Original Article

The prognostic impact of pretreatment anemia in patients with gastric cancer and nonhypoalbuminemia undergoing curative resection: a retrospective study

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Background: The influence of pretreatment anemia on the prognosis of patients with advanced gastric cancer (GC) remains controversial. We retrospectively examined the impact of pretreatment anemia on the overall survival (OS) of patients with GC with nonhypoalbuminemia undergoing curative resection.

Methods: The clinicopathological data of 2,916 patients with advanced GC who received a radical gastrectomy from 1994 to 2015 were analyzed. The patients were divided into two subgroups by hemoglobin level, <120 and ≥120 g/L. OS was analyzed using the Kaplan-Meier method, and a multivariate Cox proportional hazards model was used to identify the independent prognostic factor.

Results: A total of 1,099 patients were included in our study. The median follow-up duration was 43 (IQR, 24–66) months. The prevalence of anemia was 40.9%. Among these 1,099 patients, 505 (46.0%) had nonhypoalbuminemia. Kaplan-Meier survival analysis showed that patients with GC who were anemic had a poorer OS than patients who were not (5-year OS rate: 58.4% *vs.* 66.8%, P<0.0001). Multivariate analysis revealed that pretreatment anemia was an independent prognostic factor [hazard ratio (HR) =1.455, 95% CI, 1.013–2.09; P=0.043].

Conclusions: Our findings indicate that pretreatment anemia may serve as an independent prognostic factor for patients with advanced GC with nonhypoalbuminemia after radical gastrectomy, especially those with larger tumor size and pT3 disease.

Keywords: Gastric cancer (GC); prognosis pretreatment anemia; non-hypoalbuminemia

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Introduction

Cancer-related anemia is one of the most common comorbidities of malignancy. The prevalence of pretreatment anemia has been reported to be 30–90% in various cancers (1). Previous studies have reported that tumor-associated blood loss, bone marrow involvement, cytokine-mediated disorder, and nutritional deficiencies in iron or folic acid play a crucial role in the initiation and maintenance of cancer-related anemia (2). Pretreatment anemia is commonly observed in cancer patients and

adversely affects the quality of life (QOL) and survival of these patients (3,4).

Gastric cancer (GC) is the fifth most common cancer diagnosed worldwide. GC is the third most common cause of cancer-related deaths (5). Currently, the best strategies for GC are prevention and personalized treatments (6). To date, much effort has been devoted to searching for prognostic factors that may help to precisely calculate the risk of prognosis or recurrence in patients with GC after curative resection. In a Korean cohort that enrolled 1,688 patients with GC who underwent radical gastrectomy, the authors indicated that pretreatment anemia was an independent predictor for overall survival (OS) in TNM stage I and II GC (7). However, in a subsequent Chinese study, the researchers emphasized that it was in TNM stage III, rather than in stages I and II, that pretreatment anemia could serve as an independent prognostic factor for OS (8). Another study presented evidence that pretreatment anemia was not an independent factor for survival (9). The reasons for these inconsistencies could be complex and various across studies. One of the most important reasons for the inconsistencies could be the interference of confounding factors. Chronic occult bleeding, alimentary obstruction, severe complications, malnutrition, weight loss and renal dysfunction are common confounding factors that can also cause pretreatment anemia when initially diagnosed. To control for bias from these confounding factors, we further evaluated the prognostic influence of pretreatment anemia on the survival outcomes of patients with GC with nonhypoalbuminemia.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1649).

Methods

Patients who underwent curative resection for advanced GC between January 1994 and December 2015 were identified from the GC database of the First Affiliated Hospital of Sun Yat-sen University (FAHSYSU) in Guangzhou, China. The exclusion criteria were as follows: patients with remnant stomach cancer or recurrent carcinoma, patients with a personal history of malignancy, patients who received preoperative chemotherapy, *in situ* carcinoma, patients with stage IV and distant metastasis and patients for whom inadequate follow-up data were available. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Medical Ethics Committee of the Seventh affiliated Hospital of Sun Yat-sen University (No: KY-2020-024-01). Individual consent for this retrospective analysis was waived.

