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Original Article

Preoperative red blood cell transfusion improves treatment response and survival in patients with locally advanced esophageal cancer and iron deficiency anemia

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Abstract: Background: Locally advanced esophageal cancer presents significant treatment challenges, with iron deficiency anemia (IDA) potentially hindering the efficacy of neoadjuvant chemotherapy. This study aimed to evaluate the effect of preoperative red blood cell transfusion on tumor progression and chemotherapy response in patients with IDA. Methods: A retrospective cohort study was conducted at Shaanxi Provincial Cancer Hospital, involving 228 patients with locally advanced esophageal cancer and IDA, from August 2015 to August 2021. Patients were divided into two groups: 106 patients received preoperative red blood cell transfusions, and 122 did not. All patients underwent a standardized chemotherapy regimen followed by surgery. Hematological, immunological, and biochemical parameters, as well as chemotherapy-related adverse events, and survival outcomes were analyzed. Results: Preoperative transfusion significantly increased hemoglobin (Hb) levels ($P < 0.05$), enhanced immunological profiles (e.g., NK/T cell activity; $P < 0.05$), and reduced systemic inflammation (e.g., CRP; $P < 0.05$) after chemotherapy and operation. Overall survival and progression-free survival were notably better in the transfusion group ($P = 0.002$ and $P = 0.012$, respectively). Conclusion: Preoperative red blood cell transfusion improves hematological and immunological parameters and enhances survival outcomes in patients with locally advanced esophageal cancer and IDA.

Keywords: Esophageal cancer, iron deficiency anemia, neoadjuvant chemotherapy, red blood cell transfusion, treatment efficacy, survival outcomes

Introduction

Esophageal cancer ranks among the ten most prevalent malignancies globally and remains a major cause of cancer-related mortality, with marked geographical variations in incidence [1]. Squamous cell carcinoma and adenocarcinoma are the predominant subtypes, each with unique clinical progression and therapeutic response [2]. Despite advances in multimodal therapy, the prognosis for locally advanced esophageal cancer remains poor, often due to late-stage diagnosis and metastasis [3-5]. In response to this, neoadjuvant chemotherapy, represented by platinum-based regimens, has become a critical intervention to downstage tumors and improve surgical outcomes [6, 7]. However, treatment success is strongly influenced by the patient's hematological status. Substantial evidence indicates that iron deficiency anemia (IDA) impairs chemotherapy efficacy by inducing tumor hypoxia, which promotes resistance to platinum-based agents [8, 9]. Hypoxia-driven upregulation of hypoxia-inducible factor 1α (HIF-1α) further impairs drug uptake and DNA damage response [10, 11]. Moreover, anemia, frequently observed in cancer patients, exacerbates fatigue, reduces quality of life, and diminishes treatment responsiveness [12, 13]. Iron deficiency, primarily due to chronic blood loss, nutritional deficits, and inflammation-related changes in iron metabolism, is the leading cause of ADA in esophageal cancer patients [14].

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The implications of anemia in cancer therapy extend beyond quality-of-life considerations; substantial evidence suggests that anemia can negatively influence treatment outcomes [15]. Hypoxia, secondary to reduced hemoglobin (Hb) concentrations, enhances tumor aggressiveness and resistance to cytotoxic agents, including chemotherapy drugs [16]. Hb is crucial for oxygen transport, and its deficiency can foster hypoxic conditions in tumor microenvironments, thereby diminishing the efficacy of standard therapeutic agents [17]. Iron deficiency affects 20-45% of esophageal cancer patients, primarily due to chronic blood loss and malnutrition [18, 19]. This study focuses on locally advanced stages (IIa-IIIb), in which anemia correction may be most impactful, as tumors remain operable yet exhibit high biological aggressiveness [8]. IDA exacerbates treatment resistance in this subgroup, making early intervention crucial [8, 20]. Consequently, optimizing Hb levels through strategies such as red blood cell transfusion may therefore mitigate hypoxia and enhance tumor sensitivity to anticancer treatments.

Preoperative red blood cell transfusion is intended to correct anemia before initiating multimodal treatment [21]. This intervention is hypothesized not only to restore oxygen-carrying capacity but also to improve immunologic profiles, thereby preparing patients for neoadjuvant chemotherapy and subsequent surgery [22-24]. However, potential concerns, such as immune modulation, infection risk, and unclear long-term survival, necessitate careful evaluation of transfusion benefits versus risks [8, 25].

Although prior studies have established associations between anemia, hypoxia, and chemotherapy resistance [26-28], the specific impact of preoperative red blood cell transfusion on treatment response and survival in patients with locally advanced esophageal cancer and IDA, particularly regarding immunomodulatory mechanisms during neoadjuvant therapy, remain unclear [29, 30]. Addressing these gaps, this study aims to investigate the influence of preoperative red blood cell transfusion on disease progression and treatment response in this patient population.

Methods

Study design

This retrospective cohort study included 228 patients diagnosed with locally advanced esophageal cancer with IDA, who were treated at Shaanxi Provincial Cancer Hospital between August 2015 and August 2021. Demographic information was systematically collected from the patients' medical records. Given that this retrospective study used de-identified patient data, which poses no potential harm to participants, the requirement for informed consent was waived. Both the waiver and the study protocol were approved by the institutional ethics committee of Shaanxi Provincial Cancer Hospital, adhering to pertinent regulatory and ethical standards.

Case selection

Inclusion criteria: (1) Aged 40-75 years, corresponding to the peak incidence of esophageal cancer and reducing confounding from age-related comorbidities (e.g., frailty, cardiovascular disease) that could independently affect treatment tolerance or outcomes; (2) Pathologically confirmed locally advanced esophageal cancer (clinical stage IIa, IIIa, or IIIb) [31]; (3) Diagnosis of IDA (Hb < 13 g/dL for males; Hb < 12 g/dL for females) [32]; (4) Completion of two cycles of neoadjuvant chemotherapy followed by thoracoscopic-laparoscopic radical esophagectomy.

Exclusion Criteria: (1) Severe cardiopulmonary dysfunction; (2) Inability to tolerate intravenous chemotherapy; (3) Presence of other significant comorbidities, such as unstable cardiac disease requiring treatment, major neurological disorders, or relevant psychiatric conditions; (4) Intraoperative transfusion exceeding 2 units of RBCs (to minimize confounding effects of perioperative blood loss); (5) Alteration of the predefined chemotherapy regimen; (6) Receipt of combination therapies such as targeted therapy; (7) Prior chemotherapy or chemoradiotherapy regimens before surgery; (8) Incomplete data available during case collection.

Patients were categorized into two groups based on preoperative red blood cell transfusions, as documented in their medical records: the transfusion group (n = 106) and the non-transfusion group (n = 122). Patients in the non-transfusion group did not receive any red blood cell transfusions from the initiation of neoadjuvant chemotherapy to the time of surgery (excluding intraoperative transfusion). In contrast, patients in the transfusion group received at least one red blood cell transfusion

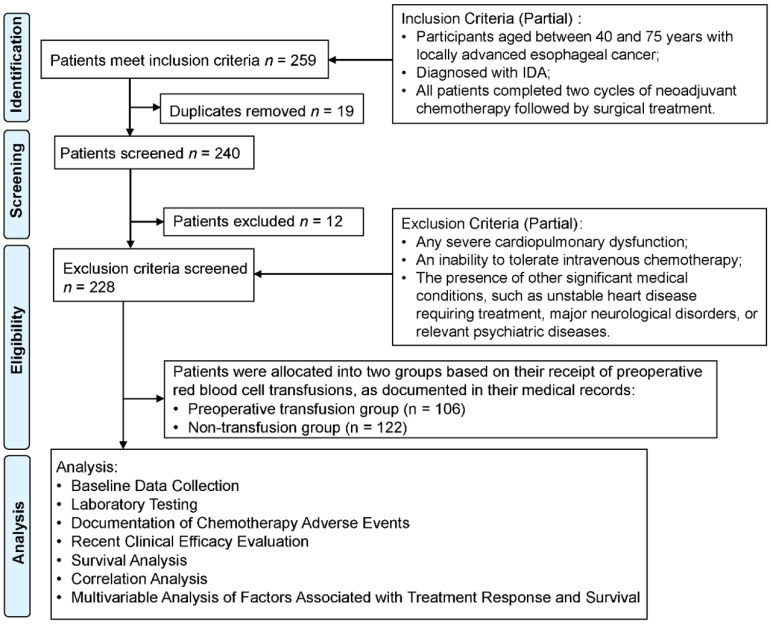

Figure 1. Study design flowchart. IDA: iron deficiency anemia.

both before neoadjuvant chemotherapy and before surgery.

