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ORIGINAL ARTICLE

Presurgical mild anemia is a risk factor for severe postoperative complications of rectal cancer surgery: A Japanese nationwide retrospective cohort study

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Abstract

Background: Anemia has negative effects on long-term outcomes of rectal cancer patients; however, its status as a risk factor for severe complications is disputed. Perioperative risks may differ based on the severity of pre-surgical anemia; nonetheless, no previous study has investigated these differences. This study identified risks of severe postoperative complications in rectal cancer patients based on severity of their pre-surgical anemia.

Materials and Methods: This study enrolled patients who underwent low anterior resection for rectal cancer and were registered in the Japanese National Clinical Database (NCD) between 2017 and 2019. Anemia severity was categorized into three levels: mild, moderate, and severe. A logistic regression model was applied to calculate the risk-adjusted odds ratio (OR) of severe complications after surgery.

Results: This study analyzed a cohort of 51 765 rectal cancer patients who underwent low anterior resection. Results showed that severe complications occurred in 10.9% of patients and were significantly more frequent in patients with anemia (13.6%) than those with normal hemoglobin levels (9.2%). Risk-adjusted ORs of severe complications in the severe, moderate, and mild anemia groups versus the normal group for males were 1.19 (95% confidence interval [CI]: 0.89–1.58), 1.47 (1.34–1.62), and 1.21 (1.12–1.31), respectively. Those for females were 1.39 (0.90–2.15), 1.64 (1.37–1.97), and 1.36 (1.16–1.58), respectively.

Conclusions: According to this large cohort study, pre-surgical anemia significantly increases the risk of severe postoperative complications in rectal cancer patients. Even mild anemia presents a significant risk.

KEYWORDS
anastomotic leakage, anemia, comorbidity, rectal cancer, surgical site infection

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1 | INTRODUCTION

Colorectal cancer is widespread and ranks as the third most frequently diagnosed cancer globally. It is also the second leading cause of cancer deaths worldwide. Rectal cancer comprises approximately one-third of all colorectal cancer cases.[1] Anemia is frequently observed in patients with rectal cancer at the time of diagnosis and is one of the reasons why rectal cancer patients seek primary care.[2] Preoperative treatments like chemoradiation or total neoadjuvant chemotherapy, which improve the prognosis of rectal cancer patients, can also cause anemia.[3] Anemia has negative effects on both short-term and long-term outcomes for patients with malignant disease.[4–6] Perioperative blood transfusions negatively affect short-term outcomes and survival of patients undergoing cancer surgery.[7,8] In addition, however, previous studies have not specifically investigated differences in perioperative risk based on anemia severity. Only Musallam et al.[9] reported that mild anemia is a risk factor for non-cardiac major surgery; however, no studies have shown that mild anemia is a risk factor for postoperative complications after colorectal surgery.

For rectal cancer patients undergoing low anterior resection, postoperative complications are common, and anastomotic leakage is the most feared, with rates ranging from 3% to 23%. It frequently necessitates additional interventions, prolongs hospital stays, and worsens prognoses.[10–13] While factors such as diabetes, smoking, bowel obstruction, and perioperative transfusion have been widely recognized as risk factors for anastomotic leakage, the relationship between preoperative anemia and severe complications, including anastomotic leakage, is still a matter of debate.[6,14–16]

The objective of this study was to assess the effect of presurgical anemia on severe postoperative complications, such as anastomotic leakage and organ/space surgical site infection (SSI), in patients with rectal cancer who underwent low anterior resection. We investigated how much the postoperative complication risk increases in patients with various severities of anemia compared to those without it. We particularly focused on whether mild anemia increases the risk of severe postoperative complications. This study analyzed data of over 50000 patients in the nationwide Japanese National Clinical Database (The National Clinical Database) and evaluated risk of postoperative complications based on severity of presurgical anemia, which was classified as mild, moderate, or severe.

2 | MATERIALS AND METHODS

2.1 | Data source

The Japanese National Clinical Database (NCD) is a nationwide, web-based, data-entry system linked to the surgical board certification system, initiated in 2011. The NCD was developed in collaboration with the National Surgical Quality Improvement Program (NSQIP) in the United States, with a shared goal of creating a standardized surgery database for quality improvement using standardized definitions of variables to collect data related to risk factors and outcomes. Patient data are maintained by the Japan Surgical Society and registered only in the NCD (http://www.ncd.or.jp/). The NCD now covers more than 97% of all surgical procedures in Japan[17] and has high data accuracy, with an overall concordance rate of 98.1%, which is equivalent to the audit of NSQIP (96.8%–98.4% in 2005–2008).[18] This retrospective cohort study included adult patients (≥18 years) who had adenocarcinomas of the rectum and underwent low anterior resection of the rectum, and who were registered in the NCD from January 1, 2017, to December 31, 2019.