Clinical data collection and processing

The following data were collected directly from our GC database by review of the medical records, and no additional calculations or processing were required: age at surgery, sex, tumor size, primary tumor site, preoperative serum carcinoembryonic antigen (CEA) level (ng/mL), Borrmann's classification, type of lymphadenectomy, degree of tumor differentiation, and follow-up status. Moreover, the postoperative pathological T stage (pT), N stage (pN), and final TNM stage were re-encoded according to the eighth American Joint Committee on Cancer TNM staging system. Peripheral blood samples were collected within 1 week before treatment from all patients. Anemia was defined as a preoperative hemoglobin (Hb) level <120 g/L according to the National Comprehensive Cancer Network (NCCN) recommendations (10). Patients were classified into two groups according to this definition: the anemic group (Hb <120 g/L) and the nonanemic group (Hb ≥120 g/L), as previously reported (11,12).

Follow-up and study end-points

After curative surgery, all patients were evaluated every three months in the first 2 years, every 6 months in the subsequent 3 years, and then every year or until death. The follow-up program was composed of a physical examination, a serum tumor marker evaluation, an endoscopy, and abdominal computed tomographic scans. The last follow-up date was December 2019.

The study end-point was OS. OS was defined as the duration from the surgery date to either the date of death or the date of the last follow-up. OS rates and 95% confidence intervals (CIs) were determined using the Kaplan-Meier estimator. The log-rank test was used to identify differences between the survival curves of different patient groups.

Statistical analysis

Values are expressed as the mean ± standard deviation (SD) for continuous variables and frequencies (percent) for categorical variables. Groups were compared using the chi-square test and Fisher's exact test. OS rates and 95% CIs were estimated via the Kaplan-Meier method and

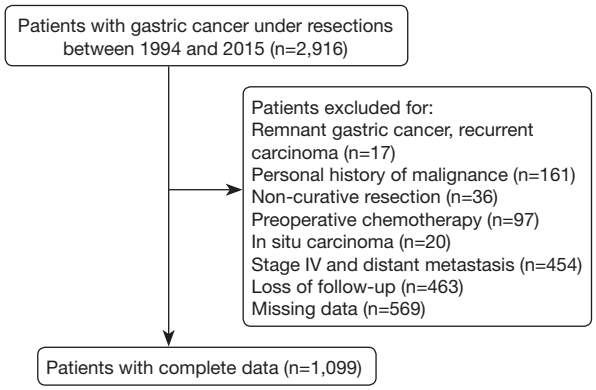

Figure 1 Flowchart describing patient enrollment and exclusion.

were compared to the log-rank test to validate the survival curves. Variables conforming to the proportional hazards assumption were enrolled in the univariate analysis, and those with P<0.1 were further included in the multivariate analysis. Multivariate analyses were also performed using the Cox proportional hazards model to identify independent prognostic factors through the enter method. All statistical tests were two-tailed, and P values less than 0.05 were considered significant. Data were analyzed using SPSS (Windows version 22.0; Chicago, IL, USA).

The following clinicopathological features were analyzed: (I) sex (male or female); (II) age at surgery (≤60 or >60 years); (III) CEA level (≤5 or >5 ng/mL); (IV) tumor size (<5 or ≥5 cm); (V) primary tumor site (lower third, middle third, upper third, or whole stomach); (VI) the depth of primary tumor invasion (pT stage); (VII) the number of positive lymph nodes (pN stage); (VIII) AJCC pathological classification (pTNM classification); (IX) the degree of tumor differentiation (well, moderate or poor); (X) Borrmann's classification of primary tumor (I, II, III, IV); and (XI) anemia (hemoglobin <120 g/L).

Results

Patient characteristics

A total of 1,099 patients met the inclusion and exclusion criteria, and the flowchart shows the selection process for the study cohort (*Figure 1*). The overall median follow-up duration was 43 (IQR, 24–66) months. *Table 1* illustrates

