



# The prognostic roles of red blood cell-associated indicators in patients with resectable gastric cancers

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**Background:** Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. This study was designed to investigate the prognostic values of red blood cell (RBC)-associated indicators, including RBC, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RBC distribution width (RDW) in resectable GC patients.

**Methods:** In this retrospective study, a total of 104 pathologically confirmed GC patients were recruited. These cases were divided into two groups according to the median values of pretreatment RBC, HGB, HCT, MCV, MCH, MCHC, or RDW. To evaluate the changes in RBC-associated indicators values after treatment, we introduced the concept of post-/pre-treatment ratios ( $\leq 1$  suggested RBC, HGB, HCT, MCV, MCH, MCHC, or RDW values were not increased after therapy, while  $>1$  represented those in increased levels).

**Results:** The lower pretreatment MCHC levels were correlated with worse overall survival (OS), while pretreatment levels of RBC, HGB, HCT, MCV, MCH, or RDW were not. The whole course of treatment (surgery plus adjuvant chemotherapy) significantly decreased the values of MCHC, and increased the values of MCV and RDW, whereas it had no obvious effects on the values of RBC, HGB, HCT, or MCH. Patients with post-/pre-treatment MCV ratio  $>1$  had an increased survival ratio. Meanwhile, post-/pre-treatment RBC, HGB, HCT, MCH, MCHC, or RDW ratios were not correlated with outcomes. Multivariate Cox regression analysis revealed that the American Joint Committee on Cancer (AJCC) stage (III), and lower pretreatment MCHC levels were independent risk factors affecting OS. The receiver operating characteristic (ROC) curve analysis showed that an MCHC value of 341.98 g/L was the optimal cutoff value for prognosis, with a sensitivity of 58.3% and a specificity of 75.0%.

**Conclusions:** Pretreatment MCHC levels could become a potential prognostic factor for resectable GC.

**Keywords:** Gastric cancer (GC); red blood cell-associated indicators (RBC-associated indicators); prognosis

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## Introduction

Gastric cancer (GC) is one of the most common malignancies in the world and the second leading cause of cancer-related death in China (1). The 5-year survival rate is 36% in patients diagnosed with the operable disease who receive perioperative chemotherapy, while that of patients in advanced or metastatic phase is only 5–20% with the mean overall survival (OS) being less than 1 year (2). Unfortunately, a lack of effective early diagnostic markers and obvious clinical symptoms leads to GC commonly being diagnosed at advanced stages (3). Therefore, it is essential to identify reliable predictive indicators for the diagnosis and follow-up of resectable GC.

Red blood cell (RBC)-related indicators include RBC, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RBC distribution width (RDW). RBC, also known as erythrocytes, can carry oxygen throughout the body and circulate in the blood. A lack of RBCs in the blood is a major characteristic of anemia, a frequent complication in cancer patients (4). HGB concentration was considered as a significant prognostic indicator in squamous cell carcinoma at several sites, like the esophagus (5), head, and neck (6). HCT is the volume percentage of RBCs in blood and could indicate anemia (7,8). MCV is a measurement of RBC size (9), which could reflect folate deficiency (10). MCH refers to a calculation of the average HGB content of each RBC, another factor correlated with anemia that represents the iron metabolism (11). MCHC is calculated by dividing the HGB by the HCT and can reflect average HGB concentration (12). RDW reflects the heterogeneity in erythrocyte size, and it is used clinically to differentiate types of anemia (13).

Several factors, including the clinical tumor stage, have been confirmed to be involved in the natural history of GC. However, tumor staging alone cannot predict GC patients' prognosis (14). A few serum indexes have attracted increasing interest as prognostic markers, like the C-reactive protein level, and platelet count (15,16). Accumulated evidence indicates that these serum biomarkers are becoming increasingly useful for monitoring and predicting early recurrence and poor prognosis (17,18).

However, the prognostic significance of the RBC-related indicators in resectable GC patients has not been well investigated thus far. Accordingly, we performed this retrospective cohort study in 104 resectable GC patients

undergoing surgery or/and adjuvant chemotherapy and systematically evaluated the prognostic value of RBC-related indicators for survival.

## Methods

### *Subjects and inclusion criteria*

The researchers retrospectively analyzed resectable GC patients who had been admitted to Soochow University's First Affiliated Hospital (Jiangsu, China) between June 2006 and July 2016. Approval for the research was given by the First Affiliated Hospital of Soochow University's medical ethics board. Clinical and clinical records of all the patients involved in the study were periodically evaluated.

In total, this study enrolled 104 resectable GC patients. Cases were surgically and pathologically confirmed. The characteristics of patients are listed in *Table 1*. Of the 104 patients, the median age was 60 (range, 30–77) years, 77 patients were male, and 27 were female. Cancer treatment was performed according to the type of tumor-nodules-metastases (TNM) and graded through the guidelines of the American Joint Committee on Cancer (AJCC). Prognostic study on OS was performed.

### *Blood samples*

Blood samples were analyzed using a hematology analyzer (Sysmex XE-2100; Sysmex, Kobe, Japan). RBC, HGB, HCT, MCV, MCH, MCHC, and RDW levels were recorded in *Table 1*. The patients were divided into two groups according to the median values of RBC, HGB, HCT, MCV, MCH, MCHC, or RDW. The post-/pre-treatment ratios were defined as the rate of pretreatment RBC-related indicators values and the corresponding ones obtained after therapy.

