions have risks for the patient, and therefore should be carefully indicated [19]. Based on this, the aim of this study is to assess how the perioperative transfusion practice influences the postoperative morbidity of patients with CRC at the Hospital de Braga, undergoing elective surgery with intention curative.

For this, 183 patients were included in the study, of which 110 developed grade I morbidity postoperatively and 73 developed grade II or higher morbidity. 38 patients received perioperative blood transfusions, with the majority of these (97.4%) developing grade II or higher postoperative morbidity. 145 patients did not receive perioperative blood transfusions, with the majority of these (75.2%) developing grade I morbidity in the postoperative period.

Clinicopathological staging determines the treatment of CRC and plays a central role in the prognosis of these patients, with T and N being two of the determinants described as having a greater influence on the prognosis of these patients [2,20]. This was not corroborated by this study, where no association was found between postoperative morbidity and T or N. This could be explained by the heterogeneity of the sample, with a reduced sample distribution in T4 (only 6 patients) and N2 (only 9 patients).

On the other hand, in agreement with some literature [4,5,7,9,17,18,21] this study also revealed the existence of a strong significant association with the number of blood transfusions perioperative ($X^2 = 63.1$, $p < 0.001$, Phi = 0.60).

A significant weak association between postoperative morbidity and tumor differentiation ($X^2 = 4.51$, $p = 0.034$, Phi = -0.017) was also demonstrated, with patients with more undifferentiated tumors presenting greater postoperative morbidity (grade II or higher). This result is in accordance with other studies. Copeland., *et al*. [22], demonstrated that patients with well-differentiated tumors had a good prognosis, as opposed to those with poorly differentiated tumors, in which shorter survival times were reported.

A significant weak association between postoperative morbidity and the type of surgical approach was also demonstrated ($X^2 = 6.15$, $p = 0.013$, Phi = -0.20), with patients undergoing laparotomic surgery having greater post-operative morbidity. With similar results, in Zhou., *et al*. [23], the existence of more postoperative complications has been described in patients with CRC undergoing laparotomic surgery, when compared to patients undergoing laparoscopic surgery.

However, when these variables were included in the multivariate analysis, only the blood transfusion variable showed statistical significance, demonstrating that an increase in the number of perioperative blood transfusions increases 100 times (95% CI 14.8 - 846, $p < 0.001$) a propensity of the patient to have a greater degree of postoperative morbidity.

When included in binary logistic regression, they allowed the creation of a predictive model capable of explaining between 34.5% (Cox and Snell's R squared) and 46.7% (Nagelkerke's R squared) of the variation in postoperative morbidity, with a greater contribution from blood transfusions (Wald equal to 19.9), through the equation:

Z = 1.11 + 4.61 × number of perioperative transfusions + 0.54 × tumor differentiation + 0.39 × surgical approach[3].

In this study sample, the performance or not of blood transfusions can influence the patients' postoperative morbidity. Thus, it is important to monitor closely patients that need blood transfusions, as well as to assess more rigorously the need for these patients to be transfused, to avoid situations where they are not strictly necessary.

Hemovigilance acquires an important role in the management of patients with CRC [24], allowing a closer surveillance of these patients, in order to act early in the development of postoperative complications. It is important to optimize hemotherapy, providing a safe and efficient transfusion practice, without adverse reactions or infections, with benefits for patients and avoiding unnecessary transfusions [25].

A prospective study would be interesting, in order to monitor transfused patients and to assess the type of complications they present.

The fact that the sample size of this study was concentrated in certain groups limited the statistical analysis performed. Since the postoperative morbidity scale consists of 7 degrees of morbidity, there was a need to dichotomize this variable into only two groups, due to the heterogeneity presented by the sample distribution, which made it impossible to analyze each group of morbidity individually. Furthermore, because this is a convenience sample, the results obtained from Hospital de Braga cannot be extrapolated at national level. Future prospective studies would be necessary to, in a controlled and homogeneous way, confirm the results presented in this retrospective study and evaluate, with a larger number of patients, the influence of transfusion practice on the different degrees of postoperative morbidity.

Conclusion

The present study revealed that 99.1% of patients with grade I postoperative morbidity were not transfused in the perioperative period. On the other hand, patients who developed grade II or higher postoperative morbidity, in 50.7% of the cases were transfused in the perioperative period.

Perioperative blood transfusions have been shown to be a significant predictor of postoperative morbidity in patients with CRC undergoing surgery with curative intent in Hospital de Braga.

[3]The probability of occurrence of the event (postoperative morbidity) is given by the equation P = 1/(1 + e^(-z (x))), where x is the number of perioperative blood transfusions.

Therefore, the need to transfuse patients with colorectal cancer must be carefully evaluated, in order to avoid unnecessary transfusions in the perioperative period and try to improve the prognosis of these patients. On the other hand, in patients with transfusion needs, there must be greater surveillance of postoperative complications, in order to provide the necessary treatment as early as possible, to avoid the occurrence of major complications that translate to organ failure or higher mortality.

Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. (IARC) IA for R on C, (OMS) WHO. GLOBOCAN 2018: Latest global cancer data. Press release 263 (2018): 13-15.
2. Kulendran M., *et al*. "Predictive and Prognostic Factors in Colorectal Cancer: A Personalized Approach". *Cancers* 3.2 (2011): 1622-1638.
3. Amato A and Pescatori M. "Perioperative Blood Transfusions and Recurrence of Colorectal Cancer". *Cochrane Database of Systematic Reviews* (2006).
4. Harlaar Joris J., *et al*. "Blood Transfusions and Prognosis in Colorectal Cancer". *Annals of Surgery* 256.5 (2012): 681-687.
5. Cata JP., *et al*. "Inflammatory Response, Immunosuppression, and Cancer Recurrence after Perioperative Blood Transfusions". *British Journal of Anaesthesia* 110.5 (2013): 690-701.
6. Wu Hsiang-Ling., *et al*. "The Impact of Blood Transfusion on Recurrence and Mortality Following Colorectal Cancer Resection: A Propensity Score Analysis of 4,030 Patients". *Scientific Reports* 8.1 (2018).
7. Compton Carolyn C., *et al*. "Prognostic Factors in Colorectal Cancer". *Archives of Pathology and Laboratory Medicine* 124.7 (2000): 979-994.
8. Vamvakas Eleftherios C and Morris A Blajchman. "Deleterious Clinical Effects of Transfusion-Associated Immunomodulation: Fact or Fiction?" *Blood* 97.5 (2001): 1180-1195.
9. Gunka Igor., *et al*. "Impact of Blood Transfusions on Survival and Recurrence in Colorectal Cancer Surgery". *Indian Journal of Surgery* 75.2 (2012): 94-101.
10. Fischer Dania., *et al*. "Red Blood Cell Transfusion and Its Alternatives in Oncologic surgery—A Critical Evaluation". *Critical Reviews in Oncology/Hematology* 134 (2019): 1-9.
11. Opelz Gerhard and Paul I Terasaki. "Improvement of Kidney-Graft Survival with Increased Numbers of Blood Transfusions". *New England Journal of Medicine* 299.15 (1978): 799-803.
12. "Clavien-Dindo Classification. Definitions (2020).
13. Chan YH. "Biostatistics 102: Quantitative Data - Parametric and Non-parametric Tests". *Singapore Medical Journal* (2003).
14. Sullivan Gail M and Richard Feinn. "Using Effect Size-or Why the P Value Is Not Enough". *Journal of Graduate Medical Education* 4.3 (2012): 279-282.

15. Kim H-Y. "Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test". *Restorative Dentistry and Endodontics* (2017).

16. Direção-Geral da Saúde. "Obesidade: otimização da abordagem terapêutica no serviço nacional de saúde". *Programa Nac para a Promoção da Aliment Saudável* (2017).

17. Van de Watering, L M G., *et al*. "Perioperative Blood Transfusions, with or Without Allogeneic Leucocytes, Relate to Survival, Not to Cancer Recurrence". *British Journal of Surgery* 88.2 (2001): 267-272.

18. Mynster Tommie and Hans Jørgen Nielsen. "Storage Time of Transfused Blood and Disease Recurrence after Colorectal Cancer Surgery". *Diseases of the Colon and Rectum* 44.7 (2001): 955-964.

19. Bonequini P and Carvalho Garcia P. "Manual de Transfusão Sanguínea para Médicos". Hemocomponentes: obtenção e usos terapêuticos (indicação) da transfusão sanguínea (2017): 36-37.

20. Chapuis PH., *et al*. "A Multivariate Analysis of Clinical and Pathological Variables in Prognosis after Resection of Large Bowel Cancer". *British Journal of Surgery* 72.9 (1985): 698-702.

21. Busch ORC., *et al*. "The Effect of Blood Transfusions on Survival after Surgery for Colorectal Cancer". *European Journal of Cancer* 31.7-8 (1995): 1226-1228.

22. Copeland Edward M., *et al*. "Prognostic Factors in Carcinoma of the Colon and Rectum". *The American Journal of Surgery* 116.6 (1968): 875-881.

23. Zhou Sicheng., *et al*. "Laparoscopic Vs Open Colorectal Cancer Surgery in Elderly Patients: Short- and Long-Term Outcomes and Predictors for Overall and Disease-Free Survival". *BMC Surgery* 19.1 (2019).

24. Antunes EM., *et al*. "Imuno hematologia" (2008).

25. Direção Geral de Saúde. "Gestão do sangue do doente; Patient Blood Management (PBM) em cirurgia eletiva". *Norma de Orientação Clínica* (2018).

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