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Correlations of Hemoglobin Level and Perioperative Blood Transfusion with the Prognosis of Gastric Cancer: A Retrospective Study

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Data Interpretation D
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Background: This study was designed to explore the correlations of hemoglobin level (Hb) and perioperative blood transfusion with the prognosis of gastric cancer (GC).

Material/Methods: Our study consisted of 210 patients with GC who all received a D2 radical operation. These patients were assigned into three groups: 68 cases in group A (blood transfusion >5 U); 59 cases in group B (blood transfusion <5 U); 83 cases in group C (without blood transfusion). A 5-year follow-up was conducted to evaluate the disease-free survival of the patients. Univariate analysis was performed to reveal the relationship between the indicators and the patients with GC. Kaplan-Meier method was employed to analyze the survival rate of patients, and Cox regression analysis was applied to determine the independent prognostic factors of GC.

Results: The univariate analysis indicated that age, perioperative blood transfusion amount, TNM staging, maximal tumor diameter, differentiation degree and invasion degree were associated with the prognosis of GC. The Kaplan-Meier curve showed that the disease-free survival rate was declined in the patients who were older, those received more amount of blood transfusion, those in advanced TNM staging, those had larger tumor diameter, and those with decreased degree of differentiation and invasion. Cox regression analysis indicated that perioperative blood transfusion, maximal tumor diameter and invasion degree were the independent factors affecting disease-free survival of the GC.

Conclusions: Our study revealed that large amount of perioperative blood transfusion leads to poor prognosis of GC.

MeSH Keywords: Blood Transfusion • Disease-Free Survival • Hemoglobin A • Perioperative Period • Prognosis

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Background

Gastric cancer (GC), developing from the lining of the stomach, is the fifth major cause of cancer incidence and also the third major cause of cancer-associated death worldwide [1]. It is recorded there are 989,600 newly diagnosed GC cases and 738,000 deaths from this disease worldwide in 2008 and approaching 70% of these cases occurred in the developing countries [2]. The 5-year survival rate of patients diagnosed with operable disease who receive perioperative chemotherapy is 36%, unfortunately, the 5-year survival of patients with advanced or metastatic GC is only 5–20% with mean overall survival no longer than one year [3,4]. Currently, surgical treatment is the most important approach for GC, and radical resection is the only means for GC patients being cured [5].

To our knowledge, the radical treatment for GC is shown to combine the radical gastrectomy together with dissection of regional lymph node, and D2 gastrectomy is now strongly recommended in the treatment for patients diagnosed with advanced GC around the world [5,6]. Unluckily, gastrectomy with lymphadenectomy often results in long operation time, overwhelmed bleeding and significant increases of minor complications [7]. During the surgery, especially perioperative period, such as gastrectomy and lymphadenectomy, blood transfusion is often required due to the complexity of GC and excessive blood loss [8,9]. Interestingly, recent evidence demonstrated that anemia was implicated in the long-term survival and prognosis of GC patients [10]. Additionally, the Hb levels could affect quality of life improvements in anemic cancer patients [11]. In this respect, understanding the potential relationship between Hb levels and perioperative blood transfusion, and prognosis of GC would help to provide the theoretic basis for the prognostic improvement of GC. However, the relationship between perioperative allogeneic blood transfusions and poor prognosis in patients with GC still remains controversial [12]. Recently, prognostic effects of perioperative blood transfusions on GC patients has been analyzed through retrospective study, while in our prospective research, we investigated the prognostic significance of Hb level and perioperative blood transfusion and how these two factors influenced the survival rate of GC patients.

