

Perioperative Risk in Colon Cancer: The Dual Burden of Tumor-Related Anemia and Cardiac Comorbidity

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Rezumat

Cancerul de colon și riscul perioperator: impactul anemiei tumorale și al comorbidității cardiace

Introducere: Cancerul de colon este o malignitate frecventă, asociată cu complicații semnificative, în special hemoragia gastrointestinală și anemia, care impun transfuzii de urgență. Scopul studiului este de a explora relația complexă dintre transfuziile de urgență la pacienții cu cancer de colon și patologia cardiacă asociată.

Metode: A fost realizat un studiu retrospectiv de tip caz-control, desfășurat între ianuarie 2020 – februarie 2024 în sud-estul României, axat pe pacienți adulți cu cancer de colon și anemie moderată/severă. Studiul a inclus pacienți cu adenocarcinom colonic în stadii avansate, cu tumori complicate ce necesitau transfuzii sanguine și a exclus cazurile cu anemie ușoară, antecedente de cancer sau transfuzii anterioare pentru aceeași afecțiune. Pacienții au fost analizați în funcție de severitatea anemiei, caracteristicile demografice și clinice, precum și rezultatele perioperatorii, cu un accent special pe impactul patologiei cardiace asociate.

Rezultate: Studiul a inclus 153 de pacienți, împărțiți în două grupuri în funcție de severitatea anemiei: anemie moderată (n=124) și anemie severă (n=29). Nu s-au identificat diferențe semnificative în ceea ce privește histopatologia sau stadiul tumoral între cele două grupuri, însă s-au constatat diferențe semnificative legate de pierderile de sânge, invazie și necesarul de transfuzii. Rezultatele postoperatorii au arătat o rată mai mare a complicațiilor, spitalizări mai lungi și mortalitate crescută în grupul cu anemie severă comparativ cu grupul anemiei moderate. În plus, comorbiditățile cardiace au fost asociate cu anemie mai severă, pierderi intraoperatorii crescute de sânge, durată mai mare a intervenției chirurgicale și necesar mai ridicat de transfuzii, precum și complicații postoperatorii mai frecvente.

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Concluzii: Anemia severă și patologiile cardiace preexistente sunt corelate cu rezultate chirurgicale mai nefavorabile, necesar mai mare de transfuzii și rate crescute ale complicațiilor.

Cuvinte cheie: cancer de colon, anemie, transfuzii, patologie cardiacă, complicații

Abstract

Background: Colon cancer is a common malignancy with significant complications, particularly gastrointestinal bleeding and anemia, requiring emergent transfusions. The aim of the study is to explore the complex relationship between emergent transfusions in colon cancer patients and their concurrent cardiac pathology.

Methods: A retrospective case-control study conducted between January 2020 - February 2024 in South-Eastern Romania focused on adult patients with colon cancer and moderate/severe anemia. The study included patients with advanced-stage colon adenocarcinoma, complicated tumors requiring blood transfusions, and excluded those with mild anemia, cancer history, or previously transfusions for the same condition. Patients were analyzed based on their anemia severity, demographic and clinical characteristics, and perioperative outcomes, with a specific focus on the impact of concurrent cardiac pathology.

Results: The study included 153 patients, divided into two groups based on anemia severity: moderate anemia (MA, n=124) and severe anemia (SA, n=29). No significant differences were found in tumor histopathology or stage between the two groups, though significant differences were observed in blood loss, invasions, and transfusion needs. Postoperative outcomes showed a higher rate of complications, longer hospital stays, and increased mortality in the SA group compared to the MA group. Additionally, cardiac comorbidities were associated with more severe anemia, increased intraoperative blood loss, longer surgery duration, and a higher need for transfusions, as well as more frequent postoperative complications.

Conclusions: Severe anemia and pre-existing cardiac conditions are linked to poorer surgical outcomes, greater transfusion requirements, and higher complication rates.

Keywords: colon cancer, anemia, transfusions, cardiac pathology, complications

Introduction

Colorectal cancer is among the most common malignancies and a leading cause of cancer mortality worldwide (1). In advanced disease, chronic tumor-related bleeding often leads to iron-deficiency anemia; a subset of patients requires preoperative transfusion to permit safe surgery (2). The coexistence of cardiac comorbidity adds complexity, narrowing hemodynamic reserve and increasing susceptibility to ischemia or volume overload during correction of anemia (3).