2.2 | Study design

The primary endpoint was the incidence of severe complications within 30 days after low anterior resection. Secondary outcomes included anastomotic leakage and organ/space SSI. Complications were categorized according to their Clavien–Dindo grade and severe complications were defined as Clavien–Dindo grade III or more. Normal hemoglobin range was defined as male: 13.5–17.0 g/dL, female: 11.5–15.0 g/dL. Anemia was classified as mild (male: 11.0–13.4 g/dL, female: 10.0–11.4 g/dL), moderate (male: 8.0–10.9 g/dL, female: 8.0–9.9 g/dL), or severe (<7.9 g/dL). In this study, males with hemoglobin of 17.0 or higher and females with 15.0 or higher were excluded from further analyses. This exclusion was made because elevated hemoglobin levels may increase the risk of thrombosis and negatively impact blood flow at the anastomosis site. However, the clinical significance of this finding remains unclear. Patients with distant metastasis were excluded as in the IVICA trial, which evaluated efficacy of preoperative intravenous and oral iron in reducing blood transfusion use in anemic patients undergoing elective colorectal cancer surgery.[19]

2.3 | Ethics and statistical analysis

This study was approved by the institutional review board of Nippon Medical School (B-2020-274). Differences between the groups were analyzed using the χ^2 test. Patients who had missing values were excluded from the analysis. Fifteen clinical factors that were considered risk factors based on results of previous studies[6,14,15] were used as adjustment factors to evaluate the risk-adjusted odds ratios (OR) for complications in each anemia severity level compared with those in the normal hemoglobin range group (the normal group). The 15 factors included age, body mass index (BMI), hypertension, diabetes, smoking, chronic obstructive pulmonary disease (COPD), ischemic cardiac disease, steroid use, preoperative transfusion, preoperative chemotherapy, preoperative radiotherapy, ASA class, T category, N category, and laparoscopic surgery. Continuous variables are shown with medians and interquartile ranges, and categorical variables are presented as numbers and proportions. A two-sided $p < 0.05$ was considered statistically significant. All statistical procedures were

conducted using R version 4.1.2 (2021; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patient backgrounds

Between 2017 and 2019, 62772 patients who underwent low anterior resection were registered in the NCD. Patients with benign diseases ($n=3966$), <18 years ($n=40$), who underwent emergency surgery ($n=543$), who lacked sufficient data regarding the depths of invasion (T) category, who had lymph node metastasis ($n=391$) or distant metastasis ($n=5384$), or who lacked sufficient observation data ($n=9$) were excluded, leaving 52439 patients. Patients with hemoglobin levels above the normal range were excluded. Finally, 33841 male and 17924 female patients were included in this study (Figure 1).

Table 1 compares demographics, preoperative variables, intraoperative variables, and surgical outcomes between male and female. Among them, 19856 patients (38.4%) had some degree of anemia, including 14957 male (44.1%) and 4899 female (27.3%).

Frequencies of death after surgery, severe complications, anastomotic leakage, and organ/space SSI were 0.47 (95% confidence interval [CI]: 0.42–0.54) %, 10.9 (95% CI: 10.6–11.1) %, 9.7 (95% CI: 9.5–10.0) %, and 6.2 (95% CI: 6.0–6.4) %, respectively. Those of males were significantly higher than those of females. Most comorbidities were also more common in males than in females. Only steroid use was higher among females than male patients. Rates of severe complications (12.9% vs. 7.0%), anastomotic leakage (12.1% vs. 5.2%), and organ/space SSI (7.7% vs. 3.5%) were higher among males than females.

3.2 | Differences in background and surgical outcomes of anemic and normal patients

Table S1 shows differences in complication frequency based on the presence or absence of anemia. Severe complications were significantly increased in patients with any degree of anemia (anemia group) compared with patients in the normal hemoglobin range (normal group) among both males (14.9% in the anemia group vs. 11.4% in the normal group) and females (9.5% in the anemia group vs. 6.0% in the normal group). Similarly, anastomotic leakage was significantly more common in patients with any degree of anemia than in patients with normal hemoglobin levels in both males (6.6% in the anemia group vs. 4.7% in the normal group) and females (9.5% in the anemia group vs. 6.0% in the normal group).

