Correlation between Low Iron Status and Clinical Characteristics in Patients with Colorectal Adenocarcinoma: Postprint

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Date: 2025-11-10T00:00:00+00:00

Abstract

Background Colorectal cancer is the second most common malignant tumor worldwide. Studies have shown that iron metabolism is involved in multiple aspects of tumor progression, including tumor cell proliferation and immune microenvironment regulation. In clinical practice, colorectal cancer patients often exhibit abnormal serum iron status, with low serum iron levels being more common. Investigating the correlation between low iron status and colorectal cancer is of great significance for personalized treatment of colorectal cancer.

Objective This study aims to comprehensively and systematically investigate the relationship between internal environment low iron status and various clinical characteristics in patients with colorectal adenocarcinoma.

Methods This study was based on a single-center registered retrospective cohort study. A total of 712 patients who were postoperatively pathologically diagnosed with colorectal adenocarcinoma at Sichuan Cancer Hospital between January 2017 and June 2023 were consecutively enrolled as study subjects. Serum iron, transferrin saturation, and various clinical characteristic indicators were collected. Based on preoperative serum iron expression levels, patients were divided into a low iron status group (low iron group, n=363) and a normal iron status control group (n=349). Propensity score matching (PSM) was used to match patients 1:1 with a caliper set at 0.2, resulting in a final matched sample of 698 cases (349 cases each in the low iron and control groups). Univariate analysis and multivariate Logistic regression analysis were employed to explore the correlation between low iron status and clinical characteristics.

Results Among the 712 patients, 363 (50.98%) were in an internal environment low iron status. Before PSM matching, there were statistically significant differences between the control and low iron groups in American Society of Anesthesiologists classification (ASA), proportion of malignant obstruction, and proportion of anemia (P<0.05). After PSM matching, differences in ASA, proportion of malignant obstruction, and proportion of anemia between the two groups remained statistically significant (P<0.05). After PSM matching, the low iron status group had higher expression levels of white blood cell count (WBC), C-reactive protein (CRP), plateletcrit (PCT), and carcinoembryonic antigen (CEA), and lower levels of lymphocyte count (LY), albumin (ALB), and serum total cholesterol (TC) compared with the control group (P<0.05). There were statistically significant differences between the two groups in tumor location, Union for International Cancer Control (UICC) TNM stage, pathological type, differentiation degree, mismatch repair (MMR) expression status, microsatellite stability status, nerve and vascular invasion, liver and lung metastasis ratios, and tumor length diameter (P<0.05). After controlling for baseline confounding factors using PSM, multivariate Logistic regression analysis was performed with anemia separated as an independent predictor variable. The analysis showed that when anemia was not included, tumor location (rectum, OR=0.410, 95%CI=0.25~0.67, P<0.01), UICC stage (OR=3.50, 95%CI=1.65~7.82, P<0.01), vascular invasion (OR=1.63, 95%CI=1.01~2.63, P=0.04), tumor length diameter (OR=1.16, 95%CI=1.03~1.30, P<0.01), ALB (OR=0.90, 95%CI=0.85~0.95, P<0.01), PCT (OR=1.12, 95%CI=1.08~1.15, P<0.01), and LY (OR=0.51, 95%CI=0.35~0.72, P<0.01) were independent influencing factors for low iron status in colorectal adenocarcinoma patients. Multivariate Logistic regression analysis after including anemia showed that anemia (OR=7.03, 95%CI=4.40~11.25, P<0.01) became an independent influencing factor for low iron status, while tumor location was no longer an independent influencing factor. The remaining factors—tumor length diameter, UICC stage , vascular invasion, and peripheral blood LY, PCT, and ALB—remained independently associated with low iron status in colorectal adenocarcinoma patients (P<0.05).