Preoperative anemia – present in up to one-third of surgical patients and frequent in gastrointestinal cancer – raises transfusion exposure and worsens short- and mid-term outcomes (4,5), with downstream effects on postoperative complications and length of stay (6). Consequently, perioperative care must balance anemia correction and cardiovascular safety (8,9). Despite broad recognition of this intersection, evidence specifically addressing tumor-related anemia requiring preoperative transfusion in patients with cardiac disease

remains limited and guidelines for this combined scenario are scarce (10-12).

This article aims to explore the relationship between emergent transfusions in complicated colon cancer and their intersection with cardiac pathology, highlighting key challenges and potential strategies for improving patient outcomes.

Material and Methods

Study Design and Population

Between January 2020 and February 2024, a retrospective study was conducted on adult patients from South-Eastern Romania who were admitted to the Surgical Department and had been diagnosed with colon cancer and secondary moderate and severe anemia. The inclusion criteria were as follows: 1) patients with complicated colon tumors; 2) histopathological result of adenocarcinoma and advanced stages (III, IV); 3) moderate and severe anemia; 4) patients who had received blood transfusions. The exclusion criteria were as

follows: 1) any personal history of cancer; 2) patients with previous surgeries; 3) previous transfusion for the same condition; 4) incomplete data.

Patients were analyzed comparatively in terms of the degree of anemia, demographic and biological characteristics, perioperative and immediate postoperative evolution. Cases were also analyzed according to the existence of cardiac disease, compared to patients without this type of comorbidity. The study flow chart is shown in Fig. 1. In this study, red blood cell transfusions were administered preoperatively as part of patient optimization prior to surgery (correction of moderate/severe anemia and hemodynamic stabilization). Intraoperative transfusions were not included in the primary exposure definition and, when present, were recorded separately as perioperative events. The primary comparisons between groups (moderate vs severe anemia; $\pm$ cardiac disease) refer to preoperative transfusions.

In accordance with international guidelines, preoperative red blood cell transfusion was indicated for patients with hemoglobin levels <7 g/dL, irrespective of symptoms. In patients with cardiac comorbidities or clinical symptoms of anemia (e.g., angina, dyspnea, hypotension, tachycardia), transfusion was initiated at Hb < 8 g/dL. In the present study, complicated colon tumors were defined as advanced-stage colonic adenocarcinomas presenting with hemorrhagic complications that required blood transfusion for preoperative optimization. Other types of complications (e.g., perforation or obstruction) were not included in this definition. For unstable patients with ongoing tumor-related bleeding, the decision was individualized, with the goal of achieving a safe hemoglobin level for surgery, generally ≥ 8 g/dL. Platelet concentrates or plasma were administered only if associated coagulopathy or thrombocytopenia was documented (4).

The World Health Organization defines anemia based on hemoglobin (Hb) concentration in the blood, with different degrees of severity, as follows: mild anemia ≥ 11 g/dL, moderate anemia 8-10.9 g/dL, severe anemia < 8 g/dL. Body Mass Index (BMI): < 18.5 = underweight, 18.5-24.9 = normal weight, 25-29.9 = overweight, ≥ 30 = obese. Age-adjusted Charlson comorbidity index (ACCI) score was used to predict the risk of mortality and was calculated from a weighted index consisting of age and the number and seriousness of comorbid diseases. Using the Clavien-Dindo classification, postoperative complications were categorized. At most, minor issues were regarded as grade II

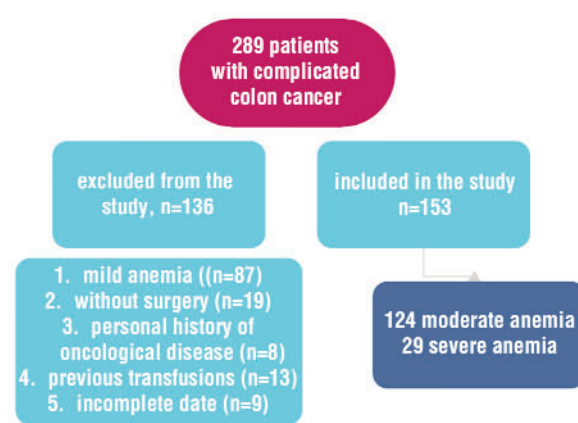


Figure 1. Flowchart visualizing recruitment of participants. Of 289 interested subjects, 153 were eligible for study inclusion.

issues. Records were kept of the clinical and pathological information (tumor staging, perineural, venous, and lymphatic invasion).

