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Original Article

Significance of perioperative allogeneic erythrocyte transfusion on the prognoses of patients with resectable esophageal squamous cell carcinomas

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Abstract: Perioperative allogeneic erythrocyte transfusion has been reported to have negative effects on the overall survival of patients with several carcinomas; however, the effects of transfusion on the prognoses of patients with esophageal cancer remain controversial. The aim of this study was to evaluate the significance of perioperative allogeneic blood transfusion and other prognostic factors for patients with resectable esophageal squamous cell carcinomas (ESCCs). The clinicopathologic data and survival outcomes of 345 patients with middle and lower thoracic ESCCs who underwent radical esophagectomies were analyzed. One hundred sixty-seven patients who received perioperative erythrocyte transfusions were compared with 178 patients who did not. The receipt of perioperative blood transfusion was associated with an increased frequency of postoperative complications ($P<0.05$). Moreover, the 5-year overall survival rates of non-transfusion patients and transfusion patients were 40.3% and 22.6%, respectively ($P<0.05$). Multivariate analyses revealed that perioperative allogeneic erythrocyte transfusion together with vascular invasion, the number of lymph node metastases, and pathological TNM stage were independent prognostic factors for the survival of patients with ESCCs ($P<0.05$). Perioperative allogeneic erythrocyte transfusions were associated with more frequent postoperative complications and poorer overall survival for patients with ESCCs who underwent radical esophagectomies.

Keywords: Esophageal squamous cell carcinoma, allogeneic erythrocyte transfusion, postoperative complications, prognosis

Introduction

Esophageal cancer (EC) is the eighth most common malignant neoplasm and sixth leading cause of cancer death worldwide and accounted for approximately 18,170 new cases and 15,450 deaths in the United States in 2014 [1, 2]. However, the morbidity and mortality are much higher in China [3]. Esophagectomy is the primary curative treatment and provides the optimal chance for long-term survival for patients diagnosed with ECs. Unfortunately, despite the administration of comprehensive treatment for EC, the majority of patients eventually develop local recurrent or distant metastatic disease, and the treatments do not improve the poor prognoses by much [4]. The overall 5-year survival rate for esophageal cancer is less than 30% [5, 6]. Many factors are responsible for the poor outcomes of patients with resectable esophageal cancer, and the confirmed prognostic indicators include vascular invasion, the depth of the tumor, lymph node status and distal metastasis [7, 8].

Transfusion has long been vital measure for ensuring the safety of surgeries during the perioperative period. However, the risks associated with allogeneic blood transfusion, such as anaphylactic reactions, infections and graft versus host disease cannot be completely avoided. Furthermore, the immunosuppressive effects caused by transfusion may have deleterious effects on the overall survivals of patients with a variety of solid tumors, and this issue has received attention [9, 10]. In recent research,

Table 1. The Relationships Between Transfusion and Clinicopathologic Features [*N*=345, *n* (%)]

	Transfusion (*n*=167, 48.4%)	Non-transfusion (*n*=178, 51.6%)	χ^2 or *t* value	*P* value
Gender				
Male	121 (72.5)	160 (89.9)	17.33[d]	<0.001
Female	46 (27.5)	18 (10.1)		
Age (y)				
<60	62 (37.1)	132 (74.2)	48.009[d]	<0.001
≥60	105 (62.9)	46 (25.8)		
Smoking history				
Index<200	76 (45.5)	88 (49.4)	0.533[d]	0.465
Index≥200	91 (54.5)	90 (50.6)		
Type of surgery				
Ivor-Lewis procedure	59 (35.3)	70 (39.3)	0.588[d]	0.443
Sweet procedure	108 (64.7)	108 (60.7)		
Tumor location				
Middle	98 (58.7)	106 (59.6)	0.027[d]	0.870
Lower	69 (41.3)	72 (40.4)		
Tumor length				
<5 cm	116 (69.5)	121 (68.0)	0.088[d]	0.766
≥5 cm	51 (30.5)	57 (32.0)		
Vascular invasion				
With	8 (4.8)	7 (3.9)	0.152[d]	0.696
Without	159 (95.2)	171 (96.1)		
Differentiation				
Good	10 (6.0)	26 (14.6)	19.588[d]	<0.001
Moderate	135 (80.8)	105 (59.0)		
Poor	22 (13.2)	47 (26.4)		
Upper incisal margin				
Positive	7 (4.2)	10 (5.6)	0.374[d]	0.541
Negative	160 (95.8)	168 (94.4)		
Depth of invasion				
Tis	2 (1.2)	6 (3.4)	9.296[d]	0.054
T_1	15 (9.0)	24 (13.5)		
T_2	20 (12.0)	29 (16.3)		
T_3	101 (60.5)	80 (44.9)		
T_4	29 (17.4)	39 (21.9)		
Lymph node status				
N_0	85 (50.9)	116 (65.2)	7.215[d]	0.007
N_1	82 (49.1)	62 (34.8)		
pTNM stage[a]				
0	2 (1.2)	6 (3.4)	3.276[d]	0.513
I	15 (9.0)	18 (10.1)		
II	61 (36.5)	67 (37.6)		
III	57 (34.1)	62 (34.8)		
IVa[b]	32 (19.2)	25 (14.0)		
Neoadjuvant therapy				
Yes	22 (13.2)	19 (10.7)	0.514[d]	0.473
No	145 (86.8)	159 (89.3)		
Adjuvant therapy				