Conclusion The internal environment iron status in colorectal adenocarcinoma patients is closely associated with tumor invasiveness (stage, neurovascular invasion, tumor length diameter) and inflammatory indicators. Rectal location and higher levels of ALB and LY are protective factors for low iron status in colorectal adenocarcinoma patients, while anemia, UICC stage , vascular invasion, larger tumor length diameter, and PCT are risk factors for low iron status.

Full Text

Correlation Analysis between Low Iron Status and Clinical Characteristics of Colorectal Adenocarcinoma Patients

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Abstract

Background
Colorectal cancer (CRC) is the second most common malignant tumor in terms of incidence worldwide. Studies have shown that iron metabolism is involved in multiple aspects of tumor progression, such as tumor cell proliferation and immune microenvironment regulation. Clinically, most CRC patients are accompanied by abnormal serum iron status, among which low serum iron levels are more common. Exploring the correlation between low iron status and colorectal cancer is of great significance for the individualized treatment of colorectal cancer.

Objective
This study aims to comprehensively and systematically investigate the relationship between the internal environment low iron status and various clinical characteristics in patients with colorectal adenocarcinoma.

Methods
Based on a single-center registered retrospective cohort study, 712 patients who were pathologically diagnosed with colorectal adenocarcinoma after surgery at Sichuan Cancer Hospital from January 2017 to June 2023 were consecutively included as research subjects. Indicators including serum iron, transferrin saturation, and various clinical characteristics were collected. Patients were divided into the low iron status group (low iron group, n=363) and the control group with normal iron status (n=349) according to the preoperative serum iron expression level. Propensity score matching (PSM) was used for 1:1 matching of patients, with a caliper set at 0.2. Finally, 698 matched samples were included (349 cases in both the low iron group and the control group). Univariate analysis and multivariate Logistic regression analysis were used to explore the correlation between low iron status and clinical characteristics.

Results
Among the 712 patients, 363 cases (50.98%) had low iron status in the internal environment. Before PSM matching, there were statistically significant differences between the control group and the low iron group in the American Society of Anesthesiologists (ASA) classification, the proportion of tumor obstruction, and the proportion of anemia ($P<0.05$). After PSM matching, the differences in ASA classification, proportion of tumor obstruction, and proportion of anemia between the two groups remained statistically significant ($P<0.05$). After PSM matching, the expression levels of white blood cell count (WBC), C-reactive protein (CRP), plateletcrit (PCT), and carcinoembryonic antigen (CEA) in the low iron status group were higher than those in the control group, while the levels of lymphocyte count (LY), albumin (ALB), and serum total choles-

terol (TC) were lower than those in the control group (P<0.05). There were statistically significant differences between the two groups in tumor location, International Union Against Cancer (UICC) TNM stage, pathological type, degree of differentiation, mismatch repair (MMR) expression status, microsatellite stability status, nerve and vascular invasion, liver and lung metastasis rates, and tumor length (P<0.05). After controlling for baseline confounding factors using PSM, anemia was separated as an independent predictive variable for multivariate Logistic regression analysis. The results showed that when anemia was not included, tumor location (rectum, OR=0.410, 95%CI=0.25-0.67, P<0.01), UICC stage IV (OR=3.50, 95%CI=1.65-7.82, P<0.01), vascular invasion (OR=1.63, 95%CI=1.01-2.63, P=0.04), tumor length (OR=1.16, 95%CI=1.03-1.30, P<0.01), ALB (OR=0.90, 95%CI=0.85-0.95, P<0.01), PCT (OR=1.12, 95%CI=1.08-1.15, P<0.01), and LY (OR=0.51, 95%CI=0.35-0.72, P<0.01) were independent influencing factors for low iron status in patients with colorectal adenocarcinoma. When anemia was included in the multivariate Logistic regression analysis, anemia (OR=7.03, 95%CI=4.40-11.25, P<0.01) became an independent influencing factor for low iron status, while tumor location was no longer an independent influencing factor. The remaining factors, including tumor length, UICC stage IV, vascular invasion, and peripheral blood LY, PCT, and ALB, were still independent factors associated with low iron status in patients with colorectal adenocarcinoma (P<0.05).