Transfusion indications followed established clinical guidelines for preoperative anemia management [33]. Specifically, hemoglobin levels below 7 g/dL necessitated transfusion; levels above 10 g/dL did not warrant transfusion unless symptomatic or at high surgical risk. For patients with Hb levels between 7-10 g/dL, the transfusion decision was based on comprehensive clinical evaluation, including symptoms such as fatigue or dyspnea, anticipated surgical risk, and overall health status. This protocol ensured adherence to current clinical standards and best practices. The study design flowchart is shown in **Figure 1**.

Treatment methods

Both groups of patients underwent a standardized regimen of neoadjuvant chemotherapy combined with surgical treatment. The protocol was as follows: on days 1, 3, and 5, patients received an intravenous infusion of 100 mg/m^2 of Etoposide (Jiangsu Hengrui Medicine Co., Ltd., National Medicine Standard H3202-5583); from days 1 to 5, an intravenous injection of 1000 mg/m^2 of 5-Fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., National Medicine Standard H31020593) was administered; Additionally, on day 1, patients received an intravenous infusion of 100 mg/m^2 of Cisplatin (Jiangsu Hansoh Pharmaceutical Group Co., Ltd., National Medicine Standard H20040813). Each treatment cycle lasted four weeks, and all patients completed two consecutive cycles. Radical esophagectomy was performed via thoracoscopic-laparoscopic approach within 4 to 6 weeks after the completion of the final chemotherapy cycle.

Follow-up

Follow-up evaluations were initiated 4 to 8 weeks after the completion of the final treatment and were conducted every 1 to 3 months thereafter. Given the three-year follow-up duration, assessments were conducted every 3 to 6 months from the first through the third postoperative year. Follow-up data were collected through outpatient and inpatient records, medical records from external hospitals, and scheduled follow-up visits. These evaluations were aimed at monitoring the patients' survival status and disease progression. The final follow-up date was August 20, 2024.

Data collection

(1) Baseline Data: Baseline demographic information for all enrolled patients was obtained from the medical record system.

(2) Laboratory Testing: Blood samples (5 mL) were collected at three time points: baseline (T0), seven days after completion of neoadjuvant chemotherapy (T1), and postoperative day 7 (T2). Laboratory parameters at T1 and T2 were derived from standardized institutional protocols requiring routine blood testing at these intervals. Deviations of ± 2 days were permitted for logistical reasons (e.g., weekend delays). Missing data (< 5% at T1/T2) were imputed using the last-observation-carried-forward (LOCF) method to minimize attrition bias. Each sample consisted of 5 mL of venous blood obtained via venipuncture.

Hematological parameters: Hb levels and red blood cell count (RBC) were measured using a Mindray BC-6800 automated hematology analyzer (Mindray, China).

Immunology parameters: Natural killer (NK) cells and T cells (CD3+ cells) were analyzed by flow cytometry using a Wellgrow Easycell 206AI flow cytometer. Lymphocyte subsets were identified using monoclonal antibodies conjugated to fluorochromes, specifically anti-CD3 FITC and anti-CD16/CD56 PE (BD Biosciences, USA).

Biochemical parameters: Ferritin, albumin, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine levels were measured using the AU5800 automatic biochemical analyzer (Olympus, Japan). Ferritin concentrations were specifically quantified using an automatic chemiluminescence instrument (New Industry MAGLUMI X8, China).

(3) Documentation of Chemotherapy-related Adverse Events: The incidence of chemotherapy-related adverse events was recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [34]. The primary adverse events monitored included gastrointestinal reactions, bone marrow suppression, hepatic and renal dysfunction, hypertension, and hypothyroidism.

(4) Recent Clinical Efficacy Evaluation: The clinical efficacy of the neoadjuvant therapy in both patient groups was assessed 3-4 weeks after the completion of two chemotherapy cycles using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [35]. Tumor response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

(5) Survival Analysis: Patients were followed until death or the study end date, with survival outcomes documented in accordance with the CAP/NCCN guidelines for esophageal cancer [36]. Overall Survival (OS) and Progression-Free Survival (PFS) were calculated as key survival endpoints.

Statistical method

Data analysis was performed using SPSS 29.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Group comparisons were performed using independent-sample t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were presented as frequencies (%) and analyzed using χ^2. Spearman's rank correlation was used to assess the relationships between preoperative transfusion and clinical outcomes.

Multivariate regression analysis was conducted to adjust for potential confounders. For short-term clinical efficacy (CR/PR vs. SD/PD), binary logistic regression was used. For survival outcomes (OS and PFS), Cox proportional hazards models were used. Variables included in the regression models were selected based on clinical relevance and biological plausibility: (1) Demographic/clinical variables: Age (continuous), sex (male vs. female), body mass index (BMI; continuous), clinical stage (IIIb vs. IIa/IIIa). (2) Treatment-related variables: Preoperative transfusion (yes/no). (3) Laboratory parameters: ΔHb (post-chemotherapy Hb at T1 - baseline Hb at T0), ΔCRP (post-chemotherapy CRP at T1 - baseline CRP at T0), ΔNK cells (T1 - T0), ΔT cells (T1 - T0). (4) Interaction term: Preoperative transfusion × ΔHb (to assess effect modification).

ΔHb reflects oxygenation improvement potentially linked to chemo-sensitization [37]; ΔCRP quantifies systemic inflammation, which promotes tumor progression [38]; ΔNK/ΔT cells capture transfusion-induced immunomodulatory effects, as NK and T cells mediate antitumor responses [39]. Proportional hazards assumptions for Cox models were verified using Schoenfeld residuals. Results were reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline demographic and clinical characteristics

Comparison of baseline demographics and clinical characteristics revealed no statistical differences between the transfusion and non-transfusion groups, including age, gender, BMI, education, employment, marital status, residence, lifestyle habits, tumor histology, lesion

Table 1. Comparison of baseline demographic and clinical characteristics between the two groups

