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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Preoperative Hematocrit (HCT) is a Novel and Simple Predictive Marker for Gastric Cancer Patients Who Underwent Radical Gastrectomy

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ABSTRACT

Background. Previous studies have suggested that preoperative anemia negatively influences survival in patients with gastric cancer (GC). We sought to investigate which anemic markers can better predict the prognosis of patients with resectable GC.

Methods. The study involved 2277 GC patients who underwent curative resection between December 2008 and December 2014. Cox regression models were used to identify the best anemic markers associated with prognosis. Time-dependent receiver operating characteristics analysis (t-ROC) and the estimated area under the curve (AUC) were used to compare the prognostic values.

Results. Of all patients, 1709 (75.1%) were male, and the median age was 61 years. Univariate analyses showed that preoperative hematocrit (HCT), hemoglobin, and mean corpuscular volume were associated with OS (all $P < 0.05$). However, in a separate analysis of individual stages, only HCT was shown to be significantly prognostic across all tumor stages (all $P < 0.05$). In the multivariate analysis, preoperative HCT remained an independent prognostic factor for GC. Low HCT was significantly associated with older age, female sex, lower body mass index, higher American Society of Anesthesiologists score, higher preoperative transfusion rate, 90-day mortality, adjuvant chemotherapy, larger tumor size, lymph node metastasis, later stage, and vascular involvement. The t-ROC curve and AUC for HCT were similar to those for the controlling nutritional status and prognostic nutritional index throughout the observation period.

Conclusions. The preoperative HCT is a novel, simple, and powerful prognostic indicator of poor outcome in patients with GC and can be used as a part of the preoperative risk stratification process.

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Gastric cancer (GC) is the fifth most common malignancy and the third-leading cause of cancer death worldwide.[1] Despite the development of diagnostic and therapeutic modalities, the postoperative long-term survival for patients with advanced GC remains poor.[2] The early detection of patients with GC who are at high risk of adverse treatment outcomes and premature mortality is the key to improving the clinical efficacy. Anemia is the most common hematologic abnormality of GC. Iron metabolism disorders, tumor-associated bleeding, abnormal catabolism of cancer patients, and nutritional deficiencies all play a

role in anemic pathogenesis.[3,4] Hemoglobin (Hb) is a common index used to evaluate anemia. Low Hb is closely related to a poor prognosis in various tumors.[5,6] As red blood cell parameters, preoperative hematocrit (HCT) and mean corpuscular volume (MCV) also are important anemic markers.[7] Only recently has MCV been proposed and investigated as a prognostic marker in patients with esophageal cancer.[8] In triple-negative breast cancer, HCT was found to be superior to Hb in terms of predicting breast cancer mortality.[9] However, to the best of our knowledge, no studies investigating the association between these two indicators and prognosis of GC have been conducted.

Anemia is closely associated with malnutrition in cancers. Previous studies have suggested that nutritional indicators, such as controlling nutritional status (COUNT) and prognostic nutritional index (PNI), can improve the prediction of clinical outcomes in GC.[10,11] However, which anemic markers can better predict the prognosis of GC patients and their superiority to the conventional nutritional indicators remain unclear. The purpose of this study was to assess the prognostic value of these anemic markers for identifying the best anemic marker and to analyze its prognostic accuracy by comparing the COUNT and PNI.

PATIENTS AND METHODS

Study Population

A retrospective review of a prospectively maintained database was performed to identify all patients undergoing radical gastrectomy at Fujian Medical University Union Hospital from December 2008 to December 2014. The case exclusion criteria were as follows: (1) no routine blood examination before surgery, (2) metastatic disease, (3) neoadjuvant chemotherapy, (4) malignant disease in other organs, and (5) incomplete/inaccurate medical records. Twenty patients (0.9%) with high HCT (HCT $>$ 50%) also were excluded because of small sample size. Consequently, 2277 patients were eligible (Supplemental Fig. 1). All surgical procedures, including D2 lymphadenectomy, were performed according to the guidelines of the Japanese Gastric Cancer Association.[12] Staging was performed according to the corresponding eighth edition of the AJCC Staging Manual.[13] Postoperative complications was defined as a state where the Clavien-Dindo classification (CDc) is $\geq$ II. Adjuvant chemotherapy using 5-fluorouracil (5-FU)-based regimens (mostly oxaliplatin with either Xeloda or S-1) was recommended to the majority of patients with advanced GC.[14,15]

