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ORIGINAL CONTRIBUTION

The Association of Preoperative Anemia and the Postoperative Course and Oncological Outcome in Patients Undergoing Rectal Cancer Surgery: A Multicenter Snapshot Study

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BACKGROUND: There is still controversy about the relationship between preoperative anemia and outcomes after rectal cancer surgery.

OBJECTIVE: The aim of this study was to analyze the association between preoperative anemia and postoperative complications and the survival of patients undergoing surgery for rectal cancer in the era of laparoscopic surgery and modern perioperative care.

DESIGN: This was a cohort study.

SETTINGS: Data were gathered from 71 hospitals in The Netherlands.

PATIENTS: Patients who underwent resection for rectal cancer in 2011, for whom preoperative hemoglobin level was registered, were included.

INTERVENTIONS(S): There were no interventions.

MAIN OUTCOME MEASURES: Short-term outcome parameters were any postoperative complication or mortality within 30 days postoperatively, and pelvic infectious complications defined as anastomotic leakage and presacral abscess. Long-term outcomes were chronic sinus diagnosed at any time during 3-year follow-up, 3-year local and distant recurrence rates, and 3-year overall survival.

RESULTS: Of 2095 patients, 1857 had a registered preoperative hemoglobin level; 576 (31%) of these patients anemic and 1281 (69%) were nonanemic. Preoperative anemia was not independently associated with postoperative complications (HR, 1.1; 95% CI, 0.9–1.4; $p = 0{\cdot}24$) or 30-day mortality (HR, 1.4, 95% CI, 0.7–2.8; $p = 0{\cdot}29$). Preoperative anemia was associated with 3-year overall survival (HR, 2.1; 95% CI, 1.7–2.5; $p < 0.0001$), after multivariable analysis (HR, 1.4; 95% CI, 1.1–1.8; $p = 0{\cdot}008$), and with local recurrence rate (HR, 1.6; 95% CI, 1.1–2.4; $p = 0.026$), but not with distant recurrence rate (HR, 1.2; 95% CI, 1.0–1.5; $p = 0.054$).

LIMITATIONS: Preoperative anemia appeared to have only limited association with postoperative and disease-specific outcome after rectal cancer surgery in contrast to published meta-analysis of small historical series.

CONCLUSIONS: Anemia is associated with overall survival. It might be considered as one of the warning signs in identifying high-risk patients. See **Video Abstract** at http://links.lww.com/DCR/A913.

KEY WORDS: Anemia; Rectal cancer; Surgery; Survival.

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Surgery remains the cornerstone of the treatment of rectal cancer with curative intent. Despite improvements in surgical technique and perioperative care, resection of rectal cancer is still associated with a substantial risk of postoperative complications.[1] Assessment and adjustment of modifiable risk factors of patients before surgery can serve as a potential window of opportunity to optimize postoperative outcome.[2] An important modifiable risk factor reflecting a patient's condition is the hemoglobin (Hb) level.[3,4] Anemia has been associated with fatigue, impaired physical performance, and increased morbidity and mortality, also in patients with rectal can-

