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Preoperative Anemia and Iron Deficiency in Elective Gastrointestinal Cancer Surgery Patients

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ABSTRACT

Background and Objectives: Preoperative anemia can impact postoperative outcomes, but its importance in gastrointestinal cancer patients, and significance of anemia etiology remains unclear. We aimed to characterize the frequency and impact of preoperative anemia, and iron-deficiency anemia (IDA), on perioperative outcomes.

Methods: We performed a retrospective cohort study of adult patients undergoing elective gastrointestinal cancer surgery. The primary outcome was the incidence of perioperative RBC transfusion. Secondary outcomes included 90-day postoperative major morbidity, ICU admission, and 90-day hospital readmission. Multivariable analyses were performed to assess the association between preoperative anemia and IDA and outcomes.

Results: Preoperative anemia was present in 55.5% of patients ($n = 15\,414$), and 58.3% of anemic patients were iron deficient. Preoperative anemia was independently associated with increased risk of RBC transfusion (RR 2.88, 95% CI 2.60–3.20), and secondary outcomes. For every preoperative hemoglobin decrease of 1 g/dL, the adjusted risk of perioperative RBC transfusion increased by 40% (RR 1.39, 95% CI 1.37–1.42).

Conclusion: Preoperative anemia is prevalent, and an independent risk factor for adverse postoperative outcomes. Decreases in preoperative hemoglobin levels elevate the risk of transfusion and adverse outcomes, supporting further study to optimize management of treatable causes of preoperative anemia including IDA.

1 | Introduction

Preoperative anemia is common in patients undergoing elective major surgery [1–3] and has been associated with adverse outcomes including post-operative mortality, morbidity, and perioperative red blood cell (RBC) transfusion [2, 4–7]. Perioperative RBC transfusion is also independently associated with adverse postoperative morbidity and mortality [8, 9]. Preoperative anemia may be caused by various etiologies including gastrointestinal (GI) blood loss, iron deficiency (ID), renal disease, or anemia of inflammation [10, 11]. For patients undergoing cancer surgery, chemotherapy, tumour type, location, and stage are additional factors that contribute to preoperative anemia [12].

GI cancers account for 35% of cancer related deaths worldwide [13]. Patients with GI cancers are frequently affected by anemia and/or ID [14, 15]. In this population, both preoperative anemia and ID without anemia have been associated with adverse short- and long-term postoperative complications, such as myocardial infarction, stroke and decreased overall survival [16, 17].

Despite the evidence demonstrating preoperative anemia is an important risk factor for perioperative adverse clinical outcomes, outstanding questions remain. The optimal screening strategy and treatment target for preoperative anemia, the impact of severity of anemia on outcomes, and the impact of iron-deficiency anemia (IDA) versus other etiologies of anemia in the GI cancer population remain less well characterized. Understanding these factors may help direct management strategies, particularly given the mixed evidence regarding the use of preoperative oral or intravenous iron [18–20].

This study sought to examine the frequency of preoperative IDA and non-ID anemia and their association with perioperative RBC transfusion and postoperative clinical outcomes in patients undergoing elective GI cancer surgery, as well as evaluate the association between preoperative hemoglobin (Hb) levels and transfusion and postoperative outcomes.

2 | Methods and Methods

2.1 | Study Design

This is a population-based retrospective cohort study using deidentified administrative health care data stored at ICES (formerly the Institute for Clinical Evaluative Sciences), an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows for the collection and analysis of health care and demographic data for health systems evaluation and improvement without consent. The use of data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*, which does not require review by a Research Ethics Board. This study is reported in accordance with the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) guidelines and the REporting of studies Conducted using Observational Routinely-collected health data (RECORD) statement [21, 22].

2.2 | Data Sources

Data for this study were obtained from multiple prospectively maintained health administrative data sets stored at ICES. All health care encounters for the province's 14 million residents are captured given the universally accessible, single-payer health care system funded by the Ontario Health Insurance Plan (OHIP) under the Canada Health Act [23]. These data sets were linked using unique encoded identifiers and analyzed at ICES. See Supporting Information S1: Table 1 for further information on data sets accessed for this study.

2.3 | Study Cohort

Adult patients (≥18 years of age) with a diagnosis of GI cancer including esophageal, gastric, small bowel, colon, rectal, hepato-biliary, and pancreatic cancer from the CIHI-DAD using International Classification of Diseases for Oncology (ICD-O-3) codes (Supporting Information S1: Table 2) were identified. Patients who underwent elective surgical resection for cancer between January 1, 2017 and January 1, 2020 were included. Follow up data were analyzed up to June 30, 2020. If multiple resection codes were identified during the study period per patient, only the first event was included. All GI surgeries were included because they share commonalities with regard to anemia frequency, underlying mechanism, and management, including etiology that can be related to the disease being surgically treated (such as luminal cancer). Exclusion criteria included patients with missing identification numbers, non-Ontario residents, those who underwent emergency surgery, or those with date of death before the index date of surgery. Patients with absent OLIS data were further excluded.

2.4 | Exposure

Preoperative anemia was defined as a preoperative Hb ≤ 13 g/dL in male and female patients and defined as the value closest to the index date of surgery, within 90 days before surgery. This definition has been adopted in recent consensus statements advocating for a preoperative Hb of ≥13 g/dL in both sexes to avoid adverse outcomes, especially in females [15, 24, 25]. ID was defined as a serum ferritin < 30 ng/mL, or a serum ferritin of <100 ng/mL and a transferrin saturation (TSAT) < 20% [24, 26].

2.5 | Outcomes

The primary outcome was the receipt of a perioperative RBC transfusion defined as receiving at least 1 RBC unit during the index hospital admission. In the CIHI-DAD, RBC transfusion is a binary variable—the timing of transfusion and number of units transfused is not captured. Secondary outcomes of interest were 90-day postoperative major morbidity, ICU admission, 90-day hospital readmission. Postoperative major morbidity was defined as the incidence of any grade 3−5 Clavien-Dindo complication (including grade 5, mortality) [27] definitions of which are included in Supporting Information S1: Table 4.