Yes	43 (25.7)	55 (30.9)	1.124[d]	0.289
No	124 (74.3)	123 (69.1)		
Level of Hb before surgery (g/L)	127.11±17.50	135.20±15.58	4.541[e]	<0.001
Level of ALB before surgery (g/L)	40.93±5.23	41.01±5.04	0.130[e]	0.897
Volume of blood loss *V*/mL	381.50±85.60	220.10±72.20	18.971[e]	<0.001
Red blood cell transfusion amount/U[c]	3.62±2.51	0	18.639[e]	<0.001
Death in the perioperative period	3 (1.8)	2 (1.1)	0.005[d]	0.943
Complications	68 (40.7)	43 (24.2)	10.829[d]	0.001
Pulmonary infection	26 (15.6)	15 (8.4)	4.197[d]	0.040
Pleural effusion	12 (7.2)	9 (5.1)	0.683[d]	0.408
Arrhythmia	9 (5.4)	8 (4.5)	0.147[d]	0.701
Anastomotic leakage	15 (9.0)	6 (3.4)	4.746[d]	0.029
Chyle leakage	6 (3.6)	5 (2.8)	0.171[d]	0.679

[a]The clinicopathologic staging was performed according to the sixth edition of the criteria established by the International Union Against Cancer (UICC) in 1997. [b]All stage IV tumors were located in the lower thoracic segment. [c]One unit equals approximately a 128-mL (115 mL-141 mL) suspension of packed red blood cells. [d]χ^2 value. [e]*t* value. pTNM: pathological tumor node metastasis; Hb: hemoglobin; ALB: albumin.

allogeneic erythrocyte transfusion has been found to be an important prognostic factor that is associated with poor outcomes in patients with carcinomas of the stomach [11], liver [12], lung [13] and the colorectum [14]. However, the significance of allogeneic erythrocyte transfusion in relation to the long-term survival of patients with EC remains controversial [10].

The aim of this study was to evaluate the significance of perioperative allogeneic erythrocyte transfusion and other possible prognostic factors on the survivals of patients with middle and lower thoracic esophageal squamous cell carcinomas (ESCCs) who underwent radical esophagectomies.