Table 1 General characteristics of 1,099 gastric cancer patients

Characteristics	No. of patients (%)
Age (years)	
≤60	604 (55.0)
>60	495 (45.0)
Gender	
Male	748 (68.1)
Female	351 (31.9)
CEA (ng/mL)	
≤5	905 (82.3)
>5	194 (17.7)
Primary site	
Upper	321 (29.2)
Middle	266 (24.2)
Lower	463 (42.1)
Whole	49 (4.5)
pT stage	
Tis	3 (0.3)
T1	170 (15.5)
T2	137 (12.5)
T3	332 (30.2)
T4	457 (41.6)
pN stage	
N0	410 (37.3)
N1	185 (16.8)
N2	214 (19.5)
N3	290 (26.4)
pTNM stage	
I	243 (22.1)
II	309 (28.1)
III	547 (49.8)
Differentiation[†]	
Well	30 (2.7)
Moderate	238 (21.7)
Poor	828 (75.3)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	No. of patients (%)
Borrmann's classification‡	
I	43 (3.9)
II	286 (26.0)
III	634 (57.7)
IV	90 (8.2)
Anemia	
No	649 (59.1)
Yes	450 (40.9)
Hypoalbuminemia§	
No	505 (46.0)
Yes	592 (53.9)

†Differentiation information missing for 3 patients (0.27%); ‡Borrmann information not applicable for 46 patients (4.0%); §Hypoalbuminemia information not applicable for 2 patients (0.18%). CEA, carcinoembryonic antigen.

the demographics and clinical features of these patients. The overall 5-year survival rate of the study cohort was 63.3%, and 624 patients were still alive at the end of our follow-up. Of these 1,099 patients, 748 (68.1%) were men. The mean age was 58.16 years (range, 21–87 years). The mean hemoglobin level was 119.97±26.14 g/L (range, 38–175 g/L), and the overall prevalence of anemia was 40.9%; 56.9% of the male patients and 43.1% of the female patients had anemia. The mean BMI (body mass index) was 21.88±3.16 (range, 13.84–34.38). The mean albumin level was 39.04±5.33 (range, 15.0–74.0). There were 243 patients in stage I, 309 patients in stage II, and 547 patients in stage III, and the corresponding numbers of pretreatment anemic patients at each stage were 61 (13.6%), 131 (29.1%), and 258 (57.3%), respectively. The general characteristics of these 1,099 patients are summarized in *Table 1*.

In the present study, Kaplan-Meier survival analysis revealed that the pretreatment anemia was correlated with a poor prognosis (5-year survival rate 58.4% *vs.* 66.8% P<0.0001, *Figure 2A*). Univariate and multivariate analysis was further performed, and revealed that pretreatment anemia was not an independent prognostic factor among the whole cohort (*Table 2*). After stratification by the level of albumin (*Figure 2A*,*B*,*C*), we found significant survival differences in GC patients with non-hypoalbuminemia (5-year survival rate 57.6% *vs.* 70.5%, P<0.0001, *Figure 2C*). However, there was no difference in prognosis between the anemic group and the non-anemic group in hypoalbuminemic patients (*Figure 2B*, P=0.446).

Among these 1,099 patients, 505 (46.0%) had nonhypoalbuminemia. Of these 505 patients, 110 (21.8%) were anemic, and the 5-year OS rate was 58.4%; 395 were nonanemic, and the 5-year OS rate was 66.8% (P<0.0001; *Figure 2A*). The baseline clinicopathologic characteristics are shown in *Table 3*.

Spearman's rank test was used to further investigate the relationship between pretreatment anemia and the clinicopathologic variables. The statistic results are shown in *Table 4*. The following variables were slightly ($|\rho|<0.5$) associated with the pretreatment hemoglobin level: sex (P<0.0001), BMI (P<0.046), tumor size (P<0.0001), pT stage (P=0.044), pN stage (P<0.0001), AJCC pathological classification (pTNM classification) (P<0.0001), degree of tumor differentiation (P=0.035), white blood cell count (WBC) (P<0.002), platelet (PLT) count (P<0.0001) and metastatic lymph node (MLN) (P<0.0001).

After stratification by tumor size (*Figure 3A*,*B*,*C*), pN stage (*Figure 4A*,*B*,*C*,*D*) and pT stage (*Figure 4E*,*F*,*G*,*H*), we found a significant survival difference between patients with a tumor size ≥5 cm (5-year survival rate 37.4% *vs.* 51.1%, P=0.041, *Figure 3C*) and those with pT3 stage tumors (5-year survival rate 46.2% *vs.* 61.0%, P=0.014, *Figure 4G*). Remarkably, in our analysis of patients with stage pN0, pN1, pN2, pN3, pT1, pT2, and pT4 GC, the current cutoff of the hemoglobin level was not associated with improved survival (P>0.05, *Figure 4A*,*B*,*C*,*D*,*E*,*F*,*H*).