2.6 | Covariates

Definitions and data set sources of covariables used in this study are listed in Supporting Information S1: Table 3. Medical comorbidity burden was assessed using the Charlson Comorbidity Index [28]. The complete list of comorbidity definitions used in our study and the components of the Charlson Comorbidity Index are included in Supporting Information S1: Table 5 and Supporting Information S1: Table 6. Race/ethnicity demographic data were not available in the health administrative data sets for the study period. For those ≥65 years,

preoperative medications including antiplatelet, anticoagulant, iron, erythropoiesis-stimulating agents, and vitamin B12 supplements were obtained from the Ontario Drug Benefit Claims (ODB) database (Supporting Information S1: Table 7). Supporting Information S1: Table 8 denotes the Canadian Classification of Intervention (CCI) codes used to define surgical approach. Baseline laboratory values (Hb, ferritin, TSAT) were defined as the first available test result in the 3 month period before surgery.

2.7 | Statistical Analysis

Differences between baseline characteristics of patients with and without preoperative anemia were assessed using standardized differences, given the large sample size and population-based design. A difference of ≥0.10 was considered to be statistically significant [29, 30]. To assess for possible clustering of patients within hospitals, we estimated the correlation coefficient under a generalized estimating equations approach; this was near zero and thus we did not further account for clustering in the final models.

First, to describe the association between the exposure of preoperative anemia and outcomes, multivariable modified Poisson regression models (Poisson regression with robust error variance) were implemented and adjusted for potential measured confounders. We used modified Poisson regression models because they can estimate the relative risk (RR) of binary outcomes when the rare events assumption is not met (i.e., for common outcomes of >10%) [31, 32]. Each model was adjusted for covariates chosen a priori based on clinical relevance and the existing literature (Supporting Information S1: Table 9). Results are presented as RR with 95% confidence intervals (CI).

Second, to investigate levels of preoperative anemia associated with outcomes, preoperative Hb was treated as a continuous variable. Multivariable logistic regression models were built to examine the association between 1 g/dL increments in preoperative Hb and RBC transfusion, and postoperative clinical outcomes, adjusting for the same covariates as in the initial models. The results are presented as RR with 95% CI and graphically with the predicted probability of the outcome plotted against the preoperative Hb.

A subgroup analysis was restricted to patients with preoperative anemia and available iron studies to examine the association between the etiology of anemia (IDA vs. non-ID anemia) and outcomes. The same models were used, with an exposure of IDA versus non-ID anemia, among patients with preoperative anemia only.

Finally, sensitivity analyses were performed. First, preoperative medications may alter the association between preoperative anemia and outcomes, but this information was only available for patients ≥ 65 years whose medication prescriptions data are available through the ODB. A sensitivity analysis restricted to patients ≥ 65 years old was performed, in which preoperative receipt of an anticoagulant and/or antiplatelet agent was added to the covariates. Second, because RBC transfusions have been independently associated with postoperative adverse events, an analysis restricted to patients who did not receive a perioperative RBC transfusion was performed.

With regard to missing data—"missing" was considered a separate category for cancer stage (35.3%) and rurality (<1%). Income quintile data and material deprivation were missing < 1% and complete case analyses were performed for analyses including those variables. All tests were two-sided with p Values of <0.05 considered as statistically significant. All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Study Population

16 621 patients undergoing elective GI cancer surgery in Ontario between January 1, 2017 and January 1, 2020 were identified. After excluding 1 207 patients with missing Hb levels in OLIS data, 15 414 patients were included. The baseline characteristics of patients with and without Hb data were similar except that the latter more commonly had colon cancer, stage I disease, and were less comorbid (Supporting Information S1: Table 10). The characteristics of included patients are detailed in Table 1. The mean age was 67.8 years (SD 12.2) and the most common diagnoses were colon (52.4%) and rectal (21.1%) cancer. Overall, 8548 (55.5%) patients had preoperative anemia. In comparison to non-anemic patients, those with anemia were more likely to be older, female, have higher comorbidity burden, and had received neoadjuvant therapy. Patients with anemia had lower mean baseline Hb (10.9 ± 2.1 g/dL vs. 14.3 ± 1.3 g/dL) and preoperative Hb (11.0 ± 1.5 g/dL vs. 14.4 ± 0.9 g/dL).

In terms of screening for iron status, preoperative ferritin levels were available for 5006 (32.5%) of all patients, and 3545 (41.5%) of patients with anemia (Table 2). Of the latter, 2069 (58.3%) patients were identified to have ID. In comparison to those with non-ID anemia, those with IDA were less likely to have received neoadjuvant therapy, be less comorbid, and have lower baseline and preoperative Hb levels (Supporting Information S1: Table 11).

3.2 | Association of Outcomes With Preoperative Anemia

Overall, 2148 (13.9%) of 15 414 patients received a perioperative RBC transfusion. Preoperative anemia was independently associated with an increased risk of perioperative RBC transfusion (adjusted RR 2.88, 95% CI 2.60–3.20) (Figure 1). When treating preoperative Hb as a continuous variable, each decrease of 1 g/dL was associated with a 39% increase in the risk of perioperative RBC transfusion (adjusted RR 1.39, 95% CI 1.37–1.42) (Figure 2A).

Preoperative anemia was also independently associated with an increased risk of 90-day postoperative major morbidity (adjusted RR 1.22, 95% CI 1.14–1.30), ICU admission (adjusted RR 1.28, 95% CI 1.18–1.39), and 90-day readmission (adjusted RR 1.14, 95% CI 1.06–1.23). For every decrease in preoperative

TABLE 1 | Baseline demographic characteristics of adult patients undergoing elective gastrointestinal cancer surgery with anemia versus those without anemia.