Next, we divided patients with anemia into three subgroups: severe, moderate, and mild anemia. Table 2 (male) and 3 (female) compare demographics, preoperative variables, intra-operative variables, and surgical outcomes for groups. The moderate and mild anemia groups constantly demonstrated an increase in severe complications >2% compared with the normal group. This tendency was observed in both males and females.

3.3 | Risk-adjusted OR to postoperative complications in relation to presurgical anemia severity

Between patients with anemia and those without, regardless of gender, significant differences were observed in age, body mass index (BMI), prevalence of hypertension, diabetes, smoking, chronic obstructive pulmonary disease (COPD), ischemic cardiac disease, steroid use, preoperative transfusion, preoperative chemotherapy, preoperative radiotherapy, ASA classification, T category, N category, and surgical procedures (Tables 2 and 3). ORs for the 15 adjustment factors associated with severe complication, anastomotic leakage, and surgical site infection are presented in Tables S2–S4.

Among males, the risk-adjusted OR for severe complications in the mild anemia group to the normal group was 1.21 (95% CI: 1.12–1.31, $p<0.001$), and that in the moderate anemia group was 1.47 (95% CI: 1.34–1.62, $p<0.001$, Figure 2A). As for females, the risk-adjusted OR for severe complications in the mild anemia group to the normal group was 1.36 (95% CI: 1.16–1.58, $p<0.001$), and that in the moderate anemia group was 1.64 (95% CI: 1.37–1.97, $p<0.001$, Figure 2A). There was no significant difference between the normal and severe anemia groups in males or females.

For males, the risk-adjusted OR for anastomotic leakage in the mild anemia group versus the normal group was 1.19 (95% CI: 1.10–1.29, $p<0.001$), and that in the moderate anemia group was 1.33 (95% CI: 1.20–1.47, $p<0.001$, Figure 2B). For females, the risk-adjusted OR for anastomotic leakage in the moderate anemia group versus the normal group was 1.66 (95% CI: 1.34–2.03, $p<0.001$). However, there was no significant difference between the mild anemia group and the normal group (OR: 1.20, 95% CI: 0.995–1.43, $p=0.053$, Figure 2B). There were also no significant differences between the normal and severe anemia groups of males or females in regard to severe complications.

The risk-adjusted OR for organ/space SSI in the male mild anemia group versus the normal group was 1.17 (95% CI: 1.06–1.29, $p=0.002$), and that in the moderate anemia group was 1.48 (95% CI: 1.31–1.67, $p<0.001$, Figure 2C). The risk-adjusted OR for organ/space SSI in the moderate female anemia group versus the normal group was 1.60 (95% CI: 1.23–2.04, $p<0.001$); however, there was no significant difference between the normal hemoglobin and mild anemia groups (OR: 1.22, 95% CI: 0.99–1.52, $p=0.06$, Figure 2C). There was no significant difference between the normal and severe anemia groups in males or females.

4 | DISCUSSION

Previous studies have not adequately examined the impact of mild anemia on postoperative complications of rectal surgery.