Data Collection

Serum samples were collected and assayed within 7 days before surgery. These included the Hb, HCT, MCV, lymphocyte counts, albumin (Alb), and total cholesterol level. According to the standard values of pretreatment Hb, HCT, and MCV,[6,8,16] patients were divided into several groups (Table 1). COUNT and PNI were derived as previously described.[10,11] The optimal cutoff value of COUNT was 2 as determined by the software X-tile (Yale University, New Haven, CT), and the cutoff value of PNI was 45 based on previous reports.[10,17]

Follow-up Evaluation

A postoperative follow-up assessment was performed every 3 months for 2 years and then every 6 months during years 2 to 5. The final follow-up evaluation was conducted in June 2018. Most routine follow-up appointments included a physical examination, laboratory testing (including cancer antigen [CA] 19-9, CA72-4, and carcinoembryonic antigen [CEA]-level measurements), chest radiography, and abdominopelvic ultrasonography or computed tomography, along with an annual endoscopic examination. Overall survival (OS) was defined as the time from surgery to death from any cause or to the time of censoring on the date of the last follow-up.

Statistical Methods

Descriptive statistics were used to summarize cohort characteristics and distributions of Hb, HCT, and MCV. Survival curves were constructed according to the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. The Cox proportional hazards regression model was applied to perform univariate and multivariate analyses. Variables found to be statistically significant ($P < 0.05$) in univariate analysis were entered into a Cox regression multivariate model using a forward conditional method. Correlations between categorical variables were analyzed using Chi squared tests, and continuous variables were analyzed using Student's t tests. The estimated area under the curve (AUC) and time-dependent receiver operating characteristic (t-ROC) curves were used to quantify the predictive accuracy.[18] All tests were two-sided, and statistical significance was inferred at a value of $P < 0.05$. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL) and R ver. 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). The "survivalROC" and "timeROC" R packages were used to estimate t-ROC curves, respectively.

TABLE 1 Baseline patient clinicopathologic characteristics

Clinicopathological features	Cases (n = 2277)
Patient characteristics	
Age (median, IQR)	61 (54–69)
Gender	
Male	1709 (75.1%)
Female	568 (24.9%)
BMI (median, IQR)	22.0 (20.2–24.0)
ASA score	
1	1431 (62.8%)
2	774 (34.0%)
3	72 (3.2%)
Tumor characteristics	
Tumor location	
Upper	544 (23.9%)
Middle	495 (21.7%)
Lower	953 (41.9%)
Mixed	285 (12.5%)
Tumor size (cm, median, IQR)	4.0 (3.0–6.0)
Histologic type	
Differentiated	515 (22.6%)
Undifferentiated	1762 (77.4%)
Vascular invasion	
Negative	1754 (77.0%)
Positive	523 (23.0%)
Perineural invasion	
Negative	1901 (83.5%)
Positive	376 (16.5%)
Signet ring cell carcinoma	377 (16.6%)
Lymph node involvement	1407 (61.8%)
T stage	
T1	569 (25.0%)
T2	251 (11.0%)
T3	716 (31.4%)
T4a	701 (30.8%)
T4b	40 (1.8%)
N stage	
N0	870 (38.2%)
N1	346 (15.2%)
N2	373 (16.4%)
N3a	412 (18.1%)
N3b	276 (12.1%)
pTNM stage	
I	652 (28.6%)
II	550 (24.2%)
III	1075 (47.2%)
Adjuvant chemotherapy	
Yes	1008 (44.3%)
No	1269 (55.7%)
Postoperative complication	
Absent	1914 (84.1%)
Present	363 (15.9%)
90-Day mortality	33 (1.4%)
Preoperative transfusion	
Yes	161 (7.1%)
No	2116 (92.9%)
Red blood cell parameter	
Hb (g/dl)	
Normal	1502 (66.0%)
Low	775 (34.0%)
MCV (fl)	
Low	288 (12.6%)
Normal	1906 (83.7%)
High	83 (3.6%)
HCT (%)	
Normal	979 (43.0%)
Low	1298 (57.0%)