Parameters	Non-transfusion group (n = 122)	Transfusion group (n = 106)	t/χ^2	P
Age (years)	57.43 ± 7.27	58.12 ± 7.04	0.731	0.466
Gender (Male/Female)	83/39	74/32	0.084	0.772
BMI (kg/m^2)	23.46 ± 3.52	23.89 ± 3.67	0.891	0.374
Education Level [n (%)]			0.188	0.910
Primary or below	27 (22.13%)	24 (22.64%)		
Secondary School	62 (50.82%)	51 (48.11%)		
College or above	33 (27.05%)	31 (29.24%)		
Employment Status [n (%)]			0.020	0.887
Employed	76 (62.30%)	67 (63.21%)		
Unemployed	46 (37.70%)	39 (36.79%)		
Marital Status [n (%)]			0.108	0.947
Married	98 (80.33%)	84 (79.24%)		
Single	14 (11.48%)	12 (11.32%)		
Divorced	10 (8.19%)	10 (9.43%)		
Current Residence [n (%)]			0.000	0.991
Urban	68 (55.74%)	59 (55.66%)		
Rural	54 (44.26%)	47 (44.34%)		
History of Alcohol Consumption (Yes/No)	45/77	41/65	0.078	0.78
History of Smoking (Yes/No)	52/70	48/58	0.163	0.686
Histological Type [n (%)]			0.095	0.953
Squamous Cell Carcinoma	96 (78.69%)	82 (77.36%)		
Adenocarcinoma	20 (16.39%)	19 (17.92%)		
Adenosquamous Carcinoma	6 (4.92%)	5 (4.72%)		
Location of Lesion [n (%)]			0.015	0.992
Upper Thoracic Segment	20 (16.39%)	18 (16.98%)		
Middle Thoracic Segment	60 (49.18%)	52 (49.06%)		
Lower Thoracic Segment	42 (34.43%)	36 (33.96%)		
Clinical Stage [n (%)]			0.015	0.992
IIa	26 (21.31%)	23 (21.70%)		
IIIa	49 (40.16%)	43 (40.57%)		
IIIb	47 (38.52%)	40 (37.74%)		
Intraoperative Transfusion [n (%)]	24 (19.67%)	18 (16.98%)	0.273	0.601

Note: BMI: Body Mass Index.

location, and clinical stage (all P > 0.05; **Table 1**). Intraoperative transfusion rates were also comparable between the two groups (19.67% vs. 16.98%, P = 0.601).

Changes in hematological and immunological parameters

The transfusion group demonstrated significantly higher post-chemotherapy Hb (T1: 13.68 vs. 11.86 g/dL, P < 0.001) and RBC levels (T1: 4.73 vs. 4.15 × 10^{12}/L, P < 0.001) compared to the non-transfusion group (**Table 2**; **Figure 2**). Additionally, NK and T cell percentages increased significantly in the transfusion group after intervention (all P < 0.05). These findings suggest that preoperative red blood cell transfusion was associated with improved hematological and immunological profiles in patients undergoing neoadjuvant chemotherapy for locally advanced esophageal cancer.

Changes in disease-related biochemical parameters

Ferritin and albumin levels were significantly higher, while CRP levels lower, in the transfu-

Table 2. Comparison of hematological and immunological parameters between the two groups

Parameters	Time	Non-transfusion group (n = 122)	Transfusion group (n = 106)	t	P
Hematology					
Hb (g/dL)	T0	11.91 ± 1.52	11.86 ± 1.47	0.233	0.816
	T1	11.86 ± 1.51	13.68 ± 1.34	9.549	< 0.001
	T2	11.35 ± 1.64	13.02 ± 1.48	8.008	< 0.001
RBC (× 10^12/L)	T0	4.16 ± 0.55	4.12 ± 0.52	0.594	0.553
	T1	4.15 ± 0.57	4.73 ± 0.51	8.136	< 0.001
	T2	3.98 ± 0.61	4.52 ± 0.56	6.848	< 0.001
Immunology					
NK Cells (% of lymphocytes)	T0	12.48 ± 3.62	12.55 ± 3.58	0.145	0.884
	T1	12.52 ± 3.41	13.97 ± 3.45	3.187	0.002
	T2	10.98 ± 3.78	12.23 ± 3.52	2.581	0.010
T Cells (CD3+ cells, % of lymphocytes)	T0	67.34 ± 8.52	67.51 ± 8.47	0.158	0.875
	T1	66.42 ± 8.58	69.29 ± 8.34	2.548	0.012
	T2	64.87 ± 8.74	67.15 ± 8.51	1.994	0.047

Note: Hb: Hemoglobin; RBC: Red Blood Cells; NK Cells: Natural Killer Cells; T0: Baseline, measurements taken before neoadjuvant chemotherapy; T1: Measurements taken 7 days after neoadjuvant chemotherapy; T2: Measurements taken on postoperative day 7.

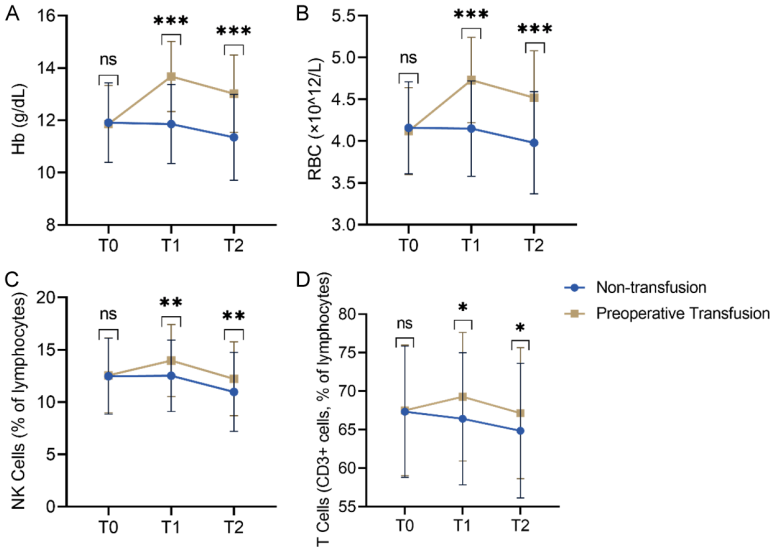

Figure 2. Comparison of hematological and immunological parameters between the two groups. A: Hb (g/dL); B: RBC (× 10^12/L); C: NK Cells (% of lymphocytes); D: T Cells (CD3+ cells, % of lymphocytes). Hb: Hemoglobin; RBC: Red Blood Cells; NK Cells: Natural Killer Cells; T1: Measurements taken 7 days after neoadjuvant chemotherapy; T2: Measurements taken on postoperative day 7; ns: No significant difference; *: P < 0.05; **: P < 0.01; ***: P < 0.001.

sion group after intervention (all P < 0.05; **Table 3**; **Figure 3**). ALT, AST, and creatinine levels were comparable between groups (all P > 0.05). Collectively, preoperative transfusion improved markers of nutritional and inflammatory status without adversely affecting hepatic or renal function.

Incidence of chemotherapy-related adverse reactions during neoadjuvant treatment

The incidence of myelosuppression was 10.66% in the non-transfusion group and 12.26% of the transfusion group (χ^2 = 0.145, P = 0.703) (**Table 4**). Gastrointestinal reactions were reported in 9.84% of patients in the non-transfusion group compared to 11.32% in the transfusion group (χ^2 = 0.133, P = 0.716). The incidence of hepatic and renal dysfunction was 9.84% in the non-transfusion group and 11.32% for the transfusion group (χ^2 = 0.133, P = 0.716). Hypertension was noted in 7.38% in the non-transfusion group and 8.49% in the transfusion group (χ^2 = 0.097, P = 0.756). Lastly, hypothyroidism occurred in 7.38% in the non-transfusion group versus 9.43% in the transfusion group (χ^2 = 0.314, P = 0.575). These findings

Table 3. Comparison of disease-related biochemical parameters between the two groups