TABLE 1. Baseline characteristics and surgical procedure

Variable	*Total cohort*		*Anemic patients*		*Nonanemic patients*		*p value*
			(Men <8.0 mmol/L, women <7.5 mmol/L)		*(Men ≥8.0 mmol/L, women ≥7.5 mmol/L)*		
	n = 1857		*n = 576*		*n = 1281*		
Age, y							<0.0001
Overall, mean (SD)	67 (11.0)		70 (11.0)		65 (10.8)		
≤60, n (%)	495 (27)		103 (18)		392 (30)		
61–70, n (%)	619 (33)		172 (30)		447 (35)		
71–80, n (%)	569 (31)		215 (37)		354 (28)		
>80, n (%)	174 (9)		86 (15)		88 (7)		
Sex, male, n (%)	1168 (63)	n = 1857	370 (64)	n = 575	798 (62)	n = 1282	0.40
Preoperative Hb, mmol/L, mean (SD)	8.2 (1.1)	n = 1857	7.0 (0.8)	n = 576	8.7 (0.6)	n = 1281	<0.0001
BMI, kg/m², overweight,[a] n (%)	985 (55)	n = 1786	267 (48)	n = 558	718 (58)	n = 1228	<0.0001
ASA classification, n (%)		n = 1814		n = 564		n = 1250	<0.0001
ASA I–II	1515 (84)		403 (71)		1112 (89)		
ASA III–IV	299 (16)		161 (29)		138 (11)		
Comorbidity, n (%)		n = 1815					
Overall	1254 (69)		443 (78)	n = 566	811 (65)	n = 1249	<0.0001
Cardiac	409 (22)		193 (44)	n = 443	216 (27)	n = 811	<0.0001
Diabetes mellitus	239 (13)		109 (25)	n = 443	130 (16)	n = 811	<0.0001
Pulmonary	213 (12)		70 (16)	n = 443	143 (18)	n = 811	0.65
Pathological TNM stage, n (%)		n = 1762		n = 551		n = 1211	0.002
Stage I (T1-2N0M0)	623 (35)		178 (32)		445 (37)		
Stage II (T3-4N0M0)	412 (23)		160 (29)		252 (21)		
Stage III (T1-4N1-2M0)	241 (14)		75 (14)		166 (13)		
Stage IV (T1-4N1-2M1)	486 (28)		138 (25)		348 (29)		
Distance to anorectal junction, n (%)		n = 1467		n = 459		n = 1009	0.27
≤3 cm	440 (30)		148 (32)		292 (29)		
3.1–7.0 cm	504 (64)		160 (35)		345 (34)		
>7 cm	523 (36)		151 (33)		372 (37)		
Preoperative treatment, n (%)		n = 1742		n = 547		n = 1195	0.028
None	191 (11)		62 (11)		129 (11)		
5 × 5 GY	861 (49)		243 (44)		618 (52)		
Chemoradiotherapy	632 (36)		219 (40)		413 (35)		
Other radiotherapy schedule	58 (4)		23 (4)		35 (3)		
Surgical procedure, n (%)		n = 1857		n = 576		n = 1281	<0.0001
Low anterior resection[a]							
With ileostomy	646 (35)		161 (28)		485 (38)		
Without ileostomy	260 (14)		66 (11)		194 (15)		
Abdominoperineal resection[a]	574 (31)		190 (33)		384 (30)		
Hartmann procedure	355 (19)		145 (25)		210 (16)		
Proctocolectomy	22 (1)		14 (2)		8 (1)		
Surgical approach, n (%)		n = 1824		n = 565		n = 1259	0.004
Open	954 (52)		326 (58)		628 (50)		
Laparoscopic	739 (40)		198 (35)		541 (44)		
Converted	121 (7)		41 (7)		80 (6)		
Additional resection for local ingrowth, n (%)	127 (7)	n = 1823	68 (12)	n = 562	59 (5)	n = 1261	<0.0001
Surgical timing, n (%)		n = 1814		n = 566		n = 1248	0.030
Elective	1786 (98)		552 (98)		1234 (99)		
Urgent	28 (1)		14 (2)		14 (1)		

Hb = hemoglobin; TEM = transanal endoscopic microsurgery.
[a]BMI ≥25 kg/m², including patient who underwent TEM followed by completion surgery.

cer.[5,6] The efficacy of preoperative treatment of anemia by means of red blood cell transfusion, erythropoiesis-stimulating agents, or iron remains a matter of debate, because the short-term advantages have not yet been shown convincingly to outweigh the potential risks (ie, oncological) and associated costs.[7,8] Furthermore, many regard anemia more as a symptom of significant tumor load and the overall weak condition of the patient, rather than a causative factor for poor outcome.[5,9]