RESULTS

Patient Characteristics

Of the 2277 GC patients included in the study, 1709 (75.1%) were male, and 568 (24.9%) were female. Their median age was 61 years (interquartile range (IQR): 54–69 years), and 1407 (61.8%) patients had lymph node involvement. The distribution of TNM stage was 652 (28.6%) of patients in stage I, 550 (24.2%) in stage II, and 1075 (47.2%) in stage III (Table 1). All patients were categorized into the following two groups according to the preoperative HCT: 979 patients (43.0%) in the normal HCT group and 1298 (57.0%) in the low HCT group. According to the preoperative Hb level, 1502 (66.0%) patients had normal Hb and 775 (34.0%) patients had low Hb. Similarly, there were 288 patients (12.6%) in the low MCV group, 1906 patients (83.7%) in the normal MCV group, and 83 patients (3.6%) in the high MCV group. Compared with the Hb and MCV group, the distribution of the HCT group was relatively balanced.

Survival Analysis

The median follow-up period was 69.0 (range 1–115) months. The 5-year OS rate for the entire cohort was 67.9%. As observed in the Kaplan–Meier curves, OS was significantly worse in patients with low HCT than in those

with normal HCT (56.8% vs. 74.9%, log-rank test: $P < 0.001$; Fig. 1a). Similarly, preoperative Hb ($P < 0.001$, Supplemental Fig. 2A) and MCV ($P = 0.013$, Supplemental Fig. 3A) were associated with OS in all stages. In a subgroup analysis, according to pTNM stage, low HCT was significantly associated with poor prognosis in each stage (all $P < 0.05$, Fig. 1b–d). Meanwhile, low Hb was strongly associated with worse OS only in stage III patients ($P < 0.05$, Supplemental Fig. 2D) but not in stage I and stage II patients (Supplemental Fig. 2B, C). However, in each stage, the Kaplan–Meier curves of the MCV group overlapped (all $P > 0.05$, Supplemental Fig. 3B–D).

HCT Independently Predicted Prognosis

In univariate analysis, all the preoperative anemic markers were associated with OS included the HCT, Hb, and MCV (all $P < 0.05$, Table 2). In addition, other variables, including age, body mass index (BMI), the American Society of Anesthesiologists (ASA) score, tumor location, size, histologic type, vascular invasion, perineural invasion, T stage, N stage, and pathological stage, had a significant effect on OS (all $P < 0.05$, Table 2). Preoperative transfusion and signet ring cell were not associated with the prognosis of GC (both $P > 0.05$, Table 2).

