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Original Article

Impact of Hemoglobin Levels on Treatment Response and Survival in Locally Advanced Rectal Cancer: A Retrospective Cohort Study

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Abstract

Introduction: This study aimed to explore the relationship between blood hemoglobin (Hb) levels and clinical factors in patients with locally advanced rectal cancer (LARC). The primary objective was to comprehensively evaluate how Hb levels influence both the response to neoadjuvant chemoradiotherapy (NACRT) and the overall survival (OS) in this patient cohort.

Methods: In this study, we examined Hb levels in patients with LARC before treatment. Survival rates were evaluated using Kaplan-Meier and life-table methods. Additionally, a multivariate analysis was conducted using Cox regression to determine hazard ratios associated with different predictors of survival. A p-value of less than 0.05 was considered statistically significant.

Results: In our study of 343 patients with LARC, most were male (59.2%) with a mean age of 58.07 years. The average Hb level was 12.70 ± 1.76 mg/dL, and 43.4% of patients had anemia. Notably, lower pre-treatment Hb levels were associated with longer intraluminal tumor . Anemic patients also experienced more obstructive symptoms (68.2%). Survival analysis revealed that patients with normal Hb levels who responded well to treatment had significantly longer overall survival. Furthermore, multivariable analysis confirmed that moderate to severe anemia was an independent predictor of lower survival rates in LARC patients.

Conclusion: This study highlights the significant impact of severe anemia on reducing survival rates in patients with advanced rectal cancer. Conversely, a favorable response to treatment improves the chances of survival. However, further research with larger patient cohorts is needed to validate these findings.

Introduction

Colorectal cancers (CRC) rank as the second leading cause of global cancer-related mortality,[1] with rectal cancer (RC) accounting for approximately 30% of all colorectal malignancies. [2]

A frequently observed symptom in cancer, cancer-related anemia, affects over 30% of cancer patients due to the presence of a chronic inflammatory state at the time of diagnosis. [3]

Anemia is prevalent in an estimated 43-48% of CRC patients,[4-7] with the majority presenting with anemia upon diagnosis. [8] Blood loss in the intestine is one of the most common causes of anemia in CRC patients, resulting in iron deficiency. [9] This deficiency amplifies the risk of poor prognosis, potentially exacerbated by tumor hypoxia. [10] Remarkably, a reduction in hemoglobin (Hb) levels within the normal range can be observed up to four years prior to a CRC diagnosis. [11,12] Importantly, the influence of anemia correction therapies on cancer outcomes remains a subject of debate. [13-18]

The intricate relationship between anemia and the pathological response to chemoradiotherapy (CRT) in various cancers, including CRC, has been a subject of investigation. This connection is multifaceted, involving factors such as tumor oxygenation, treatment delivery, and immune function. Anemia may contribute to tumor hypoxia, impede effective drug delivery to the tumor site, and compromise immune responses, potentially influencing treatment outcomes. [4-6] Anemia reduces oxygen supply to cancer cells. Since radiotherapy depends on oxygen, hypoxic tumors become more resistant to treatment. [4] Under low-oxygen conditions, HIF-1α is activated, stimulating new blood vessel formation (angiogenesis), which facilitates tumor invasion and metastasis.[19] Poor oxygenation also decreases blood flow within the tumor, hindering the effective delivery of chemotherapy drugs and increasing drug resistance in cancer cells.[20] Furthermore, anemia weakens CD8 + T cells and natural killer cells while promoting immune-suppressive macrophages, thereby impairing the body's

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Study Highlights

- Pretreatment anemia in rectal cancer serves as a straightforward and dependable predictor of survival following therapeutic interventions.
- Pretreatment anemia in rectal cancer can exacerbate tumor growth within the rectal lumen, potentially hindering its extension beyond the muscularis mucosae layer into the submucosa or muscularis propria.
- Anemia does not affect how patients respond to neoadjuvant chemoradiotherapy, but the treatment response strongly influences overall survival, regardless of anemia status.