### *Evaluation*

Computed tomography (CT) scanning was conducted every 2 months for response evaluation and analyzed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.

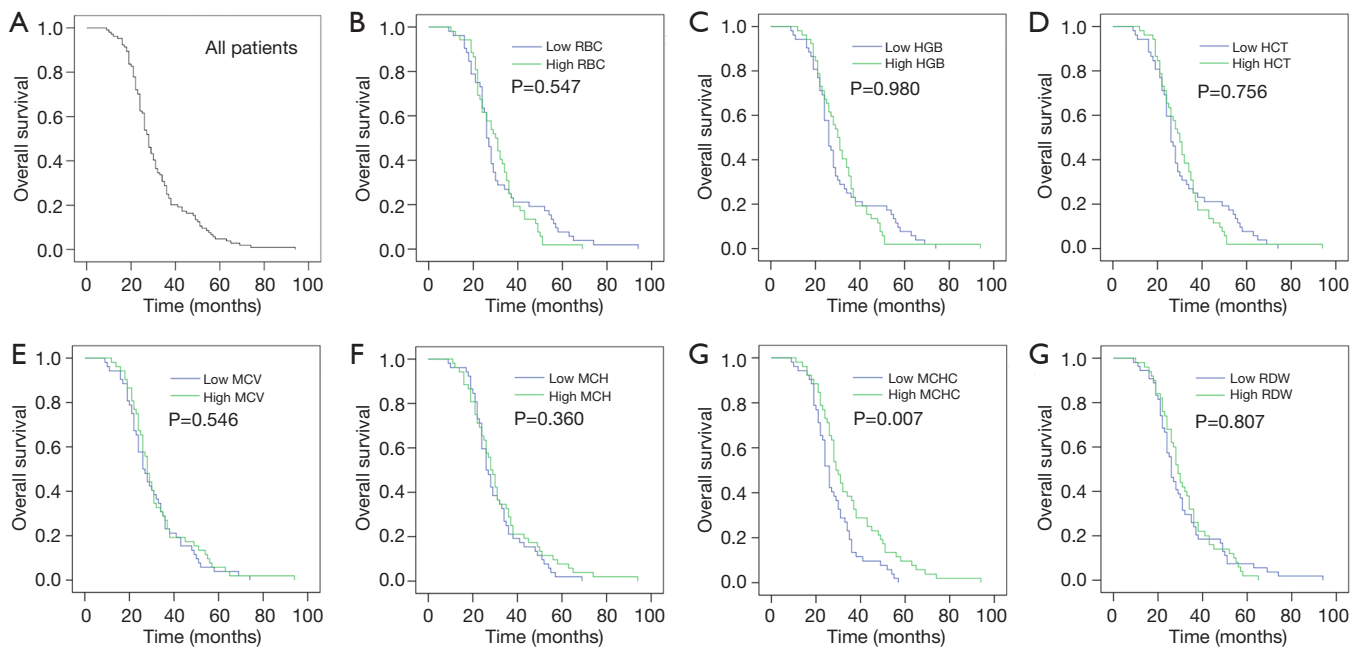
### *Follow-up*

Survival period has been estimated from the start of chemotherapy to death, or the last surgical examination.

**Table 1** Clinicopathologic features

Clinicopathologic features	n (n=104)	HGB				HCT				MCV				MCH				MCHC				RDW				RBC			
		Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value	Low (n)	High (n)	$\chi^2$	P value
Gender				14.46	0.001**			16.21	0.001**			2.451	0.117			11.26	0.001**			4.052	0.044*			3.237	0.072			11.26	0.000**
Male	77	30	47			29	48			35	42			31	46			34	43			44	33			31	46		
Female	27	22	5			23	4			17	10			21	6			18	9			10	17			21	6		
Age (years)				0.000	1.000			0.154	0.695			1.387	0.239			1.387	0.239			0.154	0.695			1.353	0.245			1.387	0.239
≤60	54	27	27			26	28			30	24			30	24			28	26			31	23			24	30		
>60	50	25	25			26	24			22	28			22	28			24	26			23	27			28	22		
Tumor size (cm)				0.474	0.491			1.316	0.251			1.316	0.251			1.316	0.251			0.053	0.819			0.000	0.993			0.053	0.819
≤5	79	38	41			37	42			42	37			37	42			40	39			41	38			40	39		
>5	25	14	11			15	10			10	15			15	10			12	13			13	12			12	13		
Depth of invasion				0.840	0.359			0.840	0.359			0.840	0.359			-	0.028*			-	0.028*			1.011	0.315			0.000	1.000
T1, T2	5	1	4			1	4			1	4			0	5			0	5			1	4			3	2		
T3, T4	99	51	48			51	48			51	48			53	47			52	47			53	46			49	50		
Lymphonodus metastasis				4.887	0.027*			3.128	0.077			0.000	1.000			0.000	1.000			0.000	1.000			0.057	0.812			3.128	0.077
N0, N1	28	19	9			18	10			14	14			14	14			14	14			14	14			18	10		
N2	76	33	43			34	42			38	38			38	38			38	38			40	36			34	42		
AJCC stage				4.685	0.030*			4.685	0.030*			0.000	1.000			0.750	0.387			0.750	0.387			0.467	0.495			6.746	0.009**
II, II	30	20	10			20	10			15	15			13	17			13	17			14	16			21	9		
III	74	32	42			32	42			37	37			39	35			39	35			40	34			31	43		

\*, P<0.05; \*\*, P<0.01. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width; AJCC, American Joint Committee on Cancer.