The current literature on the relation between preoperative anemia and the long-term postoperative outcome after rectal cancer surgery is restricted to relatively small studies with several methodological shortcomings. First, they use different survival parameters (disease-free, cancer-specific, overall). Second, they often base their conclusions on univariate analyses. Finally, they provide limited information on potential confounders for the relation between anemia and outcome. Most studies were conducted before the era of laparoscopic surgery and before the implementation of programs on enhanced recovery after surgery. A recent systematic review with meta-analysis included only 2 studies on the independent association between anemia and overall survival after rectal cancer surgery.[7,10,11] Van Halteren et al[10] included 144 patients between 1995 and 1999 among whom 30% were treated with adjuvant radiotherapy, and Lee et al[11] included 247 patients between 2002 and 2007 who had locally advanced rectal cancer and routine preoperative chemoradiotherapy, illustrating the selected populations with historical changes in treatment approach.

Therefore, the aim of this study was to analyze the association between preoperative anemia and postoperative complications, local and distant recurrence rates, and overall survival in a large multicenter follow-up study of rectal cancer surgery in The Netherlands.

METHODS

Study Design and Patient Population

The Dutch Snapshot Research Group (DSRG) performed a retrospective study in 71 Dutch hospitals, including all patients undergoing surgery for rectal cancer in 2011. The methods of this research project were described in more detail in the first article of the DSRG.[12] The foundation of the snapshot database was the obligatory national registry of the Dutch Surgical Colorectal Audit, which contains baseline characteristics and short-term postoperative outcomes (30 days) following a surgical resection.[13] These data were enhanced with diagnostic and treatment details and 3-year surgical and oncological outcomes through a Web-based application by collaborators of the DSRG. Data entry was performed by 1 or 2 residents or research nurses. In case of questions, the supervision of a consultant surgeon was available at each center. Patients with a registered pretreatment Hb level were eligible for this specific study.

Definitions and Outcome Parameters

Patients were considered anemic according to the World Health Organization criteria of anemia, defined as a Hb level <7.5 mmol/L in women and <8.0 mmol/L in men.[14] The Hb level should have been measured within 4 weeks before primary resection or start of neoadjuvant therapy.

Short-term outcome parameters were any postoperative complication or mortality within 30 days postoperatively, and pelvic infectious complications defined as anastomotic leakage and presacral abscess. Long-term outcomes were chronic sinus diagnosed at any time during the 3-year follow-up, 3-year local and distant recurrence rates, and 3-year overall survival.

TABLE 2. Surgical and oncological outcomes

Variable	Anemic patients (Men <8.0 mmol/L, women <7.5 mmol/L) n = 576		Nonanemic patients (Men ≥8.0 mmol/L), women ≥7.5 mmol/L) n = 1281		p value
Surgical, n (%)					
Overall complications <30 days	244 (43)	n = 563	436 (35)	n = 1240	0.004
Surgical septic complications[a]	91 (17)	n = 533	181 (15)	n = 1230	0.21
Cardiac complications	29 (13)	n = 230	35 (8)	n = 413	0.093
Pulmonic complications	47 (20)	n = 232	62 (15)	n = 413	0.088
Received blood transfusion during stay, n (%)	154 (28)	n = 544	110 (9)	n = 1189	<0.0001
Mortality within 30 days, n (%)	29 (5)	n = 563	21 (2)	n = 1239	<0.0001
Radical resection (R0), n (%)	534 (96)	n = 559	1176 (95)	n = 1231	0.99
Oncological,[b] HR (95% CI)					
3-year local recurrence rate	1.6 (1.1–2.4)	n = 567	0.6 (0.4–0.9)	n = 1269	0.026
3-year distant recurrence rate	1.2 (1.0–1.5)	n = 567	0.8 (0.7–1.0)	n = 1269	0.061
3-year overall survival	2.1 (1.7–2.5)	n = 568	0.5 (0.4–0.6)	n = 1272	<0.0001

[a]Anastomotic leakage, presacral abscess, abscess rectal stump, chronic sinus.
[b]Assessed by Cox regression.