Characteristic	No. (%)			
	All Patients (*N* = 15 414)	**Anemia (n = 8548)**	**No Anemia (*n* = 6866)**	**Standardized difference[a]**
Age (Mean ± SD)	67.8 ± 12.2	70.4 ± 12.3	64.6 ± 11.2	0.50
Sex				
• Female	6749 (43.8)	4622 (54.1)	2127 (31.0)	0.48
• Male	8665 (56.2)	3926 (45.9)	4739 (69.0)	0.48
Cancer site				
• Colon	8070 (52.4)	5,061 (59.2)	3009 (43.8)	0.31
• Rectum	3259 (21.1)	1343 (15.7)	1916 (27.9)	0.30
• Stomach	1102 (7.1)	706 (8.3)	396 (5.8)	0.10
• Pancreas	970 (6.3)	451 (5.3)	519 (7.6)	0.09
• Biliary	553 (3.6)	287 (3.4)	266 (3.9)	0.03
• Esophagus	502 (3.3)	332 (3.9)	170 (2.5)	0.08
• Small Bowel	496 (3.2)	208 (2.4)	288 (4.2)	0.10
• Liver	462 (3.0)	160 (1.9)	302 (4.4)	0.15
Cancer stage				
• I	2386 (15.5)	997 (11.7)	1389 (20.2)	0.24
• II	3341 (21.7)	2114 (24.7)	1227 (17.9)	0.17
• III	3480 (22.6)	2013 (23.5)	1467 (21.4)	0.05
• IV	772 (5.0)	477 (5.6)	295 (4.3)	0.06
• Missing	5435 (35.3)	2947 (34.5)	2488 (36.2)	0.04
Neoadjuvant Therapy[b]	2246 (14.6)	1383 (16.2)	863 (12.6)	0.10
Neoadjuvant Chemotherapy	1241 (8.1)	908 (10.6)	333 (4.8)	0.22
Neoadjuvant Radiation	1629 (10.6)	931 (10.9)	698 (10.2)	0.02
Neoadjuvant Chemotherapy and Radiation	624 (4.0)	456 (5.3)	168 (2.4)	0.15
Surgical approach				
• Laparoscopic	8410 (54.6)	4658 (54.5)	3752 (54.6)	0.00
• Open	6927 (44.9)	3859 (45.1)	3068 (44.7)	0.01
• Robotic	77 (0.5)	31 (0.4)	46 (0.7)	0.04
Charlson Comorbidity Index (Mean ± SD)	3.3 ± 2.0	3.5 ± 2.0	3.1 ± 1.9	0.21
Myocardial Infarction	334 (2.2)	244 (2.9)	90 (1.3)	0.11
Peripheral Vascular Disease	185 (1.2)	135 (1.6)	50 (0.7)	0.08
Chronic Kidney Disease	187 (1.2)	159 (1.9)	28 (0.4)	0.14
Liver cirrhosis	145 (0.9)	72 (0.8)	73 (1.1)	0.02
Bleeding and Coagulation Disorders	157 (1.0)	115 (1.3)	42 (0.6)	0.07
Inflammatory Bowel Disease	140 (0.9)	81 (0.9)	59 (0.9)	0.01
Congestive Heart Failure	950 (6.2)	728 (8.5)	222 (3.2)	0.23
Rural Residence	2131 (13.8)	1157 (13.5)	974 (14.2)	0.02
Income Quintile[c]				
• I	2968 (19.3)	1772 (20.7)	1196 (17.4)	0.08
• II	3170 (20.6)	1815 (21.2)	1355 (19.7)	0.04
• III	3082 (20.0)	1666 (19.5)	1416 (20.6)	0.03
• IV	3057 (19.8)	1644 (19.2)	1413 (20.6)	0.03

(Continues)

TABLE 1 | (Continued)

Characteristic	No. (%) All Patients ($N = 15\,414$)	Anemia (n = 8548)	No Anemia ($n = 6866$)	Standardized difference[a]
• V	3098 (20.1)	1627 (19.0)	1471 (21.4)	0.06
Material deprivation quintile[d]				
• I	3353 (21.8)	1772 (20.7)	1581 (23.0)	0.06
• II	3188 (20.7)	1723 (20.2)	1465 (21.3)	0.03
• III	3015 (19.6)	1660 (19.4)	1355 (19.7)	0.01
• IV	2975 (19.3)	1703 (19.9)	1272 (18.5)	0.04
• V	2744 (17.8)	1602 (18.7)	1142 (16.6)	0.06
Baseline Hb g/dL (mean ± SD)	12.4 ± 2.4	10.9 ± 2.1	14.3 ± 1.3	1.93
Preoperative Hb g/dL (mean ± SD)	12.5 ± 2.1	11.0 ± 1.5	14.4 ± 0.9	2.68
Baseline Ferritin ng/mL (mean ± SD)	110.2 ± 244.8	85.9 ± 216.4	169.0 ± 294.8	0.32
Preoperative Ferritin ng/mL (mean ± SD)	112.1 ± 227.0	92.1 ± 211.1	160.6 ± 255.2	0.29
Baseline TSAT % (mean ± SD)	0.17 ± 0.16	0.15 ± 0.15	0.27 ± 0.16	0.80
Preoperative TSAT % (mean ± SD)	0.18 ± 0.16	0.15 ± 0.15	0.27 ± 0.16	0.79

Abbreviations: Hb, Hemoglobin; SD, standard deviation; TSAT, Transferrin saturation.
[a]Standardized differences for patients with anemia versus no anemia;
[b]denotes the receipt of neoadjuvant chemotherapy and/or radiation therapy;
[c]Ranked from lowest (I) to highest (V) income quintile;
[d]Ranked from least (I) to most (V) marginalized.

TABLE 2 | Preoperative ferritin levels based on anemia and iron deficiency status.

Preoperative ferritin (ng/mL)	No. (%) IDA ($n = 2069$)	Non-IDA ($n = 1476$)	No Anemia_ID ($n = 274$)	No Anemia_Non ID ($n = 1187$)
0–29	1926 (93.1)	0 (0.0)	251 (91.6)	0 (0.0)
30–100	143 (6.9)	749 (50.8)	23 (8.4)	526 (44.3)
>100	0 (0.0)	727 (49.2)	0 (0.0)	661 (55.7)

Abbreviations: ID, iron deficiency; IDA, iron deficiency anemia.

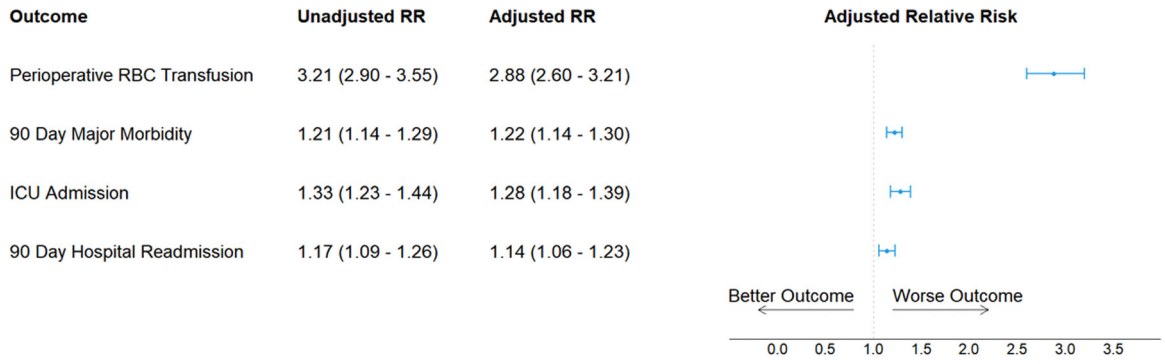

FIGURE 1 | Association between preoperative anemia and primary and secondary clinical outcomes. RR, relative risk. Results presented as RR (95% CI). Adjusted for patient age, sex, cancer stage, comorbidity index score, procedure type (open, laparoscopic, robotic), GI cancer type (separated by luminal vs. non-luminal cancers), receipt of neoadjuvant chemotherapy and/or radiation, income and marginalization quintiles, and rurality.