**Figure 1** Relationship between the status of pretreatment RBC-related indicators and the outcomes. (A) Median OS for all patients; (B) the OS according to pretreatment RBC; (C) the OS according to pretreatment HGB; (D) the OS according to pretreatment HCT; (E) the OS according to pretreatment MCV; (F) the OS according to pretreatment MCH; (G) the OS according to pretreatment MCHC; (H) the OS according to pretreatment RDW. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width.

Prognostic analyses concerning OS were conducted, and OS was identified as the time from any cause from the date it was diagnosed to death.

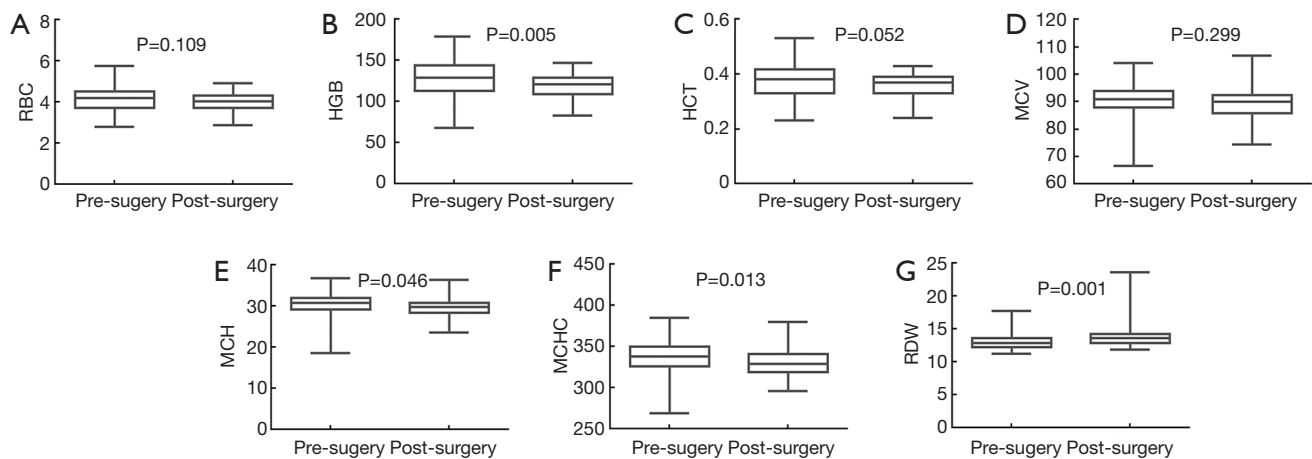
### Statistical analysis

All statistical analyses were performed using SPSS 19.0 software (Chicago, IL, USA). The  $\chi^2$  tests explored the associations between RBC-related indicators status and clinicopathologic features. For analysis of survival data, Kaplan-Meier curves were constructed, and statistical analysis was conducted using the log-rank test. The *t*-tests assessed the relationships between changes in the RBC-related indicators status and surgery or chemotherapy. The multivariate logistic regression model was employed to find the independent risk factors associated with resectable GC. All values of  $P < 0.05$  were considered statistically significant.

## Results

### *Pretreatment MCHC level was correlated with outcomes of resectable GC patients*

Median OS for all the resectable GC patients was 28 months [95% confidence interval (CI), 25.902–30.098] (Figure 1A). The Kaplan-Meier plots were used to determine the effect of pretreatment RBC, HGB, HCT, MCV, MCH, MCHC, and RDW status on OS (Figure 1B,C,D,E,F,G,H). The patients were divided into two groups according to the median value of RBC (low RBC,  $\leq 4.205 \times 10^{12}/L$  or high RBC,  $> 4.205 \times 10^{12}/L$ ), HGB (low HGB,  $\leq 129.000$  g/L or high HGB,  $> 129.000$  g/L), HCT (low HCT,  $\leq 0.380$  L/L or high HCT,  $> 0.380$  L/L), MCV (low MCV,  $\leq 90.825$  fl or high MCV,  $> 90.825$  fl), MCH (low MCH,  $\leq 30.745$  pg or high MCH,  $> 30.745$  pg), MCHC (low MCHC,  $\leq 337.935$  g/L or high MCHC,  $> 337.935$  g/L) and RDW (low RDW,