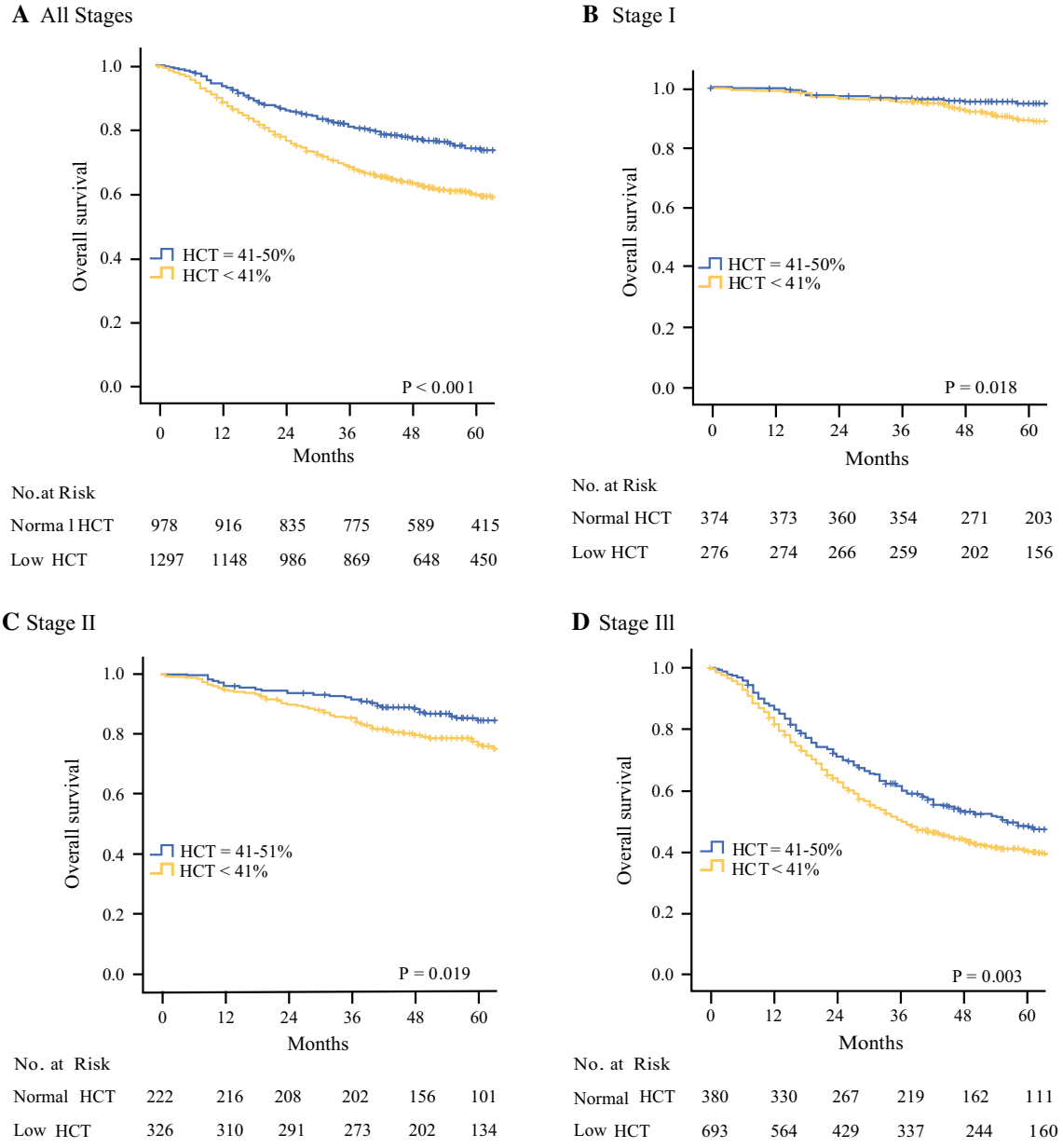


FIG. 1 Relationship between OS and HCT in all stages (**a**) and in stage I (**b**), stage II (**c**), and stage III (**d**) GC patients

TABLE 2 Univariate and multivariate cox proportional hazard regression analyses for OS

Clinicopathological features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age*	1.030 (1.023–1.037)	< 0.001	1.027 (1.020–1.034)	< 0.001
Gender		0.867		
Male	Reference			
Female	0.986 (0.838–1.161)			
BMI*	0.935 (0.913–0.958)	< 0.001	0.961 (0.938–0.984)	0.001
ASA score				
1	Reference		–	
2	1.251 (1.080–1.449)	0.003	–	0.491
3	1.494 (1.044–2.138)	0.028	–	0.389
Tumor location				
Upper	Reference		Reference	
Middle	0.918 (0.749–1.125)	0.410	0.922 (0.751–1.133)	0.441
Lower	0.625 (0.520–0.752)	< 0.001	0.825 (0.684–0.995)	0.044
Mixed	1.546 (1.251–1.910)	< 0.001	1.333 (1.072–1.659)	0.010
Tumor size (cm)	1.017 (1.015–1.020)	< 0.001	1.007 (1.004–1.010)	< 0.001
Histologic type				
Differentiated	Reference		–	
Undifferentiated	1.295 (1.081–1.552)	0.005	–	0.276
Vascular invasion				
Negative	Reference		–	
Positive	1.845 (1.586–2.146)	< 0.001	–	0.967
Perineural invasion				
Negative	Reference		–	
Positive	1.754 (1.482–2.075)	< 0.001	–	0.893
Signet Ring Cell Carcinoma				
No	Reference			
Yes	0.988 (0.818–1.195)	0.904		
T stage				
T1	Reference		NA	
T2	2.200 (1.438–3.367)	< 0.001		
T3	5.728 (4.161–7.886)	< 0.001		
T4a	10.999 (8.053–15.021)	< 0.001		
T4b	16.745 (10.471–26.779)	< 0.001		
N stage				
N0	Reference		NA	
N1	1.776 (1.326–2.380)	< 0.001		
N2	3.282 (2.556–4.216)	< 0.001		
N3a	6.814 (5.446–8.524)	< 0.001		
N3b	11.204 (8.885–14.129)	<0.001		
pTNM stage				
I	Reference		Reference	
II	2.912 (2.095–4.048)	< 0.001	2.697 (1.927–3.775)	< 0.001
III	10.632 (7.986–14.156)	< 0.001	9.028 (6.675–12.212)	< 0.001
Adjuvant chemotherapy				
No	Reference		Reference	
Yes	1.157 (1.002–1.336)	0.047	0.714 (0.616–0.828)	< 0.001