Material and Methods

Patients

A total of 210 GC patients (128 males and 82 females, age between 36 and 79 years, with median age of 60 years) with complete follow-up data, diagnosed and treated in Spinal Surgical Diagnosis and Treatment Center, The Central Hospital of Hubei Enshi Tujia and Miao Autonomous Prefecture between October 2008 and December 2010, were enrolled into our study. The degree of differentiation was: 49 well differentiated cases, 62 moderately differentiated cases, and 99 poorly differentiated cases. Tumor location was: 65 cases located in gastric antrum area, 79 cases located in gastric antrum junction, and 66 cases located in fundus ventriculi or gastric body region. TNM staging [13] was: 47 cases in Stage I, 49 cases in Stage II, and 144 cases in Stage III. Tumor diameter was: 121 cases at <5 cm and 89 cases at ≥5 cm. The degree of invasion was: 34 cases at T1 level, 28 cases at T2 level, 78 cases at T3 level, and 70 cases at T4 level. According to the amount of blood transfused during the perioperative period, the patients were divided into three groups with 68 cases in group A (blood transfusion >5 U), 59 cases in group B (blood transfusion <5 U), and 83 cases in group C (without blood transfusion). Diagnostic criteria [14] was hard mass with nodules in the upper abdomen accompanied by tenderness and lymph node enlargement at the left clavicle; reduction of gastric juices and decreased gastric acidity; 60–80% showing persistent positive fecal occult blood tests. Inclusion criteria was: patients confirmed as GC by preoperative gastroscopy and tissue biopsy; patients receiving no anti-tumor therapy before the operation; and patients undergoing laparoscopic operation or open D2 radical gastrectomy. Exclusion criteria: was patients receiving preoperative anti-tumor therapies including neoadjuvant chemotherapy and radiation therapy; advanced patients undergoing palliative operation; and patients with other metabolic diseases like diabetes mellitus, hyperthyroidism, and hypothyroidism. This study was approved by the Ethics Committee of Spinal Surgical Diagnosis and Treatment Center, The Central Hospital of Hubei Enshi Tujia and Miao Autonomous Prefecture, and informed consent was obtained from each participant.

Operation method

After endotracheal intubation with general anesthesia, the patient was placed in the supine position with legs set apart. The incision was about 15–20 cm in the middle of the abdomen, then, the abdomen was cut step by step, such that the abdominal cavity was comprehensively explored. The D2 radical gastrectomy for GC was performed in accordance with *Japanese classification of gastric carcinoma: 3rd English edition*[15], and the lymph nodes in 11p, 7, 9, 8a, 12a and 12p group were cleared from left to right and from down to up. Catheters and peritoneal drainage tubes were indwelled after the operation. Adjuvant chemotherapy of capecitabine combined with oxaliplatin was performed postoperatively for patients, except for patients who could not take combined chemotherapy. The concentration of capecitabine was 1,000 mg/m^2. Patients were expected to take capecitabine two times per day, after a meal, once in the morning and once in the evening for 14 consecutive days. An intravenous infusion of 130 mg/m^2 oxaliplatin was given on the first day of capecitabine therapy, and 21 days was considered one cycle; there were a total of six cycles.

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Peripheral venous blood was collected in the hospital for routine blood examination from each patient within 24 hours prior to their radical resection. Preoperative Hb was detected by blood cell detection classification technique [16], and the patients with less than 6 g/dL Hb were assigned to the severe anemia group, while the patients with more than 6 g/dL Hb were classified into the non-severe anemia group. In addition, patients with ≥3.5 g/dL albumin (ALB) were regarded as normal, and patients with ≥6.5 g/dL total protein (TP) were also recognized as normal.

Follow-up

Follow-up was performed by telephone, letter, or visit starting from the day when the patient discharged from the hospital to death or loss of access. Five years was defined as the statistical follow-up period for recurrence. The follow-up included the general condition of the patients, postoperative treatments, and detailed records for the diagnosis of recurrence including time of recurrence and location of recurrence. The clinical pathological data were then grouped, and the disease-free survival rate was calculated using the life table method.

Statistical analysis

All data were analyzed by SPSS (SPSS Inc., Chicago, IL, USA) 20.0 statistical software. Measurement data were demonstrated by mean ± standard deviation, with the comparison between two groups analyzed by *t*-test, and comparison among different groups analyzed by independent sample *t*-test; count data were expressed as a percentage or rate and examined by χ^2 test; Kaplan-Meier method was applied for single-factor survival analysis, log-rank was used in significant level analysis among all groups, and Cox regression was adopted in evaluation of the influence of multiple factors on the prognosis of GC patients. The level of significance was set as $p<0.05$.