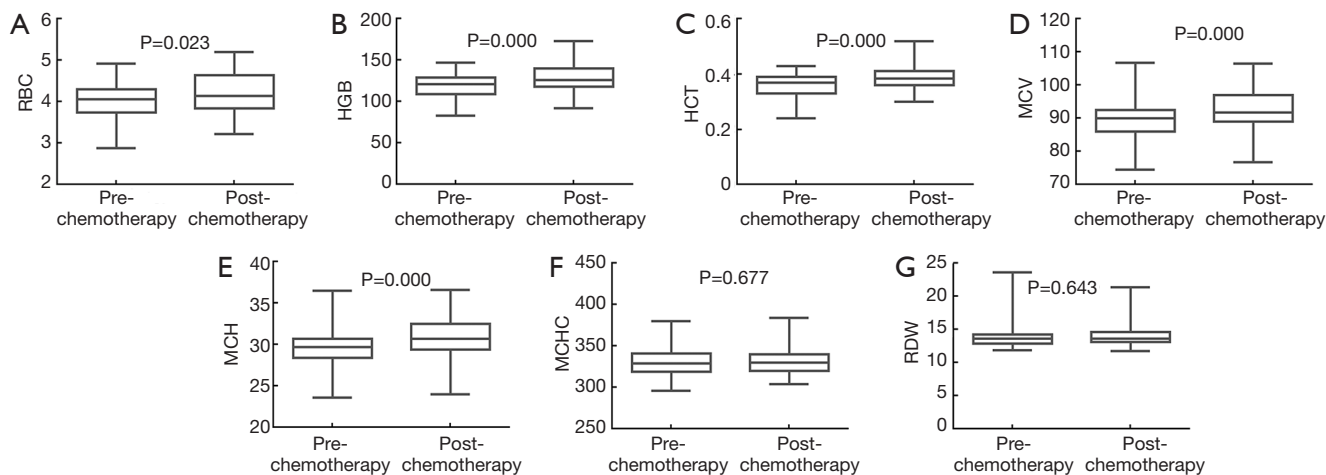


**Figure 2** Effects of surgery on the status of RBC-related indicators. (A) Surgery had no influence on the value of RBC; (B) surgery decreased the value of HGB. (C) surgery had no influence on the value of HCT; (D) surgery had no influence on the value of MCV; (E) surgery decreased the value of MCH; (F) surgery decreased the value of MCHC; (G) surgery increased the value of RDW. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width.

$\leq 12.900\%$  or high RDW,  $>12.900\%$ ). The median OS of the high RBC group was 30 months (95% CI, 24.952–35.048), while that of the low RBC group was 26 months (95% CI, 24.233–27.767) ( $P=0.547$ ). The median OS of the high HGB group was 30 months (95% CI, 26.467–33.533), while that of the low HGB group was 26 months (95% CI, 22.980–29.020) ( $P=0.980$ ). The median OS of the high HCT group was 30 months (95% CI, 26.469–33.531), while that of the low HCT group was 26 months (95% CI, 23.432–28.568) ( $P=0.756$ ). The median OS of the high MCV group was 28 months (95% CI, 25.646–30.354), while that of the low MCV group was 26 months (95% CI, 21.962–30.038) ( $P=0.546$ ). The median OS of the high MCH group was 28 months (95% CI, 24.971–31.029), while that of the low MCH group was 26 months (95% CI, 22.859–29.141) ( $P=0.360$ ). The median OS of the high MCHC group was 29 months (95% CI, 26.173–31.827), while that of the low MCHC group was 26 months (95% CI, 24.096–27.904) ( $P=0.007$ ). The median OS of the high RDW group was 29 months (95% CI, 26.403–31.597), while that of the low RDW group was 26 months (95% CI, 23.606–28.394) ( $P=0.807$ ). Thus, the patients with high pretreatment MCHC levels had increased survival ratio. However, pretreatment levels of RBC, HGB, HCT, MCV, MCH, and RDW had no effects on OS.

#### *Effects of surgery on the values of RBC-related indicators*

The relationships between changes in the RBC-related indicators levels and surgery are respectively presented in *Figure 2*. The median value of RBC was  $4.205 \times 10^{12}/L$  ( $4.060 \times 10^{12}/L$ – $4.330 \times 10^{12}/L$ ) before surgery, and  $4.060 \times 10^{12}/L$  ( $3.950 \times 10^{12}/L$ – $4.185 \times 10^{12}/L$ ) after surgery ( $P=0.109$ ). The median value of HGB was 129.000 (123.170–134.830) g/L before surgery, and 121.000 (116.003–125.997) g/L after surgery ( $P=0.005$ ). The median value of HCT was 0.380 (0.365–0.390) L/L before surgery, and 0.370 (0.350–0.380) L/L after surgery ( $P=0.052$ ). The median value of MCV was 90.825 (90.265–92.400) fl before surgery, and 90.115 (88.902–90.920) fl after surgery ( $P=0.299$ ). The median value of MCH was 30.745 (30.001–31.210) pg before surgery, and 29.700 (29.321–30.180) pg after surgery ( $P=0.046$ ). The median value of MCHC was 337.935 (334.375–341.980) g/L before surgery, and 328.700 (325.240–333.659) g/L after surgery ( $P=0.013$ ). The median value of RDW was 12.900% (12.635–13.100%) before surgery, and 13.580% (13.300–13.800%) after surgery ( $P=0.001$ ). Surgery significantly decreased the values of HGB, MCH, and MCHC, and increased the value of RDW, while it had no obvious effects on the values of RBC, HCT, or MCV.



**Figure 3** Effects of adjuvant chemotherapy on the status of RBC-related indicators. (A) Chemotherapy increased the value of RBC; (B) chemotherapy increased the value of HGB; (C) chemotherapy increased the value of HCT; (D) chemotherapy increased the value of MCV; (E) chemotherapy increased the value of MCH; (F) chemotherapy had no influence on the value of MCHC; (G) chemotherapy had no influence on the value of RDW. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width.