Univariate and multivariate Cox proportional hazard regression models were used to further identify the possible independent clinicopathological variables in patients with GC with nonhypoalbuminemia. Nine prognostic risk factors were determined in the univariate analysis, including sex, CEA level, primary tumor site, pT stage, pN stage, pTNM stage, degree of tumor differentiation, Borrmann's classification, and anemia. Nevertheless, three factors that were independently associated with OS were revealed through the multivariate analysis: pT stage (P=0.018), pN stage (P<0.0001), and anemia (HR =1.455, 95% CI, 1.013–2.09; P=0.043) (*Table 5*).

Discussion

It is still controversial whether pretreatment anemia

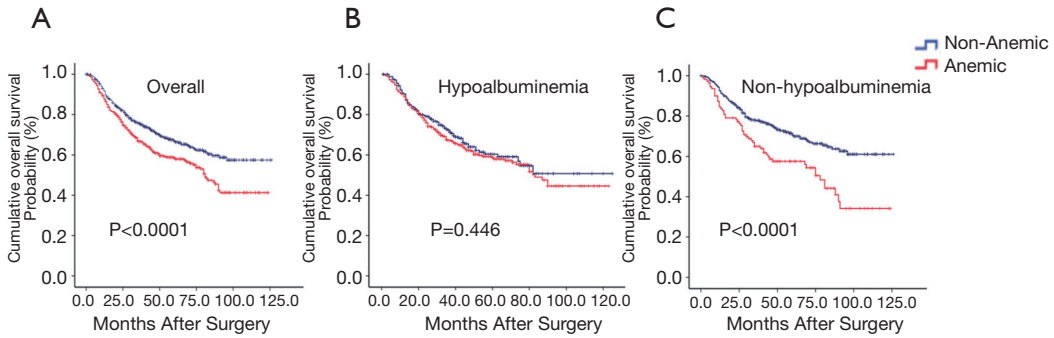

Figure 2 Kaplan-Meier curves of pretreatment anemia in the entire cohort (A), hypoalbuminemic patients (B) and non-hypoalbuminemic patients (C).

Table 2 Univariate and multivariate analysis for overall survival in the entire cohort

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		<0.0001		0.004
≤60	Referent		Referent	
>60	1.477 (1.212–1.800)		1.353 (1.100–1.664)	
Gender		0.034		0.197
Male	Referent		Referent	
Female	1.248 (1.016–1.533)		1.156 (0.928–1.440)	
CEA (ng/mL)		<0.0001		0.213
≤5	Referent		Referent	
>5	1.782 (1.419–2.238)		1.162 (0.917–1.473)	
Primary site		<0.0001		0.132
Upper	0.410 (0.283–0.595)	<0.0001	0.932 (0.598–1.454)	0.757
Middle	0.265 (0.178–0.394)	<0.0001	0.679 (0.430–1.074)	0.098
Lower	0.260 (0.179–0.377)	<0.0001	0.804 (0.516–1.253)	0.335
Whole	Referent		Referent	
pT stage		<0.0001		0.034
Tis	Referent		Referent	
T1	73.581 (0.0001–2.064E+20)	0.843	123.677 (0.0001–5.932E+24)	0.857
T2	146.144 (0.0001–4.092E+20)	0.818	161.706 (0.0001–7.744E+24)	0.849
T3	555.289 (0.0001–1.552E+21)	0.771	315.904 (0.0001–1.514E+25)	0.829
T4	799.257 (0.0001–2.233E+21)	0.758	402.749 (0.0001–1.931E+25)	0.822