Hb level by 1 g/dL, the adjusted risk of 90-day postoperative major morbidity, ICU admission, and hospital readmission increased by 7% (RR 1.07, 95% CI 1.05–1.09), 5% (RR 1.05, 95% CI 1.03–1.08), and 4% (RR 1.04, 95% CI 1.02–1.06), respectively (Figure 2B–D).

3.3 | Sub-Group Analysis: Preoperative ID Anemia

Overall, 3545 patients had anemia and iron studies available, of which 2069 (58.3%) had iron-deficiency (Table 2). In this

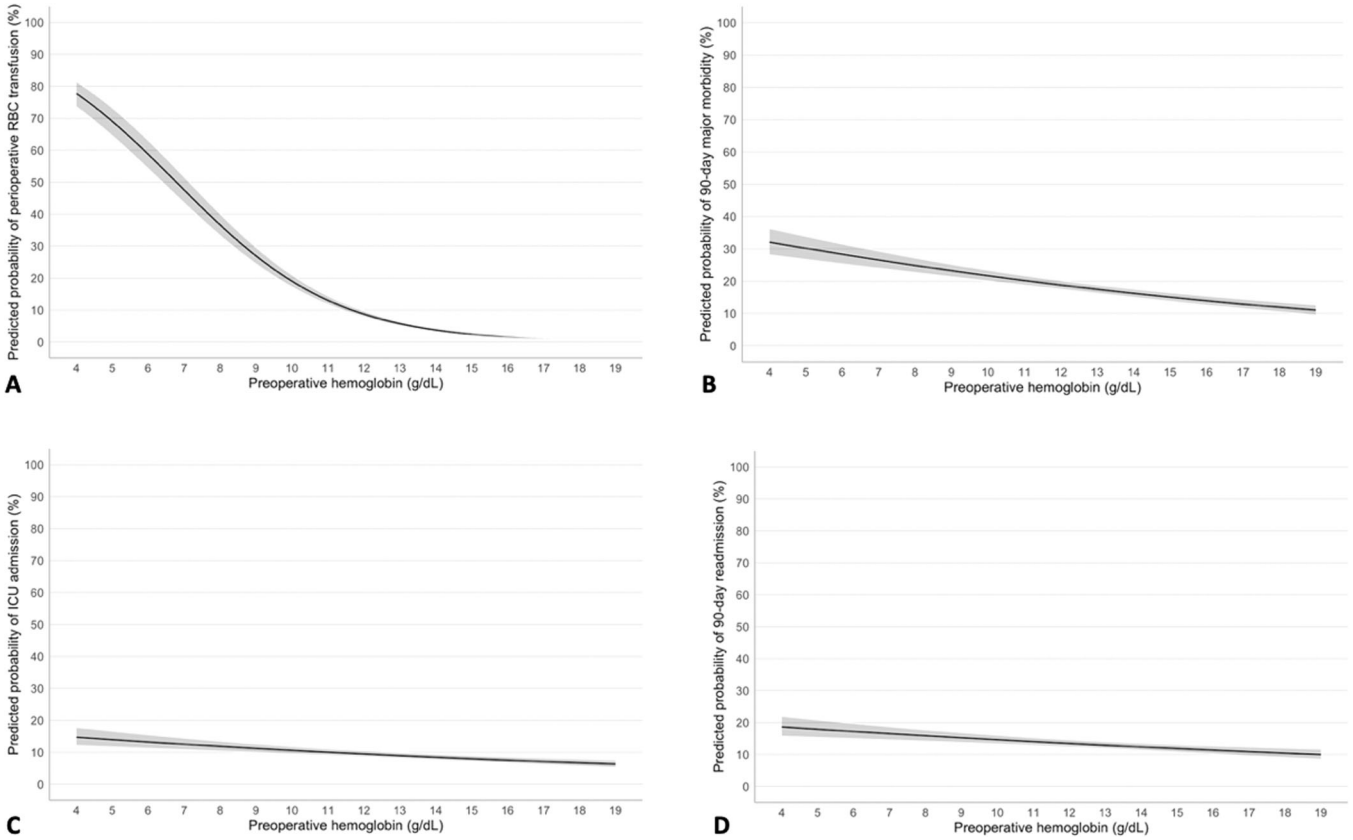

FIGURE 2 | Association between preoperative hemoglobin level (g/dL) and adjusted predicted probability of perioperative RBC transfusion (A) 90-day postoperative major morbidity (B), ICU admission (C), and 90-day hospital readmission (D). Results presented as RR (95% CI). Adjusted for patient age, sex, cancer stage, comorbidity index score, procedure type (open, laparoscopic, robotic), GI cancer type (separated by luminal vs. non-luminal cancers), receipt of neoadjuvant chemotherapy and/or radiation, income and marginalization quintiles, and rurality.

sub-group of patients with preoperative anemia, the etiology of anemia, IDA compared to non-ID anemia, was not associated with increased perioperative risk of RBC transfusion (adjusted RR 1.09, 95% CI 0.96–1.25), 90 day postoperative major morbidity (adjusted RR 0.95, 95% CI 0.84–1.08) or 90 day hospital readmission (adjusted RR 0.96, 95% CI 0.82–1.12) (Figure 3).

3.4 | Sensitivity Analyses

When restricting the analysis to patients ≥ 65 years old ($n = 9789$) and adjusting for antiplatelet/anticoagulant medications, preoperative anemia remained independently associated with perioperative RBC transfusion (RR 2.83, 95% CI 2.48–3.23). When restricting the analysis to patients who did not receive a perioperative RBC transfusion ($n = 13\,267$), preoperative anemia remained independently associated with increased risk of 90-day postoperative major morbidity (adjusted RR 1.11, 95% CI 1.03–1.20).