Results

Comparisons of clinicopathological characteristics of GC patients in the three groups

The differences in age, preoperative Hb, TNM staging, differentiation degree, maximal tumor diameter, and invasion degree were significant among the three groups (A: blood transfusion >5 U; B: blood transfusion <5 U; C: without blood transfusion). The amount of perioperative blood transfusion was significantly elevated in the patients who were older, those who had declined Hb levels, those in advanced TNM stage, those who had larger tumor diameter, and those with higher degree of invasion (all $p<0.05$). However, the differences in gender, preoperative ALB and TP, and tumor location were not statistically significant among the three groups (all $p>0.05$) (Table 1).

Comparisons of Hb levels of GC patients in the three groups

There was no significant difference in age, gender, TNM staging, maximal tumor diameter, differentiation degree, tumor location, and invasion degree between the severe anemia group and non-severe anemia group (all $p>0.05$) (Table 2).

Univariate analysis of the 5-year disease-free survival of GC patients

As shown in the single-factor analysis, gender, preoperative ALB, TP and Hb, and tumor location failed to have an effect on the prognosis of GC (all $p>0.05$) while age, perioperative blood transfusion amount, TNM staging, maximal tumor diameter, differentiation degree and invasion degree were associated with the prognosis of GC (all $p<0.05$) (Table 3). Kaplan-Meier analysis of enrolled age, perioperative blood transfusion amount, TNM staging, maximal tumor diameter, differentiation degree and invasion degree found that the disease-free survival rate was significantly lower in the patients who were older, those who received larger volume of blood transfusion, those in advanced TNM stage, those who had larger tumor diameter, and those with higher degree of differentiation and invasion (all $p<0.05$) (Figure 1).

Cox regression analysis of the independent prognostic factors for GC patients

All variables in the univariate analysis were added into Cox risk ratio function. It was suggested that the independent factors affecting disease-free survival of the GC patients were as follows: perioperative blood transfusion amount ($p<0.05$, the median disease-free survival was 28 months for the patients with more than 5 U perioperative blood transfusion, 41 months for the patients with less than 5 U perioperative blood transfusion, and 48 months for the patients with no blood transfusion), maximal tumor diameter ($p<0.05$, the median disease-free survival was 32 months for the patients with maximal tumor diameter more than 5 cm and 52 months for the patients with maximal tumor diameter less than 5 cm) and invasion degree ($p<0.05$, the median disease-free survival was 27 months for the patients at T4 levels, 42 months for the patients at T3 levels, 48 months for the patients at T2 levels, and 53 months for patients at T1 level). However, age, gender, preoperative ALB, TP and Hb, differentiation degree, TNM staging, and tumor location were non-major prognostic factors (Table 4).

Discussion

In this study, we recruited 210 GC patients as our study population to investigate the prognostic impacts of Hb level and

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Table 1. Comparisons of clinicopathological characteristics of patients with gastric cancer among the group A (blood transfusion >5 μ), group B (blood transfusion <5 μ) and group C (without blood transfusion).

Characteristic	Group A (n=68)	Group B (n=59)	Group C (n=83)	*P* value
Age (years)				<0.001
<60	16	23	59	
≥60	52	36	24	
Gender				0.915
Male	41	35	52	
Female	27	24	31	
Preoperative ALB (g/dl)	36.05±3.21	35.21±3.24	34.92±4.01	0.142
Preoperative TP (g/dl)	66.17±4.15	65.39±4.27	65.62±5.01	0.602
Preoperative Hb (g/dl)	6.97±2.18	9.15±2.72	10.52±2.14	<0.001
TNM staging				0.003
I	6	15	26	
II	13	14	22	
III	49	30	35	
Tumor diameter				0.004
<5 cm	28	38	55	
≥5 cm	40	21	28	
Differentiation degree				<0.001
Well-differentiated	12	9	28	
Moderately differentiated	13	16	33	
Poorly differentiated	43	34	22	
Tumor location				0.973
Gastric antrum	22	19	24	
Gastric antrum junction	25	23	31	
Other	21	17	28	
Invasion degree				<0.001
T1	11	11	12	
T2	1	1	26	
T3	9	26	43	
T4	47	21	2	

ALB – albumin; TP – total protein; Hb – hemoglobin; TNM – tumor node metastasis

perioperative blood transfusion on gastric cancer (GC) patients. On the basis of the preoperative Hb level, intraoperative blood transfusion, and follow-up, we concluded that perioperative blood transfusion was a risk factor for the prognosis of GC patients, indicating that a larger volume of perioperative blood transfusion may shorten the disease-free survival of patients. However, we did not find a relationship between Hb level and prognosis of GC. Previous studies have shown that the amount of blood transfusion of patients receiving curative surgery for GC was related to the long-term prognosis based on the predicated outcomes of all-cause mortality, cancer-related death and recurrence [9,17].