Study Endpoints

- The primary endpoint was to analyze statistical differences regarding the clinical, demographic characteristics and the perioperative outcomes according to the type of anemia: moderate or severe.
- The secondary endpoint was to evaluate biological and postoperative characteristics depending on the existence of cardiac disease.

Ethical Approval

In compliance with the Declaration of Helsinki on human testing, the study was authorized by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies. All patients gave their informed consent when they were enrolled (approval no. 11/4.7.2024).

Statistical Analysis

Descriptive statistics were used to describe the profile of study participants. Quantitative variables were described using the mean and standard deviation. Meanwhile, qualitative variables were summarized as frequencies and percentages. Group comparisons were performed using the χ^2 test or Mann-Whitney U test. A p-value <0.05 was considered statistically significant. For transparency, intraoperative transfusions were tabulated separately and were not entered in the primary exposure

variable. The SPSS statistical software package for Windows version 28.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

Included in the study for analysis were 153 patients, distributed into 2 groups, with moderate anemia (MA, n=124) and with severe anemia (SA, n=29). The baseline demographics and comorbidity of the patients depending on the degree of anemia included in the study are provided in *Table 1*. The mean age of the patients in the study was approximately equal for both groups of patients, regardless of the degree of anemia (MA: 64.03 ± 9.98; 65.66±11.24: SA). Most patients with MA

were classified as being in the 6th decade of age, followed by patients in the 5th decade of age, and most patients with SA were classified as being in the 6th and 7th decades of age. The distribution of cases by gender was in favor of females (MA, 57.3% vs SA, 65.5%). The mean weight was approximately equal for the two groups (MA: 26.61±3.94, SA: 26.09±3.76), as was the distribution according to weight groups.

A third of patients, regardless of anemia status, were tobacco users, and over half of the patients had a Mediterranean diet. The mean ACCI (Adjusted Age-Adjusted Charlson Comorbidity Index) score of patients with MA was 4.42 ± 1.37 and 4.52 ± 1.33 with SA. The most common blood type of the patients was A positive (*Fig. 2*). Preoperative RBC transfusion (mL) was significantly higher in the severe anemia group compared to the moderate anemia group (674.8 ± 98.3 vs 403.2 ± 71.3 mL; $p < 0.001$). Intraoperative transfusions, when required, were recorded separately and were not part of the primary exposure.

The histopathological characteristics and stage of the tumors were not influenced by the different degrees of anemia (*Table 2*). The most common location of tumors was the cecum in MA patients and the ascending colon in SA patients. There were no statistically significant differences in disease stage ($p=0.156$) or lymphatic invasion ($p=0.331$). There were statistically significant differences between the two groups regarding blood loss ($p=0.035$), perineural (0.035), and venous invasions ($p=0.027$). Regarding the type of surgical approach, most patients underwent open procedure, and minimally invasive surgery was indicated in selected cases in a small percentage (MA: 11.3%, SA: 10.3%).

Table 1. Baseline demographics and comorbidity of the patients depending on the degree of anemia

Variables	Moderate anemia (n=124)	Severe anemia (n=29)	p-value
Age (y)*	64.03±9.98	65.66±11.24	0.547
< 50 years	11 (8.9)	3 (10.3)	
50 – 59 years	30 (24.2)	4 (13.8)	
60 – 69 years	47 (37.9)	10 (34.5)	
70 – 79 years	29 (23.4)	10 (34.5)	
≥ 80 years	7 (5.6)	2 (6.9)	
Gender			0.421
Male	53 (42.7)	10 (34.5)	
Female	71 (57.3)	19 (65.5)	
BMI (kg/m ²)*	26.61±3.94	26.09±3.76	0.409
Underweight	4 (3.2)	1 (3.4)	
Normal weight	39 (31.5)	9 (31)	
Overweight	56 (45.2)	13 (44.8)	
Obesity Grade I	23 (18.5)	5 (17.2)	
Obesity Grade II	2 (1.6)	1 (3.4)	
Obesity Grade III	0	0	
Smokers	43 (34.7)	9 (31)	0.141
Alcohol abuse	14 (11.3)	3 (10.3)	0.022
Dietary status			0.403
Mediterranean	91 (73.4)	19 (65.5)	
Hypercaloric	33 (26.6)	10 (34.5)	
Weight loss, < 6 Months	52 (41.9)	12 (41.4)	0.113
Physical activity	34 (27.4)	10 (34.5)	0.455
DM	14 (11.3)	1 (3.4)	0.359
Hypertension	21 (16.9)	4 (13.8)	0.176
ACCI (Mean±SD*)	4.42±1.37	4.52±1.33	0.122
0-1	0	0	
2-3	34 (27.4)	5 (17.2)	
4-5	67 (54)	18 (62)	
≥ 6	23 (18.6)	6 (20.7)	
10-YS*	42.66±29.31	38.18±29.21	0.711
Platelet count (mcL)*	258.57±92.43	266.59±98.09	0.174
RBC concentrate transfusion (g) preoperative*	403.2±71.3	674.8±98.3	< 0.001