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
pN stage		<0.0001		<0.0001
N0	Referent		Referent	
N1	2.033 (1.366–3.025)	<0.0001	1.280 (0.792–2.068)	0.314
N2	4.372 (3.115–6.137)	<0.0001	2.512 (1.441–4.379)	0.001
N3	9.989 (7.355–13.566)	<0.0001	5.067 (2.850–9.007)	<0.0001
pTNM stage		<0.0001		0.841
I	Referent	<0.0001	Referent	
II	4.297 (2.427–7.609)	<0.0001	1.272 (0.519–3.120)	0.599
III	15.513 (9.065–26.546)	<0.0001	1.240 (0.399–3.853)	0.710
Differentiation		<0.0001		0.872
Well	Referent		Referent	
Moderate	3.038 (0.953–9.677)	0.06	1.142 (0.346–3.771)	0.827
Poor	5.278 (1.693–16.454)	0.004	1.218 (0.375–3.952)	0.743
Borrmann's classification		<0.0001		0.063
I	0.448 (0.261–0.768)	0.004	0.955 (0.526–1.733)	0.880
II	0.199 (0.138–0.286)	<0.0001	0.588 (0.386–0.896)	0.014
III	0.463 (0.349–0.615)	<0.0001	0.731 (0.520–1.028)	0.072
IV	Referent		Referent	
Anemia		<0.0001		0.217
Yes	1.431 (1.175–1.744)		1.141 (0.925–1.407)	
No	Referent		Referent	

CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

is associated with poor survival in advanced GC. We retrospectively analyzed a large cohort of Chinese patients with GC who underwent curative resection at our single center to resolve this issue. The prevalence of anemia in our cohort was 40.4%, consistent with a large European survey (12). We found that pretreatment anemia was significantly correlated with poor OS in GC patients with nonhypoalbuminemia. Moreover, we determined that pretreatment anemia was an independent prognostic predictor for OS in these patients through a multivariate analysis.

Our findings were similar to those of previous studies, which have shown a correlation between pretreatment anemia and OS. In a cohort of 504 patients with advanced GC, Zhang *et al.* reported that almost 61% of the patients had pretreatment anemia, and a lower hemoglobin level indicated a poorer OS (HR =1.37, P=0.037) (13). However, it is noteworthy that there was a high rate of pretreatment anemia in their cohort. In a recent study, 27.0% of patients in the cohort were anemic, and Liu *et al.* found that preoperative anemia was independently related to poor OS in patients with TNM stage III GC rather than stage I and II GC (8). Similarly, the same trend can be seen in non-alimentary tract cancer. In a study of 2,123 breast cancer patients, the incidence of anemia was 25.2%, and pretreatment anemia was an independent prognostic factor for lymph node metastasis-free survival, relapse-free survival and OS (11). Of note, anemia is more common

Table 3 Baseline characteristics of pretreatment anemia among non-hypoalbuminemia patients

Characteristics	Anemic	Nonanemic	χ^2	P
Total	110 (21.8%)	395 (78.2%)		
Age (years)			0.111	0.739
≤60	74 (67.3%)	259 (65.6%)		
>60	36 (32.7%)	136 (34.4%)		
Gender			28.207	<0.0001
Male	53 (48.2%)	295 (74.7%)		
Female	57 (51.8%)	100 (25.3%)		
CEA (ng/mL)			1.146	0.284
≤5	95 (86.4%)	324 (82.0%)		
>5	15 (13.6%)	71 (18.0%)		
Primary site[†]			3.249	0.343
Upper	27 (24.5%)	122 (30.9%)		
Middle	33 (30.0%)	90 (22.8%)		
Lower	46 (41.8%)	171 (43.3%)		
Whole	4 (3.6%)	12 (3.0%)		
pT stage			8.792	0.057
Tis	1 (0.9%)	1 (0.3%)		
T1	12 (10.9%)	86 (21.8%)		
T2	14 (12.7%)	55 (13.9%)		
T3	40 (36.4%)	120 (30.4%)		
T4	43 (39.1%)	133 (33.7%)		
pN stage			16.923	0.001
N0	34 (30.9%)	173 (43.8%)		
N1	11 (10.0%)	72 (18.2%)		
N2	28 (25.5%)	74 (18.7%)		
N3	37 (33.6%)	76 (19.2%)		
pTNM stage			13.265	0.001
I	20 (18.2%)	120 (30.4%)		
II	24 (21.8%)	114 (28.9%)		
III	66 (60.0%)	161 (40.8%)		
Differentiation[†]			5.145	0.076
Well	1 (0.9%)	16 (4.1%)		
Moderate	20 (18.2%)	97 (24.6%)		
Poor	89 (80.9%)	281 (71.3%)		
Borrmann's classification[‡]			3.210	0.353
I	1 (0.9%)	13 (3.4%)		
II	28 (26.4%)	119 (31.4%)		
III	68 (64.2%)	223 (58.8%)		
IV	9 (8.5%)	24 (6.3%)		

[†]Differentiation information missing for 1 patients (0.19%). [‡]Borrmann information missing for 20 patients (3.9%). CEA, carcinoembryonic antigen.