In our study, the amount of perioperative blood transfusion was significantly elevated with increased age, declined Hb, enhanced TNM stage, enlarged tumor diameter, and strengthened invasion degree. According to Yamashita et al., patients diagnosed with advanced GC commonly present with both hematogenous

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Table 2. The relationship between hemoglobin levels and clinicopathological characteristics of patients with gastric cancer.

Characteristic	Preoperative Hb level		*P* value
	Severe anemia group (n=53)	Non-severe anemia group (n=157)	
Age (years)			0.581
<60	23	75	
≥60	30	82	
Gender			0.229
Male	36	92	
Female	17	65	
TNM staging			0.211
I	8	39	
II	16	33	
III	29	85	
Tumor diameter			0.429
<5 cm	33	88	
≥5 cm	20	69	
Differentiation degree			0.148
Well-differentiated	16	33	
Moderately differentiated	18	44	
Poorly differentiated	19	80	
Tumor location			0.093
Gastric antrum	14	51	
Gastric antrum junction	16	63	
Other	23	43	
Invasion degree			0.169
T1	13	21	
T2	4	24	
T3	20	58	
T4	16	54	

Hb – hemoglobin; TNM – tumor node metastasis.

and lymphatic metastatic progression [18], possibly leading to difficulties in surgery such as excessive blood loss and greater incidence of postoperative complications compared with the patients with early stage of GC. Previous research reported by Kanda et al. indicated that GC patients with older age, lower preoperative Hb levels, larger tumor size, more deep invasion, and higher pathological UICC stage were more likely to receive blood transfusions, which is indirectly consistent with our results [19].

Importantly, by Cox regression analysis, we also find that the perioperative blood transfusion amount was the independent factor affecting disease-free survival of GC patients. It has been suggested that perioperative blood transfusion is connected with inflammatory response as well as immunosuppression, and developing postoperative morbidity may occur in patients who received blood transfusion [20]. Blood transfusion inhibits cellular immunity by decreasing cutaneous delayed-type

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Table 3. Univariate analysis of the 5-year disease-free survival rate.

Characteristic	5-year PFS rate	*P* value
Age (years)		0.033
<60	53.06% (52/98)	
≥60	38.39% (43/112)	
Gender		0.588
Male	43.75% (56/128)	
Female	47.56% (39/82)	
Preoperative ALB (g/dL)		0.995
<35	45.26% (43/95)	
≥35	45.22% (52/115)	
Preoperative TP (g/dL)		0.132
<65	46.74% (43/92)	
≥65	36.44% (43/118)	
Perioperative blood transfusion		<0.001
Blood transfusion >5 μ	22.06% (15/68)	
Blood transfusion <5 μ	37.29% (22/59)	
Without blood transfusion	69.88% (58/83)	
Preoperative Hb		0.755
Severe anemia group	43.40% (23/53)	
Non-severe anemia group	45.86% (72/157)	
TNM staging		0.007
I	63.83% (30/47)	
II	46.94% (23/49)	
III	36.84% (42/114)	
Maximal tumor diameter		0.004
<5 cm	53.72% (65/121)	
≥5 cm	33.71% (30/89)	
Differentiation degree		0.006
Well-differentiated	61.22% (30/49)	
Moderately differentiated	50.00% (31/62)	
Poorly differentiated	34.34% (34/99)	
Tumor location		0.644
Gastric antrum	43.08% (28/65)	
Gastric antrum junction	43.04% (34/79)	
Other	50.00% (33/66)	
Invasion degree		
T1	58.80%	<0.001
T2	71.40%	
T3	55.10%	
T4	17.10%	

PFS – disease-free survival; ALB – albumin; TP total protein; Hb – hemoglobin; TNM – tumor node metastasis.