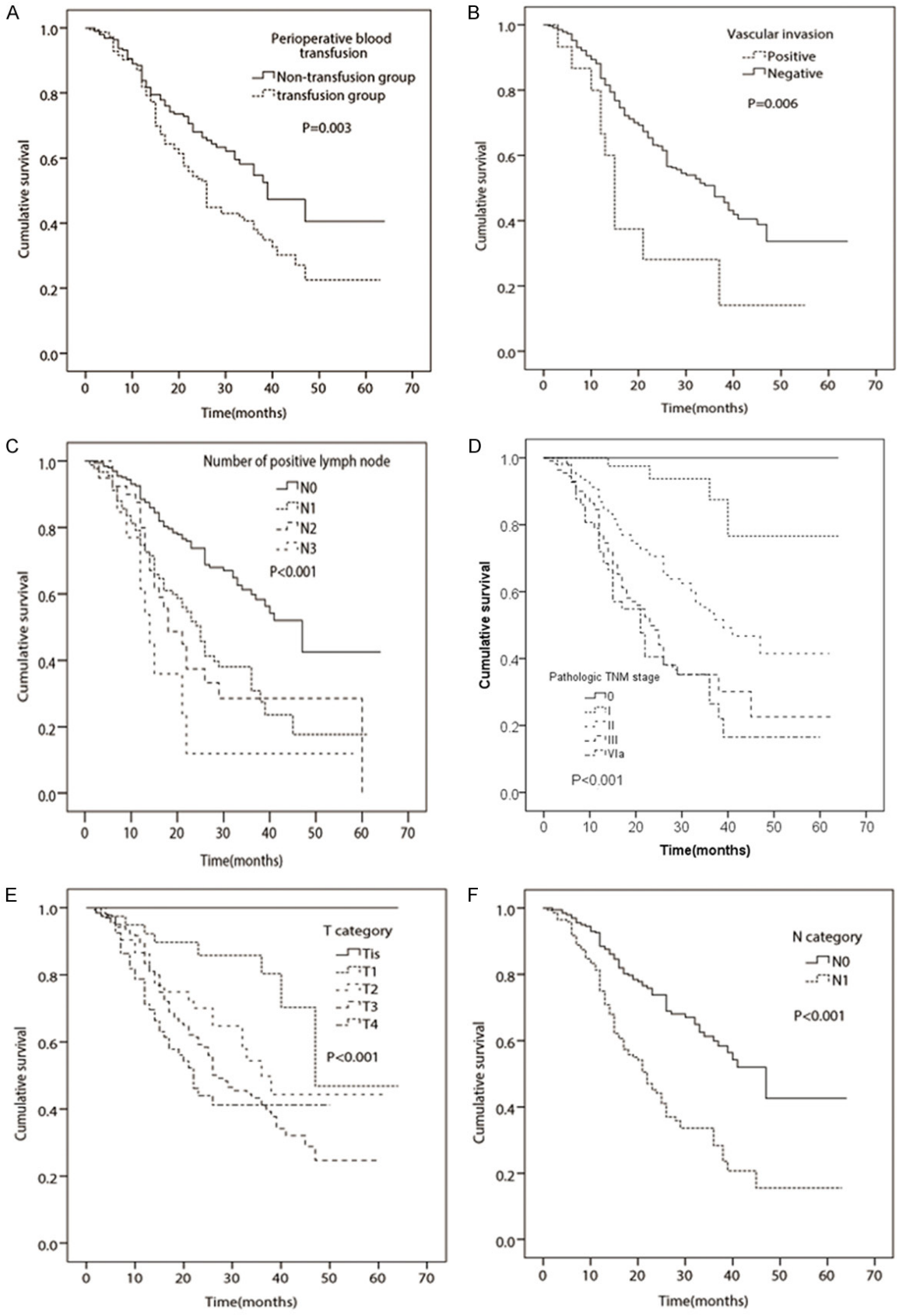
Materials and methods

Patients and criteria

A total of 358 consecutive patients diagnosed with middle and lower thoracic ESCCs who underwent radical esophagectomies from January 2007 to January 2011 at the First Affiliated Hospital of Xi'an Jiaotong University were retrospectively reviewed in this study. All patients had postoperatively pathologically confirmed squamous cell carcinomas of the middle and lower thoracic ESCC. A subset of 13 patients who lacked complete clinicopathological information was excluded from the study. Therefore, 345 patients with complete records were included in the analysis. The patients were divided into two groups according to whether they received perioperative allogeneic red blood cell transfusions. One hundred sixty-seven patients received allogeneic erythrocyte transfusion and 178 patients did not.

Clinicopathological features and survival data

The clinicopathological and survival data were collected from the patients' medical records, and a database of patients with ESCC who underwent esophagectomy that included the following general information of the patients was created: age; gender; cigarette smoking; tumor factors, such as tumor location, length, differentiation, and depth of invasion (T category), lymph node involvement (N category), distant metastasis and pathologic TNM stage; and perioperative factors, such as the volume of blood loss, the volume of the red blood cell transfusion, postoperative complications (a major complication was collected for one patient), hemoglobin (Hb) and albumin (ALB) levels before surgery, and the type of surgery (Ivor-Lewis surgical procedure consisted of celiotomy for gastric conduit preparation prior, then performed esophagectomy through right posterolateral or anterolateral thoracotomy, and finally intrathoracic anastomosis; Sweet surgical procedure consisted of gastric conduit preparation transhiatal through left posterolateral thoracotomy, esophagectomy and intrathoracic anastomosis subsequently). Additionally, neoadjuvant and adjuvant therapy were also involved in. The overall survival (OS) time was calculated from the date of surgery to the last