Parameters	Time	Non-transfusion group (n = 122)	Preoperative Transfusion group (n = 106)	t	P
Ferritin (ng/mL)	T0	29.54 ± 10.45	29.78 ± 10.63	0.167	0.867
	T1	29.87 ± 10.72	76.34 ± 20.48	20.995	< 0.001
	T2	28.15 ± 11.02	72.46 ± 19.87	20.399	< 0.001
Albumin (g/dL)	T0	3.87 ± 0.35	3.89 ± 0.36	0.44	0.660
	T1	3.88 ± 0.37	4.12 ± 0.34	5.192	< 0.001
	T2	3.76 ± 0.41	4.01 ± 0.38	4.763	< 0.001
CRP (mg/L)	T0	6.67 ± 3.21	6.72 ± 3.28	0.125	0.901
	T1	6.71 ± 3.34	5.85 ± 2.17	2.332	0.021
	T2	7.82 ± 3.16	6.13 ± 2.24	4.691	< 0.001
ALT (U/L)	T0	28.45 ± 10.23	28.67 ± 10.41	0.161	0.873
	T1	28.57 ± 10.54	29.34 ± 10.62	0.549	0.583
	T2	30.12 ± 11.07	29.85 ± 10.78	0.191	0.849
AST (U/L)	T0	32.54 ± 11.32	32.78 ± 11.54	0.158	0.874
	T1	32.67 ± 11.65	33.45 ± 11.78	0.502	0.616
	T2	34.12 ± 12.04	33.85 ± 11.87	0.167	0.867
Creatinine (mg/dL)	T0	0.92 ± 0.18	0.93 ± 0.19	0.456	0.649
	T1	0.93 ± 0.19	0.95 ± 0.20	0.709	0.479
	T2	0.91 ± 0.20	0.94 ± 0.21	1.157	0.248

Note: CRP: C-reactive Protein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T0: Baseline, measurements taken before neoadjuvant chemotherapy; T1: Measurements taken 7 days after neoadjuvant chemotherapy; T2: Measurements taken on postoperative day 7.

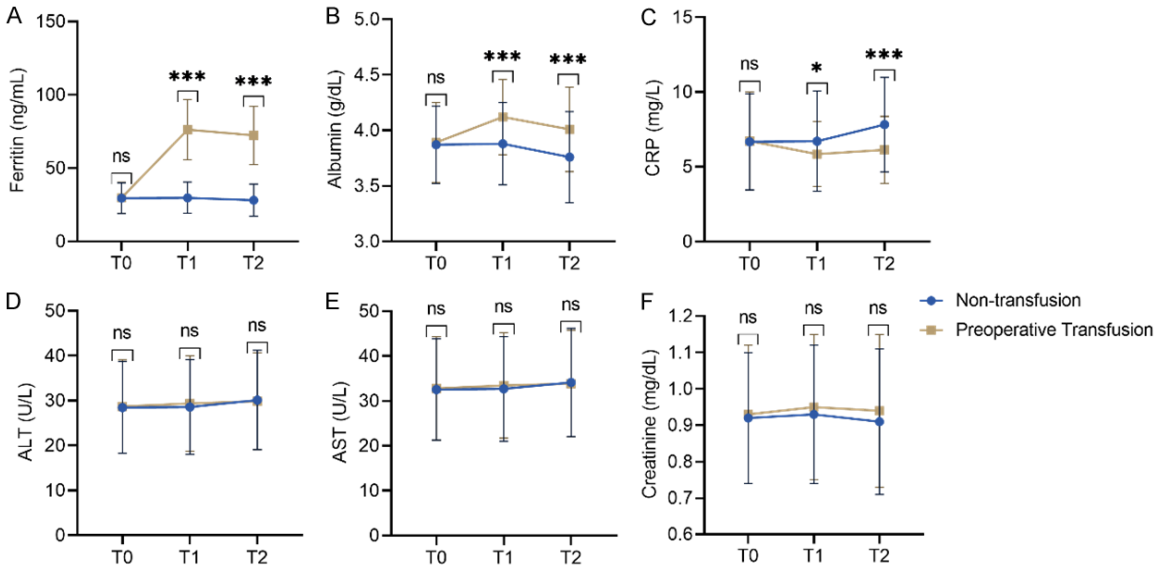

Figure 3. Comparison of disease-related biochemical parameters between the two groups. A: Ferritin (ng/mL); B: Albumin (g/dL); C: CRP (mg/L); D: ALT (U/L); E: AST (U/L); F: Creatinine (mg/dL). CRP: C-reactive Protein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T0: Baseline, measurements taken before neoadjuvant chemotherapy; T1: Measurements taken 7 days after neoadjuvant chemotherapy; T2: Measurements taken on postoperative day 7; ns: No significant difference; *: P < 0.05; ***: P < 0.001.

suggest that preoperative red blood cell transfusion did not significantly increase the risk of chemotherapy-related adverse reactions during neoadjuvant treatment.

Table 4. Comparison of chemotherapy-related adverse reactions during neoadjuvant treatment between the two groups

Parameters	Non-transfusion group (n = 122)	Transfusion group (n = 106)	χ^2	P
Myelosuppression	13 (10.66%)	13 (12.26%)	0.145	0.703
Gastrointestinal reactions	12 (9.84%)	12 (11.32%)	0.133	0.716
Hepatic and renal dysfunction	12 (9.84%)	12 (11.32%)	0.133	0.716
Hypertension	9 (7.38%)	9 (8.49%)	0.097	0.756
Hypothyroidism	9 (7.38%)	10 (9.43%)	0.314	0.575

Table 5. Comparison of short-term clinical efficacy between the two groups

Parameters	Non-transfusion group (n = 122)	Transfusion group (n = 106)	χ^2	P
Recent clinical efficacy			10.159	0.017
CR	10 (8.20%)	12 (11.32%)		
PR	44 (36.07%)	57 (53.77%)		
SD	56 (45.90%)	29 (27.36%)		
PD	12 (9.84%)	8 (7.55%)		

Note: CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

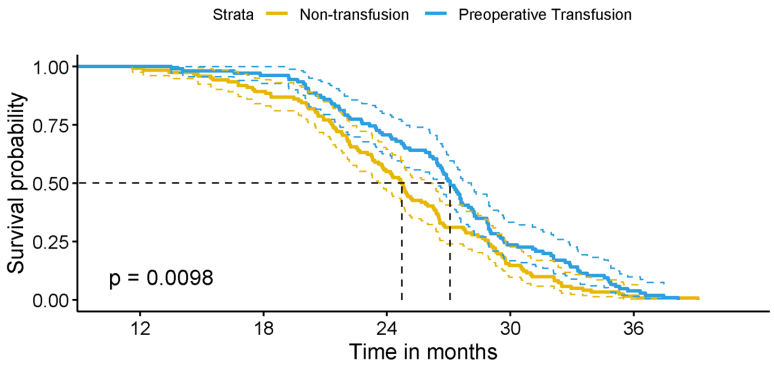

Figure 4. Kaplan-Meier Overall Survival (OS) curves stratified by preoperative transfusion. The shaded regions represent 95% confidence intervals.

Short-term clinical efficacy evaluation after neoadjuvant chemotherapy

In the transfusion group, 11.32% of patients achieved a CR, compared to 8.20% in the non-transfusion group (**Table 5**). PR rates were 53.77% in the transfusion group, notably higher than 36.07% in the non-transfusion cohort. Conversely, 45.90% of the patients in the non-transfusion group experienced SD, compared to 27.36% in the transfusion group. PD was observed in 9.84% of non-transfusion patients and 7.55% of those in the transfusion cohort.

The short-term clinical efficacy, assessed two weeks after completion of neoadjuvant chemotherapy, demonstrated a significant difference between the two groups (χ^2 = 10.159, P = 0.017). These results indicate that preoperative red blood cell transfusion was associated with improved short-term tumor response in patients with locally advanced esophageal cancer.