ability to combat tumors. [21] Oxygen deficiency in anemic patients slows wound healing, heightens infection risk, and increases the likelihood of postoperative complications. [22]

The treatment strategies for RC have undergone adaptation to address the higher local recurrence rates observed in earlier treatment paradigms. This adaptation reflects the principles of personalized medicine. [7]

The landscape of treatment approaches for locally advanced rectal cancer (LARC) is dynamically evolving. Within the context of caring for patients with LARC, several pivotal decision-making junctures come into play. These include pre-treatment assessments, evaluations following neoadjuvant therapy, and post-surgery follow-up procedures. [8]

Studies indicate that changes in Hb levels can have significant implications for patients with RC. Therefore, this study was conducted to examine the relationship between blood Hb levels and various clinical and pathological factors in patients with LARC. Our primary focus was to investigate how Hb levels influence the response to neoadjuvant chemoradiotherapy (NACRT) and the overall survival (OS) of LARC patients. The findings of this study are expected to provide insights into the current status of patients in the studied region and contribute to optimizing Hb level management as part of a comprehensive cancer treatment approach. In the future, these findings may also support larger-scale studies aimed at developing new therapeutic strategies and improving the quality of life for cancer patients.

Methods

Patients and Study Design

We conducted a retrospective review of the medical records of 343 consecutive LARC patients at the Radiation and Medical Oncology Center of Tabriz University Hospital from February 2007 to March 2017.

This study received approval from the Ethics Committee of Tabriz University of Medical Sciences (ID. 1403/412), Iran.

All patients received radiotherapy once a day, with doses of either 50.4 Gy in 28 fractions or 45 Gy in 25 fractions. Patients requiring neoadjuvant radiotherapy underwent surgery 4-6 weeks after completing radiotherapy. For adjuvant radiotherapy, patients received treatment 6-8 weeks after surgery. [9]

Pretreatment Hb levels were retrieved from medical records, recorded before the initiation of NACRT or before surgery in patients undergoing adjuvant CRT. These data were obtained alongside clinical and tumor characteristics.

Inclusion and Exclusion Criteria

The inclusion criteria encompassed histopathologically confirmed rectal cancer, a complete blood count at the time of diagnosis (baseline), and comprehensive follow-up data. Exclusion criteria involved incomplete data, synchronous malignancies, and clinical stage IV.

Definition of Parameters

Anemia: Defined as per the World Health Organization (WHO) standards, characterized by Hb levels below 13 g/dL for men and below 12 g/dL for women. Mild anemia typically presents with Hb levels ranging from 11 to 12.9 g/dL in men and 11 to 11.9 g/dL in women. Moderate to severe anemia is classified as Hb levels below 10.9 g/dL.

Mean Corpuscular Volume (MCV): Anemia categorized based on MCV values of erythrocytes as microcytic (MCV < 80 fL), normocytic (MCV 80–100 fL), or macrocytic (MCV > 100 fL).[10]

Red Cell Distribution Width (RDW): RDW classification is based on the RDW value, with normal ranging from 11.6% to 14.5%, low being below 11.6%, and high being above 14.5%.

Obstruction: Rectal obstruction initially suspected through patient history and physical examination, confirmed by abdominal CT with oral contrast. [11] Partial obstruction was defined based on colonoscopy reports noting difficulty in passing the scope through the mass.

Cancer Stage: Clinical stage was defined according to the 8th edition of the AJCC (American Joint Committee on Cancer) criteria (cTNM). [12]

Tumor Regression Grade (TRG): Categorized into four groups (TRG0-3) following the Ryan classification. [13]

Tumor Location: Determined based on proximity to the anal verge, with the lower rectum < 5 cm, middle rectum 5-10 cm, and upper rectum 10-15 cm. [14]

Statistical Analysis

We conducted a comprehensive statistical analysis encompassing various aspects:

Descriptive Statistics: Fundamental demographic characteristics, patient data, and Hb levels were presented with mean values accompanied by standard deviations (SD). Categorical and ordinal data were reported as ratios. It is important to note that Hb values for RC patients typically refer to the most recent test conducted before diagnosis.