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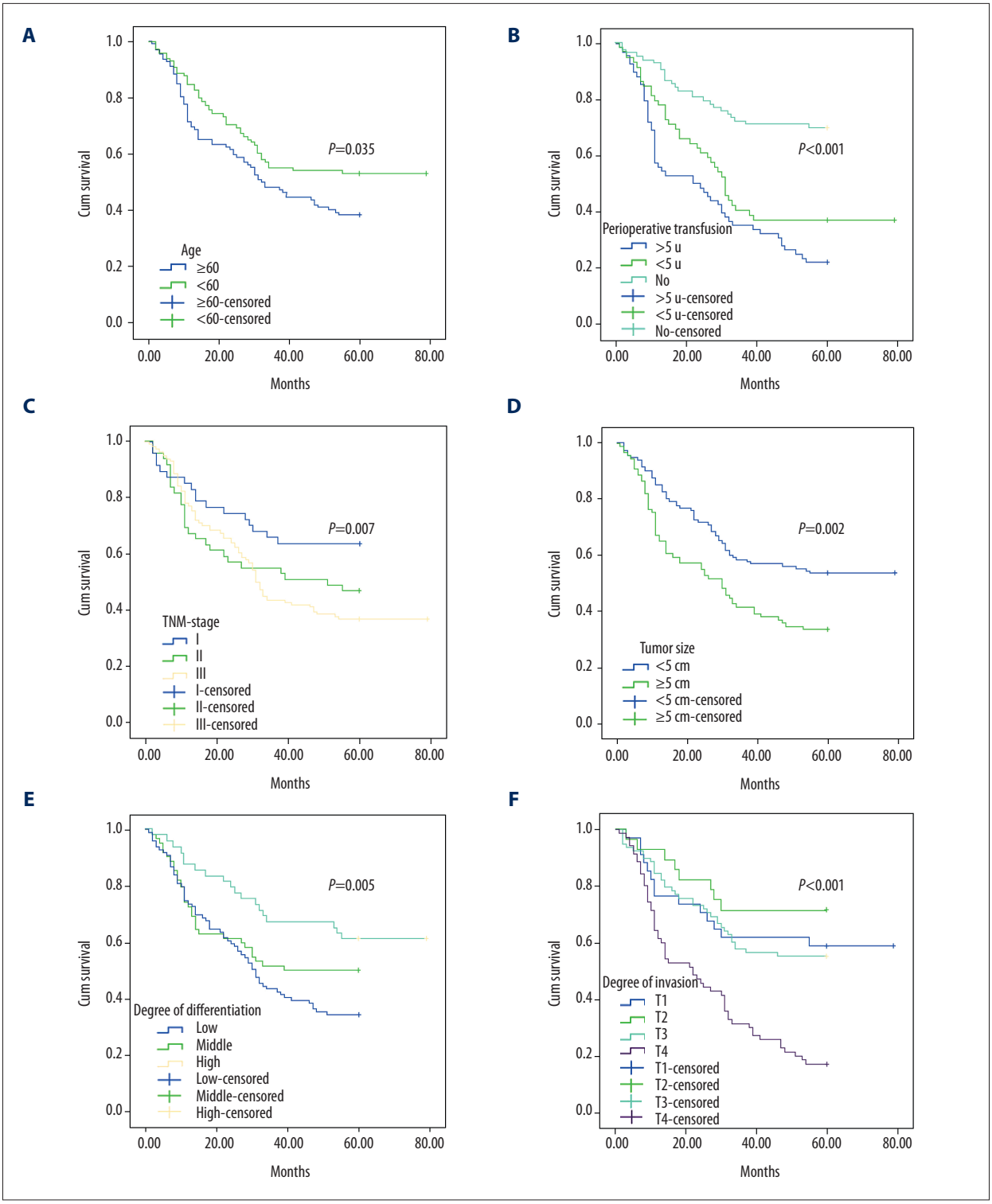

Figure 1. The relationship between clinicopathological characteristics and disease-free survival. (**A**) relationship between age and disease-free survival; (**B**) relationship between amount of perioperative blood transfusion and disease-free survival; (**C**) relationship between TNM staging and disease-free survival; (**D**) relationship between tumor diameter and disease-free survival; (**E**) relationship between differentiation degree and disease-free survival; (**F**) relationship between invasion degree and disease-free survival.