Variables are expressed as number with percentages in parentheses unless indicated otherwise. *Values are mean (standard deviation). y: years; BMI: Body Mass Index; DM: Diabetes Mellitus; ACCI: Age-adjusted Charlson Comorbidity Index; SD: Standard Deviation; YS: years survival; RBC: red blood cells. RBC transfusion values refer to preoperative transfusions; intraoperative transfusions were recorded separately and were not included in the primary exposure. Values in italics indicate statistical significance ($p < 0.050$).

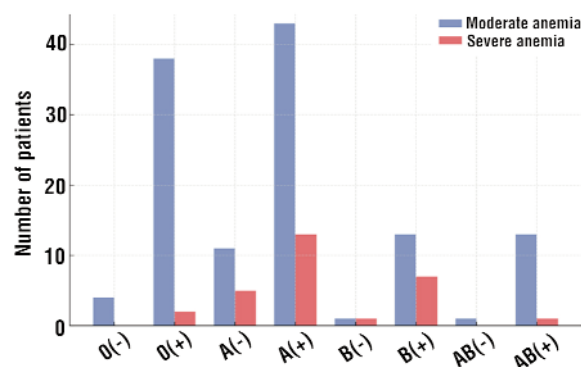


Figure 2. Blood type distribution in colon cancer patients with moderate versus severe anemia

Table 2. Comparison of histopathological and perioperative elements of the patients depending on the degree of anemia

Variables	Moderate anemia (n=124)	Severe anemia (n=29)	p-value
Localization			0.250
Cecum	56 (45.2)	8 (27.6)	
Ascending	23 (18.5)	15 (51.7)	
Transverse	15 (12.1)	2 (6.9)	
Descending	16 (12.9)	1 (3.4)	
Sigmoid	14 (11.3)	3 (10.3)	
Operation time (min)*	202.31±20.36	203.79±17.41	0.134
Estimate blood loss (ml)*	149.31±38.72	133.15±36.25	0.035
Procedure			0.108
Open	110 (88.7)	26 (89.7)	
Laparoscopic	14 (11.3)	3 (10.3)	
Stage			0.156
III	82 (66.1)	23 (79.3)	
IV	42 (33.9)	6 (20.7)	
Lymphatic invasion	41 (33.1)	8 (27.6)	0.331
Venous invasion	92 (74.2)	6 (20.7)	0.027
Perineural invasion	32 (25.8)	7 (24.1)	0.035

Variables are expressed as number with percentages in parentheses unless indicated otherwise *mean ±SD (Standard Deviation). min: minutes; ml: milliliters. Values in *italics* indicate statistical significance ($p < 0.050$).

Postoperative complications in patients with advanced colon cancer and secondary anemia are presented in *Table 3*, *Fig. 3*. The occurrence of postoperative complications was significantly lower in patients without MA compared with patients with SA ($p=0.021$). According to the Clavien-Dindo classification, major complications were identified in one patient with MA and in one patient with SA, both patients having anastomotic leakage with intraperitoneal abscess requiring reintervention. Between the two study groups, there were significant statistical differences regarding postoperative hospital stay (MA: 9.60 ± 2.32 , SA: 11.16 ± 3.11 ; $p < 0.001$), reoperation (MA: 3.2% vs SA: 6.8%, $p=0.041$), and 30-day mortality (MA: 0.8% vs SA: 6.8%; $p=0.004$). Bowel transit and mobility resumed later in patients who had severe anemia, compared to patients with moderate anemia ($p<0.001$).