Analysis of variables: Differences in qualitative variables were assessed using the chi-square test or Fisher exact test, while quantitative data employed methods such as one-way ANOVA or the Kruskal-Wallis test based on the

distribution of the data. Survival outcomes were analyzed using the Kaplan-Meier and life-table methods, and group comparisons were performed using the log-rank test. Multiple variables were assessed using Cox proportional hazard regression to determine their influence on survival. Hazard ratios and confidence intervals were calculated to evaluate the strength of these influences. Model assumptions, including the proportional hazards assumption, were not formally tested. The statistical analyses were performed using IBM SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY). A p-value less than 0.05 was considered statistically significant, indicating meaningful associations or differences in the data.

Results

This study comprised 343 patients diagnosed with RC, consisting of 203 (59.2%) males and 140 females, with an average age at diagnosis of 58.07 (±14.06) years. Among these patients, 184 (53.6%) received NACRT, while 102 (29.7%) received adjuvant chemoradiotherapy (ACRT). Seven patients underwent surgery only, and 50 patients received CRT only (non-cooperation). A comprehensive overview of patients' characteristics and group comparisons is presented in Table 1.

The mean Hb level was 12.70 (±1.76) g/dL. More than 50% of patients had normal Hb levels, while 149 patients presented with pretreatment anemia, predominantly normocytic followed by microcytic ($P<0.001$). Males exhibited a higher average Hb level compared to females (13.19 vs. 11.98 g/dL, $P<0.001$). The most common clinical symptom was the presence of blood in the stool (79.6%). Over 60% of patients had red blood cells of similar size (normal RDW). Tumors were predominantly located in the middle rectum, at an average distance of 8 cm (range, 1–15 cm) from the anal verge (65.12%). Of the patients, 173 (50.4%) had nodal involvement, and 181 (52.8%) had a clinical stage of T3N0 or higher (regional).

Association Analysis: No significant associations were observed between Hb levels and age, onset symptoms, histology grade, clinical tumor stage, NACRT, or recurrence (Table 1). Regarding pathologic response scoring, data were available for 92 of the 184 (50%) patients were available. Among them, 40 (21.7%) patients achieved TRG 0-1 (7 TRG 0), while 52 (28.3%) achieved TRG 2-3 (39 TRG 3). There was no difference in TRG between anemic and non-anemic patients ($P=0.96$). Hb levels demonstrated a direct relationship with MCV but an inverse relationship with RDW value ($P<0.001$). The median intraluminal tumor length was 4 cm, with most RC tumor lengths being ≤4 cm. A significant inverse relationship existed between pretreatment Hb levels and intraluminal tumor length ($P<0.001$). Obstructive symptoms were more common in anemic patients compared to non-anemic patients (68.2% vs. 31.8%, $P=0.03$). A detailed analysis of survival and comparisons based on Hb status in RC patients is presented in Table 2. The median survival time for all patients was 72.03 months (range, 48.94–95.12 months). Out of the patients, 130 died during the follow-up period. The 1, 3, 5, and 10-year OS rates were 89%, 56%, 56%, and 43%, respectively. Patients under 50 years old exhibited better survival rates compared to patients aged 50 or older ($P<0.001$). Patients experiencing abdominal pain had worse survival rates compared to those without abdominal pain ($P<0.001$). Kaplan-Meier survival analysis (Figure 1) revealed that patients with normal Hb levels had significantly longer lifespans than anemic cancer patients ($P<0.001$), while no statistically significant relationship was observed between MCV, RDW, and survival ($P>0.05$).

The comparison of survival rates based on Hb status indicated that anemia increased the risk of death, holding significance in the presence of all variables ($P<0.05$) (Table 2). For example, elderly patients (HR = 1.43) suffering from anemia faced a substantially higher risk of death compared to their counterparts (Figure 2).