TABLE 2 continued

Clinicopathological features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Postoperative complication				
Absent	Reference		–	
Present	1.300 (1.084–1.560)	0.005	–	0.415
Preoperative transfusion				
No	Reference			
Yes	1.278 (0.998–1.636)	0.052		
Hb (g/dl)				
Normal	Reference		–	
Low	1.726 (1.498–1.990)	< 0.001	–	0.329
MCV (fl)				
Low	Reference		–	
Normal	1.311 (1.078–1.594)	0.007	–	0.274
High	1.127 (0.777–1.636)	0.529	–	0.344
HCT (%)				
Normal	Reference		Reference	
Low	1.744 (1.501–2.027)	< 0.001	1.234 (1.059–1.440)	0.007

*Analysed as a continuous variable

NA indicates not included in the multivariate analysis due to interference of these indices with pTNM stage

However, multivariate analyses revealed that HCT was the only independent anemic marker for OS (hazard ratio 1.246, 95% confidence interval 1.069–1.452, $P = 0.005$, Table 2). Other independent prognostic factors included age, BMI, tumor location, size, vascular invasion, perineural invasion, TNM stage, and adjuvant chemotherapy (all $P < 0.05$, Table 2). In addition, low HCT was also an independent risk factor for CSS in patients with GC by multivariate analysis (hazard ratio 1.180, 95% confidence interval 1.006–1.030, $P = 0.042$, Supplemental Table 1).

Correlations Between HCT and Clinicopathological Features

Table 2 shows the correlations between the HCT and clinicopathological factors. The HCT had significant associations with unfavorable clinicopathological factors. Low HCT was associated with older age, female sex, low BMI, high American Society of Anesthesiologists (ASA) scores, higher preoperative transfusion rate, 90-day mortality, and adjuvant chemotherapy rate (all $P < 0.05$, Table 2). Regarding tumor factors, larger tumor size, more lymph node metastasis, advanced pTNM stage, and vascular invasion were significantly associated with low HCT (all $P < 0.05$, Supplemental Table 2). However, in separate analysis of each clinicopathological factor, the prognostic value of the HCT was consistent (Fig. 2).

Comparison and Association of HCT with Nutritional Indicators (COUNT and PNI)

Of all patients, 2193 had COUNT and PNI values available for analysis. COUNT and PNI values were divided into four group according to quartiles. Normal HCT was significantly associated with lower COUNT and higher PNI (all $P < 0.001$, Supplemental Fig. 4). T-ROC curves were generated to compare the prognostic accuracy of the HCT and nutritional indicators (COUNT and PNI). The t-ROC curve and AUC values of the HCT were comparable to those of the COUNT and PNI throughout the observation period (all $P > 0.05$, Fig. 3).

DISCUSSION

Recently, increasing evidence has shown that anemia is associated with worse survival in a wide variety of malignancies.[19–21] As a frequent hematologic abnormality in cancer patients, the main indication for anemia is abnormal red blood cell parameters, including Hb, HCT, and MCV.[22] Previous studies have found that preoperative Hb, HCT, and MCV can be prognostic markers in many cancers.[6,8,9] However, the prognostic value of MCV and Hb in GC remains unclear. In a large cohort of resectable GC patients, our findings demonstrate that Hb, HCT, and MCV were all associated with OS, but only preoperative HCT was an independent predictor, and its prognostic value was consistent in each stage. As far as we