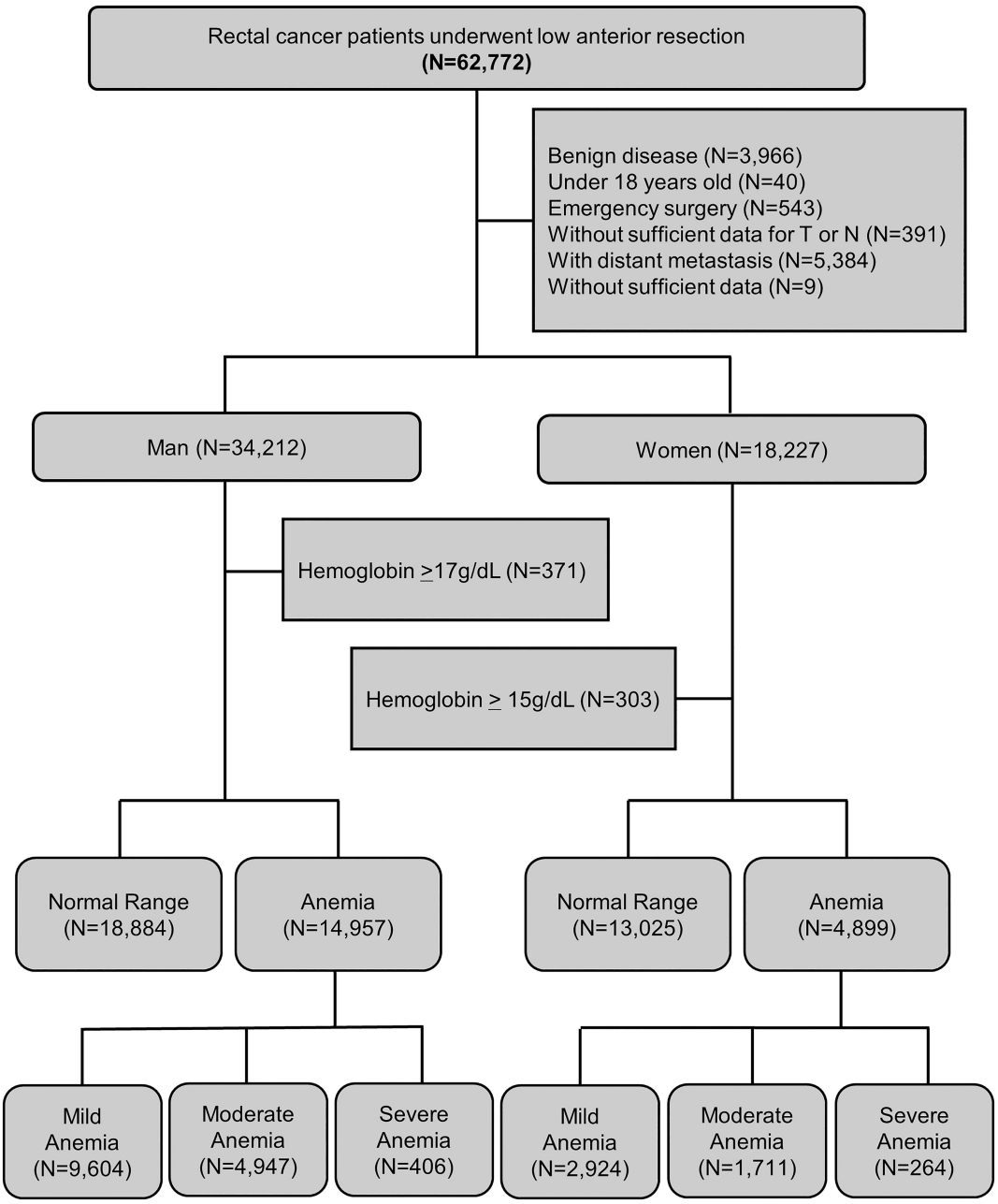

FIGURE 1 Flow diagram.

This study assessed the degree of risk that anemia severity poses for severe complications following low anterior resection for rectal cancer. These findings demonstrated that even mild anemia increases the incidence of severe complications. These results underscore the importance of preoperative evaluation and management of anemia, as well as the need to consider anemia as a risk factor in future clinical trials in this field. While the increase in risk may appear small, it could have significant implications for patient outcomes, considering the high prevalence of anemia in rectal cancer patients.[20,21]

The present study demonstrated that mild anemia increases the risk of postoperative severe complications. Despite the high frequency of colorectal cancer patients having anemia, the presence of anemia was not included in patient backgrounds of many randomized clinical trials examining short-term outcomes of rectal cancer surgery.[10,22–24] In addition, in many studies, only severe and moderate anemia have been examined as a risk factor[25–27] or anemia severity classification was lacking altogether.[28,29] Therefore, the present study focused on severities of anemia in patients with rectal cancer and demonstrated that mild anemia is a risk factor for severe postoperative complications. The findings of this study provide valuable information to help healthcare providers optimize perioperative care for patients with rectal cancer and to develop guidelines for managing preoperative anemia. While various institutions have attempted to introduce patient blood management (PBM),[20] further studies are needed to determine the best strategies for managing

TABLE 1 Baseline characteristics and surgical outcome of patients.