Tumor size, obstruction, T stage, lymph node involvement, clinical cancer stage, NACRT, recurrence, and onset symptoms were all significant predictors of OS ($P<0.05$) (Table 2).

The study also evaluated the tumor's pathologic response to NACRT by dichotomizing patients based on their TRG (good = TRG0 and TRG1; poor = TRG2 and TRG3). The 5-year OS rates were 93% and 52% in patients with good and poor responses, respectively ($P=0.01$, Figure 3).

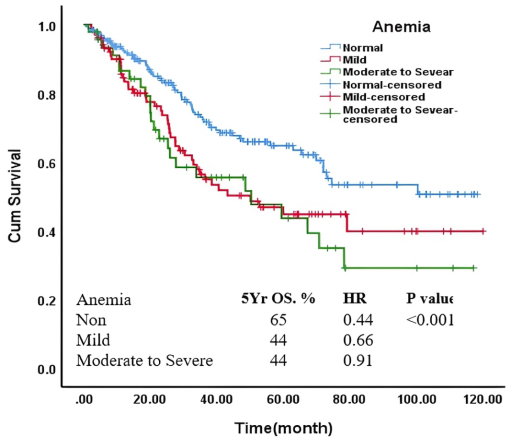

Figure 1. Survival analysis of patients stratified by hemoglobin levels using Kaplan–Meier method and Log-Rank test

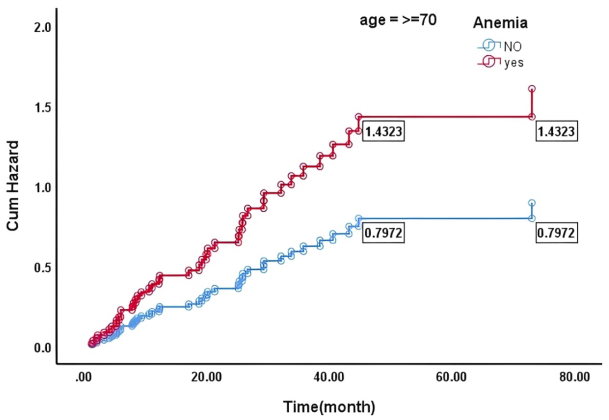

Figure 2. HR analysis by anemia status in patients Aged ≥ 70 using Kaplan–Meier and Log-Rank test

Table 1. Patients' characteristics and comparing non anemic vs anemia rectal cancer patients.

Variables		N	Non Anemic	Anemic	*P* value
			N (%)	N (%)	
Age	<50	101	57(29.38)	44(29.53)	0.98
	50-69	162	92(47.42)	70(46.98)	
	≥70	80	45(23.20)	35(23.49)	
Sex	Female	140	77(39.69)	63(42.28)	0.66
	Male	203	117(60.31)	86(57.72)	
MCV	<80 fL	56	10(5.43)	46(35.38)	<0.001
	80-100 fL	255	172(93.48)	83(63.85)	
	>100 fL	3	2(1.09)	1(0.77)	
RDW	Normal	120	86(64.66)	34(35.05)	<0.001
	Low	5	1(0.75)	4(4.12)	
	High	105	46(34.59)	59(60.82)	
location	Upper	40	22(14.57)	18(16.82)	0.54
	Middle	168	101(66.89)	67(62.62)	
	Lower	50	28(18.54)	22(20.56)	
Size	>4(cm)	88	42 (41.18)	46 (60.53)	0.006
	≤4(cm)	90	60 (58.82)	30 (39.47)	
Obstruction	No	241	146(75.65)	95(64.63)	0.034
	Complete	22	7(3.63)	15 (10.20)	
	Partial	76	39(20.21)	37(25.17)	
T Stage	≤T2	107	62(31.96)	45(30.20)	0.19
	T3	142	84(43.30)	58(38.93)	
	T4	25	9(4.64)	16(10.74)	
N Stage	N0	170	97(50)	73(48.99)	0.47
	N1	173	97(50)	76(51.01)	
TNM Stage	Localized	124	74(38.14)	50(33.56)	0.65
	Regional	181	100(51.55)	81(54.36)	
Grade	Well. diff	237	139(82.28)	98(78.40)	0.14
	Moderate. diff	46	23(14.11)	23(18.40)	
	Poor. diff	5	1(0.61)	4(3.20)	
Neoadjuvant	Yes	184	111(57.22)	73(48.99)	0.08
	NO	159	83(42.78)	76(51.01)	
TRG	TRG0,1	40	26(43.3)	14(43.8)	0.96
	TRG2,3	52	34(56.7)	18(56.2)	
Adjuvant	Yes	102	60(30.93)	42(28.19)	0.33
	NO	241	134(69.07)	107(71.81)	
Recurrence	NO	244	141(73.82)	103(71.53)	0.71
	Yes	91	50(26.18)	41(28.47)	
Onset symptoms	Blood in the stool	273	160(82.47)	113(75.84)	0.43
	Altered bowel habit	34	17(8.76)	17(11.41)	
	Abdominal pain	21	9(4.64)	12(8.05)	