4 | Discussion

In this large population-based cohort study, preoperative anemia was prevalent and present in over half of patients with both luminal and non-luminal malignancies undergoing elective GI cancer surgery. In patients with anemia, 58% were identified to have IDA, but only one-third of all patients had any preoperative ferritin testing available. Preoperative anemia was independently associated with a higher risk of RBC transfusion, with a dose-response relationship; each decrease in preoperative Hb of 1 g/dL was associated with a 40% increase in the risk of RBC transfusion. Similar continuous associations were identified between preoperative anemia and 90-day postoperative major morbidity, ICU admission, and readmission, with risk increased by 7%, 5%, and 4%, for each decrease of 1 g/dL in preoperative Hb, respectively. The type of anemia, whether IDA or non-ID anemia, was not independently associated with perioperative RBC transfusions or post-operative outcomes, potentially indicating that anemia, regardless of etiology, plays a role in perioperative outcomes. These findings are important to bolster efforts to improve uptake of, and set goals for, perioperative patient blood management programs as well as future research.

We observed a similar rate of preoperative anemia and IDA relative to the existing literature on GI cancers [15, 33–37]. This indicates face validity for our assessment of preoperative anemia. While the finding of an association between preoperative anemia and outcomes within the GI cancer patient population have previously been reported, our study adds new information regarding the severity of anemia. Prior studies have observed that preoperative anemia is independently associated with adverse clinical and RBC transfusion outcomes [1–5]. However, in previous studies, different definitions of anemia were used

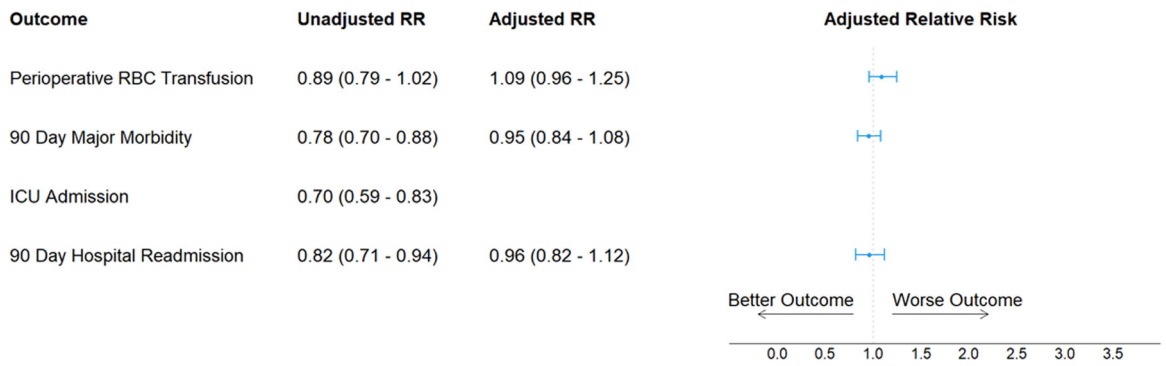

FIGURE 3 | Associations between preoperative IDA versus non-IDA on primary and secondary clinical outcomes. RR, relative risk. Results presented as RR (95% CI). Results presented as RR (95% CI). Adjusted for patient age, sex, cancer stage, comorbidity index score, procedure type (open, laparoscopic, and robotic), GI cancer type (separated by luminal vs. non-luminal cancers), receipt of neoadjuvant chemotherapy and/or radiation, income and marginalization quintiles, and rurality. Multivariable analysis unable to be performed for ICU admission due to low outcome number.

for male and female patients, and preoperative anemia was examined as a dichotomous variable. In our study we used the same Hb threshold of <13 g/dL to define anemia in male and female patients, consistent with international consensus statements advocating for the same definition in both sexes to avoid predisposing females to adverse outcomes [24, 25, 38]. We also used a novel approach by examining preoperative Hb as a continuous variable. This provides a more nuanced and precise assessment of the association of degree of anemia with outcomes. Patient blood management programs often aim to correct anemia altogether however, depending on the level of anemia and timelines to surgery, this may not be possible [10, 39]. As a result, some may be discouraged to intervene and not consider blood management interventions preoperatively. Our result suggests that even modest improvements in preoperative Hb can be associated with improved outcomes. This supports the need for timely preoperative anemia identification and management for all patients undergoing GI surgery because even small gains in Hb levels could make a difference [4, 24, 40].

We further explored whether the etiology of anemia, IDA or non-ID anemia, was associated with outcomes. ID is the most common cause of anemia worldwide, and frequently identified in patients with GI malignancies both at time of diagnosis and/or during treatment [14, 15, 41–43]. In our study 58.3% of anemic patients were identified to be iron deficient, however only a third of all patients (32.5%) had any preoperative ferritin testing performed. As such, the prevalence of ID (with or without anemia) within our cohort is likely underestimated. Our low ferritin testing rate despite the high prevalence of anemia suggest that ID is under-tested and under-diagnosed in this patient population. Investigation into a patient's underlying iron status is important considering that IDA is treatable and should be treated regardless of whether a patient is going for surgery [26]. In patients undergoing cardiac surgery, ID in the presence or absence of anemia has been associated with increased postoperative mortality, perioperative RBC transfusion, and postoperative fatigue [44–46]. In patients with colorectal cancer, severe ID regardless of anemia status has been examined, but not found to be associated with postoperative complications [17]. Among patients with preoperative anemia in our study, IDA was not associated with outcomes compared to non-ID anemia, including perioperative RBC transfusion. This does not examine whether IDA compared to no anemia, or non-ID anemia compared to no anemia, is associated with outcomes. It is acknowledged that our definitions of ID (serum ferritin of <30 ng/mL, or if available—serum ferritin of <100 ng/mL and TSAT < 20%) were strict; half of patients characterized as "non-IDA" had serum ferritin levels of 30–100 ng/mL in the absence of an available TSAT. As such it is possible that a subset of patients with ID were included in the non-ID anemia group, attenuating potential differences. Nevertheless, these results report for the first time on the question of the etiology of preoperative anemia and outcomes for GI surgery. We did not identify a difference in outcomes between IDA and non-IDA, possibly due to the low rate of screening for ID and other causes of anemia. Differences in the ability to correct Hb preoperatively and their effect on outcomes between etiology fell beyond the scope of this study but could be investigated in future efforts.