	ALL ($n=51765$)	Male ($n=33841$)	Female ($n=17924$)
Preoperative factors			
Hemoglobin (%)			
Normal	31909 (61.6)	18884 (55.8)	13025 (72.7)
Mild	12528 (24.2)	9604 (28.4)	2924 (16.3)
Moderate	6658 (12.9)	4947 (14.6)	1711 (9.5)
Severe	670 (1.3)	406 (1.2)	264 (1.5)
Age category (%)			
≤64	17392 (33.6)	11432 (33.8)	5960 (33.3)
65–74	19527 (37.7)	13496 (39.9)	6031 (33.6)
75≤	14846 (28.7)	8913 (26.3)	5933 (33.1)
BMI category (%)			
Normal 18.5–24.9 kg/m^2	33760 (65.2)	22500 (66.5)	11260 (62.8)
Underweight <18.5 kg/m^2	5847 (11.3)	2877 (8.5)	2970 (16.6)
Overweight 25 kg/m^2≤	12158 (23.5)	8464 (25.0)	3694 (20.6)
Hypertension (%)	20120 (38.9)	14013 (41.4)	6107 (34.1)
Diabetes (%)	10010 (19.3)	7634 (22.6)	2376 (13.3)
Smoking (%)	11571 (22.4)	9703 (28.7)	1868 (10.4)
COPD (%)	1855 (3.6)	1555 (4.6)	300 (1.7)
ICD (%)	1571 (3.0)	1332 (3.9)	239 (1.3)
Steroid use (%)	409 (0.8)	223 (0.7)	186 (1.0)
Preoperative transfusion (%)	558 (1.1)	348 (1.0)	210 (1.2)
Preoperative chemotherapy (%)	3793 (7.3)	2670 (7.9)	1123 (6.3)
Preoperative radiotherapy (%)	1838 (3.6)	1294 (3.8)	544 (3.0)
ASA PS 3, 4, 5 (%)	5670 (11.0)	4170 (12.3)	1500 (8.4)
T category 3, 4 (%)	32184 (62.2)	21323 (63.0)	10861 (60.6)
N positive (%)	19788 (38.2)	12835 (37.9)	6953 (38.8)
Intra-operative factors			
Laparoscopic (%)	42064 (81.3)	27544 (81.4)	14520 (81.0)
Intra-operative transfusion (%)	2344 (4.5)	1405 (4.2)	939 (5.2)
Outcomes			
Surgical related deaths (%)	245 (0.5)	182 (0.5)	63 (0.4)
Severe complication (%)	5626 (10.9)	4375 (12.9)	1251 (7.0)
Anastomotic leakage (%)	5028 (9.7)	4096 (12.1)	932 (5.2)
Organ/Space SSI (%)	3219 (6.2)	2598 (7.7)	621 (3.5)
Transfusion after surgery (%)	1024 (2.0)	702 (2.1)	322 (1.8)

Abbreviations: ASA, American Society for Anesthesiologists; COPD, chronic obstructive pulmonary disease; ICD, ischemic cardiac disease.

preoperative anemia in patients undergoing low anterior resection for rectal cancer.

In males, even mild anemia significantly increases the risk of anastomotic leakage. For females, while mild anemia was not a statistically significant risk factor ($p=0.053$), it still may be a clinically relevant factor that warrants attention. For both genders, the anastomotic leakage rate in the mild anemia group was only 1% higher than in the group with normal hemoglobin levels. Nonetheless, this detail is crucial to enhance patient outcomes and to reduce anastomotic leakage incidence in patients with rectal cancer undergoing low anterior resection. Given the profound impact of anastomotic leakage after rectal cancer surgery on prognosis and diminished quality of life, even such a minor difference deserves attention. Huisman et al.[30] reported that there are seven risk factors for anastomotic leakage in colorectal surgery, and that anemia is the most important. They defined anemia in males as a hemoglobin level below 10.5 g/dL. In the study of Sparreboom et al., which included 36929 Dutch patients with colorectal cancer, anemia was not found to be a risk

TABLE 2 Baseline characteristics and surgical outcomes of men (categorized by the severity of anemia).