Conclusion

The internal environment iron status of patients with colorectal adenocarcinoma is closely associated with tumor invasiveness (including tumor stage, neurovascular invasion, and tumor length) as well as inflammatory indicators. Rectal tumor location, along with higher levels of albumin (ALB) and lymphocyte count (LY), are protective factors against low iron status in patients with colorectal adenocarcinoma. In contrast, anemia, UICC stage IV, vascular invasion, longer tumor length, and higher plateletcrit (PCT) are risk factors for low iron status.

Keywords

Colorectal neoplasms; Colorectal adenocarcinoma; Tumor microenvironment; Internal environment iron; Hypoferremic state

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Introduction

As the second leading cause of cancer-related mortality worldwide, colorectal cancer has long been a major focus of global medical research. According to statistics, the incidence and mortality rates of colorectal cancer in China rank second and fifth respectively among all malignant tumors, with both the number of cases and deaths continuing to increase annually, though the exact mechanisms of its development remain incompletely understood [1]. In recent years, with deepening research into tumor pathogenesis, increasing attention has been paid to the tumor microenvironment and overall metabolic status of the body. During colorectal cancer development, iron is considered a key regulatory factor in tumor progression, where both excess and deficiency can lead to different pathological conditions. As an essential trace element, iron participates in vital processes including oxygen transport, cellular respiration, and immune regulation. The mechanism of ferroptosis in colorectal cancer, which is directly related to internal environment iron, represents a current research hotspot [2-3].

Colorectal cancer patients often exhibit abnormal iron status. Multiple studies have shown that excessive intestinal iron can increase intracellular oxidative stress and lipid peroxidation, promoting oncogene activation through pathways such as protein modification and DNA damage, while also providing iron for cancer cell proliferation and facilitating tumor development [4-5]. However, statistics indicate that serum iron levels are generally low in colorectal cancer patients, and the relationship between internal environment low iron status and colorectal cancer has not been fully evaluated [6].

Current research on the relationship between colorectal cancer and low iron status has certain limitations. Existing studies have primarily focused on the association between decreased transferrin and ferritin levels and certain characteristics of colorectal cancer, neglecting comprehensive analysis of serum iron status and deficiency across multiple clinicopathological factors. There are also deficiencies in sample scope, research methodology, and results interpretation [7-8]. Serum iron directly reflects the availability of iron in the internal environment, and its level is crucial for maintaining basic cellular physiological functions. Therefore, this study examined preoperative serum iron and related indicators in colorectal adenocarcinoma patients, combined with multiple clinicopathological factors for correlation analysis, aiming to provide reference for comprehensive treatment strategies and to offer thorough, systematic research findings on the relationship between colorectal adenocarcinoma and internal environment low iron status.

Methods

Study Design This study was based on a single-center registered retrospective cohort. We consecutively enrolled 712 colorectal cancer surgery patients diagnosed and registered at Sichuan Cancer Hospital from January 2017 to June 2023. Inclusion criteria were: (1) patients who underwent surgical treatment at Sichuan Cancer Hospital with postoperative pathological confirmation of colorectal adenocarcinoma; (2) patients who received a single colorectal cancer surgical treatment regimen; (3) patients with one or more blood test records before surgery; and (4) patients with complete medical records. Exclusion criteria were: (1) patients who had received treatments or non-therapeutic behaviors in the past six months that could significantly affect observation indicators (such as blood transfusion, iron therapy, chemotherapy, massive blood loss, severe infection, etc.); and (2) patients who underwent endoscopic surgery or neoadjuvant therapy. This study was approved by the Medical Ethics Committee of Sichuan Cancer Hospital (approval number: SCCHEC-02-2024-069), and all patients and their families provided informed consent.