Abbreviations: MCV, Mean Corpuscular Volume; RDW, Red Cell Distribution Width; TNM, tumor, lymph nodes and metastasis; TRG, Tumor Regression Grade

Multivariable analysis confirmed that age≥70 at diagnosis, abdominal pain, moderate to severe anemia, complete obstruction, clinical T4 stage, and recurrence were independent predictors of RC survival. Conversely, lymph node involvement and regional stage were not predictive (Table 3).

Discussion

Anemia constitutes a significant health challenge, particularly in low- and middle-income countries. [15]

In the context of cancer, it is noteworthy that more than sixty-five percent of cancer patients are susceptible to developing anemia. [16]

The chief driver of anemia in cancer patients lies in the aggressive behavior of cancer cells. [17] These cells not only directly suppress hematopoiesis by infiltrating the bone marrow but also produce cytokines that induce functional

Table 2. Comparison of 5-year overall survival (OS) rate and hazard ratio (HR), between anemic and non-anemic rectal cancer patients.

Variable		Survival. % 1, 3, 5, 10 Yr	*P* value	Non Anemic	Anemic	*P* value
				5Yr OS.% (HR)		
Age	<50	93, 72, 65, 41		67 (0.32)	51(0.58)	0.001
	50-69	94, 70, 59, 51		67(0.40)	55(0.72)	
	≥70	75, 46, 38, 34		59(0.79)	14(1.43)	
Sex	Female	92, 66, 48, 33		62(0.56)	28(0.95)	0.002
	Male	87, 65, 61, 51		61(0.39)	53(0.64)	
MCV	<80 fL	87, 56, 48, -	0.204	27(0.48)	53(0.75)	0.009
	80-100 fL	90, 67, 58, 43		62(0.45)	42(0.79)	
	>100 fL	100, 67, 00, -		-	-	
RDW	Normal	94, 68, 60, 43	0.94	61(0.42)	44(0.72)	0.002
	Low	100, 100, 67, -		100(0.28)	50(0.49)	
	High	86, 64, 62, 55		73(0.34)	54(0.58)	
location	Upper	81, 61, 49, 41	0.58	42(0.56)	41(0.97)	0.001
	Middle	91, 65, 54, 39		63(0.48)	35(0.84)	
	Lower	89, 60, 56, 44		59(0.40)	39(0.70)	
Size	≤4(cm)	98, 79, 71, 50	0.004	75(0.61)	62(1.01)	0.004
	>4(cm)	86, 64, 54, 52		60 (0.46)	49(0.77)	
Obstruction	No	94, 71, 61, 52	<0.001	59(0.41)	40(0.67)	0.005
	Partial	81, 52, 44, -		16 (0.62)	27(1.02)	
	Complete	68, 54, 54, 45		71 (0.44)	23(0.73)	
T Stage	≤T2	98, 70, 58, 48	<0.001	66(0.45)	41(0.72)	0.009
	T3	85, 62, 55, 38		65(0.50)	42(0.80)	