There were no statistically significant differences between the two groups regarding the association of BMI with the existence of cardiac conditions ($p=0.190$). Patients with cardiac conditions presented a higher percentage of severe anemia (20%) compared to non-cardiac patients (18.5%). Intraoperative blood loss ($p=0.020$) and surgical duration ($p=0.049$) were increased in patients with cardiac conditions as a comorbidity. Cardiac patients had a higher need for transfusions compared to non-cardiac patients (559.22 ± 64.37 vs 450.81 ± 75.44 , $p=0.034$). Postoperative complications were more frequently diagnosed in cardiac patients (60% compared to 41.66%, $p=0.036$) (*Table 4*, *Fig. 4*).

Table 3. Postoperative outcomes of the patients depending on the degree of anemia

Variables	Moderate anemia (n=124)	Severe anemia (n=29)	p-value
ICU stay (pod)*	2.28±0.51	3.34±0.55	<0.001
First bowel movement (pod)*	2.65±0.78	3.76±0.71	<0.001
First flatus (pod)*	2.68±0.32	3.76±0.88	<0.001
Postoperative hospital stay*	9.60±2.32	11.16±3.11	<0.001
Any postoperative complication	52 (41.8)	20 (69)	0.021
Reoperation	4 (3.2)	2 (6.8)	0.041
30-day mortality	1 (0.8)	2 (6.8)	0.004

With percentages in parentheses unless indicated otherwise, *Values are mean (standard deviation). ICU, Intensive Care Unit; pod, postoperative day. Values in *italics* indicate statistical significance ($p < 0.005$).

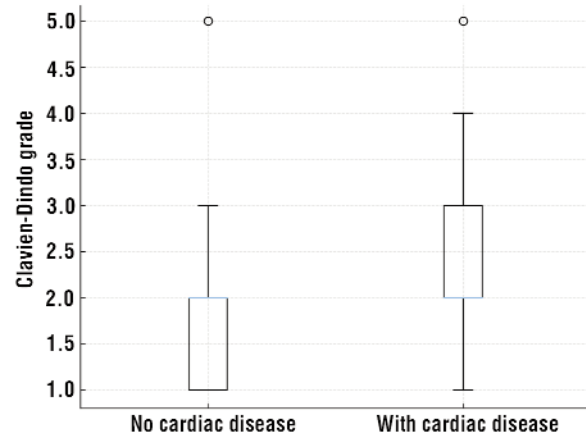

Figure 3. Comparative boxplot of the Clavien–Dindo distribution for patients with and without cardiac comorbidities

Table 4. Clinico-biological and postoperative characteristics of the patients in the study according to the existence of cardiac disease

Variables	Cardiac disease		p-value
	Without (-) n=108	With (+) n=45	
BMI (kg/m ²)	26.7±3.88	26.1±3.94	0.190
Anemia*			0.017
Moderate	88 (81.5)	36 (80)	
Severe	20 (18.5)	9 (20)	
Platelet count (mcL)	258.74±83.43	263.33±114.43	0.057
Stage*			0.844
III	75 (69.4)	30 (66.7)	
IV	33 (30.6)	15 (33.3)	

Values are mean (standard deviation), unless indicated otherwise *number with percentage. BMI: body mass index; RBC: Red Blood Cells. Values in *italics* indicate statistical significance ($P < 0.005$).