	Normal ($n=18884$)	Mild ($n=9604$)	Moderate ($n=4947$)	Severe ($n=406$)
Preoperative factors				
Age (years, median [IQR])	66 [58, 72]	71 [65, 77]	73 [67, 79]	72 [66, 79]
Age category (%)				
≤64	8269 (43.8)	2216 (23.1)	870 (17.6)	77 (19.0)
65–74	7372 (39.0)	4005 (41.7)	1954 (39.5)	165 (40.6)
75≤	3243 (17.2)	3383 (35.2)	2123 (42.9)	164 (40.4)
BMI category (%)				
Normal 18.5–24.9	12169 (64.4)	6703 (69.8)	3346 (67.6)	282 (69.5)
Underweight <18.5	937 (5.0)	1045 (10.9)	822 (16.6)	73 (18.0)
Overweight ≥25 kg/m^2	5778 (30.6)	1856 (19.3)	779 (15.7)	51 (12.6)
Hypertension (%)	6988 (37.0)	4500 (46.9)	2359 (47.7)	166 (40.9)
Diabetes (%)	3756 (19.9)	2400 (25.0)	1381 (27.9)	97 (23.9)
Smoking (%)	5767 (30.5)	2677 (27.9)	1168 (23.6)	91 (22.4)
COPD (%)	687 (3.6)	559 (5.8)	294 (5.9)	15 (3.7)
ICD (%)	470 (2.5)	499 (5.2)	349 (7.1)	14 (3.4)
Steroid use (%)	88 (0.5)	87 (0.9)	46 (0.9)	2 (0.5)
Preoperative transfusion (%)	14 (0.1)	41 (0.4)	213 (4.3)	80 (19.7)
Preoperative chemotherapy (%)	1054 (5.6)	1223 (12.7)	381 (7.7)	12 (3.0)
Preoperative radiotherapy (%)	608 (3.2)	527 (5.5)	155 (3.1)	4 (1.0)
ASA PS 3, 4, 5 (%)	1394 (7.4)	1407 (14.7)	1266 (25.6)	103 (25.4)
T category 3, 4 (%)	10284 (54.5)	6641 (69.1)	4042 (81.7)	356 (87.7)
N positive (%)	6433 (34.1)	3860 (40.2)	2335 (47.2)	207 (51.0)
Intra-operative factors				
Laparoscopic (%)	16123 (85.4)	7581 (78.9)	3576 (72.3)	264 (65.0)
Intra-operative transfusion (%)	185 (1.0)	325 (3.4)	766 (15.5)	129 (31.8)
Outcomes				
Surgical related deaths (%)	55 (0.3)	53 (0.6)	68 (1.4)	6 (1.5)
Severe complication (%)	2148 (11.4)	1322 (13.8)	844 (17.1)	61 (15.0)
Anastomotic leakage (%)	2103 (11.1)	1222 (12.7)	716 (14.5)	55 (13.5)
Organ/Space SSI (%)	1300 (6.9)	768 (8.0)	496 (10.0)	34 (8.4)
Transfusion after surgery (%)	134 (0.7)	213 (2.2)	313 (6.3)	42 (10.3)

Abbreviations: ASA, American Society for Anesthesiologists; COPD, chronic obstructive pulmonary disease; ICD, ischemic cardiac disease.

factor for leakage. This may be attributed to inclusion of patients with both rectal and colon cancer.[31] These findings suggest that the definition of anemia and its impact on anastomotic leakage may vary depending on the location of colorectal cancer and the patient population. This further highlights the need to consider anemia as a risk factor in patients with rectal cancer undergoing low anterior resection and to conduct further studies to establish clear guidelines for managing anemia in specific patient populations.

This study revealed that the rate of anastomotic leakage in rectal cancer patients undergoing low anterior resection is higher in males than females, regardless of the degree of anemia. In all categories, normal hemoglobin (11.8% vs. 4.7%), mild (13.8% vs. 5.8%), and moderate anemia (17.1% vs. 8.0%), the rate of anastomotic leakage for males is more than twice that of females. This confirms that being male is a risk factor for anastomotic leakage, as previous studies have demonstrated.[30,31]

This study highlights the need to correct preoperative anemia so as to minimize or prevent postoperative complications. Although there is limited evidence, some studies suggest that preoperative iron supplementation may be effective in reducing the perioperative transfusion

TABLE 3 Baseline characteristics and surgical outcomes of women (categorized by the severity of anemia).

	Normal (*n* = 13025)	Mild (*n* = 2924)	Moderate (*n* = 1711)	Severe (*n* = 264)
Preoperative factors				
Age (years, median [IQR])	68 [59, 75]	73 [65, 81]	75 [67, 82]	74 [64, 82]
Age category (%)				
≤64	4851 (37.2)	696 (23.8)	346 (20.2)	67 (25.4)
65–74	4625 (35.5)	864 (29.5)	473 (27.6)	69 (26.1)
≥75	3549 (27.2)	1364 (46.6)	892 (52.1)	128 (48.5)
BMI category (%)				
Normal 18.5–24.9	8316 (63.8)	1766 (60.4)	1034 (60.4)	144 (54.5)
Underweight <18.5	1788 (13.7)	683 (23.4)	420 (24.5)	79 (29.9)
Overweight 25≤	2921 (22.4)	475 (16.2)	257 (15.0)	41 (15.5)
Hypertension (%)	8316 (63.8)	1766 (60.4)	1034 (60.4)	144 (54.5)
Diabetes (%)	4184 (32.1)	1132 (38.7)	698 (40.8)	93 (35.2)
Smoking (%)	1567 (12.0)	467 (16.0)	298 (17.4)	44 (16.7)
COPD (%)	1469 (11.3)	261 (8.9)	115 (6.7)	23 (8.7)
ICD (%)	202 (1.6)	64 (2.2)	33 (1.9)	1 (0.4)
Steroid use (%)	130 (1.0)	56 (1.9)	47 (2.7)	6 (2.3)
Preoperative transfusion (%)	118 (0.9)	34 (1.2)	31 (1.8)	3 (1.1)
Preoperative chemotherapy (%)	23 (0.2)	30 (1.0)	109 (6.4)	48 (18.2)
Preoperative radiotherapy (%)	711 (5.5)	286 (9.8)	122 (7.1)	4 (1.5)
ASA PS 3, 4, 5 (%)	373 (2.9)	126 (4.3)	43 (2.5)	2 (0.8)
T category 3, 4 (%)	754 (5.8)	388 (13.3)	308 (18.0)	50 (18.9)
N positive (%)	7046 (54.1)	2172 (74.3)	1410 (82.4)	233 (88.3)
Intra-operative factors				
Laparoscopic (%)	10982 (84.3)	2167 (74.1)	1200 (70.1)	171 (64.8)
Intra-operative transfusion (%)	249 (1.9)	228 (7.8)	380 (22.2)	82 (31.1)
Outcomes				
Surgical related deaths (%)	18 (0.1)	17 (0.6)	21 (1.2)	7 (2.7)
Severe complication (%)	785 (6.0)	257 (8.8)	184 (10.8)	25 (9.5)
Anastomotic leakage (%)	607 (4.7)	170 (5.8)	137 (8.0)	18 (6.8)
Organ/Space SSI (%)	396 (3.0)	120 (4.1)	93 (5.4)	12 (4.5)
Transfusion after surgery (%)	105 (0.8)	84 (2.9)	103 (6.0)	30 (11.4)