#### Effects of adjuvant chemotherapy on the values of RBC-related indicators

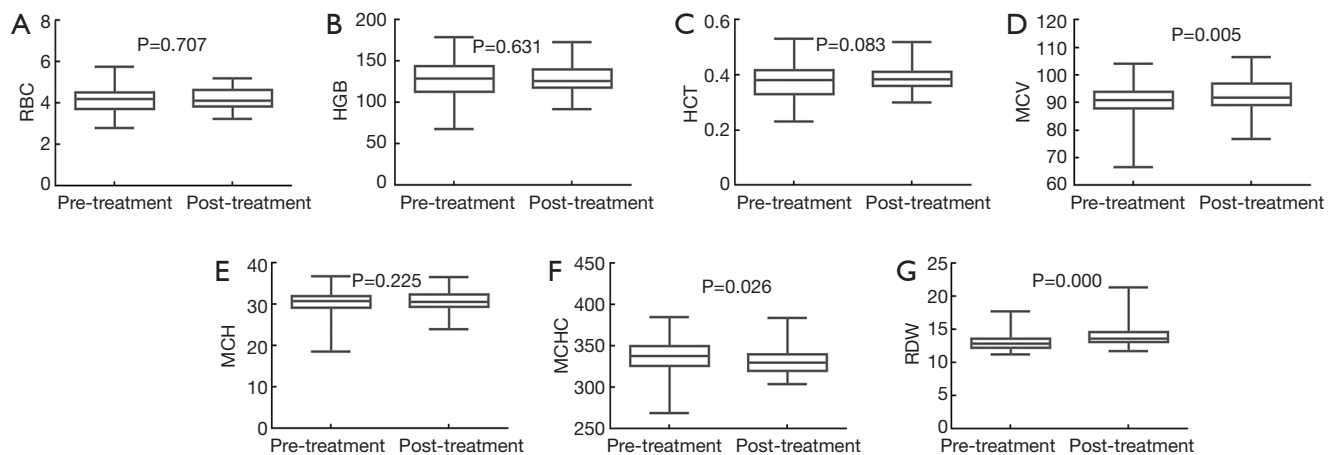
The effects of adjuvant chemotherapy on the levels of the RBC-related indicators are shown in *Figure 3*. The median value of RBC was  $4.060 \times 10^{12}/L$  ( $3.950 \times 10^{12}/L$ – $4.185 \times 10^{12}/L$ ) before adjuvant chemotherapy, and  $4.130 \times 10^{12}/L$  ( $4.005 \times 10^{12}/L$ – $4.239 \times 10^{12}/L$ ) after adjuvant chemotherapy ( $P=0.023$ ). The median value of HGB was 121.000 (116.003–125.997) g/L before adjuvant chemotherapy, and 126.000 (122.839–130.161) g/L after adjuvant chemotherapy ( $P=0.000$ ). The median value of HCT was 0.370 (0.350–0.380) L/L before adjuvant chemotherapy, and 0.385 (0.370–0.400) L/L after adjuvant chemotherapy ( $P=0.000$ ). The median value of MCV was 90.115 (88.902–90.920) fl before adjuvant chemotherapy, and 91.700 (90.790–93.160) fl after adjuvant chemotherapy ( $P=0.000$ ). The median value of MCH was 29.700 (29.321–30.180) pg before adjuvant chemotherapy, and 30.695 (30.200–31.000) pg after adjuvant chemotherapy ( $P=0.000$ ). The median value of MCHC was 328.700 (325.240–333.659) g/L before adjuvant chemotherapy and 330.315 (325.240–332.000) g/L after adjuvant chemotherapy ( $P=0.677$ ). The median value of RDW was 13.580% (13.300–13.800%) before adjuvant chemotherapy and 13.640% (13.500–13.940%) after adjuvant chemotherapy ( $P=0.643$ ). Adjuvant chemotherapy significantly increased the values of RBC, HGB, HCT,

MCV, and MCH, while it had no obvious effect on the value of MCHC or RDW.

#### Effects of the whole course of treatment on the values of RBC-related indicators

The effects of the whole course of treatment (surgery plus adjuvant chemotherapy) on the values of the RBC-related parameters are presented in *Figure 4*. The median value of RBC was  $4.205 \times 10^{12}/L$  ( $4.060 \times 10^{12}/L$ – $4.330 \times 10^{12}/L$ ) before treatment, and  $4.130 \times 10^{12}/L$  ( $4.005 \times 10^{12}/L$ – $4.239 \times 10^{12}/L$ ) after treatment ( $P=0.707$ ). The median value of HGB was 129.000 (123.170–134.830) g/L before treatment, and 126.000 (122.839–130.161) g/L after treatment ( $P=0.631$ ). The median value of HCT was 0.380 (0.365–0.390) L/L before treatment, and 0.385 (0.370–0.400) L/L after treatment ( $P=0.083$ ). The median value of MCV was 90.825 (90.265–92.400) fl before treatment, and 91.700 (90.790–93.160) fl after treatment ( $P=0.005$ ). The median value of MCH was 30.745 (30.001–31.210) pg before treatment, and 30.695 (30.200–31.000) pg after treatment ( $P=0.225$ ). The median value of MCHC was 337.935 (334.375–341.980) g/L before treatment, and 330.315 (325.240–332.000) g/L after treatment ( $P=0.026$ ). The median value of RDW was 12.900% (12.635–13.100%) before treatment, and 13.640% (13.500–13.940%) after treatment ( $P=0.000$ ). The whole course of treatment significantly decreased the value





**Figure 4** Effects of the whole course of treatment on the status of RBC-related indicators. (A) The whole course of treatment had no influence on the value of RBC; (B) the whole course of treatment had no influence on the value of HGB; (C) the whole course of treatment had no influence on the value of HCT; (D) the whole course of treatment increased the value of MCV; (E) the whole course of treatment had no influence on the value of MCH; (F) the whole course of treatment decreased the value of MCHC; (G) the whole course of treatment increased the value of RDW. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width.

of MCHC and increased the values of MCV and RDW, whereas it had no obvious effects on the values of RBC, HGB, HCT, or MCH.