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Table 4. Cox regression analysis of the independent prognostic factors for gastric cancer.

Variable	B	SE	*P* value	OR	95%CI
Age	0.009	0.206	0.963	1.010	0.674–1.512
Gender	0.075	0.204	0.713	1.078	0.722–1.609
Preoperative ALB	–0.015	0.029	0.596	0.985	0.931–1.042
Preoperative TP	0.003	0.022	0.896	1.003	0.961–1.047
Perioperative blood transfusion	1.049	0.319	0.001	2.855	1.529–5.333
Preoperative Hb	0.025	0.045	0.579	1.025	0.938–1.120
TNM stage	0.055	0.125	0.658	1.057	0.827–1.351
Tumor diameter	0.463	0.199	0.020	1.589	1.077–2.347
Differentiation degree	0.008	0.113	0.941	1.008	0.808–1.259
Tumor location	–0.055	0.127	0.668	0.947	0.738–1.215
Invasion degree	0.247	0.107	0.022	1.280	1.037–1.579

B – regression coefficient; SE – standard error; ALB – albumin; TP – total protein; Hb – hemoglobin; TNM – tumor node metastasis; OR – odds ratio; CI – confidence interval.

hypersensitivity, reduction of T-cell proliferation, and inactivation of natural killer cell function, as well as driving the immune system toward a T-helper 2 response from a T-helper 1 response [21]. In addition, it has been found that after blood transfusion, non-specific immune responses, including natural killer cells, inhibition of T lymphocyte activity, and stimuli for antibody production, may suppress the differentiation of lymphocyte and production of lymphokines which restrict the mixed lymphocyte reaction and phagocyte function, resulting in poor prognosis, tumor reoccurrence, and decreased survival rates of GC patients [19,22]. Moreover, blood transfusion could promote the proliferation of tumors through inducing angiogenesis [8]. For example, Patel et al. indicated that blood transfusion stimulated endothelial cell proliferation and angiogenesis [23]. Park et al. reported that patients receiving perioperative blood transfusion were significantly older, had more comorbidity, and were more likely to have advanced disease [24]. Interestingly, the findings obtained from Cox regression analysis implied that maximal tumor diameter and invasion degree were independent factors affecting disease-free survival of GC patients. A former study also considered that the tumor size was an importantly independent prognostic factor for GC patients and pointed out that more concern should be paid to its role in the treatment of GC [25]. At the same time, another research study demonstrated that density of tumor-infiltrating lymphocytes could serve as an independent predictor of regional lymph node metastasis as well as survival in GC patients [26]. Additionally, there was no significant association found between Hb levels and clinicopathological characteristics. Cancer-related anemia is now thought to be caused by a complex interaction between the tumor cell population and the immune system, which ultimately disrupts normal erythropoiesis [27]. Different from our results, Tchekmedyian et al. found that anemia, common in cancer care, was usually related to worsened quality of life and declined physical function, indicating potentially important implications of anemia as a variable which affects the efficacy of cancer therapies [28]. Thus, with regard to the role of Hb level in the prognosis of GC, further investigations, including larger sample sizes, are needed.

Conclusions

We demonstrated that perioperative blood transfusion was negatively related to prognosis of GC patients, indicating that a larger amount of perioperative blood transfusion leads to poorer prognosis of GC. Unfortunately, an association between the Hb level and the prognosis of GC was not found, thus further studies should pay more attention to this subject. Besides, in the clinical setting, proper operative blood transfusion ought to be performed based on the specific condition of patients to achieve better postoperative quality of life. There were some limitations to our study. First, five years of follow-up was a relatively short period, longer periods of follow-up are needed to reveal the long-term influences of perioperative blood transfusion. In addition, the difference in the effect of laparoscopic radical gastrectomy and open radical gastrectomy on postoperative survival should be taken into consideration. Moreover, our finding that preoperative Hb level was not a prognostic factor for GC may have resulted from the differences in samples in severe anemia group and non-severe anemia group, and the fact that there are too many patients in advanced disease stage in our study.

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Conflicts of interests

None.

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