Postoperative survival analysis

Kaplan-Meier survival analysis revealed a significant difference in OS between the transfusion and non-transfusion groups (P = 0.002) (**Figure 4**). The mean OS was 26.91 ± 5.18 months in the transfusion group compared to 24.74 ± 5.32 months in the non-transfusion group. Survival curves, stratified by transfusion status, consistently showed improved longevity in the transfusion cohort.

Patients in the preoperative transfusion group had a mean PFS of 19.92 ± 4.58 months, significantly longer than 18.43 ± 4.26 months in the non-transfusion group (t = 2.531, P = 0.012 (**Figure 5**). These results suggest that preoperative red blood cell transfusion may extend the period of disease control and improve long-term outcomes in patients with locally advanced

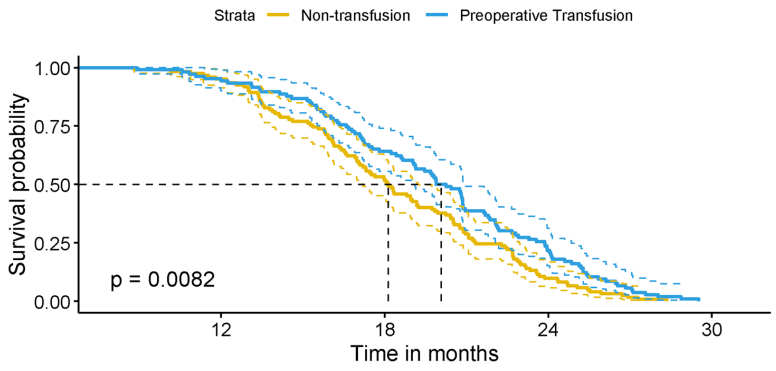

Figure 5. Kaplan-Meier Progression-Free Survival (PFS) curves stratified by preoperative transfusion. The shaded regions represent 95% confidence intervals.

esophageal cancer undergoing neoadjuvant chemotherapy.

Correlation analysis

Spearman correlation analysis revealed a moderate positive correlation between preoperative transfusion and short-term clinical efficacy (rho = 0.184, P = 0.005), indicating that transfusion may enhance the immediate response to neoadjuvant chemotherapy (**Figure 6**). Furthermore, transfusion was significantly correlated with OS (rho = 0.194, P = 0.003) and PFS (rho = 0.162, P = 0.014), suggesting potential benefits in both survival duration and disease control. These findings collectively emphasize the benefits of correcting IDA through preoperative red blood cell transfusion on treatment response and survival outcomes.

Multivariable analysis of factors associated with treatment response and survival

Logistic regression demonstrated that preoperative transfusion (OR = 2.412, 95% CI: 1.307-4.452, P = 0.005) and ΔHb (OR = 1.148 per 1 g/dL increase, 95% CI: 1.032-1.278, P = 0.011) were independently associated with improved short-term clinical efficacy (CR/PR vs. SD/PD) after adjusting for age, sex, BMI, and clinical stage, while advanced clinical stage (IIIb) was inversely correlated with treatment response (OR = 0.482, 95% CI: 0.263-0.884, P = 0.018) (**Table 6**).

Cox proportional hazards analysis identified preoperative transfusion (HR = 0.537, 95% CI: 0.374-0.772, P = 0.001) and ΔHb (HR = 0.892 per 1 g/dL increase, 95% CI: 0.813-0.979, P = 0.016) as protective factors. In contrast, advanced stage (IIIb) (HR = 1.824, 95% CI: 1.221-2.725, P = 0.003) and elevated ΔCRP (HR = 1.102 per 1 mg/L increase, 95% CI: 1.018-1.193, P = 0.015) predicted worse survival (**Table 7**). Similar trends were observed for PFS, with preoperative transfusion (HR = 0.621, 95% CI: 0.452-0.853, P = 0.003) and ΔHb (HR = 0.921, 95% CI: 0.857-0.989, P = 0.024) associated with reduced risk of disease progression.

Discussion

One of the most notable findings of this study was the beneficial effect of preoperative red blood cell transfusion on hematological and immunological parameters. The transfusion group exhibited increased Hb and red blood cell levels post-transfusion, which likely improved tissue oxygen delivery and enhanced the efficacy of neoadjuvant chemotherapy. Hypoxia within tumor microenvironment is well-documented to promote resistance to therapies, as adequate oxygenation is crucial for the bioactivity of many chemotherapeutic agents [40-42]. By ameliorating anemia-related hypoxia, transfusions could disrupt hypoxia-mediated pathways that facilitate tumor survival and chemoresistance [43, 44]. This improvement in oxygenation could enhance the cytotoxicity of chemotherapeutic agents such as Etoposide, 5-Fluorouracil, and Cisplatin, thereby potentiating tumor cell kill and improving treatment responses as observed in the increased rates of CR and PR in the transfusion group.

Moreover, beyond hematological improvements, red blood cell transfusions was associated with improved immunological parameters, particularly enhancing NK cell and T cell (CD3+) activity. These immune subsets play pivotal roles in cancer surveillance and mediating response to immunogenic treatments. Iron deficiency has been associated with impaired immune function; hence, correction of anemia may restore effective immune surveillance and antitumor immune responses during chemotherapy [44-46]. Recent studies have shown that iron deficiency reduces the expression of