Patient Grouping Based on preoperative serum iron expression levels, patients were divided into a low iron status group (low iron group, n=363) and a control group with normal iron status (n=349). The low iron group was defined as: male serum iron $ $10.6 µg/L, female serum iron $ $7.8 µg/L, or functional iron deficiency with transferrin saturation (TSAT) $ $20% [9-10]. The control group was defined as: male serum iron >10.6 µg/L, female serum iron >7.8 µg/L, and TSAT >20%.

Observation Indicators We retrieved data on patients' gender, age, BMI, smoking status, American Society of Anesthesiologists Physical Status Classification System (ASA) grade, postoperative pathological results, mismatch repair (MMR) expression, as well as peripheral blood hemoglobin (Hb), serum iron (SI), transferrin saturation (TSAT), white blood cell count (WBC), total protein (TP), albumin (ALB), lymphocyte count (LY), C-reactive protein (CRP), total cholesterol (TC), triglyceride (TG), plateletcrit (PCT), and carcinoembryonic antigen (CEA). Colorectal cancer staging was performed according to the TNM staging system published by the Union for International Cancer Control (UICC): pTNM stage from postoperative pathology reports and M stage at evaluation. The minimum values of Hb, SI, and TSAT detected within one week after diagnosis of colorectal adenocarcinoma until before surgery were used, along with the last preoperative measurements of blood proteins, CRP, WBC, LY, PCT, and tumor markers. Using minimum values minimized the risk of unrecorded iron supplementation as a confounding factor.

Statistical Methods Data analysis was performed using SPSS 26 (Chinese version) statistical software. Normally distributed measurement data were expressed as ($\bar{x} \pm s$) and compared between groups using independent samples t-test; count data were expressed as relative numbers and compared using ^{2} test. Python (3.12.1) was used for linear regression and heatmap analysis of tumor pathological results and serum iron levels. After univariate analysis of the 712 collected patients, propensity score matching (PSM) was used for 1:1 matching to control for baseline confounding factors. Matching variables included factors with statistically significant differences from univariate analysis, with a caliper set at 0.2. Intergroup differences were reassessed after matching. Finally, 698 matched samples (349 cases each in the low iron group and control group) were included for multivariate Logistic regression analysis. Missing data evaluation was performed on the dataset: the proportion of complete cases was 96.68%, and multiple imputation models were used with five complete variables and the outcome variable iron status, with accuracy tested using Monte Carlo methods for error analysis. $P<0.05$ was considered statistically significant.

Results

Patient Characteristics Among the 712 patients in this study, 363 (50.98%) were classified as having low iron status, comprising 363 cases in the low iron group and 349 cases in the control group. Before PSM matching, there were statistically significant differences between the control and low iron groups in ASA classification, proportion of tumor obstruction, and proportion of anemia ($P<0.05$), while no statistically significant differences were found in gender, age, smoking proportion, BMI, or proportion of hypertension or diabetes ($P>0.05$). After PSM matching, the differences in ASA classification, proportion of tumor obstruction, and proportion of anemia between the two groups remained statistically significant ($P<0.05$), as shown in Table 1 .

Blood Test Indicators After Matching After matching, the low iron status group showed higher expression levels of WBC, CRP, PCT, and CEA compared with the control group, while LY, ALB, and TC levels were lower than in the control group, with statistically significant differences ($P<0.05$). There were no statistically significant differences between the two groups in TP and TG ($P>0.05$), as shown in Table 2 .

Comparison of Tumor Pathological Features There were statistically significant differences between the two groups in tumor location, UICC TNM stage, pathological type, degree of differentiation, MMR status, microsatellite stability status, nerve and vascular invasion, liver and lung metastasis rates, and tumor length ($P<0.05$), as shown in Table 3 .