While routine administration of IV iron has not demonstrated a benefit on transfusion rates or mortality in abdominal surgery, in colorectal cancer surgery, there is evidence to suggest that IV iron in comparison to oral supplementation or standard of care may result in larger increase in Hb level and decrease perioperative RBC transfusion [18, 19, 33, 47, 48]. In the most recent randomized controlled trial (PREVENTT), IV iron was administered routinely (not specifically to patients with IDA) at a median 14 days preoperatively with an average Hb increase of 5 g/L with no differences in postoperative complications [18]. Notable, a decreased risk of readmission to hospital was observed in those patients treated with IV iron, suggesting that treatment with IV iron may have occurred too late in the preoperative phase [18]. Although the data are still uncertain, they do not definitively rule out benefits of treating preoperative anemia. ID is a treatable cause of preoperative anemia which should be managed; early identification and timely management before surgery should be pursued [24, 26].

This study has limitations. The data were not collected specifically to answer the research question and thus can lack details. While we adjusted for key measured covariates such as patient comorbidities in our analysis, unmeasured confounding cannot be avoided. For instance, we were missing certain tumour factors and the indication for, or Hb level before, transfusion. Such details may lessen the magnitude of the associations observed. We could not obtain preoperative medication information for the entire cohort because the

ODB claims are only available for individuals ≥ 65 years or on disability, but we conducted a sensitivity analysis on this subgroup of patients that did not alter the findings. We also could not address whether time to surgery post neoadjuvant therapy influenced preoperative anemia, and any preoperative management of anemia, such as iron supplementation which was not reliably available in the data sets. We included all GI surgeries which may differ in terms of complexity and baseline risk of RBC transfusion and postoperative morbidity. The procedures share commonalities with regard to anemia frequency, underlying mechanism, and management. We adjusted for the type of procedure based on surgical approach and disease in the multivariable models, but could not adjust for estimated blood loss which was not available in the data set. Our data set is obtained from a large provincial retrospective data set which encompasses data from various academic and community institutions across Ontario; as such transfusion practices may vary based on individual institutional policies, and individual surgeon practice. Additionally, based on our definition of anemia as a Hb < 13 g/dL in both sexes we observed high rates of anemia in our study population with 68% and 45% of female and male patients respectively being anemic. While similarly high anemia rates in female patients have been observed in previous studies, the high rates of anemia in our population may influence the generalizability of our results [15]. Future studies assessing the prevalence of preoperative anemia that similarly avoid sex based definitions to define anemia will be of benefit to compare our findings. Finally, while our study suggests that there is an association between the degree of preoperative anemia and transfusion as well as clinical outcomes such as postoperative morbidity, given the retrospective nature of this work we are unable to assess whether preoperative correction of anemia with interventions such as iron supplementation would lead to an improvement in these outcomes.

Despite these limitations, the strengths of this study include the large cohort of over 15 000 patients with both luminal and non-luminal GI malignancies and high-quality administrative data sets. Future work on efforts to better identify preoperative anemia and ID in the early preoperative setting, as well as prospective observational or randomized controlled trials to delineate the impact of anemic and non-anemic ID in GI cancer patients, and more importantly its treatment on additional patient-centered outcomes such as fatigue, and postoperative quality of life will be of benefit to better address how to optimally manage anemia and ID within this population. Moreover, the observation that the degree of preoperative anemia is associated with RBC transfusion and postoperative outcomes supports patient blood management recommendations for early identification and treatment of preoperative anemia to result in incremental increases in Hb level before surgery.

5 | Conclusion

Preoperative anemia and IDA are very common in patients undergoing elective GI cancer surgery, however iron status testing may be under-utilized in the preoperative setting contributing to under-recognition of treatable ID in this patient population. Preoperative anemia is independently associated with increased risks of perioperative RBC transfusion, 90-day postoperative major morbidity, ICU admission, and hospital readmission. Notably, each decrease of preoperative Hb by 1 g/dL was associated with significant increases in perioperative RBC transfusion, and 90-day postoperative major morbidity, ICU admission, and hospital readmission which suggests that any correction in preoperative Hb levels may contribute to improving patient outcomes. Our work supports efforts for early detection, investigation into treatable causes, and early management of preoperative anemia before GI cancer surgery to mitigate adverse outcomes.

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Conflicts of Interest

Y. L. has research funding from Canadian Blood Services and Octapharma and consulting fees from Choosing Wisely Canada. The remaining authors declare no conflicts of interest.

Data Availability Statement

The data set from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

References

1. K. M. Musallam, H. M. Tamim, T. Richards, et al., "Preoperative Anaemia and Postoperative Outcomes in Non-Cardiac Surgery: a Retrospective Cohort Study," *The Lancet* 378, no. 9800 (2011): 1396–1407, https://doi.org/10.1016/S0140-6736(11)61381-0.

2. D. M. Baron, H. Hochrieser, M. Posch, et al., "Preoperative Anaemia Is Associated with Poor Clinical Outcome in Non-Cardiac Surgery Patients," *British Journal of Anaesthesia* 113, no. 3 (2014): 416–423, https://doi.org/10.1093/bja/aeu098.

3. A. A. Klein, T. J. Collier, M. S. Brar, et al., "The Incidence and Importance of Anaemia in Patients Undergoing Cardiac Surgery in the Uk - the First Association of Cardiothoracic Anaesthetists National

Audit," *Anaesthesia* 71, no. 6 (2016): 627–635, https://doi.org/10.1111/anae.13423.

4. M. M. Mueller, H. Van Remoortel, P. Meybohm, et al., "Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference," *JAMA* 321, no. 10 (2019): 983–997, https://doi.org/10.1001/jama.2019.0554.

5. A. J. Fowler, T. Ahmad, M. K. Phull, S. Allard, M. A. Gillies, and R. M. Pearse, "Meta-Analysis of the Association between Preoperative Anaemia and Mortality after Surgery," *British Journal of Surgery* 102, no. 11 (2015): 1314–1324, https://doi.org/10.1002/bjs.9861.

6. W. S. Beattie, K. Karkouti, D. N. Wijeysundera, and G. Tait, "Risk Associated with Preoperative Anemia in Noncardiac Surgery," *Anesthesiology* 110, no. 3 (2009): 574–581, https://doi.org/10.1097/ALN.0b013e31819878d3.

7. J. Freedman, K. Luke, M. Escobar, L. Vernich, and J. A. Chiavetta, "Experience of a Network of Transfusion Coordinators for Blood Conservation (Ontario Transfusion Coordinators [Ontrac])," *Transfusion* 48, no. 2 (2008): 237–250, https://doi.org/10.1111/j.1537-2995.2007.01515.x.

8. V. A. Ferraris, "Surgical Outcomes and Transfusion of Minimal Amounts of Blood in the Operating Room," *Archives of Surgery* 147, no. 1 (2012): 49–55, https://doi.org/10.1001/archsurg.2011.790.