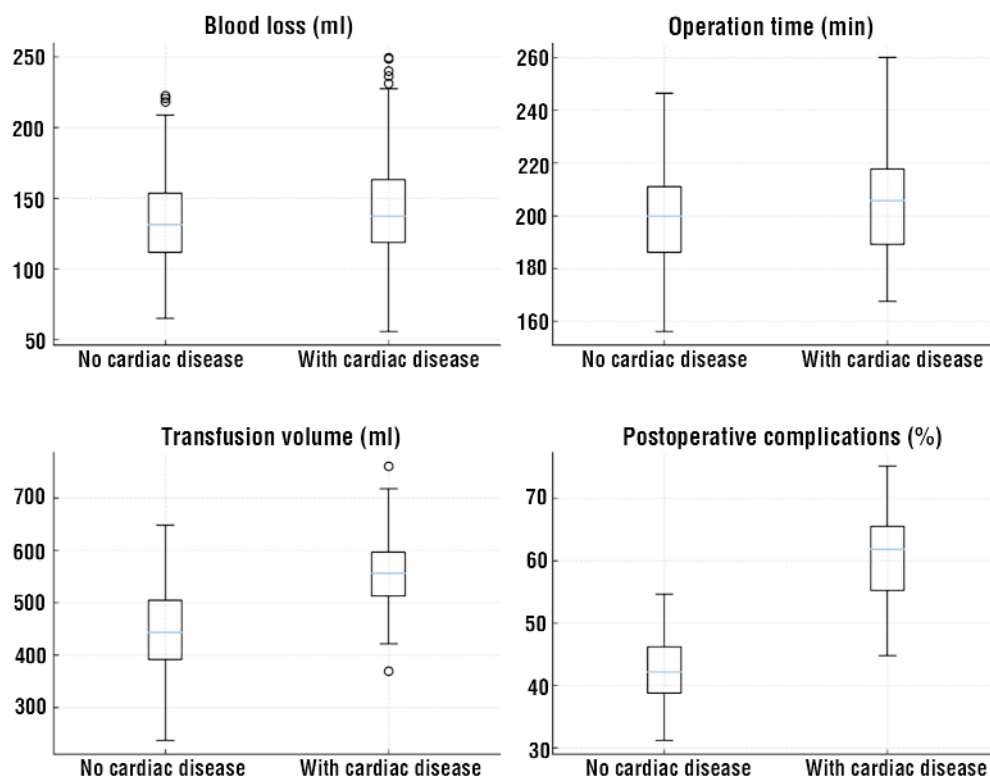


Figure 4. Comparative distribution of perioperative outcomes in colon cancer patients with and without cardiac comorbidity.

Discussion

Colorectal cancer is still one of the biggest causes of cancer-related illness and death globally (13). Anemia is one of the most common systemic consequences that patients encounter as the disease progresses because of persistent blood loss, dietary deficits, and inflammatory processes that are endemic to malignancy (14,15). In this cohort of 153 patients with complicated colon cancer, severe anemia and cardiac comorbidity were each associated with worse perioperative outcomes. Compared to moderate anemia, severe anemia showed higher complications, longer length of stay, more reoperations, and higher 30-day mortality. Cardiac comorbidity was linked to increased blood loss, longer operative time, greater transfusion requirements, and higher complication rates. These findings quantify the additive risk conferred by anemia severity and cardiac disease.

In addition to impairing physiological resilience, this hematologic impairment frequently increases the need for perioperative blood transfusions,

which have been linked to negative outcomes such as a higher risk of postoperative infections, tumor recurrence, and a lower overall survival rate (13,15). The presence of severe anemia was significantly correlated with an increased incidence of post-operative complications, a finding consistent with previous studies suggesting that anemia impairs wound healing, delays recovery, and increases the risk of infections and other adverse events (16,17). Beyond transfusion, preoperative optimization of anemia should also include other evidence-based measures, particularly for iron-deficiency anemia. Strategies such as intravenous iron supplementation, erythropoiesis-stimulating agents, and nutritional support represent valuable tools within the framework of Patient Blood Management and have been shown to reduce transfusion requirements and improve perioperative outcomes in colorectal cancer surgery (4).

Postoperative ileus is a common complication that significantly prolongs hospital stays and increases healthcare resource utilization (18).

Anemic patients often exhibit reduced oxygen-carrying capacity and impaired tissue perfusion, which can compromise the healing of the intestinal anastomosis and reduce the neuromuscular function of the gastrointestinal tract (19). Moreover, anemia may exacerbate fatigue and impair mobilization, both of which are essential for early return of bowel function (20). This delay in gastrointestinal transit not only increases the risk of postoperative complications such as nausea, vomiting, and abdominal distension, but it also impedes nutritional intake, thereby affecting overall recovery and functional outcomes (19,20). In the present study, patients with severe anemia displayed a notably delayed return of bowel function and reduced postoperative mobility, underscoring the detrimental impact of anemia on recovery following colorectal cancer surgery. These findings emphasize the critical need for early recognition and management of severe anemia in the preoperative setting.

Patients with cardiovascular disease are more prone to hemodynamic instability during surgery, which may result in increased blood loss and a greater need for transfusions (21,22). In addition, our study identified cardiac disease as a significant factor in perioperative risk; patients with cardiac comorbidities required a higher volume of blood transfusions, experienced longer surgeries, and had increased intraoperative blood loss. The combined effect of cardiac disease and anemia appears to create a compounded risk for patients undergoing colon cancer surgery (23,24). These patients may require more intensive perioperative management, including careful monitoring of cardiac function and more aggressive transfusion strategies to stabilize both anemia and cardiovascular health (25). Given the increased incidence of postoperative complications and the prolonged recovery observed in cardiac patients, it is crucial to develop tailored, multidisciplinary care plans that address both oncologic and cardiovascular concerns (26).