	T4	61, 30, 30, -		60 (NA)	18(NA)	
N Stage	N0	92, 70, 61, 52	<0.001	68(0.39)	47(0.66)	0.002
	N1	86, 61, 50, 32		51(0.55)	35(0.94)	
Grade	Well. diff	91, 67, 61, 45	0.59	65(0.43)	41(0.73)	0.002
	Moderate. diff	88, 64, 57, 30		72(0.38)	37(0.65)	
	Poor. diff	80, 80, 40, 40		NA (0.32)	50(0.56)	
TNM Stage	Localized	92, 69, 58, 49	<0.001	68(0.43)	54(0.74)	0.002
	Regional	85, 58, 48, 31		63 (0.57)	34(0.99)	
Neoadjuvant	Yes	93, 69, 54, 41	0.012[B]	60(0.70)	45(0.42)	0.003
	NO	85, 61, 49, 44		60(0.51)	38(0.82)	
TRG	TRG0, 1	97, 94, 93, 56	0.01	95(0.05)	86(0.15)	0.01
	TRG2, 3	94, 87, 52, 40		48(0.73)	57(0.55)	
Recurrence	NO	88, 71, 64, 54	<0.001	74(0.34)	50(0.53)	0.02
	Yes	94, 51, 17, -		18(0.99)	17(1.52)	
Onset symptoms	Blood in the stool	91, 70, 61, 49	<0.001	65(0.39)	50(0.65)	<0.001
	Altered bowel habit	78, 53, 41, 29		56(0.67)	17(1.11)	
	Abdominal pain	80, 29, 22, 7		18 (1.99)	12(1.99)	

Abbreviations: MCV, Mean Corpuscular Volume; RDW, Red Cell Distribution Width; TNM, tumor, lymph nodes and metastasis; TRG, Tumor Regression Grade

iron deficiency, leading to a decrease in red blood cell production and a shortened lifespan for these cells. [18] Moreover, the infiltration of cancer cells into tumor sites can result in chronic blood loss, further exacerbating the burden of anemia.

Pretreatment anemia stands out as a high-risk factor for adverse outcomes in numerous cancer types. [23-28] It is plausible that increased radiation resistance in tumors may give rise to a more aggressive tumor phenotype by exacerbating tumor hypoxia. [29]

Gastrointestinal tumors, including RC, often exhibit more severe anemia as a paraneoplastic manifestation than other cancer types. [30]

In this research , we directed our attention toward discerning the potential prognostic value of pretreatment anemia specifically in RC patients. Our findings revealed that pretreatment anemia was prevalent in 43.3% of our patients, a higher incidence than previously reported (30%). [31,32]

We discovered a substantial inverse correlation between

Table 3. prognostic factors for Rectal cancer specific survival from 2007 to 2017 (N=343).