rate,[29] postoperative complication rate, and hospital length of stay.[9,32] Other investigations, such as the PREVENTT study found that preoperative intravenous iron was not superior to a placebo in reducing the need for blood transfusions when given to patients with anemia 10–42 days prior to elective major abdominal surgery.[33] However, that study included patients with anemia of varying severity; thus, the benefit of iron supplementation for patients with mild anemia is not clear. Additionally, the median time from randomization to surgery was 15 days. This term may be too short because anemia was corrected in only 21% (42 of 244) of patients. Despite this, there were significantly fewer rehospitalizations in the intervention group. The IVICA trial, which included anemic patients with non-metastatic colorectal adenocarcinoma, demonstrated that intravenous iron did not reduce the blood transfusion requirement, but was more effective than oral iron at treating preoperative anemia and iron deficiency in patients undergoing colorectal cancer surgery; however, this study did not include patients who did not receive iron supplementation.[19] The HepciFer trial, a randomized controlled trial, which included 50 patients undergoing liver surgery concluded that intravenous ferric carboxymaltose administration did not result in a significant increase of hemoglobin levels 7 days after surgery.[34]

This study had additional limitations that should be considered when interpreting the results. The limited number of patients with severe anemia restricted evaluation of the risk of severe complications

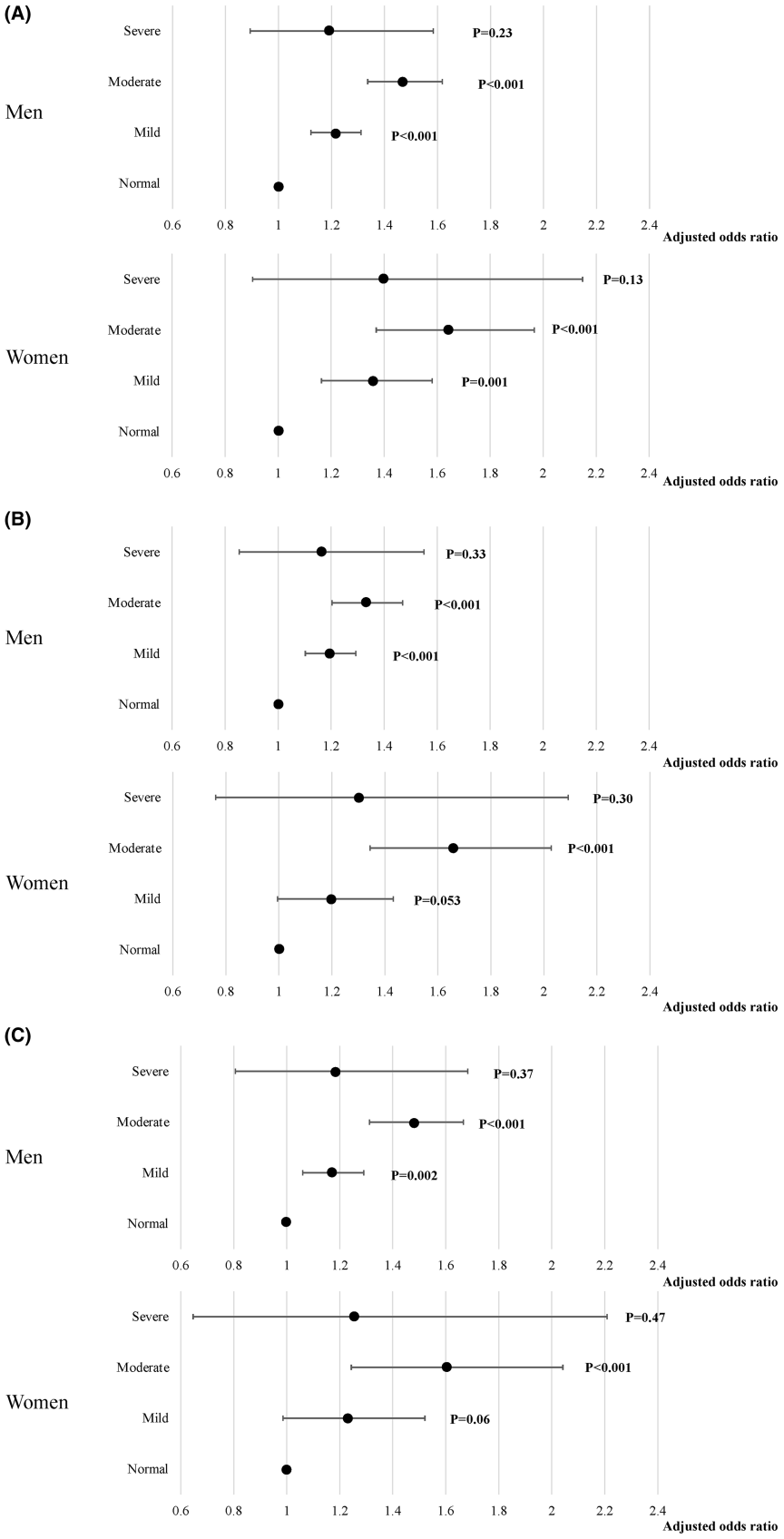

FIGURE 2 (A) Effect of preoperative anemia on severe complications (Clavien–Dindo grade ≥ III). (B) Effect of preoperative anemia on anastomotic leakage. (C) Effect of preoperative anemia on deep/organ surgical site infection. Fifteen risk adjustment factors (described in Section 2) were used to calculate risk-adjusted odds ratios based upon anemia severity. Mild anemia was defined as 11.0–13.4 g/dL in men and 10.0–11.4 g/dL in women. Moderate anemia was defined as 8.0–10.9 g/dL in men and 8.0–9.9 g/dL in women. Severe anemia was defined as ≥7.9 g/dL in both men and women.