Multivariate Logistic Regression Analysis of Factors Influencing Low Iron Status Since iron deficiency has a clear unidirectional causal relationship with the development of anemia [11-12], this study separated anemia as an independent predictive variable in the regression analysis. Factors showing statistically significant differences after univariate analysis and PSM matching were included as independent variables (assignment: tumor location: ascending colon=1, transverse colon=2, descending colon=3, rectum=4; UICC stage: stage I=1, stage II=2, stage III=3, stage IV=4; vascular invasion: no invasion=1, invasion=2; measurement data assigned actual measured values), with iron status as the dependent variable (assignment: normal iron status=1, low iron status=2). Multivariate Logistic regression analysis showed that tumor location (rectum), tumor length, UICC stage IV, vascular invasion, and peripheral blood LY, PCT, and ALB were independent factors associated with low iron status in colorectal adenocarcinoma patients ($P<0.05$), as shown in Table 4 .

Multivariate Logistic regression analysis including anemia showed that anemia became an independent influencing factor for low iron status, while tumor location was no longer an independent factor. Tumor length, UICC stage IV, vascular invasion, and peripheral blood LY, PCT, and ALB remained independent factors associated with low iron status in colorectal adenocarcinoma patients ($P<0.05$), as shown in Table 5 .

Heatmap analysis revealed a clear downward trend in serum iron levels with different tumor locations and stage progression (Figure 1 [Figure 1: see original paper]).

Discussion

Previous studies have suggested that iron deficiency in colorectal cancer patients is caused by intraluminal tumor bleeding, malignancy-induced inflammation, or a combination of both, though no definitive conclusion has been reached [6,12-13]. Currently, the relationship between iron deficiency and colorectal cancer progression has been partially explained from biological and immunological perspectives. Tumor cell proliferation requires substantial nutrients, with iron being one of the essential nutrients, but the mechanisms by which tumor cells acquire iron may change. On one hand, tumor cells may upregulate the expression of certain iron transport proteins, enhancing their iron uptake capacity and leading to relatively reduced available iron content in the tumor microenvironment, resulting in internal environment low iron status. On the other hand, tumor cells may induce immune responses that alter iron distribution in the body, such as macrophage polarization and Treg population changes, increasing iron production and export to the tumor microenvironment and reducing iron in the internal environment [14-15]. From the perspective of overall body metabolism, colorectal cancer patients may experience iron metabolism disorders and low iron status due to tumor consumption and inadequate nutritional intake [4].

This study focused on colorectal adenocarcinoma patients and, after controlling for baseline confounding factors through PSM and multivariate Logistic regression analysis, found that UICC stage IV, ALB, and PCT levels were independent influencing factors for low iron status ($P<0.05$). Heatmap analysis results also showed that colorectal adenocarcinoma pathological stage was an independent influencing factor for internal environment low iron status, with significant differences in both T stage and M stage between the low iron and control groups. Multivariate Logistic regression analysis including anemia verified that tumor location was an independent influencing factor for low iron status, with tubular adenocarcinomas of the ascending and transverse colon being more prone to bleeding than those of the descending colon, sigmoid colon, and rectum, leading to greater iron loss and more severe systemic inflammatory responses [11-12,16]. This study found no significant relationship between lymph node metastasis and low iron status in colorectal adenocarcinoma, but patients with distant metastasis showed more pronounced internal environment low iron status [14,17]. Meanwhile, LY in the low iron group was significantly lower than in the control group, while the number of patients with vascular invasion and mean PCT were higher than in the normal group.