#### *Changes in MCV level after the whole course of treatment could predict outcomes of resectable GC patients*

The Kaplan-Meier plots were used to determine the effects of changes of RBC, HGB, HCT, MCV, MCH, MCHC, and RDW status on OS (Figure 5A,B,C,D,E,F,G). The median OS of patients whose RBC level increased following the whole course of treatment was 26 months (95% CI, 24.387–27.613), while that of the not-increased group was 31 months (95% CI, 26.885–35.115) ( $P=0.525$ ). The median OS of patients whose HGB level increased following the whole course of treatment was 26 months (95% CI, 23.040–28.960), while that of the not-increased group was 31 months (95% CI, 26.896–35.104) ( $P=0.413$ ). The median OS of patients whose HCT level increased following the whole course of treatment was 27 months (95% CI, 25.323–28.677), while that of the not-increased group was 30 months (95% CI, 23.141–36.859) ( $P=0.885$ ). The median OS of patients whose MCV levels increased following the whole course of treatment was 31 months (95% CI, 27.336–34.664), while that of patients with decreased MCV was 26 months (95% CI, 25.038–26.962)

( $P=0.046$ ). The median OS of patients whose MCH level increased following the whole course of treatment was 26 months (95% CI, 22.758–29.242), while that of the not-increased group was 28 months (95% CI, 25.376–30.624) ( $P=0.597$ ). The median OS of patients whose MCHC level increased following the whole course of treatment was 26 months (95% CI, 20.456–31.544), while that of the not-increased group was 28 months (95% CI, 24.886–31.114) ( $P=0.448$ ). The median OS of patients whose RDW level increased following the whole course of treatment was 26 months (95% CI, 24.247–27.753), while that of the not-increased group was 33 months (95% CI, 28.199–37.801) ( $P=0.372$ ). Thus, the patients with increased MCV levels had an increased survival ratio. However, changes in RBC, HGB, HCT, MCH, MCHC, and RDW levels had no effects on OS.

#### *Prognostic factors for resectable GC*

Univariate analysis demonstrated that lymphonodus metastasis (N2) [hazard ratio (HR) 2.116; 95% CI, 1.316–3.403;  $P=0.002$ ], AJCC stage (III) (HR, 2.764; 95% CI 1.641–4.657;  $P=0.000$ ), and low pretreatment MCHC levels (HR, 1.704; 95% CI 1.138–2.549;  $P=0.010$ ) were significant risk factors for a worse prognosis (Table 2). In multivariate analysis, AJCC stage (III) (HR, 3.518; 95% CI, 1.054–

**Table 2** Univariate and multivariate logistic regression analysis of resectable GC risk factors

Risk factors	OS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (female or male)	0.714 (0.457-1.115)	0.139	–	–
Age (>60 or ≤60 years)	1.015 (0.992-1.038)	0.192	–	–
Tumor size (>5 or ≤5 cm)	0.848 (0.538-1.337)	0.478	–	–
Depth of invasion (T3-4 or T1-2)	2.062 (0.745-5.705)	0.164	–	–
Lymphonodus metastasis (N2 or N0-1)	2.116 (1.316-3.403)	0.002**	0.803 (0.251-2.569)	0.712
AJCC stage (III or I-II)	2.764 (1.641-4.657)	0.000**	3.518 (1.054-11.744)	0.041*
Pre-treatment HGB (≤129.000 or >129.000 g/L)	0.995 (0.668-1.482)	0.980	–	–
Pre-treatment HCT (≤0.380 or >0.380 L/L)	0.940 (0.632-1.401)	0.940	–	–
Pre-treatment MCV (≤90.825 or >90.825 fl)	1.123 (0.762-1.655)	0.557	–	–
Pre-treatment MCH (≤30.745 or >30.745 pg)	1.195 (0.807-1.768)	0.374	–	–
Pre-treatment MCHC (≤337.935 or >337.935 g/L)	1.704 (1.138-2.549)	0.010*	1.705 (1.124-2.586)	0.012*
Pre-treatment RDW (≤12.900% or >12.900%)	1.049 (0.708-1.553)	0.813	–	–
Pre-treatment RBC (≤4.205×10 <sup>12</sup> /L or >4.205×10 <sup>12</sup> /L)	0.887 (0.595-1.324)	0.559	–	–
Post/pre-treatment HGB ratio (≤1 or >1)	0.852 (0.575-1.264)	0.426	–	–
Post/pre-treatment HCT ratio (≤1 or >1)	0.972 (0.655-1.443)	0.888	–	–
Post/pre-treatment MCV ratio (≤1 or >1)	1.484 (0.993-2.217)	0.054	1.258 (0.833-1.900)	0.275
Post/pre-treatment MCH ratio (≤1 or >1)	0.903 (0.611-1.333)	0.607	–	–
Post/pre-treatment MCHC ratio (≤1 or >1)	0.852 (0.558-1.303)	0.461	–	–
Post/pre-treatment RDW ratio (≤1 or >1)	0.815 (0.513-1.294)	0.386	–	–
Post/pre-treatment RBC ratio (≤1 or >1)	0.883 (0.596-1.309)	0.536	–	–

\*, P<0.05; \*\*, P<0.01. GC, gastric cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval; RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width; AJCC, American Joint Committee on Cancer.