caused by severe anemia. Due to the lack of information on the grade of anastomotic leakage, it was difficult to compare those results with other studies. Additionally, factors that could impact anemia, such as preoperative blood biochemistry test results and the use of nonsteroidal anti-inflammatory drugs, were not included in the analysis. It is also important to note that Japanese patients typically have a lower

BMI than Western patients and many do not receive preoperative radiotherapy. Moreover, the study did not examine the distance of the tumor from the anal verge or the method of anastomosis, which could impact anastomotic leakage rates.[14] Surgery-related deaths were not included in the analysis because the number of events was too small to perform multivariable regression analysis. The present study does not offer specific details regarding the timing of the hemoglobin measurements. Data entered into the NCD must have been acquired no more than 90 days before surgery and must be the most recent values. In situations where a transfusion or an iron supplement was given, it is likely that in many cases blood was taken after this administration, and transiently elevated hemoglobin values were then recorded. The NCD does not have accurate data regarding the covering stoma. A covering stoma has the potential to contribute to a reduced rate of anastomotic leakage by preventing fecal matter from passing through the anastomosis. Additionally, in cases of mild anastomotic leakage, it makes clinical symptoms less likely to appear. Finally, the definition of anemia differs between the World Health Organization (WHO) and the NCD. According to the WHO, males with hemoglobin levels ≤13.0 g/dL and females with ≤12.0 g/dL are considered anemic. However, the NCD classifies anemia in males as ≤13.5 g/dL and ≤11.5 g/dL in females.

5 | CONCLUSIONS

Pre-surgical anemia significantly increases the risk of severe postoperative complications in patients undergoing low anterior resection for rectal cancer. It is noteworthy that even mild anemia is a significant risk factor.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENTS

Approval of the research protocol: This study was approved by the Ethics Committee for the local Institutional Review Board of Nippon Medical School (Approval No. B-2020-274).
Informed Consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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