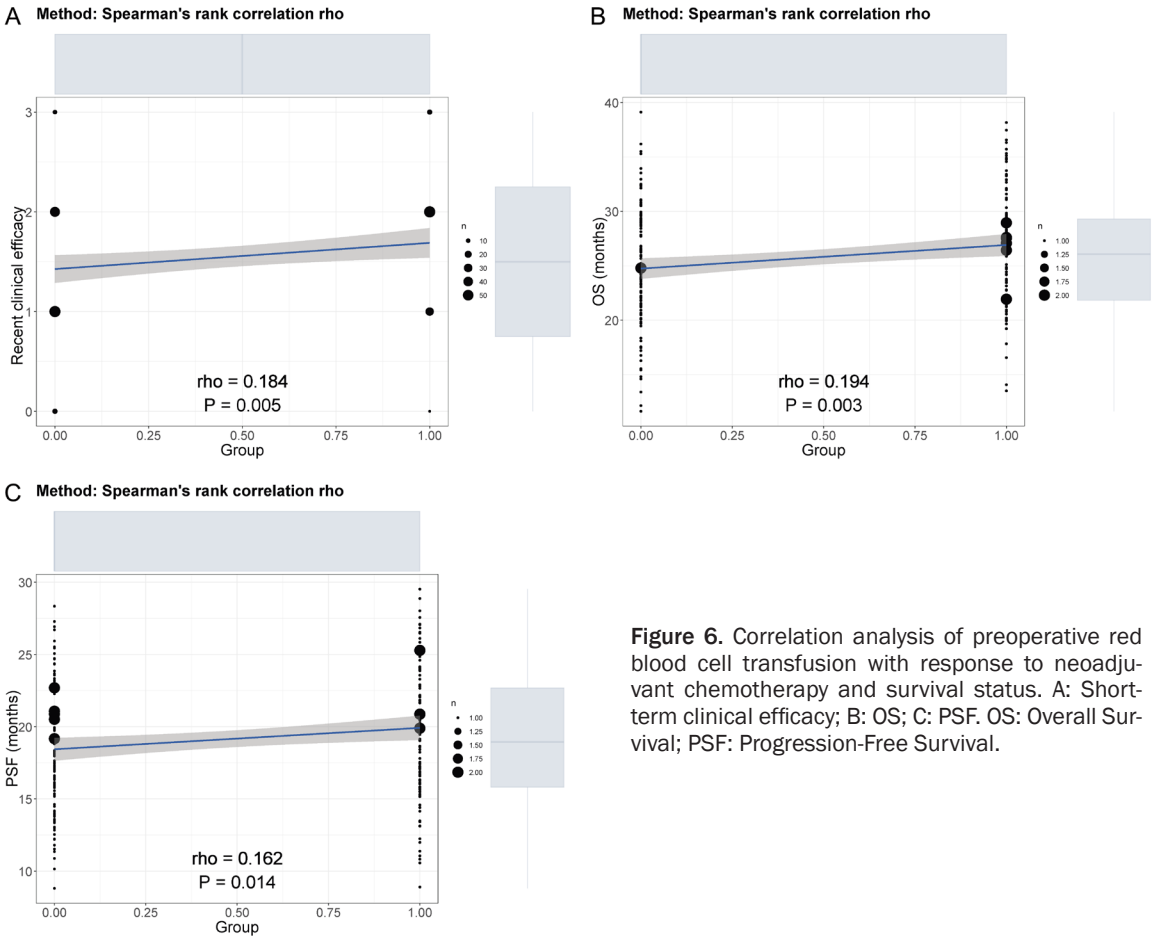

Figure 6. Correlation analysis of preoperative red blood cell transfusion with response to neoadjuvant chemotherapy and survival status. A: Short-term clinical efficacy; B: OS; C: PSF. OS: Overall Survival; PSF: Progression-Free Survival.

Table 6. Multivariable logistic regression for short-term clinical efficacy (CR/PR vs. SD/PD)

Variable	OR	95% CI	P
Age (per 1-year increase)	0.985	0.941-1.031	0.512
Male sex	1.204	0.693-2.092	0.509
BMI (per 1 kg/m^2)	1.038	0.957-1.126	0.382
Clinical stage IIIb	0.482	0.263-0.884	0.018
Preoperative transfusion	2.412	1.307-4.452	0.005
ΔHb (per 1 g/dL)	1.148	1.032-1.278	0.011
ΔCRP (per 1 mg/L)	0.972	0.898-1.052	0.480
ΔNK cells (%)	1.021	0.962-1.083	0.491
ΔT cells (%)	1.015	0.978-1.053	0.433

Note: BMI: Body Mass Index; Hb: Hemoglobin; CRP: C-reactive Protein; NK Cells: Natural Killer Cells; ΔHb/ΔCRP/ΔNK/ΔT cells: T1 (post-chemotherapy) - T0 (baseline).

co-stimulatory molecules on immune cells, impairing their activation and cytotoxicity [47, 48]. Additionally, iron deficiency alters cytokine production, leading to suboptimal immune responses [49]. The observed increase in immune cell percentages post-transfusion aligns with these hypotheses, suggesting that transfusions not only mitigate functional iron deficiency but also restore immune competence that commonly compromised in anemic cancer patients. For instance, a study by Aguilar-Nascimento et al. [50] demonstrated that correcting anemia through transfusion improved the functionality of NK cells and CD8+ T cells in anemic cancer patients. Similarly, Rodgers et al. [51] reported that iron supplementation and subsequent correction of anemia enhanced T cell proliferation and cytokine production, further supporting the immunoregulatory role of iron in antitumor responses.

Furthermore, the study also evaluated various biochemical parameters that serve as indicators of systemic inflammation and nutritional status. The increase in ferritin levels following transfusion was consistent with the correction of iron deficiency, while the improved albumin levels suggest a favorable shift in nutritional status. Elevated albumin has been associated with improved surgical outcomes and reduced

Table 7. Multivariable cox regression for Overall Survival (OS) and Progression-Free Survival (PFS)

Variable	OS			PFS		
	HR	95% CI	P	HR	95% CI	P
Age (per 1-year)	1.012	0.975-1.051	0.539	1.008	0.971-1.047	0.672
Male sex	1.158	0.792-1.695	0.451	1.104	0.761-1.601	0.602
BMI (per 1 kg/m^2)	0.972	0.912-1.036	0.385	0.984	0.926-1.046	0.612
Clinical stage IIIb	1.824	1.221-2.725	0.003	1.652	1.121-2.434	0.011
Preoperative transfusion	0.537	0.374-0.772	0.001	0.621	0.452-0.853	0.003
ΔHb (per 1 g/dL)	0.892	0.813-0.979	0.016	0.921	0.857-0.989	0.024
ΔCRP (per 1 mg/L)	1.102	1.018-1.193	0.015	1.075	0.998-1.158	0.058
ΔNK cells (%)	0.981	0.933-1.032	0.450	0.989	0.942-1.039	0.674
ΔT cells (%)	0.976	0.945-1.008	0.137	0.984	0.954-1.015	0.309

Note: BMI: Body Mass Index; Hb: Hemoglobin; CRP: C-reactive Protein; NK Cells: Natural Killer Cells; ΔHb/ΔCRP/ΔNK/ΔT cells: T1 (post-chemotherapy) - T0 (baseline).

complications, further underscoring the potential systemic benefits of transfusion in this patient cohort [50, 52]. Additionally, the reduction in CRP levels observed in the transfusion group indicates a decrease in systemic inflammation, a factor frequently linked to improved treatment outcomes and reduced cancer progression risk. Together, reduced systemic inflammation and improved nutritional status are possible mechanisms through which preoperative transfusion exerts its beneficial effects, facilitating better responses to anticancer therapies [53, 54].

Interestingly, despite the known risks associated with blood transfusion, such as potential immune modulation and an increased risk of infections, the incidence of chemotherapy-related adverse effects did not significantly differ between the transfusion and non-transfusion groups. This finding supports the safety and feasibility of employing transfusions as part of the preoperative optimization strategy for with locally advanced esophageal cancer and IDA. Nonetheless, larger, prospective studies are warranted to validate these safety profile of transfusions and further delineate the long-term immunologic consequences of transfusion in this context.

The observed improvements in OS and PFS in the transfusion group was particularly noteworthy, highlighting a potential clinical benefit that merits consideration in treatment planning. These survival advantages may be attributed to various factors, including enhanced chemotherapeutic efficacy via increased oxygen delivery, improved immune function, and other indirect effects like better overall patient condition that allows for optimal dosing and timing of subsequent clinical interventions. Furthermore, the correlation analysis supports the notion that transfusions have a supportive role in maximizing the effectiveness of neoadjuvant chemotherapy, enabling patients to sustain better therapeutic outcomes over time.

Our findings contribute to the evolving understanding of anemia management in oncology by demonstrating that preoperative red blood cell transfusion not only alleviates anemia-related symptoms but also enhances chemotherapy response and survival outcomes in locally advanced esophageal cancer. This aligns with recent studies highlighting anemia correction as a modulator of tumor hypoxia and immune function [8, 51, 55]. For instance, Lee et al. [56] reported that hemoglobin optimization mitigates hypoxia-driven chemoresistance in breast cancer, while Watanabe et al. [57] demonstrated improved responses to immune checkpoint inhibitor in transfused patients. Our work extends these observations to esophageal cancer, emphasizing anemia correction as a therapeutic adjunct rather than solely a supportive measure.

While our study provides valuable insights into the role of preoperative red blood cell transfusion in treating locally advanced esophageal cancer, several limitations should be acknowledged. As a retrospective cohort study, inherent selection bias may limit the generalizability of the findings. The analysis was confined to a

specific group of patients and may not be applicable to broader populations with varying degrees of anemia or differing chemotherapy regimens. Additionally, this study lacks data on long-term outcomes and potential transfusion-related complications, and potential confounding factors, such as comorbidities and nutritional status, were not comprehensively addressed. Finally, the absence of a randomized controlled design precludes definitive conclusions regarding causal relationship between transfusion and improved treatment outcomes. Future prospective studies are needed address these limitations.