A
Perioperative blood transfusion
Non-transfusion group
transfusion group
P=0.003
Cumulative survival
Time(months)
B
Vascular invasion
Positive
Negative
P=0.006
Cumulative survival
Time(months)
C
Number of positive lymph node
N0
N1
N2
N3
P<0.001
Cumulative survival
Time(months)
D
Pathologic TNM stage
0
I
II
III
VIa
P<0.001
Cumulative survival
Time(months)
E
T category
Tis
T1
T2
T3
T4
P<0.001
Cumulative survival
Time(months)
F
N category
N0
N1
P<0.001
Cumulative survival
Time(months)

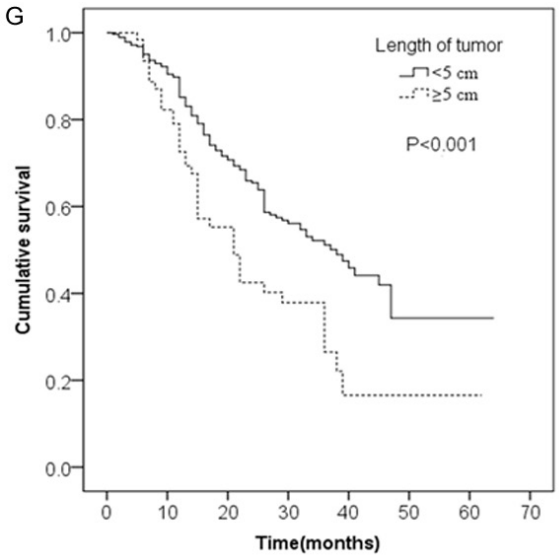


Figure 1. Kaplan-Meier analyses of the prognostic factors for the 345 patients with resectable esophageal squamous cell carcinomas (ESCCs). Perioperative allogeneic erythrocyte transfusion (A), vascular invasion (B), number of positive lymph nodes (C), pathological TNM stage (D), T category (E), N category (F) and tumor length (G) were significantly associated with the overall survival of the patients with middle and lower thoracic ESCCs who underwent radical esophagectomies.

follow-up of death, and the last follow-up assessments were conducted in December 2014. The pathological stages of the ECs were performed according to the sixth edition of the criteria established by American Joint Committee on Cancer and International Union Against Cancer (AJCC/UICC).

Statistical analysis

The statistical analyses were performed with the SPSS version 19.0 software (IBM, Chicago, IL, USA). Values for the continuous data are expressed as the means ± the standard errors and were compared using two-sample *t*-tests or Mann-Whitney *U* tests. Categorical data were evaluated with the chi-square test or Fisher's exact test. Univariate analyses of the overall survival were performed with the Kaplan-Meier method and compared with log-rank tests. The factors that were found to be significant ($P<0.05$) in the univariate analyses were included in a multivariate analysis using a backward stepwise procedure. The multivariate analysis of survival was performed with the Cox proportional hazard model. *P* values below 0.05 were considered statistically significant.

Results

Comparison of clinicopathological features

A total of 345 patients with complete data and confirmed ESCCs who underwent radical esophagectomy were enrolled in this research. There were 281 (81.4%) males and 64 (18.6%) females, and the median age at operation was 59.3 years with a range of 37 to 80 years. According to the criteria for pathological stage classification, the majority of the patients had advanced disease; a total of 304 (88.1%) patients had stage II-IVa disease. Moreover, 33 patients (9.6%) were classified as stage I, and 8 patients were stage 0.

The clinicopathological features of the 345 patients were compared between the two groups, and the results are displayed in **Table 1**. The analyses revealed that allogeneic blood transfusions were performed more frequently in patients over the age of 60 years ($P<0.001$), and the proportion of patients who received blood transfusion was significantly higher in female, compared with non-transfusion patients ($P<0.001$). Additionally, allogeneic blood transfusions were associated with the lymph node metastases ($P=0.007$) and differentiation ($P<0.001$). However, there were no significant differences in smoking history, vascular invasion, the depth of tumor invasion, neoadjuvant therapy, adjuvant therapy, or pathologic TNM stage between the two groups.