This relationship between low iron status and tumor invasiveness may be related to the following factors: (1) The immunosuppressive or immune-inducing effects formed by low iron status in the tumor microenvironment may promote tumor progression; (2) Low iron status may affect platelet function and PCT, thereby altering the tumor microenvironment [18]. On one hand, low iron affects normal platelet function, potentially leading to abnormal coagulation status in the tumor microenvironment, promoting thrombosis, and creating favorable conditions for tumor cell survival and metastasis. On the other hand, elevated PCT may alter the distribution and concentration of cytokines and growth factors in the tumor microenvironment, which in turn affect tumor cell proliferation, invasion, and metastasis capabilities. Simultaneously, tumor cells may secrete certain substances that affect platelet function and quantity, further regulating iron metabolism and platelet status in the tumor microenvironment, forming a complex interaction network [17-19]. (3) Low iron status may limit the supply of iron ions required for ferroptosis, enabling tumor cells to evade ferroptosis and gain survival advantages. Conversely, the body may regulate iron metabolism through compensatory mechanisms to adapt to the low iron environment, which may interfere with the expression and function of ferroptosis-related proteins, further affecting the ferroptosis process in tumor cells [3,14]. For example, changes in the expression of certain iron transport proteins may affect intracellular iron uptake and storage, thereby influencing ferroptosis sensitivity. This abnormal regulation of ferroptosis may be associated with increased tumor invasiveness and metastasis, providing favorable conditions for colorectal adenocarcinoma progression [3].

In this study, ALB also showed a close relationship with low serum iron status (OR=0.90, 95%CI=0.85-0.95, P=0.04). Under iron deficiency conditions, the body may reduce ALB synthesis to conserve energy and resources, leading to decreased blood ALB levels. Additionally, iron can indirectly affect ALB synthesis and secretion by influencing liver metabolic function. ALB levels and functional status also affect iron metabolism. Low ALB levels may reduce iron transport and utilization efficiency, making iron more prone to accumulation or deficiency in the body. ALB can also affect iron transport and storage by regulating transferrin activity. Combined with previous research findings [11,20], it can be concluded that low iron is a factor contributing to deteriorating systemic nutritional status in cancer patients.

In this study, inflammatory indicators (WBC, LY, PCT) were significantly higher in the low iron group compared with the control group, which to some extent confirms that malignancy-induced inflammation leads to low iron status in the body [11,13,18]. No significant gender difference was observed between the two groups, which differs from previous studies and may be related to physiological baseline differences between sexes in defining low iron status [7-8,21]. Low iron status accompanied by worse clinical presentation and physical performance was validated in univariate analysis ($P<0.05$) but was not confirmed in multivariate analysis [7]. Colorectal adenocarcinoma patients with mismatch repair deficiency (including microsatellite low and high instability) were more likely to be in low iron status. Low iron status may be correlated with tumor cell differentiation degree, where lower differentiation may lead to lower internal environment iron concentration, which may be related to the previously established relationship between tumor invasiveness and iron level [19]. Contrary to predictions that ulcerative bleeding leads to iron loss, there was no significant correlation between pathological classification of colorectal adenocarcinoma (medullary type, constrictive type, protruding type, ulcerative type) and low iron status [11,13].

This study has several limitations: (1) The data were derived from a single center, resulting in insufficient sample representativeness; (2) There was high selectivity in patient inclusion.

This study confirms that low iron status in colorectal adenocarcinoma patients is not simply related to a single factor but involves the interaction of multiple clinical factors affecting tumor development, progression, and metastasis. The results suggest that in terms of treatment, considering the relationship between internal environment low iron status and colorectal adenocarcinoma, iron metabolism could be modulated to improve immune function and inhibit tumor invasion and metastasis. For example, drug interventions could be used to regulate iron transport protein activity, or appropriate iron supplementation could be administered to improve patients' iron status while avoiding negative effects from iron overload. Iron status could also serve as an important prognostic indicator. When evaluating patient prognosis, clinicians may consider patients' iron status and iron metabolism-related factors to more accurately predict disease progression and recurrence risk.

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Author Contributions: LUO Hao and LUO Yajun proposed the main research objectives, conceived and designed the study; LUO Hao was responsible for study implementation, statistical analysis, and manuscript writing; YANG Yi collected and organized data and prepared figures and tables; HU Hai was responsible for quality control and review of the article and overall supervision.

Conflict of Interest: The authors declare no conflict of interest.

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(Received: March 10, 2025; Revised: August 20, 2025)

Note: Figure translations are in progress. See original paper for figures.