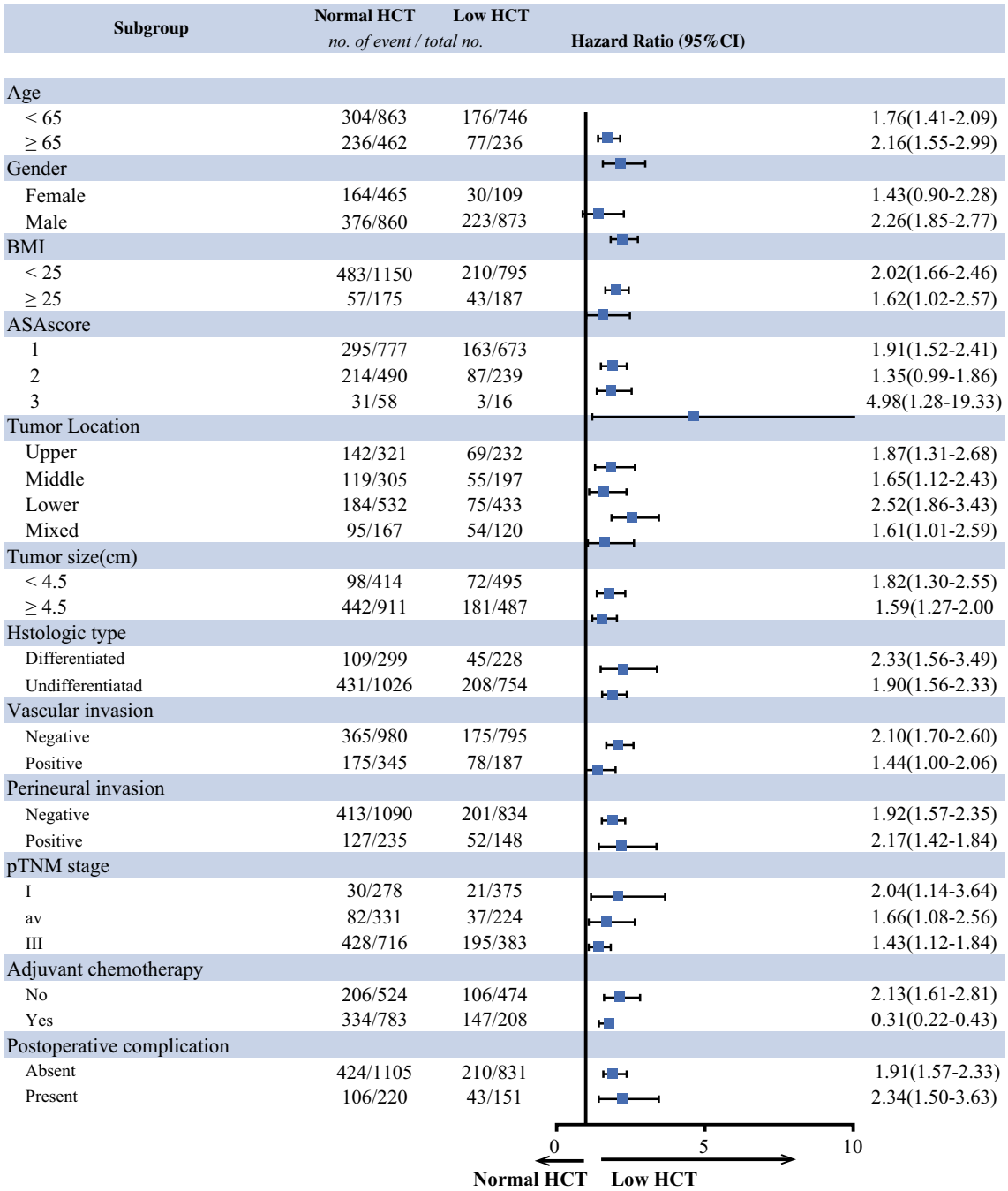
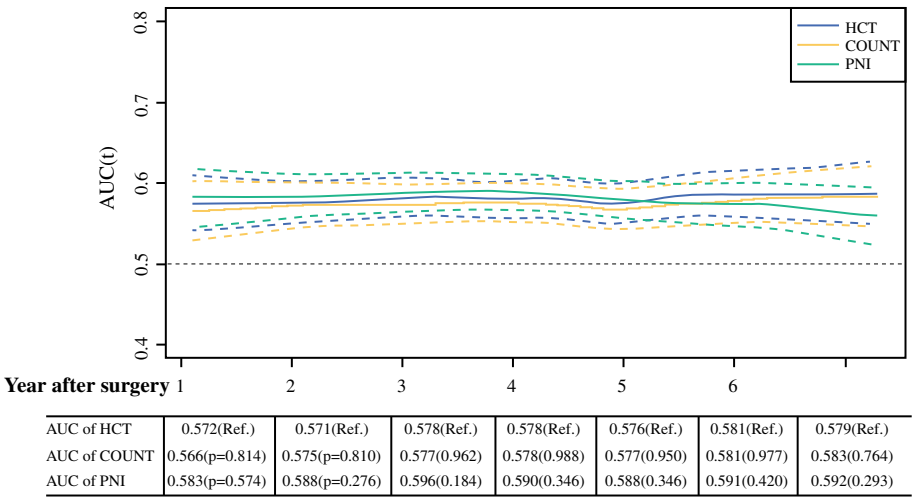