Baseline characteristics such as age, sex, BMI, ASA classification,[15] comorbidity (overall, cardiac, diabetes mellitus, pulmonary), TNM stage according to the American Joint Committee on Cancer,[16] and neoadjuvant and adjuvant therapy were recorded, besides type, approach, and urgency of surgery.

Statistical Analysis

All analyses were performed using SPSS (version 20.0; SPSS Inc, Chicago, IL). For continuous data, normality was assessed visually. Normally distributed variables were described with mean and SDs and the independent *t* test was used to compare differences between the anemic and nonanemic patients. Non-normally distributed continuous variables were described with their median and interquartile range, and differences were assessed with the Mann-Whitney *U* test. Dichotomous and categorical outcomes were compared with the χ^2 test. Actuarial survival and recurrence rates were assessed using the Kaplan-Meier method and differences were evaluated using the log-rank test. The independent relation between anemia and the outcomes was assessed by means of a Cox multiple regression model, including potential confounders for this relation. Confounders were defined according to risk factors previously described in literature: age, sex, BMI, ASA score, TNM stage, comorbidity, preoperative treatment, additional resection, surgical approach, and surgical procedure. Potential confounders were defined as those variables that were associated with both anemia and each of the outcomes, expressed with a *p* value <0.1. For each outcome, this could imply that different potential confounders were included in the model. Throughout the analyses, a *p* value of <0.05 was considered statistically significant.

TABLE 3. Logistic regression overall complications within 30 days

Variable	Patients (N = 1857) n (%)	Univariable analysis HR	Univariable 95% CI	Univariable p value	Multivariable analysis HR	Multivariable 95% CI	Multivariable p value
Sex-specific anemia	575 (31)	1.4	1.1–1.7	0.001	1.1	0.9–1.4	0.24
Age, y							
<60	495 (27)	1					
61–70	619 (33)	1.1	0.8–1.4	0.49			
71–80	569 (31)	1.2	0.9–1.6	0.13			
>80	174 (9)	1.6	1.1–2.3	0.009	1.3	0.9–2.0	0.15
Sex, female	690 (37)	0.7	0.6–0.9	0.001	0.7	0.6–0.9	0.001
BMI, obese	997 (54)	1.1	0.9–1.3	0.29			
ASA score							
ASA I–II	1516 (82)	1					
ASA III–IV	299 (16)	2.3	1.8–2.9	<0.0001	1.9	1.4–2.5	<0.0001
TNM stage							
Stage I	496 (27)	1					
Stage II	368 (20)	1.1	0.9–1.5	0.32			
Stage III	30 (2)	1.0	0.8–1.4	0.79			
Stage IV	639 (34)	1.0	0.8–1.3	0.69			
Overall comorbidity	1254 (67)	1.4	1.1–1.7	0.003	1.2	0.9–1.5	0.16
Preoperative treatment							
None	191 (10)	1					
5 × 5 GY	861 (46)	1.1	0.8–1.5	0.41			
Chemoradiotherapy	632 (34)	0.9	0.6–1.9	0.91			
Other radiotherapy schedule	54 (3)	1.0	0.6–1.3	0.63			
Additional resection for local ingrowth	68 (12)	1.3	0.9–2.0	0.088	1.4	0.9–2.1	0.094
Surgical approach							
Open	440 (24)	1					
Laparoscopic	505 (27)	0.7	0.5–0.8	<0.0001	0.7	0.6–0.9	0.001
Converted	523 (28)	0.9	0.6–1.4	0.81			
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1					
Without ileostomy	66 (11)	1.0	0.7–1.3	0.98			
Abdominoperineal resection	190 (33)	0.9	0.7–1.2	0.46			
Hartmann procedure	145 (25)	1.1	0.8–1.4	0.69			
Proctocolectomy	14 (2)	2.3	1.0–5.8	0.053	1.9	0.8–4.7	0.15

RESULTS

Baseline Characteristics

Of the total Snapshot cohort of 2095 patients, 1857 patients were eligible for the present analysis based on known preoperative Hb level. Median completeness of the data at hospital level was 100% (interquartile range, 96.7–100). The mean age was 67 (±11.1) years and 1168 (63%) were men. The mean Hb level in men was 8.4 (±1.1) mmol/L and 7.9 (±0.9) mmol/L in women. Based on the sex-specific cutoff, 575 (31%) patients were anemic.