Variables		Univariate analysis		Multivariate analysis	
		HR [95% CI]	*P*-Value	HR [95% CI]	*P*-Value
Age,	<50	1 [Reference]	<0.001	1 [Reference]	<0.001
	50-69	0.96 [0.63-1.47]	0.86	1.08 [0.69-1.71]	0.73
	≥70	2.07 [1.33-3.24]	0.001	2.98 [1.84-4.82]	<0.001
Anemia	Non	1 [Reference]	0.008	1 [Reference]	0.01
	Mild	1.65 [1.12-2.42]	0.01	1.58 [1.04-2.41]	0.03
	Mod- Severe	1.85 [1.16-2.98]	0.01	1.91 [1.15-3.17]	0.01
Obstruct	No	1 [Reference]	0.002	1 [Reference]	0.09
	Partial	1.8[0.93-3.32]	0.08	1.13[0.49-2.57]	0.77
	Complete	2.03[1.39-2.95]	0.000	1.53[1.03-2.26]	0.03
Size	≤4(cm)	1 [Reference]	0.004	1 [Reference]	0.11
	>4(cm)	0.64[0.39-1.06]	0.09	0.78[0.45-1.33]	0.36
T Stage	≤T2	1 [Reference]	<0.001	1 [Reference]	0.11
	T3	1.38 [0.91-2.08]	0.13	0.91 [0.53-1.58]	0.75
	T4	3.32 [1.83-6.05]	<0.001	2.43 [0.98-6.04]	0.06
N Stage	N0	1 [Reference]	-	1 [Reference]	-
	N1	1.63 [1.15-2.30]	0.006	0.73 [0.24-2.22]	0.58
TNM Stage	Localized	1 [Reference]	0.001	1 [Reference]	0.16
	Regional	1.59 [1.11-2.30]	0.01	1.92 [0.56-6.67]	0.30
Recurrence	NO	1 [Reference]	<0.001	1 [Reference]	<0.001
	Yes	2.25 [1.56-3.23]	<0.001	2.15[1.46-3.18]	<0.001
Onset symptoms	Blood in the stool	1 [Reference]	<0.001	1 [Reference]	0.007
	Altered bowel habit	1.79 [1.09-2.94]	0.02	1.76 [1.02-3.04]	0.04
	Abdominal pain	2.96 [1.71-5.13]	<0.001	2.63 [1.42-4.87]	0.002

Abbreviations: TNM, tumor, lymph nodes and metastasis

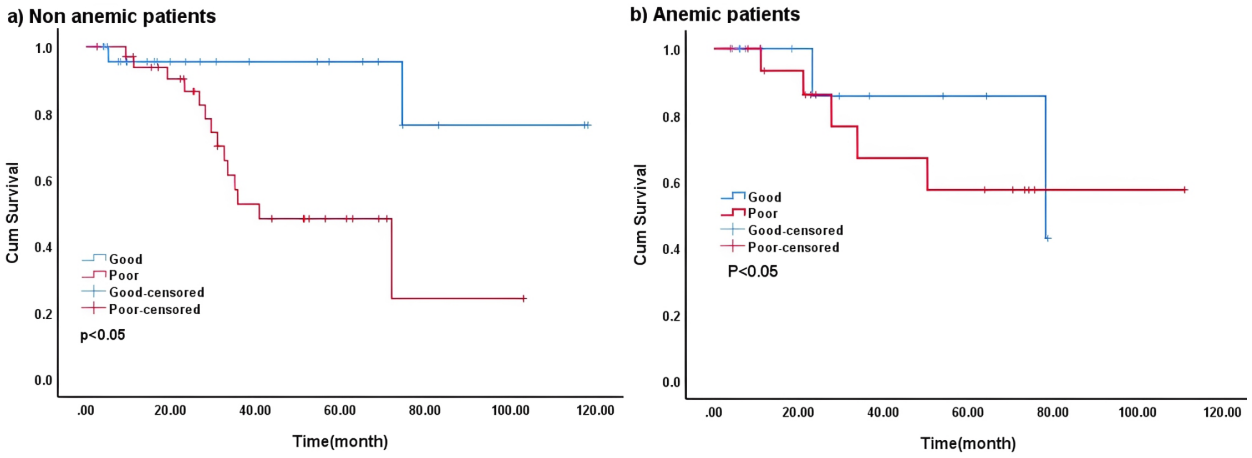

Figure 3. Overall survival curves are shown for categories of (a) Non anemic patients, (b) Anemic patients was dichotomized as good response (Good) or poor response (Poor) using Kaplan–Meier and Log-Rank test

pretreatment Hb levels and intraluminal tumor length, as well as the risk of an obstructing tumor. These factors are intimately linked with poor prognosis. Intriguingly, we found no association between Hb levels and tumor TNM stage. [33-35] This suggests that anemia likely amplifies the intraluminal dimensions of the tumor but is less likely to incite tumor invasion into outermost layers or adjacent tissues and lymphatic spread, characteristic of TNM stages II and III. Therefore, it appears that chronic hypoxia induced by anemia may exacerbate tumor growth within the lumen by slowing cellular differentiation and increasing proliferation in the more superficial areas, potentially preventing its spread beyond the muscular mucosal layer to the submucosa or muscularis propria.