11.744; P=0.041) and low pretreatment MCHC levels (HR, 1.705; 95% CI, 1.124-2.586; P=0.012) were found to be independently associated with worse survival.

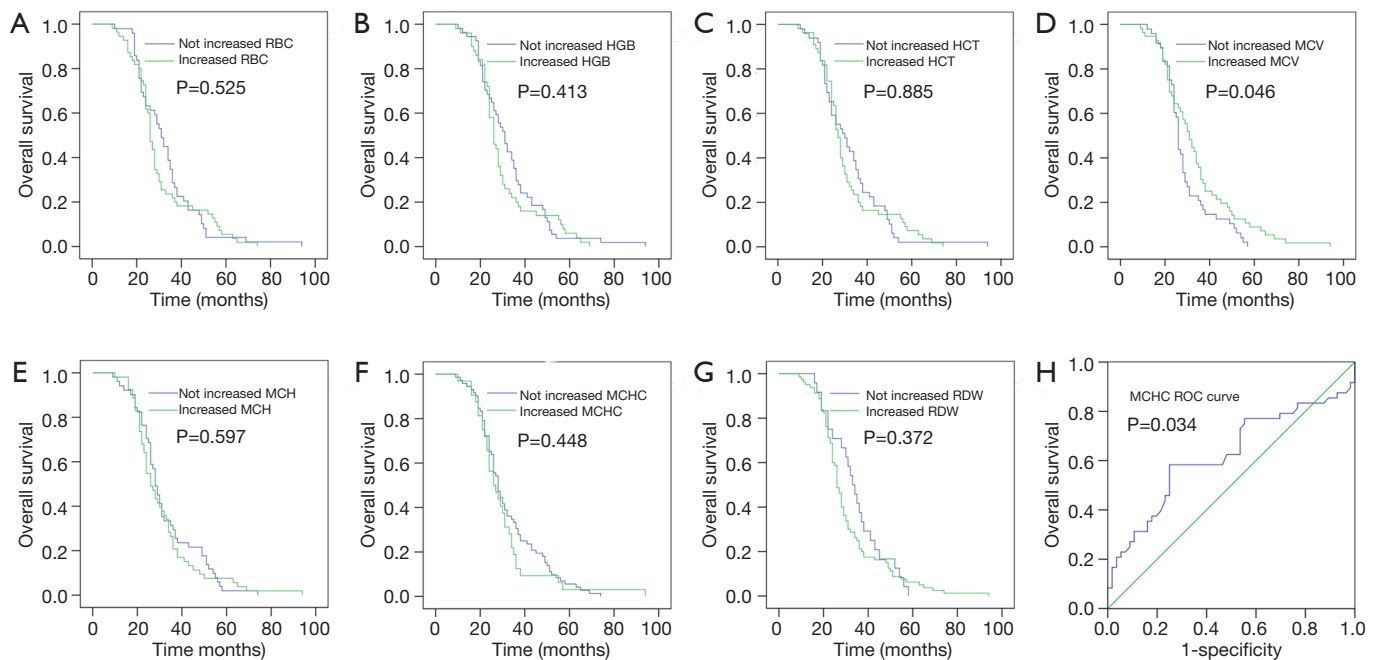
#### **Specificity and sensitivity of baseline parameters on predicting resectable GC**

The receiver operating characteristic (ROC) curve analysis (Figure 5H) showed that the area under the curve (AUC) for predicting resectable GC of MCHC was 0.621 (95% CI, 0.509-0.733; P<0.034). The optimal cutoff point of MCHC was 341.98 g/L, with a sensitivity of 58.3% and a specificity of 75.0%.

#### **Discussion**

RBC is a part of person's complete blood count, and it can circulate in blood and carry oxygen throughout the body (4). A long-term retrospective study indicated that low RBC levels could predict poor survival in postoperative patients with liver cancer (19). Another analysis has indicated that the low RBC level of deglycating enzymes could be implicated in malignant colon mucosal transformation (20). The underlying mechanism was reported by Quemener *et al.* (21). He showed that alterations in RBC rheological properties could result in hemolysis, which was common in cancer-bearing hosts. In turn, the products of hemolysis





**Figure 5** Relationship between the status of changes in RBC-related indicators after the whole course of treatment and the outcomes. (A) The OS according to changes in RBC; (B) the OS according to changes in HGB; (C) the OS according to changes in HCT; (D) the OS according to changes in MCV; (E) the OS according to changes in MCH; (F) the OS according to changes in MCHC; (G) the OS according to changes in RDW; (H) schematic of the ROC curve for prediction by pretreatment MCHC value. RBC, red blood cell; OS, overall survival; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width; ROC, receiver operating characteristic.

were related to the advanced/aggressive nature of cancers. Our present study revealed that neither surgery nor the whole course of treatment had significant effects on serum RBC level, while adjuvant chemotherapy significantly increased the value of RBC. Likewise, neither the amount of pretreatment nor the RBC post-/pretreatment ratio had an effect on OS.

HGB was proposed as an independent prognostic factor for survival in a variety of malignancies. Low HGB concentration could indicate impaired outcomes for patients with carcinoma of the bladder (22), endometrium (23), and ovaries (24). As indicated in a previous report by Grimm *et al.* (25), HGB level could be decreased by inflammatory cytokines, which were released by tumor cells and might be able to decrease erythropoietin production and shorten the survival of RBCs. In the current study, we found no association between pretreatment HGB levels and the outcome of resectable GC patients. Surgery significantly decreased the value of HGB. On the contrary, chemotherapy significantly increased the value of HGB,

making the HGB value remain stable during the whole course of treatment. Change in HGB level represented by post-/pre-treatment HGB had no significant impact on OS.