The baseline characteristics of the total cohort, as well as the anemic and nonanemic groups, are displayed in Table 1. Anemic patients were older (mean age 70 vs 65 years, $p < 0.0001$), were significantly more often ASA III to IV (29% vs 11%, $p < 0.0001$), were less frequently overweight (48% vs 58%, $p < 0.0001$), had more overall comorbidity (78% vs 65%, $p < 0.0001$), had more cardiac comorbidity (44% vs 27%, $p < 0.0001$), and had diabetes mellitus more often (25% vs 16%, $p < 0.0001$).

Treatment Characteristics

Preoperative therapy differed significantly, with anemic patients receiving chemoradiotherapy more often (40% vs 35%) and short-course radiotherapy less often (44% vs 52%) ($p = 0.028$). The surgical procedure also differed significantly between the 2 groups. Anemic patients more often underwent a Hartmann procedure (25% vs 16%, $p < 0.0001$), and the surgical approach was more often open (58% vs 50%, $p = 0.004$). These results are summarized in Table 1.

Short-term Outcome

Short-term outcomes for both groups are shown in Table 2. Patients with anemia experienced significantly more overall complications (43% vs 35%, $p = 0.004$). Pelvic in-

TABLE 4. Logistic regression postoperative mortality within 30 days

Variable	Patients (N = 1857) n (%)	Univariable analysis HR	Univariable analysis 95% CI	Univariable analysis p value	Multivariable analysis HR	Multivariable analysis 95%CI	Multivariable analysis p value
Sex-specific anemia	575 (31)	3.1	1.8–5.6	<0.0001	1.4	0.7–2.8	0.29
Age, y							
<60	495 (27)	1					
61–70	619 (33)	3.6	0.8–16.8	0.10			
71–80	569 (31)	12.3	2.9–51.9	0.001	13.2	1.7–101.2	0.013
>80	174 (9)	18.3	4.1–82.9	<0.0001	11.1	1.3–97.9	0.030
Sex, female	1168 (63)	0.4	0.2–0.8	0.008	0.3	0.1–0.8	0.010
BMI, obese	997 (54)	0.9	0.5–1.5	0.63			
ASA score							
ASA I–II	1516 (82)	1					
ASA III–IV	299 (16)	5.4	3.1–9.6	<0.0001	2.2	1.1–4.5	0.029
TNM stage							
Stage I	496 (27)	1					
Stage II	368 (20)	1.2	0.6–2.6	0.62			
Stage III	30 (2)	1.9	0.9–4.3	0.098	1.5	0.6–3.8	0.37
Stage IV	639 (34)	0.9	0.4–2.1	0.88			
Overall comorbidity	1254 (67)	5.3	1.9–14.8	0.001	2.9	0.8–9.9	0.091
Preoperative treatment							
None	191 (10)	1					
5×5 GY	861 (46)	0.5	0.2–1.0	0.07	0.8	0.3–1.9	0.62
Chemoradiotherapy	632 (34)	0.2	0.1–0.6	0.001	0.4	0.1–1.4	0.16
Other radiotherapy schedule	54 (3)	0.3	0.0–2.2	0.22			
Additional resection for local ingrowth	68 (12)	0.9	0.3–2.9	0.85			
Surgical approach							
Open	440 (24)	1					
Laparoscopic	505 (27)	0.7	0.4–1.4	0.35			
Converted	523 (28)	1.1	0.4–3.1	0.89			
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1					
Without ileostomy	66 (11)	2.2	0.9–5.6	0.080			
Abdominoperineal resection	190 (33)	1.8	0.8–4.0	0.15			
Hartmann procedure	145 (25)	2.3	1.0–5.3	0.060	1.0	0.4–2.6	0.97
Proctocolectomy	14 (2)	9.7	2.5–38.2	0.001	6.0	1.2–28.6	0.026