The present study, along with several others on RC, has shown that pretreatment anemia does not have a significant impact on the pathological response to NACRT.[26] The exact reason for this finding remains unclear, but it may be related to the unique biological characteristics of rectal tumors, which are possibly less

affected by hypoxia compared to other tumor types. Additionally, standardized treatment protocols—such as optimized radiation and chemotherapy doses—might help mitigate the negative effects of hypoxia. It is also possible that the degree of hypoxia in these cases was not sufficient to induce treatment resistance.[36,37]

While only a few studies have explored the relationship between Hb levels and survival in RC patients,[2,25,30,38]our research aligns with two other studies indicating that preoperative anemia is a prognostic factor for survival. [25,38] For instance, in a study of 138 patients with RC who underwent NACRT, Tunce et al. observed that non-anemic patients had a significantly better prognosis than anemic ones. [25] Similarly, a recent study involving 96 patients with LARC who underwent preoperative CRT followed by radical surgery identified preoperative Hb level as a prognostic factor for survival.[38] These findings underscore the potential of pretreatment anemia as a straightforward and reliable predictor. However, the precise mechanisms underpinning the association between anemia and poor prognosis remain elusive, with hypotheses pointing towards exacerbated tumor hypoxia and heightened radio resistance of tumor cells. Notably, a similarly sized study in the UK found no association between Hb levels and survival. [30]

NACRT stands as the standard treatment for LARC.[39] Our results emphasize the direct link between pathological response to NACRT and OS rate, a relationship that holds true for both anemic and non-anemic patients. Several studies have reported associations between TRG and OS [40,41], corroborating our findings. However, it is important to note that other studies have yielded conflicting results, with no significant association between TRG and 5-year OS. [39,42] Hence, the clinical significance of pathological response remains a matter of debate.

Our multivariate analysis identified both mild anemia (HR = 1.58, 95% CI = 1.04-2.41; $P = 0.03$) and severe anemia (HR = 1.91, 95% CI = 1.15-3.17; $P = 0.01$) as independent prognostic factors for OS. These findings underscore the potential of pretreatment anemia as a straightforward and reliable predictor of post-therapeutic intervention survival in RC patients.

The difference between univariate and multivariate results may be due to multicollinearity, confounding variables, and limited statistical power. Stronger predictors like age or recurrence may overshadow others, while correlations among variables such as T, N, and TNM can reduce individual significance in multivariate models. This highlights the importance of careful interpretation within statistical and clinical frameworks.

Limitations

The findings of this study should be interpreted in light of several limitations. First, it is a single-center, retrospective study. Furthermore, since we focused on patients with stage I to III RC, our study population does not reflect cases with metastatic disease.

Conclusion

This study has unveiled an intriguing inverse relationship between the severity of anemia and OS rates among RC patients. Furthermore, it has shed light on the noteworthy connection between a positive pathological response to NACRT and enhanced survival outcomes. Notably, our findings suggest that anemia's predominant influence may be confined to tumor size within the luminal space, rather than its propensity for invasion into adjacent tissues. However, it is essential to underscore that these observations warrant validation through larger-scale studies with extended follow-up periods to provide more robust insights into the complex interplay between anemia and RC prognosis.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval

This study was granted approval by the Ethics Committee of Tabriz University of Medical Sciences under reference ID, IR.TBZMED. REC .1403/412.

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