HCT is the proportion of blood volume that is occupied by red blood anemia, and is usually part of a complete blood count (26). Previous reports have demonstrated that a low HCT level was relevant to worse survival in many cancer diseases, including renal cell carcinoma (27) and breast cancer (26). Hypoxia was one of the underlying mechanisms in which HCT functioned as a prognostic factor for malignant diseases (26). Due to the reduced oxygen-carrying capacity, oxygen delivery reduces at a lower HCT level and further leads to the production of hypoxia (28). Meanwhile, the parallel relationship between cancer progression and hypoxia was reported (29). In the present study, although surgery and the whole course of treatment had no significant effect on the value of HCT, adjuvant chemotherapy could increase the HCT levels. We also found that neither the pretreatment nor the post-/pre-treatment ratio of HCT could affect OS on resectable GC

patients.

MCV refers to the volume of RBCs. It has been long recognized as a biomarker for a variety of malignant diseases, like esophageal squamous cell carcinoma (30) and colorectal cancer (31). To our knowledge, MCV is a marker of internal folate concentration. Zheng *et al.* demonstrated that the deficiency of folate could result in aberrant DNA methylation, which has been proposed as a predictor of clinical outcome in cancer patients (30). In our study, we found that the pretreatment of MCV levels did not affect the OS of resectable GC patients. The whole course of treatment significantly increased the levels of MCV. Chemotherapy might have led to the upregulation of MCV, because surgery had no impact on MCV status. In contrast to earlier studies, we found that patients with increased MCV levels had increased survival ratio.

MCH is a measurement of the average HGB content of each RBC (11). One small-scale retrospective study revealed that a low MCH level was associated with worse survival in hepatectomized patients with hepatocellular carcinoma (11), and MCH was shown to be a marker of iron metabolism. As demonstrated in previous reports, abnormalities in iron metabolism might be crucial in cancer progression (32,33). In the present study, surgery significantly decreased the value of MCH, while chemotherapy significantly increased the value, leaving MCH values unchanged during the whole course of treatment. However, pretreatment MCH levels and post-/pre-treatment ratio of MCH had no significant effects on OS.

MCHC is calculated by dividing the MCH by the MCV and can reflect the average value of HGB concentration (12). A retrospective study was conducted and demonstrated that lower MCHC level was associated with unfavorable prognosis of resectable lung cancer (12). It is well known that MCHC is one of the key indicators of anemia, a frequent complication of cancer patients (4). Tumor cells produce anemia by secreting soluble molecules such as interleukin-1, interferon- $\gamma$ , and tumor necrosis factor that may cause hemolysis, erythropoiesis suppression, and erythropoietin response deficiency on progenitor erythroid cells (12). Thus, it is not surprising to find out the parallel association between low MCHC and worse outcomes in cancer patients. Consistent with previous studies, our study showed that high pretreatment MCHC levels predicted better outcomes of resectable GC patients. The whole course of treatment significantly reduced MCHC rates. The decline of MCHC was mainly attributable to surgery, since chemotherapy had no impact on MCHC status. Both

univariate and multivariate analyses demonstrated that low pretreatment MCHC level was one of the independent risk factors in early GC patients. Moreover, the ROC curve analysis showed that the pretreatment MCHC value of 341.98 g/L was considered to be the optimal cutoff value for prognosis, with a sensitivity of 58.3% and a specificity of 75.0%.

RDW is one of the most common blood parameters, which reflects the degree of heterogeneity of erythrocyte volume (also known as anisocytosis) (34). Accumulated evidence indicates that RDW could be a prognostic factor for various malignancies, like gastric (35), lung (13), and ovarian cancers (36). RDW has been reported to have a close association with many pathophysiological conditions, such as anemia, inflammation, and early nutritional deficiencies via changes in erythropoiesis (37). To the best of our knowledge, cancer can induce chronic inflammation and malnutrition (37). Also, anemia is another frequent complication in cancer patients (4). These findings reflect a widely accepted hypothesis that increased RDW level could be a marker of worse outcomes in cancer patients. Our study found that the whole course of treatment increased the level of RDW, and this change mainly resulted from surgery since chemotherapy had no impact on RDW status. However, no significant association was found between survival and pretreatment or the post/pre-treatment ratio of RDW.

A few limitations in this study should be addressed. First, this is a retrospective analysis, and the data were collected from only a single medical center. Secondly, although all measurements were taken in the same laboratory, a certain bias arising from the long study period cannot be completely excluded. Finally, the case number was insufficient.

In conclusion, our present study investigated the predictive values of RBC-related indicators in resectable GC patients and found that high pretreatment MCHC levels were a favorable predictor of OS. In comparison, both the univariate analysis and the multivariate analysis showed that the low level of MCHC pretreatment was an independent risk factor impacting OS. Since MCHC is an inexpensive and easily accessible indicator, our findings offer a new and valuable clue to evaluating prognosis in resectable GC.

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### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.46>). The authors have no conflicts of interest to declare.

*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. Ethics approval for the study was granted by the Medical Ethics Committees of the First Affiliated Hospital of Soochow University [No. (2019)015].

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