Comparison of perioperative related indicators

The pre-operative Hb levels of the transfusion and non-transfusion groups were 127.11±17.50 g/L and 135.20±15.58 g/L, respectively. The blood loss volumes during surgery between the two groups were 381.50±85.60 mL and

Table 2. Univariate Analyses of the 5-year Overall Survivals of Patients with ESCCs

Feature	Cases	Median survival (month)	5-year overall survival rate (%)	*P* value
Gender				
Male	281	39.3	33.3	0.254
Female	64	33.5	30.1	
Age (y)				
<60	194	39.2	33.7	0.122
≥60	151	32.4	30.0	
Smoking				
Index<200	164	38.0	37.1	0.146
Index≥200	181	31.5	28.7	
Type of surgery				
Ivor-Lewis procedure	129	36.8	35.9	0.691
Sweet procedure	216	32.1	30.7	
Perioperative blood transfusion				
Transfusion	167	27.8	22.6	0.003
Non-transfusion	178	39.5	40.3	
Tumor length				
<5 cm	237	40.9	38.0	<0.001
≥5 cm	108	23.8	18.7	
Tumor location				
Middle	204	33.6	30.3	0.277
Lower	141	37.8	34.0	
Differentiation				
Good	36	33.1	25.0	0.292
Moderate	240	39.0	36.1	
Poor	69	24.1	20.7	
Vascular invasion				
Positive	15	17.1	15.5	0.006
Negative	330	37.8	38.2	
Upper incisal margin				
Positive	17	28.4	26.2	0.666
Negative	328	38.8	35.2	
Depth of tumor invasion (T category)				
Tis	8		100	<0.001
T_1	39	47.0	50.0	
T_2	49	37.3	45.5	
T_3	181	27.8	24.7	
T_4	68	21.6	40.2	
Regional lymph node status (N category)				
N_0	201	47.5	45.1	<0.001
N_1	144	23.0	18.9	
Number of positive lymph nodes[a]				
N_0	201	47.5	45.1	<0.001
N_1	77	25.3	20.8	
N_2	38	19.0	0	
N_3	29	15.3	10.0	

220.10±72.20 mL, respectively. The mean perioperative blood transfusion amount in the transfusion patients was 3.62±2.51 U. The incidences of total postoperative complications (including pulmonary infection, pleural effusion, arrhythmia, anastomotic leakage, and chyle leakage) in transfusion and non-transfusion groups were 40.7% and 24.2%, respectively. Furthermore, the incidences of pulmonary infection in transfusion and non-transfusion groups were 15.6% and 8.4%, respectively, and the incidences of anastomotic leakage in transfusion and non-transfusion groups were 9.0%, 3.4%, respectively. All of these differences between the two groups were significant. However, there were no significant differences in the preoperative ALB levels or mortality in perioperative period between the two groups.

Prognostic factors for long-term survival

The median follow-up time was 42.2 months and ranged from 3 to 68 months. The median survival time of the 345 patients was 35.5 months, and the overall 5-year survival rate was 31.4%. The 5-year overall survival rates of the non-transfusion patients and transfusion patients were 40.3% and 22.6%, respectively. This difference in survival

pTNM stage				
0	8		100	<0.001
I	33		75.2	
II	128	42.8	45.1	
III	119	24.0	24.4	
IV[a]	57	21.7	19.8	
Neoadjuvant therapy				
Yes	41	39.2	34.5	0.226
No	304	34.1	30.7	
Adjuvant therapy				
Yes	98	38.2	36.6	0.084
No	247	33.6	29.8	
Complications				
Yes	111	30.7	28.6	0.125
No	234	38.8	34.8	
Pulmonary infection				
Yes	41	29.8	30.0	0.792
No	304	37.0	32.9	
Pleural effusion				
Yes	21	34.6	29.8	0.668
No	324	35.8	32.0	
Arrhythmia				
Yes	17	33.2	32.7	0.724
No	328	37.0	30.3	
Anastomotic leakage				
Yes	21	27.8	26.9	0.107
No	324	36.9	33.8	
Chyle leakage				
Yes	11	29.6	28.7	0.224
No	334	35.8	33.2	

pTNM: pathological tumor node metastasis; [a]N_0: no lymph node metastasis; N_1: one or two lymph node metastases; N_2: three to six lymph node metastases; and N_3: more than six lymph node metastases.

between the two groups was significant (P=0.003).