9. A. C. Bernard, D. L. Davenport, P. K. Chang, T. B. Vaughan, and J. B. Zwischenberger, "Intraoperative Transfusion of 1 U to 2 U Packed Red Blood Cells Is Associated with Increased 30-day Mortality, Surgical-Site Infection, Pneumonia, and Sepsis in General Surgery Patients," *Journal of the American College of Surgeons* 208, no. 5 (2009): 931–937e2 ,; discussion 938-9, https://doi.org/10.1016/j.jamcollsurg.2008.11.019.

10. Y. Lin, "Preoperative Anemia-Screening Clinics," *Hematology* 2019, no. 1 (2019): 570–576, https://doi.org/10.1182/hematology.2019000061.

11. J. Abraham, R. Sinha, K. Robinson, V. Scotland, and D. Cardone, "Aetiology of Preoperative Anaemia in Patients Undergoing Elective Cardiac Surgery-The Challenge of Pillar One of Patient Blood Management," *Anaesthesia and Intensive Care* 45, no. 1 (2017): 46–51, https://doi.org/10.1177/0310057X1704500107.

12. R. S. Weber, N. Jabbour, and R. C. G. Martin, "Anemia and Transfusions in Patients Undergoing Surgery for Cancer," *Annals of Surgical Oncology* 15, no. 1 (2008): 34–45, https://doi.org/10.1245/s10434-007-9502-9.

13. M. Arnold, C. C. Abnet, R. E. Neale, et al., "Global Burden of 5 Major Types of Gastrointestinal Cancer," *Gastroenterology* 59, no. 1 (2020): 335–349.e15, https://doi.org/10.1053/j.gastro.2020.02.068.

14. H. Ludwig, S. Van Belle, P. Barrett-Lee, et al., "The European Cancer Anaemia Survey (Ecas): a Large, Multinational, Prospective Survey Defining the Prevalence, Incidence, and Treatment of Anaemia in Cancer Patients," *European Journal of Cancer* 40, no. 15 (2004): 2293–2306, https://doi.org/10.1016/j.ejca.2004.06.019.

15. M. Muñoz, M. J. Laso-Morales, S. Gómez-Ramírez, M. Cadellas, M. J. Núñez-Matas, and J. A. García-Erce, "Pre-Operative Haemoglobin Levels and Iron Status in a Large Multicentre Cohort of Patients Undergoing Major Elective Surgery," *Anaesthesia* 72, no. 7 (2017): 826–834, https://doi.org/10.1111/anae.13840.

16. M. J. Wilson, M. van Haaren, J. J. Harlaar, et al., "Long-Term Prognostic Value of Preoperative Anemia in Patients with Colorectal Cancer: A Systematic Review and Meta-Analysis," *Surgical Oncology* 26, no. 1 (2017): 96–104, https://doi.org/10.1016/j.suronc.2017.01.005.

17. M. J. Wilson, J. W. T. Dekker, J. J. Harlaar, J. Jeekel, M. Schipperus, and J. J. Zwaginga, "The Role of Preoperative Iron Deficiency in Colorectal Cancer Patients: Prevalence and Treatment," *International Journal of Colorectal Disease* 32, no. 11 (2017): 1617–1624, https://doi.org/10.1007/s00384-017-2898-1.

18. T. Richards, R. R. Baikady, B. Clevenger, et al., "Preoperative Intravenous Iron to Treat Anaemia before Major Abdominal Surgery (Preventt): a Randomised, Double-Blind, Controlled Trial," *The Lancet* 396, no. 10259 (2020): 1353–1361, https://doi.org/10.1016/S0140-6736(20)31539-7.

19. B. D. Keeler, J. A. Simpson, O. Ng, et al., "Randomized Clinical Trial of Preoperative Oral Versus Intravenous Iron in Anaemic Patients with Colorectal Cancer," *British Journal of Surgery* 104, no. 3 (2017): 214–221, https://doi.org/10.1002/bjs.10328.

20. E. A. Dickson, B. D. Keeler, O. Ng, A. Kumar, M. J. Brookes, and A. G. Acheson, "Preoperative Intravenous Iron Therapy and Survival after Colorectal Cancer Surgery: Long-Term Results from the Ivica Randomised Controlled Trial," *Colorectal Disease* 22, no. 12 (2020): 2018–2027, https://doi.org/10.1111/codi.15342.

21. E. I. Benchimol, L. Smeeth, A. Guttmann, et al., "The Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement," *PLoS medicine* 12, no. 10 (2015): e1001885, https://doi.org/10.1371/journal.pmed.1001885.

22. E. von Elm, D. G. Altman, M. Egger, et al, "The Strengthening the Reporting of Observational Studies in Epidemiology (Strobe) Statement: Guidelines for Reporting Observational Studies," *PLoS Med* 4, no. 10 (2007): e296, https://doi.org/10.1371/journal.pmed.0040296.

23. Government of Canada. *Canada Health Act*. Government of Canada, (2020), https://www.canada.ca/en/health-canada/services/health-care-system/canada-health-care-system-medicare/canada-health-act.html.

24. M. Muñoz, A. G. Acheson, M. Auerbach, et al., "International Consensus Statement on the Peri-Operative Management of Anaemia and Iron Deficiency," *Anaesthesia* 72, no. 2 (2017): 233–247, https://doi.org/10.1111/anae.13773.

25. A. C. Weyand, P. T. McGann, and M. Sholzberg, "Sex Specific Definitions of Anaemia Contribute to Health Inequity and Sociomedical Injustice," *The Lancet Haematology* 9, no. 1 (2022): e6–e8, https://doi.org/10.1016/S2352-3026(21)00351-3.

26. K. Hands, J. Daru, C. Evans, et al., "Identification and Management of Preoperative Anaemia in Adults: A British Society for Haematology Guideline Update," *British Journal of Haematology* 205, no. 1 (2024): 88–99, https://doi.org/10.1111/bjh.19440.

27. D. Dindo, N. Demartines, and P. A. Clavien, "Classification of Surgical Complications: a New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey," *Annals of Surgery* 240, no. 2 (2004): 205–213, https://doi.org/10.1097/01.sla.0000133083.54934.ae.

28. M. E. Charlson, P. Pompei, K. L. Ales, and C. R. MacKenzie, "A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation," *Journal of Chronic Diseases* 40, no. 5 (1987): 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.

29. P. C. Austin, "Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research," *Communications In Statistics - Simulation and Computation* 38, no. 6 (2009): 1228–1234, https://doi.org/10.1080/03610910902859574.