Table 4 Spearman's rank test of the correlation between hemoglobin levels and clinical characteristics

Characteristics	P (Hb)	P
Age	–0.015	0.739
Sex	0.236	<0.0001
CEA	–0.048	0.285
BMI	–0.103	0.046
Tumor size	0.157	<0.0001
Primary site	0.024	0.596
pT stage	0.09	0.044
pN stage	0.16	<0.0001
pTNM stage	0.158	<0.0001
Differentiation	0.094	0.035
Borrmann'classification	0.074	0.103
WBC	–0.141	0.002
PLT	0.215	<0.0001
MLN	0.172	<0.0001

CEA, carcinoembryonic antigen; BMI, body mass index; WBC, white blood cell count; PLT, platelet; MLN, metastatic lymph node.

in alimentary tract cancer than in non-alimentary tract cancer (14), and various factors can lead to anemia, which might be related to tumors (large size and deep invasion), patients (malnutrition, weight loss, and renal dysfunction), or complications (obstruction, bleeding, and perforation). These findings may indicate that the function of anemia in relation to cancer-specific survival is different and complicated in alimentary tract cancer compared to the role of anemia in non-alimentary tract cancer. Researchers found

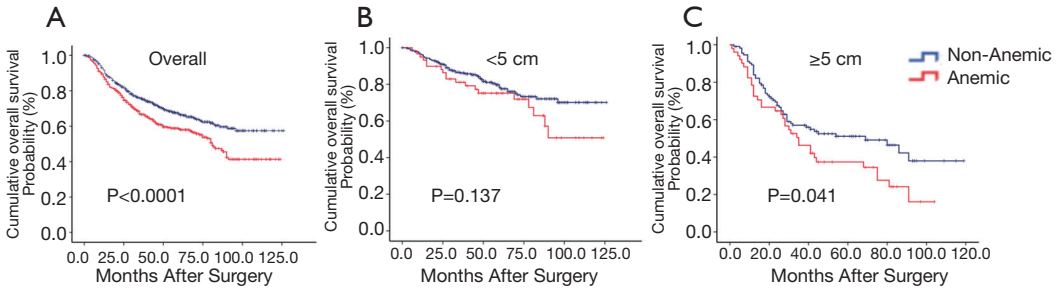

Figure 3 Kaplan-Meier curves of pretreatment anemia in nonhypoalbuminemia patients among groups: (A) overall; (B) tumor size <5 cm; (C) tumor size ≥5 cm.