Conclusion

Preoperative red blood cell transfusion significantly improves hematological parameters, immune function, and survival outcomes in patients with locally advanced esophageal cancer and iron deficiency anemia. These benefits likely arise from hypoxia mitigation, immune function restoration, and systemic inflammation reduction. While the retrospective design limits causal inference, our findings advocate for integrating anemia correction into multimodal treatment protocols. Prospective trials are needed to validate transfusion strategies and refine patient selection criteria.

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Disclosure of conflict of interest

None.

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References

[1] Hulshof MCCM, Geijsen ED, Rozema T, Oppedijk V, Buijsen J, Neelis KJ, Nuyttens JJME, van der Sangen MJC, Jeene PM, Reinders JG, van Berge Henegouwen MI, Thano A, van Hooft JE, van Laarhoven HWM and van der Gaast A. Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO Study). J Clin Oncol 2021; 39: 2816-2824.

[2] Kato K, Machida R, Ito Y, Daiko H, Ozawa S, Ogata T, Hara H, Kojima T, Abe T, Bamba T, Watanabe M, Kawakubo H, Shibuya Y, Tsubosa Y, Takegawa N, Kajiwara T, Baba H, Ueno M, Takeuchi H, Nakamura K and Kitagawa Y; JCOG1109 investigators. Doublet chemotherapy, triplet chemotherapy, or doublet chemotherapy combined with radiotherapy as neoadjuvant treatment for locally advanced oesophageal cancer (JCOG1109 NExT): a randomised, controlled, open-label, phase 3 trial. Lancet 2024; 404: 55-66.

[3] Li Q, Liu T and Ding Z. Neoadjuvant immunotherapy for resectable esophageal cancer: a review. Front Immunol 2022; 13: 1051841.

[4] Thakur B, Devkota M and Chaudhary M. Management of locally advanced esophageal cancer. JNMA J Nepal Med Assoc 2021; 59: 409-416.

[5] Watanabe M, Otake R, Kozuki R, Toihata T, Takahashi K, Okamura A and Imamura Y. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Surg Today 2020; 50: 12-20.

[6] Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, Mao W, Xiang J, Han Y, Chen Z, Yang H, Wang J, Pang Q, Zheng X, Yang H, Li T, Zhang X, Li Q, Wang G, Chen B, Mao T, Kong M, Guo X, Lin T, Liu M and Fu J. Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced esophageal squamous cell carcinoma: the NEOCRTEC5010 randomized clinical trial. JAMA Surg 2021; 156: 721-729.

[7] Yang W, Niu Y and Sun Y. Current neoadjuvant therapy for operable locally advanced esophageal cancer. Med Oncol 2023; 40: 252.

[8] Nandakumar S, Singh N, Tharani AR, Pankiw M and Brezden-Masley C. Intravenous iron and iron deficiency anemia in patients with gastrointestinal cancer: a systematic review. PLoS One 2024; 19: e0302964.

[9] Kaur T, Upadhyay J, Nandave M, Alsayari A, Alshehri SA, Pukale S, Wahab S, Ahmad W, Rashid S and Ansari MN. Exploring progress in iron supplement formulation approaches for treating iron deficiency anemia through bibliometric and thematic analysis. Heliyon 2024; 10: e29058.

[10] Ghosh R, Samanta P, Sarkar R, Biswas S, Saha P, Hajra S and Bhowmik A. Targeting HIF-1α by natural and synthetic compounds: a promising

approach for anti-cancer therapeutics development. Molecules 2022; 27: 5192.
[11] Luo Z, Tian M, Yang G, Tan Q, Chen Y, Li G, Zhang Q, Li Y, Wan P and Wu J. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. Signal Transduct Target Ther 2022; 7: 218.
[12] Chardalias L, Papaconstantinou I, Gklavas A, Politou M and Theodosopoulos T. Iron deficiency anemia in colorectal cancer patients: is preoperative intravenous iron infusion indicated? A narrative review of the literature. Cancer Diagn Progn 2023; 3: 163-168.
[13] Rudzki J, Polewka M, Agopsowicz P, Nowak A, Porada M and Czempik PF. Current approach to the management of preoperative iron deficiency anemia in colorectal cancer patients: a review of literature. Pol Przegl Chir 2024; 96: 67-74.
[14] Abiri B and Vafa M. Iron deficiency and anemia in cancer patients: the role of iron treatment in anemic cancer patients. Nutr Cancer 2020; 72: 864-872.
[15] Aktaş BY, Ata EB, Çeşmeci E, Çakır İY, Coşkunpınar M, Tahillioğlu Y, Güner G, Güven DC, Arık Z, Kertmen N, Dizdar Ö, Yalçın Ş and Aksoy S. Seven-year single-center experience of the efficacy and safety of ferric carboxymaltose in cancer patients with iron-deficiency anemia. Curr Oncol 2023; 30: 9689-9700.
[16] Al-Hassi HO, Ng O, Evstatiev R, Mangalika M, Worton N, Jambrich M, Khare V, Phipps O, Keeler B, Gasche C, Acheson AG and Brookes MJ. Intravenous iron is non-inferior to oral iron regarding cell growth and iron metabolism in colorectal cancer associated with iron-deficiency anaemia. Sci Rep 2021; 11: 13699.
[17] Berg EP, Mohammed A, Shipp ZJ and Tenegra JC. Colorectal cancer screening and iron deficiency anemia. Prim Care 2023; 50: 481-491.
[18] Blonk L, Gooszen JAH, Fakkert RA, Eshuis WJ, Rietveld SCM, Wierdsma NJ, Straatman J, van Berge Henegouwen MI and Gisbertz SS. Micronutrient deficiencies and anemia in the follow-up after gastroesophageal cancer surgery. Dis Esophagus 2024; 37: doae053.
[19] Kumar A, Sharma E, Marley A, Samaan MA and Brookes MJ. Iron deficiency anaemia: pathophysiology, assessment, practical management. BMJ Open Gastroenterol 2022; 9: e000759.
[20] Basak T and Kanwar RK. Iron imbalance in cancer: intersection of deficiency and overload. Cancer Med 2022; 11: 3837-3853.
[21] Bhurosy T, Jishan A, Boland PM, Lee YH and Heckman CJ. Underdiagnosis of iron deficiency anemia among patients with colorectal cancer: an examination of electronic medical records. BMC Cancer 2022; 22: 435.
[22] Făgărășan V, Andraș D, Amarinei G, Seicean RI, Bințințan VV, Dindelegan GC and Căinap CI. Absolute and functional iron deficiency in colon cancer: a cohort study. Medicina (Kaunas) 2022; 58: 1202.
[23] Koh JS and Song IC. Functional iron deficiency anemia in patients with cancer. Blood Res 2024; 59: 26.
[24] Krieg S, Loosen S, Krieg A, Luedde T, Roderburg C and Kostev K. Association between iron deficiency anemia and subsequent stomach and colorectal cancer diagnosis in Germany. J Cancer Res Clin Oncol 2024; 150: 53.
[25] Lin PC, Shih HH, Chen YT and Chang YT. Iron-deficiency anemia caused by duodenal paraganglioma in an adolescent. Kaohsiung J Med Sci 2022; 38: 716-718.
[26] Osmola M, Gierej B, Mleczko-Sanecka K, Jończy A, Ciepiela O, Kraj L, Ziarkiewicz-Wróblewska B and Basak GW. Anemia, iron deficiency, and iron regulators in pancreatic ductal adenocarcinoma patients: a comprehensive analysis. Curr Oncol 2023; 30: 7722-7739.
[27] Park HM, Lee J, Lee SY, Kim CH and Kim HR. Intravenous versus oral iron supplementation for iron deficiency anemia in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy: a study protocol for a randomized controlled trial. Trials 2024; 25: 771.
[28] Patel SG. Iron deficiency anemia and hematochezia are red flags for colorectal cancer in young patients. Gastroenterology 2022; 162: 2101-2102.
[29] Phipps O, Brookes MJ and Al-Hassi HO. Iron deficiency, immunology, and colorectal cancer. Nutr Rev 2021; 79: 88-97.
[30] Talboom K, Borstlap WAA, Roodbeen SX, Bruns ERJ, Buskens CJ, Hompes R, Tytgat KMAJ, Tuynman JB, Consten ECJ, Heuff G, Kuiper T, van Geloven AAW, Veldhuis GJ, van der Hoeven JAB, Gerhards MF, Sietses C, Spinelli A, van de Ven AWH, van der Zaag ES, Westerterp M, van Westreenen HL, Dijkgraaf ML, Juffermans NP and Bemelman WA; FIT collaborative group. Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anaemia in patients with colorectal cancer (FIT): a multicentre, open-label, randomised, controlled trial. Lancet Haematol 2023; 10: e250-e260.
[31] DiSiena M, Perelman A, Birk J and Rezaizadeh H. Esophageal cancer: an updated review. South Med J 2021; 114: 161-168.
[32] Iolascon A, Andolfo I, Russo R, Sanchez M, Busti F, Swinkels D, Aguilar Martinez P, Bou-Fakhredin R, Muckenthaler MU, Unal S, Porto G, Ganz T, Kattamis A, De Franceschi L, Cappellini MD, Munro MG and Taher A; from