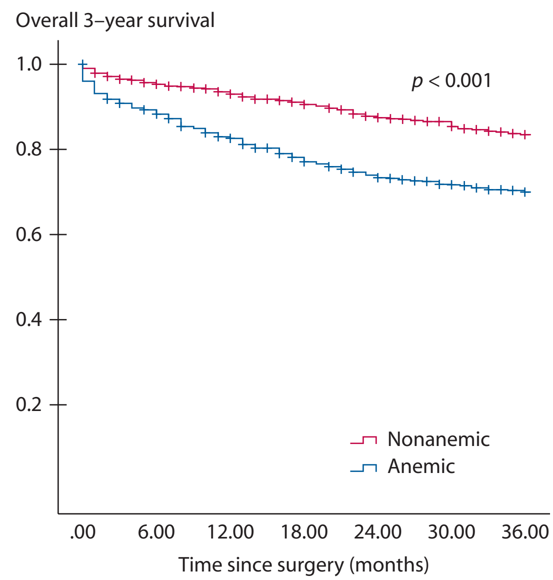
fectious complications consisting of anastomotic leakage, presacral abscess, abscess on top of the rectal stump, and chronic sinus formation did not differ significantly (17% vs 15%, $p = 0.21$). Age, sex, ASA score, comorbidity, additional resection, surgical approach, and type of procedure were associated with preoperative anemia and pelvic septic outcomes. In the multivariable analysis, preoperative anemia was not independently associated with postoperative complications (HR, 1.1; 95% CI, 0.9–1.4; $p = 0.24$; Table 3).

A higher mortality rate within 30 days was observed in anemic patients (5% vs 2%, $p < 0.0001$). After correction for age, sex, ASA score, TNM stage, comorbidity, preoperative radiotherapy, and surgical procedure, preoperative anemia was not independently associated with 30-day mortality (HR, 1.4; 95% CI, 0.7–2.8; $p = 0.29$; Table 4).

Long-term Outcomes

On the long term, anemic patients had significantly lower overall 3-year survival rates (71% vs 84%, $p < 0.0001$; Fig. 1). After correction for age, ASA score, TNM stage, radical resection, comorbidity, preoperative radiotherapy, blood transfusion during hospital stay, surgical approach, and surgical procedure, anemia was independently associated with 3-year overall survival (HR, 1.4; 95% CI, 1.0–1.8; $p = 0.008$). Preoperative anemia was associated with 3-year local recurrence rate (HR, 1.6; 95% CI, 1.1–2.4; $p = 0.026$) but not with distant recurrence rate (HR, 1.2; 95% CI, 1.0–1.5; $p = 0.054$).

Results are visualized in Tables 2 and 5.



Numbers at risk

Anemic	567	498	460	417	383	353	318
Nonanemic	1271	1206	1158	1102	1045	1004	909

FIGURE 1. Kaplan-Meier analysis of 3-year overall survival.

DISCUSSION

The results of this study illustrate that preoperative anemia was not independently associated with postoperative complications in patients undergoing surgery for rectal cancer. However, preoperative anemia still appeared to be independently associated with lower 3-year overall survival, although with a HR of 1.4. The clinical relevance of anemia as a solitary factor has become limited but could still be considered as one of the warning signs for an overall frail state of patients with rectal cancer.

This study investigating preoperative Hb level in patients with rectal cancer clearly supports the existing evidence of anemia being a perilous sign for poor overall condition.[2,3,7] Patients with preoperative anemia were older, had higher ASA scores, and had comorbidities more often.