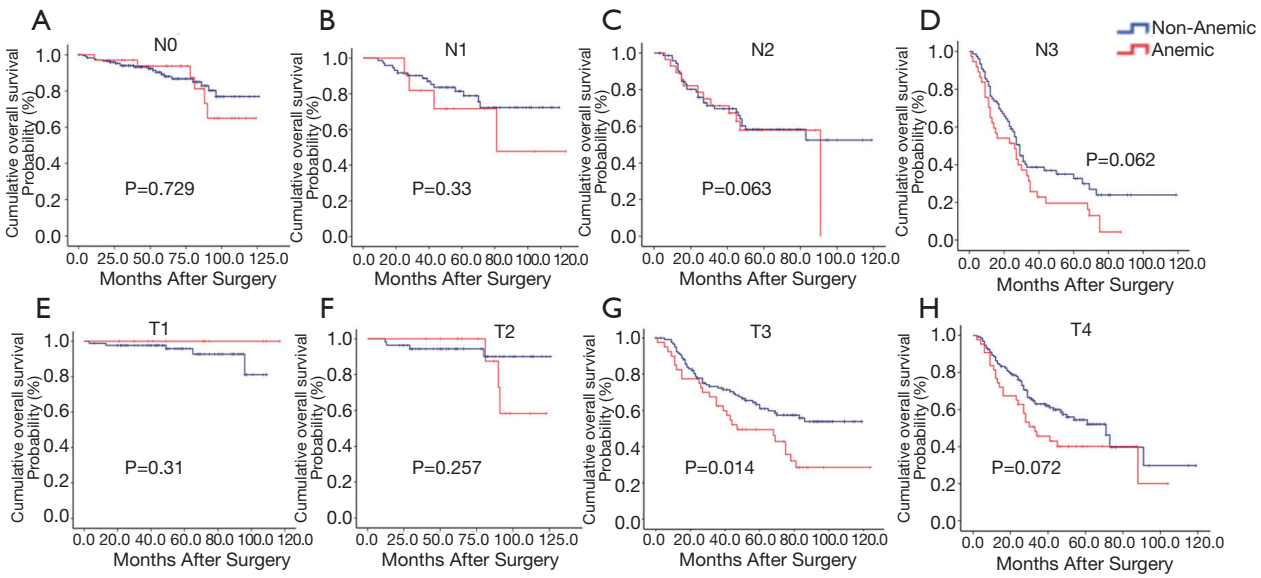

Figure 4 Kaplan-Meier curves of pretreatment anemia in nonhypoalbuminemia patients among groups: (A) pN0 stage; (B) pN1 stage; (C) pN2 stage; (D) pN3 stage; (E) pT1 stage; (F) pT2 stage; (G) pT3 stage; (H) pT4 stage.

Table 5 Univariate and multivariate analysis for overall survival in nonhypoalbuminemia patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.118		0.520
≤60	Referent		Referent	
>60	1.279 (0.940–1.742)		1.114 (0.801–1.550)	
Sex		0.012		0.614
Male	Referent		Referent	
Female	1.486 (1.091–2.023)		1.094 (0.771–1.554)	

Table 5 (*continued*)

Table 5 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
CEA (ng/mL)		0.001		0.164
≤5	Referent		Referent	
>5	1.789 (1.254–2.551)		1.300 (0.898–1.883)	
Primary site		<0.0001		0.171
Upper	0.240 (0.133–0.433)	<0.0001	0.594 (0.278–1.269)	0.179
Middle	0.155 (0.083–0.290)	<0.0001	0.476 (0.223–1.017)	0.055
Lower	0.137 (0.076–0.248)	<0.0001	0.476 (0.225–1.008)	0.053
Whole	Referent		Referent	
pT stage		<0.0001		0.018
Tis	Referent		Referent	
T1	188.555 (0.0001–1.962E+38)	0.901	206.052 (0.0001–1.094E+39)	0.902
T2	325.956 (0.0001–3.388E+38)	0.891	298.867 (0.0001–1.584E+39)	0.895
T3	1828.043 (0.0001–1.894E+39)	0.859	1232.511 (0.0001–6.544E+39)	0.869
T4	2629.209 (0.0001–2.724E+39)	0.852	1835.670 (0.0001–9.754E+39)	0.862
pN stage		<0.0001		<0.0001
N0	Referent		Referent	
N1	1.790 (0.995–3.219)	0.052	1.322 (0.668–2.620)	0.423
N2	3.947 (2.418–6.442)	<0.0001	2.885 (1.324–6.284)	0.008
N3	10.815 (6.962–16.802)	<0.0001	7.449 (3.307–16.776)	<0.0001
pTNM stage		<0.0001		0.363
I	Referent		Referent	
II	4.833 (2.250–10.377)	<0.0001	2.439 (0.434–13.703)	0.311
III	14.939 (7.292–30.603)	<0.0001	1.657 (0.824–3.334)	0.157
Differentiation		0.014		0.706
Well	Referent		Referent	
Moderate	2.593 (0.621–10.820)	0.191	0.853 (0.179–4.075)	0.842
Poor	4.052 (1.003–16.372)	0.05	0.717 (0.151–3.401)	0.675
Borrmann's classification		<0.0001		0.243
I	0.304 (0.105–0.882)	0.028	1.048 (0.307–3.586)	0.940
II	0.163 (0.092–0.290)	<0.0001	0.555 (0.280–1.102)	0.092
III	0.478 (0.303–0.754)	0.002	0.826 (0.456–1.498)	0.529
IV	Referent		Referent	
Anemia		<0.0001		0.043
Yes	1.811 (1.313–2.498)		1.455 (1.013–2.090)	
No	Referent		Referent	

CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

that severe pretreatment anemia was significantly associated with low albumin (15). Albumin constitutes up to two-third of total plasma protein and is responsible for the transport and binding of many molecules. Vascular damage caused by tumor can lead to loss of both albumin and hemoglobin. Inflammatory factors released by tumor enhance vascular permeability, which would induce a larger shift of albumin and hemoglobin from the vascular to the interstitial space. What is more, a lack of albumin might result in higher levels of free folate and vitamin B12, which would cause anemia. We divided our cohort into hypoalbuminemia and nonhypoalbuminemia groups to reduce the bias associated with chronic occult bleeding, alimentary obstruction, severe complications, malnutrition, weight loss, and renal dysfunction. We further verified the role of pretreatment anemia in patients with GC with nonhypoalbuminemia who underwent radical surgery. Therefore, our results might be more prudent in illustrating the prognostic importance of pretreatment anemia in GC.

Furthermore, after stratification by the AJCC/TNM stage, pT stage, pN stage and tumor size in patients with GC with nonhypoalbuminemia, pretreatment anemia further significantly stratified survival in the pT3 stage group and the tumor size ≥5 cm group. Both of these factors are associated with the malignancy of the tumor. These findings were consistent with those of previous studies (16,17), which indicated that pretreatment anemia might be a potential biomarker for a high tumor burden and an aggressive tumor phenotype.

Over the past decades, researchers have focused on clarifying the potential mechanistic relationships between anemia and poor survival outcomes. To date, several hypotheses have been proposed. First, anemia can attenuate the capacity of the blood to transport oxygen, which results in a hypoxic tumor microenvironment (18). A hypoxic tumor microenvironment is a common feature in cancer and plays an important role in the unfavorable prognosis of solid tumors (19). Hypoxia-inducible factor-1 (HIF-1) is a key protein that responds to hypoxia. Its expression increases as the pathologic stages progress, and its expression is higher in poorly differentiated lesions than in well-differentiated lesions (20,21). HIFs or hypoxia signaling pathways are associated with many of the hallmarks of cancer (22), including angiogenesis (23), reprogramming energy metabolism (24), immune escape (24), activating invasion and distant metastasis (25), sustaining proliferative signaling, resisting cell death, and genome instability (26). Second, cancer-related inflammation has attracted increasing attention in recent years (27). Inflammatory cytokines released by tumor-associated macrophages, including tumor necrosis factor (TNF), interleukin (IL), and gamma interferon (γ-IFN), can not only inhibit the synthesis of erythropoietin (EPO) but also the release of stored iron and the proliferation of erythroid progenitor cells. Moreover, these inflammatory cytokines could lead to an increase in hepcidin (28), which binds to macrophages in the reticuloendothelial system and hinders the release of iron to transferrin. This is the so-called anemia of inflammation (29), which is typically unresponsive to iron interventions.

We examined the effect of pretreatment anemia on the OS of patients with GC with nonhypoalbuminemia undergoing curative resection in our innovative study. We found that pretreatment anemia was correlated with poor prognosis and could serve as an independent predictive factor of outcome. Stratification analyses by TNM stage and tumor size revealed that pretreatment anemia could provide better prognostic information for patients with a larger tumor size and pT3 GC than those with other stages. Moreover, evaluating patients with GC with nonhypoalbuminemia may obviate possible confounding factors associated with non-cancer-related anemia, thus increasing the statistical power and providing more robust results.

Nevertheless, our study had some limitations. First, our study was a retrospective study; the cohort included patients who were treated at our center between January 1994 and December 2015. Over time, surgical procedures, surgical instruments, surgical skills, examinations of lymph nodes and adjuvant chemotherapies have all developed, which may have introduced bias. Second, one of the most important sources of heterogeneity—the heterogeneous treatment protocols among the included studies—may weaken our results. Third, we lacked cancer-specific survival and recurrence-free survival data. Therefore, further studies are required to verify our findings.

In conclusion, our data suggest that pretreatment anemia may serve as an independent prognostic factor in patients with advanced GC with nonhypoalbuminemia after radical gastrectomy, especially those with larger tumor size and pT3 disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Medical Ethics Committee of the Seventh affiliated Hospital of Sun Yat-sen University (No: KY-2020-024-01). All patient records and information were anonymized and deidentified prior to analysis. Individual consent for this retrospective analysis was waived.

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