EHA-SWG Red Cell and Iron. Recommendations for diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia. Hemasphere 2024; 8: e108.
[33] Connor JP, Destrampe E, Robbins D, Hess AS, McCarthy D and Maloney J. Pre-operative anemia and peri-operative transfusion are associated with poor oncologic outcomes in cancers of the esophagus: potential impact of patient blood management on cancer outcomes. BMC Cancer 2023; 23: 99.
[34] Freites-Martinez A, Santana N, Arias-Santiago S and Viera A. Using the common terminology criteria for adverse events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 2021; 112: 90-92.
[35] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.
[36] National Health Commission of The People's Republic of China. National guidelines for diagnosis and treatment of esophageal carcinoma 2022 in China (English version). Chin J Cancer Res 2022; 34: 309-334.
[37] Çobanoğlu B, Balsak A and Kandaz M. Effect of baseline hemoglobin level on prognosis in nasopharyngeal cancer patients receiving chemoradiotherapy. 2023. doi: 10.47191/ijmscrs/v3-i7-21.
[38] Șiancu P, Oprinca GC, Vulcu AC, Pătran M, Croitoru AE, Tănăsescu D, Bratu D, Boicean A and Tănăsescu C. The significance of C-reactive protein value and tumor grading for malignant tumors: a systematic review. Diagnostics (Basel) 2024; 14: 2073.
[39] Mavers M, Maas-Bauer K and Negrin RS. Invariant natural killer t cells as suppressors of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Front Immunol 2017; 8: 900.
[40] Dzobo K, Senthebane DA and Dandara C. The tumor microenvironment in tumorigenesis and therapy resistance revisited. Cancers (Basel) 2023; 15: 376.
[41] Bayat M and Nahand JS. Battlegrounds of treatment resistance: decoding the tumor microenvironment. Naunyn Schmiedebergs Arch Pharmacol 2025; [Epub ahead of print].
[42] Hu J, Li X, Yang L and Li H. Hypoxia, a key factor in the immune microenvironment. Biomed Pharmacother 2022; 151: 113068.
[43] Ramli NA, Iberahim S, Che Ismail AA and Hussin H. Incidence of anemia and red blood cell (RBC) transfusion requirement in breast cancer. Caspian J Intern Med 2023; 14: 237-248.
[44] Petrelli F, Ghidini M, Ghidini A, Sgroi G, Vavassori I, Petrò D, Cabiddu M, Aiolfi A, Bonitta G, Zaniboni A and Rausa E. Red blood cell transfusions and the survival in patients with cancer undergoing curative surgery: a systematic review and meta-analysis. Surg Today 2021; 51: 1535-1557.
[45] Zheng Y, Zhang W, Chen Y, Yang X and Dong R. Impact of perioperative red blood cell transfusion on the prognosis of patients with epithelial ovarian cancer. Heliyon 2023; 9: e23081.
[46] Chen X, Zhou H and Lv J. The importance of hypoxia-related to hemoglobin concentration in breast cancer. Cell Biochem Biophys 2024; 82: 1893-1906.
[47] Liu Y, Wu A, Yu B, He J, Yu J, Mao X, Zheng P, Luo Y, Luo J, Pu J, Yan H and Chen D. The influence of iron nutrition on the development of intestine and immune cell divergency in neonatal pigs. J Anim Sci Biotechnol 2024; 15: 111.
[48] Sharma G, Sharma A, Kim I, Cha DG, Kim S, Park ES, Noh JG, Lee J, Ku JH, Choi YH, Kong J, Lee H, Ko H, Lee J, Notaro A, Hong SH, Rhee JH, Kim SG, De Castro C, Molinaro A, Shin K, Kim S, Kim JK, Rudra D and Im SH. A dietary commensal microbe enhances antitumor immunity by activating tumor macrophages to sequester iron. Nat Immunol 2024; 25: 790-801.
[49] Lin Y, Song Y, Zhang Y, Li X, Kan L and Han S. New insights on anti-tumor immunity of CD8(+) T cells: cancer stem cells, tumor immune microenvironment and immunotherapy. J Transl Med 2025; 23: 341.
[50] Aguilar-Nascimento JE, Zampieri-Filho JP and Bordin JO. Implications of perioperative allogeneic red blood cell transfusion on the immune-inflammatory response. Hematol Transfus Cell Ther 2021; 43: 58-64.
[51] Rodgers GM. Update on iron supplementation in patients with cancer-related anemia. Expert Rev Hematol 2024; 17: 505-514.
[52] Mispelbaum R, Hattenhauer ST, Brossart P and Heine A. Red blood cell transfusions impact response rates to immunotherapy in patients with solid malignant tumors. Front Immunol 2022; 13: 976011.
[53] Chang L, Cheng Q, Ma Y, Wu C, Zhang X, Ma Q, He L, Li Q and Tao J. Prognostic effect of the controlling nutritional status score in patients with esophageal cancer treated with immune checkpoint inhibitor. J Immunother 2022; 45: 415-422.
[54] Yan K, Wei W, Shen W, Du X, Zhu S, Zhao H, Wang X, Yang J, Zhang X and Deng W. Combining the systemic inflammation re-

sponse index and prognostic nutritional index to predict the prognosis of locally advanced elderly esophageal squamous cell carcinoma patients undergoing definitive radiotherapy. J Gastrointest Oncol 2022; 13: 13-25.
[55] Badran O, Cohen I and Bar-Sela G. The impact of iron on cancer-related immune functions in oncology: molecular mechanisms and clinical evidence. Cancers (Basel) 2024; 16: 4156.
[56] Lee CL, Tsai CH, Yeh DC, Lin CS, Li YF and Tzeng HE. Hemoglobin level trajectories in the early treatment period are related with survival outcomes in patients with breast cancer. Oncotarget 2017; 8: 1569-1579.
[57] Watanabe H, Kano K, Hashimoto I, Tanabe M, Onuma S, Morita J, Nagasawa S, Kanematsu K, Aoyama T, Yamada T, Ogata T, Rino Y, Saito A and Oshima T. Intraoperative blood loss impacts recurrence and survival in patients with locally advanced esophageal cancer. Anticancer Res 2023; 43: 5173-5179.