However, at the heart of the scientific debate concerning anemia lies the question of whether it is a confounding symptom reflecting an overall poor physical state and progressed oncological disease, or whether anemia itself could be a causative factor. In this study, anemia was independently associated with lower 3-year overall survival rate, although a hazard ratio of 1.4 has limited clinical relevance. These results provide 3 key observations offering an indication for further research at the level of pathophysiology, medical treatment, and a holistic approach to clinical practice.

First, from the perspective of pathophysiology, these results are limited in providing more in-depth information about the origin of the anemia and its treatment. A previous study by Wilson et al[7] illustrated that anemia can be caused by intestinal blood loss and iron deficiency. The latter can be subdivided in absolute (decreased nutritional intake) and functional (decreased uptake from duodenum and system inflammation causing storage of iron in enterocytes) iron deficiency.[17] The cause of anemia determines the optimal treatment, but this might be difficult to determine in the individual patient and might even be multifactorial. Furthermore, Hb levels are not static and require follow-up in time. The database that was used only provided a single preoperative Hb value, which impedes the possibility to differentiate between patients with acute or chronic anemia. Similarly, there was no attributive information on the Hb values after neoadjuvant therapy. This is hard to retrieve from retrospective studies, because relevant data are often not well registered, indicating the need for better prospective data.

It is possible that a percentage of these patients received iron (oral or intravenous), erythropoiesis stimulants, or a blood transfusion preoperatively, which may have influenced the results. Although anemia is a risk factor in itself, several studies have illustrated that both iron, erythropoiesis stimulants, and blood transfusion also have

TABLE 5. Cox Regression 3-year overall survival

	Patients	Univariable analysis			Multivariable analysis		
Variable	n (%)	HR	95% CI	p value	HR	95% CI	p value
Sex-specific anemia	575 (31)	2.1	1.7–0.5	<0.0001	1.4	1.1–1.8	0.008
Age, y							
<60	495 (27)	1.0					
61–70	619 (33)	1.1	0.8–1.5	0.67			
71–80	569 (31)	1.9	1.5–2.6	<0.0001	1.4	1.0–2.0	0.039
>80	174 (9)	3.6	2.5–5.0	<0.0001	2.0	1.3–3.2	0.001
Sex, female	690 (37)	0.8	0.7–1.1	0.14			
BMI, obese	997 (54)	0.9	0.7–1.1	0.31			
ASA score							
ASA I–II	1516 (82)	1.0					
ASA III–IV	299 (16)	2.8	2.3–3.6	<0.0001	2.6	1.9–3.6	<0.0001
TNM stage							
Stage I	496 (27)	1.0					
Stage II	368 (20)	2.0	1.4–2.7	<0.0001	1.7	1.2–2.5	0.002
Stage III	30 (2)	2.9	2.0–4.0	<0.0001	2.9	2.0–4.2	<0.0001
Stage IV	639 (34)	2.7	2.0–3.6	<0.0001	2.6	1.9–3.6	<0.0001
Radical resection							
R0	1710 (96)	1.0					
R 1–2	80 (4)	4.1	3.0–5.6	<0.0001	2.4	1.7–3.5	<0.0001
Comorbidity overall	1254 (67)	1.8	1.4–2.3	<0.0001	1.1	0.8–1.5	0.49
Preoperative treatment							
None	191 (10)	1.0					
5 × 5 GY	861 (46)	0.5	0.4–0.7	<0.0001	0.7	0.5–1.1	0.15
Chemoradiotherapy	632 (34)	0.9	0.5–1.6	0.84			
Other radiotherapy schedule	54 (3)	0.6	0.4–0.9	0.003	2.6	1.9–3.6	0.95
Septic complications	69 (12)	1.2	0.9–1.5	0.31			
Blood transfusion during stay	264 (15)	3.1	2.5–4.0	<0.0001	1.7	1.3–2.2	<0.0001
Surgical approach							
Open	505 (27)	1.0			1.0		
Laparoscopic	440 (24)	0.7	0.6–0.9	0.004	0.9	0.7–1.2	0.55
Converted	523 (28)	1.3	0.9–1.9	0.17			
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1.0					
Without ileostomy	66 (11)	1.1	0.7–1.7	0.60			
Abdominoperineal resection	190 (33)	2.1	1.6–2.7	<0.0001	1.7	1.3–2.4	0.001
Hartmann procedure	145 (25)	2.8	2.1–3.8	<0.0001	1.5	1.1–2.1	0.018
Proctocolectomy	14 (2)	5.4	2.9–10.1	<0.0001	2.4	1.1–5.2	0.021