FIG. 2 Relationship between HCT and overall survival in various strata

know, the present study represents the single largest consecutive GC cohort to investigate and compare the prognostic value of these red blood cell parameters.

HCT is the proportion of blood volume that is occupied by red blood cells. At this time, only one study is available regarding the relationship between MCV and prognosis of cancer. Chen et al.[9] reported that HCT was superior to Hb for predicting triple-negative breast cancer mortality. In this study, the cutoff value of HCT was determined by X-tile software based on their own cohort. However, in our study, the standard value was used as the cutoff value of HCT, Hb, and MCV, because we considered that it can enhance the value of the current results for universal application. Our findings demonstrate that preoperative HCT is an independent predictor of OS for patients with GC undergoing curative surgical resection. The study also revealed some interesting associations between the HCT and clinicopathologic features previously shown to be



AUC of HCT	0.572(Ref.)	0.571(Ref.)	0.578(Ref.)	0.578(Ref.)	0.576(Ref.)	0.581(Ref.)	0.579(Ref.)
AUC of COUNT	0.566(p=0.814)	0.575(p=0.810)	0.577(0.962)	0.578(0.988)	0.577(0.950)	0.581(0.977)	0.583(0.764)
AUC of PNI	0.583(p=0.574)	0.588(p=0.276)	0.596(0.184)	0.590(0.346)	0.588(0.346)	0.591(0.420)	0.592(0.293)

FIG. 3 Time-dependent ROC curves for the HCT, COUNT, and PNI

predictive of worse outcomes. These include older age, higher TNM stage, larger tumor size, and vascular invasion. This finding suggests that the low HCT may be associated with tumor proliferation and metastatic potential. Previous studies have shown that the later the tumor stage, the greater the probability of GC bleeding, and due to different degrees of arterial invasion in the elderly patients, the ability for vasoconstriction is decreased and bleeding easily occurs.[23] Low HCT also was associated with older age and low BMI. Therefore, for elderly GC patients with low BMI, attention should be paid to monitoring preoperative HCT and strengthen nutritional status to improve the postoperative prognosis. Although HCT was associated with a number of variables, the relationship between MCV and OS was not modified by any other clinicopathological factors, which suggested that HCT was a stable predictor of prognosis in patients with GC. To date, only preliminary hypotheses have been introduced to explain why HCT may confer prognostic information. We propose several additional mechanisms. First, at a lower HCT level, oxygen transport decreases due to the reduced oxygen carrying capacity, which contributes to the development of hypoxia.[24] By inducing proteomic and genomic changes, hypoxia may increase the proliferative and metastatic potential.[25,26] Second, Prosnitz et al.[27] found that hypoxia has been linked to radiotherapy and chemotherapy resistance, because oxygen is essential for the cytotoxic activities of these treatments. Previous studies have shown that some chemotherapeutic drugs, such as platinum chemotherapy drugs and etoposide, have oxygen-dependent killing effects on cancer cells.[28,29] Therefore, hypoxia of tumors can lead to decreased chemosensitivity and increased drug resistance. Although patients with neoadjuvant chemotherapy has been excluded, there are still 44.3% of the patients in this study receiving 5-FU-based adjuvant chemotherapy (mostly oxaliplatin with either Xeloda or S-1) after surgery. Therefore, preoperative anemia-induced hypoxia may affect the efficacy of adjuvant chemotherapy and lead to poor prognosis of GC. Therefore, hypoxia in tumor tissue may be an important cause of poor prognosis for GC patients with low HCT.[30] Finally, low HCT was related to malnutrition before treatment. In this study, patients with low HCT were significantly associated with low BMI, low PNI, and high COUNT, which further confirmed that the decrease of HCT might reflect the state of preoperative malnutrition. Previous studies have suggested that preoperative malnutrition negatively influences prognosis after gastrectomy.[11,31,32] Therefore, HCT plays an important role in the prognosis of GC. In clinic, accurate pretreatment staging is essential for treatment decision. Our study found that preoperative HCT is an independent prognostic factor for GC, which can affect the prognosis of GC patients in each stage. Therefore, as novel and easily obtainable prognostic marker, preoperative HCT can be used as a supplement to the pathological stages and provide a more accurate prognosis.