30. M. Mamdani, K. Sykora, P. Li, et al., "Reader's Guide to Critical Appraisal of Cohort Studies: 2. Assessing Potential for Confounding," *BMJ (Clinical research ed.)* 330, no. 7497 (2005): 960–962, https://doi.org/10.1136/bmj.330.7497.960.

31. G. Zou, "A Modified Poisson Regression Approach to Prospective Studies with Binary Data," *American Journal of Epidemiology* 159, no. 7 (2004): 702–706, https://doi.org/10.1093/aje/kwh090.

32. L. A. McNutt, C. Wu, X. Xue, and J. P. Hafner, "Estimating the Relative Risk in Cohort Studies and Clinical Trials of Common Outcomes," *American Journal of Epidemiology* 157, no. 10 (2003): 940–943, https://doi.org/10.1093/aje/kwg074.

33. M. Laso-Morales, C. Jericó, S. Gómez-Ramírez, et al., "Preoperative Management of Colorectal Cancer-Induced Iron Deficiency Anemia in Clinical Practice: Data from a Large Observational Cohort," *Transfusion* 57, no. 12 (2017): 3040–3048, https://doi.org/10.1111/trf.14278.

34. V. Roberts, I. Deftereos, B. Mahbub, et al., “Anaemia and Its Impact on Colorectal Cancer Patients: How Can We Better Optimize Surgical Outcomes,” *ANZ journal of surgery* 91, no. 5 (2021): 280, https://doi.org/10.1111/ans.16774.

35. X. Liu, H. Qiu, Y. Huang, et al., “Impact of Preoperative Anemia on Outcomes in Patients Undergoing Curative Resection for Gastric Cancer: a Single-Institution Retrospective Analysis of 2163 Chinese Patients,” *Cancer Medicine* 7, no. 2 (2018): 360–369, https://doi.org/10.1002/cam4.1309.

36. S. W. Leichtle, N. J. Mouawad, R. Lampman, B. Singal, and R. K. Cleary, “Does Preoperative Anemia Adversely Affect Colon and Rectal Surgery Outcomes,” *Journal of the American College of Surgeons* 212, no. 2 (2011): 187–194, https://doi.org/10.1016/j.jamcollsurg.2010.09.013.

37. X. Huang, Y. Yang, Y. Chen, et al., “Preoperative Anemia or Low Hemoglobin Predicts Poor Prognosis in Gastric Cancer Patients: A Meta-Analysis,” *Disease Markers* 2019 (2019): 7606128, https://doi.org/10.1155/2019/7606128.

38. M. Muñoz, S. Gómez-Ramírez, S. Kozek-Langeneker, et al., “Fit to Fly’: Overcoming Barriers to Preoperative Haemoglobin Optimization in Surgical Patients,” *British Journal of Anaesthesia* 115, no. 1 (2015): 15–24, https://doi.org/10.1093/bja/aev165.

39. K. Pavenski, A. Howell, C. D. Mazer, G. M. T. Hare, and J. Freedman, “Ontrac: A 20-Year History of a Successfully Coordinated Provincewide Patient Blood Management Program: Lessons Learned and Goals Achieved,” *Anesthesia & Analgesia* 135, no. 3 (2022): 448–458, https://doi.org/10.1213/ANE.0000000000006065.

40. J. S. Chin, J. Mayhew, L. A. Rumble, et al., “Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management,” in *Program in Evidence-Based Care Evidence-Based Series No. 17-3 Version 2* Vol. 3 (Toronto, ON: Cancer Care Ontario, 2008): 25.

41. W. M. Gardner, C. Razo, T. A. McHugh, et al., “Prevalence, Years Lived with Disability, and Trends in Anaemia Burden By Severity and Cause, 1990-2021: Findings from the Global Burden of Disease Study 2021,” *The Lancet Haematology* 10, no. 9 (2023): e713–e734, https://doi.org/10.1016/S2352-3026(23)00160-6.

42. S. R. Pasricha, J. Tye-Din, M. U. Muckenthaler, and D. W. Swinkels, “Iron Deficiency,” *The Lancet* 397, no. 10270 (2021): 233–248, https://doi.org/10.1016/S0140-6736(20)32594-0.

43. S. Krieg, S. Loosen, A. Krieg, T. Luedde, C. Roderburg, and K. Kostev, “Association between Iron Deficiency Anemia and Subsequent Stomach and Colorectal Cancer Diagnosis in Germany,” *Journal of Cancer Research and Clinical Oncology* 150, no. 2 (2024): 53, https://doi.org/10.1007/s00432-023-05534-z.

44. P. Piednoir, N. Allou, F. Driss, et al., “Preoperative Iron Deficiency Increases Transfusion Requirements and Fatigue in Cardiac Surgery Patients: a Prospective Observational Study,” *European Journal of Anaesthesiology* 28, no. 11 (2011): 796–801, https://doi.org/10.1097/EJA.0b013e32834ad97b.

45. J. Rössler, F. Schoenrath, B. Seifert, et al., “Iron Deficiency Is Associated with Higher Mortality in Patients Undergoing Cardiac Surgery: a Prospective Study,” *British Journal of Anaesthesia* 124, no. 1 (2020): 25–34, https://doi.org/10.1016/j.bja.2019.09.016.

46. L. F. Miles, S. A. Kunz, L. H. Na, S. Braat, K. Burbury, and D. A. Story, “Postoperative Outcomes Following Cardiac Surgery in Non-Anaemic Iron-Replete and Iron-Deficient Patients - an Exploratory Study,” *Anaesthesia* 73, no. 4 (2018): 450–458, https://doi.org/10.1111/anae.14115.

47. P. M. H. Kam, C. W. H. Chu, E. M. Y. Chan, O. L. Liu, and K. H. Kwok, “Use of Intravenous Iron Therapy in Colorectal Cancer Patient with Iron Deficiency Anemia: a Propensity-Score Matched Study,” *International Journal of Colorectal Disease* 35, no. 3 (2020): 521–527, https://doi.org/10.1007/s00384-020-03508-y.

48. H. Lederhuber, L. H. Massey, S. Abeysiri, et al., “Preoperative Intravenous Iron and the Risk of Blood Transfusion in Colorectal Cancer Surgery: Meta-Analysis of Randomized Clinical Trials,” *The British Journal of surgery* 111, no. 1 (2024): 1–11, https://doi.org/10.1093/bjs/znad320.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.