potential harmful effects, both in the short term (wound healing) and on oncologic outcomes (recurrence) in the long term.[18–20]

Second, from a medical treatment perspective, it has been concluded that not treating patients with anemia should be considered to be inferior.[21] However, current evidence is still not conclusive about the real impact of preoperative treatment of anemia on postoperative and long-term outcome in rectal cancer, as well as on the optimal type of treatment. Further prospective randomized research is needed to investigate the effect of anemia, in particular, of iron supplementation in patients who have rectal cancer with preoperative iron deficiency anemia to investigate its effects on both postoperative outcomes and survival.[22]

Last, concerning a holistic approach to clinical practice, preoperative anemia should not be regarded as a solitary risk factor. Because it is representative of a multifactorial deteriorated physical state, preoperative anemia should be considered as a warning sign, indicating a patient group that might benefit from some type of prehabilitation.[2] Especially in the perioperative phase, in which the body is put at significant stress levels, the effects of anemia put the patient at increased risk for complications. Hemoglobin plays a key role in the transport of oxygen toward tissues.[23] Impaired oxygen supply leads to decreased wound healing, muscle performance, and overall fatigue, which are detrimental, especially for oncological patients undergoing surgery.[3,24,25] More specifically, iron serves both as a building block for Hb and plays an important role in oxidative metabolism of muscle performance.[23] Consequently, iron supplementation can play a crucial role in a prehabilitation program (consisting of exercise, nutritional support, and psychological enhancement),[26–28] because it will potentially affect cardiorespiratory and muscle strength endurance and overall fatigue.[29,30] Furthermore, iron supplementation could potentially be a quick win if compared with the challenges that might be faced when implementing preoperative interventions such as physical training and nutritional support (eg, compliance, logistical issues, costs).[31]

Although this snapshot study was an elegant way to establish a quick overview with a large number of patients, representing the current state of this specific clinical field, it is important to mention several limitations of this study. Because of retrospective data collection, relevant data were missing to some extent. Measuring preoperative Hb levels was also not part of a standardized protocol but measured as part of routine daily practice. This collaborative research was not specifically designed to look at preoperative anemia, for which reason we were not informed about preoperative treatment of anemia and changes in Hb level during the whole treatment period, including neoadjuvant therapy. Unfortunately, we are not able to retrieve additional data from the participating centers, because the data set was anonymized after data collection was completed in 2015. Despite these shortcomings, this study adds substantially to the available literature on this topic, because of being the largest cohort until now and the representativeness for current practice related to recently collected data. The design results in a similar follow-up duration for included patients, without historical changes as observed in longitudinal cohort studies. Furthermore, this study has a high external validity due to its multicenter design and unselected patient population.

CONCLUSION

In conclusion, this multicenter cohort study including 1857 patients undergoing surgery for rectal cancer illustrates lower overall 3-year survival in patients with preoperative anemia after correction for confounding factors. However, the effect of anemia as a solitary factor seems to be of relatively limited clinical relevance. Assessment and adjustment of preoperative anemia and its cause could serve both as a warning sign, and as a potential element of a wider prehabilitation program for patients with rectal cancer undergoing surgery.

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