Univariate analyses performed using the Kaplan-Meier method revealed that the length of the tumor, vascular invasion, the depth of tumor invasion, regional lymph node involvement, the number of lymph node metastases (N_0=0, N_1=1-2, N_2=3-6, and N_3≥7), pathological TNM stage, and perioperative allogeneic erythrocyte transfusion were associated with significant differences in survival between the two groups (P<0.05). The Kaplan-Meier cumulative survival curves are illustrated in **Figure 1**. Gender, age, smoking history, tumor location, tumor differentiation, incisal margin status, type of surgical procedure, neoadjuvant and adjuvant therapy, and postoperative complications were not significantly related to the overall survival (P>0.05, **Table 2**).

Multivariate analysis revealed that perioperative allogeneic erythrocyte transfusion (HR: 1.386, P=0.011), vascular invasion (HR: 0.482, P=0.024), the number of lymph node metastases (HR: 1.404, P=0.009), and pTNM stage (HR: 1.736, P= 0.033) were independent prognostic factors for the survival of the patients with middle and lower thoracic ESCCs (**Table 3**).

Discussion

Negative effects of the immunosuppressive effect of allogeneic blood transfusion on the long-term survivals of patients with a variety of solid tumors have been reported [11-14]. Moreover, in combination with the trauma caused by surgery and anesthesia in the perioperative period, this immunosuppressive effect results in greater frequencies of postoperative complications among transfusion patients [15, 16]. However, surgeons typically make decisions regarding transfusions in haste to ensure the safety of the operation. Therefore, a portion of researchers have declared that measures should be taken to avoid perioperative allogeneic blood transfusions, such as preoperative autologous blood collection and the perioperative use of recombinant human erythropoietin (rHu-EPO) stimulation with ferric oxide and vitamin B12 supplementation [17].

Previous studies have established the possible mechanisms responsible for the poor out-

Table 3. Multivariate analysis of the prognostic factors affecting the overall survivals of patients with esophageal carcinomas using a cox regression model

Risk factor	*SE*	Wald	*P* value	Hazard ratio	95% *CI*
Tumor length	0.106	0.226	0.635	0.951	0.772-1.171
Vascular invasion	0.323	5.111	0.024	0.482	0.256-0.907
T category	0.333	0.146	0.702	1.136	0.591-2.183
N category	0.332	0.944	0.331	0.724	0.378-1.388
Number of positive LN	0.129	6.895	0.009	1.404	1.090-1.808
pTNM stage	0.259	4.548	0.033	1.736	1.046-2.881
Perioperative blood transfusion	0.129	6.394	0.011	1.386	1.076-1.784

SE: standard error; *CI*: confidence interval; LN: lymph node; pTNM: pathological tumor node metastasis.

comes of patients who received allogeneic red blood cells transfusions. Allogeneic blood transfusions can not only increase the number and activity of suppressor T lymphocytes but can also reduce the function of natural killer cells, and these effects can obviously reduce the non-specific immune response and ultimately result in increases in the frequencies of cancer recurrence and metastasis [18-20]. Quigley et al. found that endothelial cells co-cultured with allogeneic leukocytes can reduce the expression of intercellular adhesion molecules (ICAMs) [21], which are important factors that decrease the metastatic potential of cancer cells as confirmed in previous studies [22]. Thus, the hypothesis that leukocyte-depleted transfusions may eliminate the negative influence on survival has been proposed [23]. Additionally, Patel et al. found that allogeneic red cell transfusions can obviously increase the levels of serum vascular endothelial growth factor (VEGF) [24], and VEGF has been confirmed to play an important role in the promotion of tumor angiogenesis in previous studies [25]. Furthermore, increases in the risk of thrombosis and alterations of the microenvironment of the tumor due to transfusion may also contribute to the poor survivals of patients with ESCC [26, 27].