To evaluate the clinical value of HCT as a surrogate marker for the patient's nutritional status, our study further investigated the relationship between HCT and nutritional markers in GC. This study highlighted a direct relationship between HCT and nutritional factors, including COUNT and PNI. As traditional nutritional markers, COUNT and PNI have been reported to be associated with survival in GC.[11,32] Therefore, the current study also attempted to clarify the prognostic value of the HCT compared with that of the COUNT and PNI. The t-ROC curve and AUC values suggested that the HCT was similar to the COUNT and PNI in terms of predicting the long-term prognosis of GC patients. However, COUNT and PNI are complex parameters, which limits their clinical application. Thus, as a

simple and easily available parameter, the HCT may be used as an alternative to the COUNT or PNI to improve the prediction of clinical outcomes. For patients with low preoperative HCT, preoperative nutritional support and postoperative systemic adjuvant therapy should be considered to improve long-term survival. However, malnutrition was associated with many factors, including albumin, hemoglobin, cholesterol, etc.[6,33,34] So, we believe that comprehensive nutritional support should be used to improve preoperative nutritional status, rather than preoperative transfusion alone. At present, whether preoperative anemia correction therapy can affect the prognosis of GC remains controversial.[35,36] In our study, we found that preoperative transfusion was not associated with the prognosis of GC, which indicated that increasing preoperative HCT by transfusion alone may not significantly improve the prognosis of GC. This also may be related to the lower number of patients (7.1%) with preoperative transfusions in this study. Therefore, whether the improvement of HCT by preoperative transfusion can improve the prognosis of GC still needs a lot of prospective studies to confirm.

This study has some limitations. First, it was a retrospective study and thus may have been subject to selection bias; however, the cohort represents the largest known consecutive cohorts used in the study of anemic markers. Second, whether all patients were in the same state before blood sampling is unclear, so patients with neoadjuvant therapy were excluded. Finally, due to the lack of data on limits plastics and Borrmann type, we cannot evaluate the impact of these clinicopathological factors on the prognostic value of HCT. The proportion of patients with low Hb and MCV was lower than that of patients with low HCT, which also may affect the outcomes. Despite these limitations, our study is the first to demonstrate that preoperative HCT can predict the prognosis of GC better than Hb and MCV can. Additionally, as a simple and easily available anemic marker, the HCT may be used as an alternative to the nutritional markers to better stratify patients and help to guide clinical decision-making for patients with GC.

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AUTHOR CONTRIBUTIONS Lin JX, Lin JP, Zheng CH, Huang CM, and Li P conceived of the study, analyzed the data, and drafted the manuscript. Tu RH, Li P, Xie JW, Wang JB, and Li P helped revise the manuscript critically for important intellectual content; Lu J, Chen QY, Cao LL, and Lin M helped collect data and design the study.

CONFLICT OF INTEREST There are no conflicts of interest or financial ties to disclose from any of author.

HUMAN RIGHTS STATEMENT All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

INFORMED CONSENT Informed consent or substitute for it was obtained from all patients for being included in the study.

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