The results of this study suggest that the management of severe anemia and cardiac comorbidities should be a key consideration in the preoperative and perioperative care of colon cancer patients. Clinicians should consider more aggressive anemia management, such as optimizing hemoglobin levels prior to surgery, to reduce the risk of complications associated with low blood volume. Furthermore, the significant differences in blood loss, transfusion requirements, and postoperative complications between cardiac and non-cardiac patients highlight the need for a multidisciplinary

approach to managing these patients. Cardiology, oncology, and transfusion medicine teams should collaborate to ensure the best outcomes for patients with both cancer and cardiovascular disease. Optimizing cardiac function, managing anemia, and minimizing surgical stress are all essential components of improving postoperative recovery and reducing mortality.

Limitations

One of the limitations of our study was the limited number of cases that were analyzed after meeting the inclusion and exclusion requirements. Using these results alone to make adjustments to the preoperative care colon cancer patients would be premature. While the present study provides relevant insights, further prospective, multicenter research is needed to validate these observations and to establish standardized management strategies. An important limitation of our study is that we did not differentiate anemia subtypes; we focused exclusively on tumor-related moderate and severe anemia that required preoperative transfusion. Further research is needed to refine transfusion protocols and develop more effective strategies for managing the complex interactions between anemia, surgery, and cardiac disease in colon cancer patients.

Conclusion

In conclusion, this study highlights the critical role of both anemia severity and cardiac disease in shaping postoperative outcomes in complicated colon cancer patients. Severe anemia and pre-existing cardiac conditions are both independently associated with worse surgical outcomes, increased transfusion needs, and higher rates of complications. These findings highlight the need for follow-up and further research, ideally through multicenter studies employing additional investigative tools, in order to refine perioperative management strategies for colon cancer patients with anemia and cardiac comorbidity.

Authors' Contributions

Conceptualization: Nicoleta Leopa, Andrea Badea, Razvan Catalin Popescu, Mihaela Pundiche, Viorel Ispas, Irinel Raluca Parepa; methodology: Nicoleta Leopa, Razvan Catalin Popescu, Mihaela Pundiche, Mihaela Botnariuc, Stefan Paitici, Dimitrie Busu, Cristina Tocia, Sorina Ispas;

software, Nicoleta Leopa; validation: Nicoleta Leopa, Razvan Catalin Popescu, Mihaela Pundiche, Andrea Badea, Viorel Ispas, Stefan Paitici, Irinel Raluca Parepa; formal analysis, Nicoleta Leopa, Stefan Paitici; investigation: Nicoleta Leopa, Razvan Catalin Popescu, Andrea Badea, Nicoleta Leopa, Mihaela Pundiche, Mihaela Botnariuc, Sorina Ispas; resources: Nicoleta Leopa, Razvan Catalin Popescu, Mihaela Pundiche, Mihaela Botnariuc, Cristina Tocia, Andrei Dumitru, Ioana Popescu, Irinel Raluca Parepa; data curation: Nicoleta Leopa, Cristina Tocia, Andrei Dumitru, Ioana Popescu, Dimitrie Busu, Sorina Ispas; writing—original draft preparation Nicoleta Leopa, Andrea Badea, Razvan Catalin Popescu, Mihaela Pundiche, Viorel Ispas, Cristina Tocia, Stefan Paitici; writing—review and editing: Nicoleta Leopa, Andrea Badea, Razvan Catalin Popescu, Mihaela Pundiche, Viorel Ispas, Andrei Dumitru; visualization: Nicoleta Leopa, Razvan Catalin Popescu, Mihaela Pundiche, Mihaela Botnariuc, Ioana Popescu, Dimitrie Busu; supervision: Nicoleta Leopa, Stefan Paiciti, Andrea Badea, Mihaela Pundiche, Razvan Catalin Popescu, Irinel Raluca Parepa, Sorina Ispas; administration: Nicoleta Leopa, Andrea Badea, Razvan Catalin Popescu, Viorel Ispas, Mihaela Pundiche. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interests

None to declare.

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