In the current study, allogeneic blood transfusion was significantly correlated with gender ($P<0.001$), age ($P=0.002$), differentiation ($P<0.001$), regional lymph node status ($P=0.007$), preoperative Hb level ($P<0.001$), blood loss volume during surgery ($P<0.001$; **Table 1**). Which shown that female patients over the age of 60 years were more likely to receive blood transfusion. Additionally, patients diagnosed with lymph node metastasis was closely associated with transfusion. Furthermore, preoperative Hb level and blood loss volume were also important transfusion-related factors. Although allogeneic blood transfusion was obviously affected by other variables, the multivariate analysis revealed that allogeneic blood transfusion was a significant independent predictive factor for patients with ESCC (**Tables 2** and **3**), which presented a strong evidence that allogeneic blood transfusion had a negative effect on the survival of ESCC. Naturally, prophylactic preoperative rHu-EPO treatment and the minimization of surgical trauma seemed to be vital for decreasing the frequency of perioperative transfusion based on the observed differences between the two groups. More attention should be focused on patients who receive perioperative transfusions even if they present with early-stage disease. Additionally, in this research, we also found that the postoperative complications including pulmonary infection and anastomotic leakage occurred more frequently in the patients who received allogeneic erythrocyte transfusions than in the patients who did not receive transfusions, which shown that pulmonary infection and anastomotic leakage were also significant transfusion-related factors. Measures should be taken to reduce the incidence of this complications to avoid the allogeneic blood transfusion. Typically, postoperative complications seem to be related to the general preoperative condition of the patient and surgical trauma and reflect the perioperative mortality to a certain extent. However, Nozoe et al. found that a high incidence of postoperative complications predicted poor long-term survivals for patients with ESCCs [15], but this result was not confirmed in the current study. Furthermore, we found that the vascular invasion, as well as the number of lymph node metastases and pTNM stage also significantly affected long-term survival of ESCC patients, and these observations are consistent with previous research results [7, 8].

The present study found that patients with ESCCs who did not receive allogeneic blood transfusions exhibited significantly better overall survival than the patients who received blood transfusions. Ling et al. reported that one unit (U) of blood transfusion is the cutoff value for affecting the prognoses of patients [28]. Furthermore, some researchers have identified blood transfusions of 2 U or more as a predictive factor in ESCC patients [29-31]. In contrast, Swisher et al. demonstrated that the association between greater transfusion volumes and poor survival is actually attributable to an increase in the frequency of postoperative complications [16]. However, it remains questionable whether this different result was caused by a statistical accident or simply reflects the circumstances that necessitate transfusions. Therefore, a prospective trial regarding the effects of allogeneic blood transfusions on the survival of ESCC patients should be performed to clarify these controversial results.

Moreover, we observed the expected results that the number of lymph node metastases and not the locations of the lymph node metastases was an important factor for predicting the long-term survival of ESCC patients based on multivariate analysis. Therefore, the new N classification system of the seventh edition of the AJCC from 2009 may have better predictive value for patients with ESCC who undergo radical esophagectomy [32]. However, we used the older criteria to stage the patients in this study because the majority of the patients were diagnosed with ESCC prior to the emergence of the new standards. In addition, we found that patients with ESCC received neoadjuvant and adjuvant therapy did not present significant advantages of overall survival in this research, a possible explanation due to that patients received neoadjuvant or adjuvant therapy are more likely to emerge with advanced stage disease in our institution. Further researches are required to identify this in larger, longer-term studies.

As a retrospective study in single institution, limitations are unavoidable. Disease-free survival (DFS) and other possible transfusion-related factors were not included in the analyses. To eliminate the effects of these factors and confirm the effect of perioperative allogeneic erythrocyte transfusion on the prognoses of patients with resectable ESCCs, a carefully designed prospective study should be performed.

In summary, our study indicates that perioperative allogeneic erythrocyte transfusion in addition to vascular invasion, the number of lymph node metastases, and pathological TNM stage are independent predictive factors of the long-term survival of patients with middle and lower thoracic ESCCs. Moreover, we found that allogeneic blood transfusion was associated with an increase in the incidence of postoperative complications. As allogeneic blood transfusion is obviously affected by other variables, a prospective trial is needed to confirm these results regarding an issue that has received far less attention than it deserves. Furthermore, measures should be adopted to avoid allogeneic blood transfusions to improve the outcomes of the patients who undergo radical esophagectomy.

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Disclosure of conflict of interest

None.

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