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***Retrospective Study*****Prognostic Significance of the Preoperative Hemoglobin to Albumin Ratio for the Short-term Survival of Gastric Cancer Patients who Underwent D two Radical Resection**

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**Abstract****BACKGROUND**

Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied.

**AIM**

To investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

**METHODS**

Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software.

## RESULTS

HAR was independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ( $P < 0.001$ ). Low HAR was markedly related to high stage (OR = 0.45 for II vs. I; OR = 0.48 for III vs. I), T classification (OR = 0.52 for T4 vs. T1), and large tumor size (OR = 0.51 for  $\geq 4$  cm vs.  $< 4$  cm) (all  $P < 0.05$ ). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820.

## CONCLUSION

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

**Key Words:** gastric cancer; hemoglobin to albumin ratio; short-term survival; prognosis; nomogram

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**Core Tip:** Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied. Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software. HAR was independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ( $P < 0.001$ ). Low HAR was markedly related to high

stage (OR = 0.45 for II vs. I; OR = 0.48 for III vs. I), T classification (OR = 0.52 for T4 vs. T1), and large tumor size (OR = 0.51 for  $\geq 4$  cm vs.  $< 4$  cm) (all  $P < 0.05$ ). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820. Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

## **INTRODUCTION**

For resectable GC, radical surgery and adjuvant therapy are the standard therapies [1-2]. The postoperative prognosis is evaluated by the American Joint Committee on Cancer (AJCC) TNM classification system [3-4]. However, prognostic factors such as age, tumor size, and tumor location are not considered in the prediction of individual survival. Moreover, the prognosis of patients in the same stage with similar treatment regimens varies greatly [5-6]. Therefore, it is necessary to develop a comprehensive and accurate prognostic evaluation system to predict the prognosis of GC patients, which is of great significance in selecting individualized treatment plans for these patients. In addition, studies have shown that the prognosis of cancer is not only correlated with tumor characteristics but also to the nutritional status and systemic inflammation of patients [7-8]. The systemic inflammatory response can affect the progression and metastasis of tumors [9]. Recently, studies also found that malnutrition is associated with decreased immunity, which increases the incidence of complications and mortality postoperatively, leading to poor postoperative prognosis in cancer patients [10-11]. Hemoglobin and albumin are used as the two most common indicators of nutritional status. Various perioperative nutritional parameters have been confirmed as independent prognostic factors in GC patients who underwent D2 Radical Resection [12]. Low hemoglobin levels can lead to tumor hypoxia, which can accelerate tumor growth and promote the angiogenesis of tumor cells [13]. Low serum albumin concentration was an independent risk factor affecting the survival of GC patients [14]. In addition, low serum albumin levels can impair cellular immune function, leading to poor prognosis in cancer patients [15]. Studies have demonstrated that preoperative low serum albumin and hemoglobin levels are closely associated with the poor prognosis of malignant tumors [16-17] ; the high preoperative C-Reactive protein to albumin ratio (CAR) was related to poor outcome in patients with GC [18-19]. However, the clinical value of the hemoglobin to albumin ratio (HAR) in the prognosis of GC patients with D2 radical resection has not been reported. Nomogram can provide

the overall probability of specific outcomes for individual patients and provide more accurate predictions than the traditional TNM staging system, thereby improving personalized treatment decisions [20-21]. Therefore, the aim of this study was to investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

## **MATERIALS AND METHODS**

### **Patient characteristics**

The clinical and follow-up data of 312 GC patients who underwent D2 radical resection in our hospital were collected from January 2017 to January 2019. Tumor markers, serum albumin and fibrinogen levels, and blood cell counts, including hemoglobin, neutrophils, platelets, and lymphocytes, were extracted at the first admission. The HAR, platelet to hemoglobin ratio (PHR), platelet to lymphocyte ratio (PLR), platelet to albumin ratio (PAR), fibrinogen to lymphocyte ratio (FLR), albumin to fibrinogen ratio (AFR), hemoglobin to fibrinogen ratio (HFR), platelet to fibrinogen ratio (PFR), neutrophil to lymphocyte ratio (NLR) and albumin to lymphocyte ratio (ALR) were calculated. According to the median HAR value, GC patients were divided into a high HAR group and a low HAR group. The stage of postoperative patients was based on the AJCC TNM classification system. Survival time was calculated from the day of surgery to the last follow-up. After surgery, all patients were followed up every three months for the first two years and then every six months until five years. The last follow-up date was March 1, 2020.

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### **Inclusion and exclusion criteria**

The inclusion criteria were as follows: 1. patients with GC were diagnosed by pathology after surgery; and 2. neoadjuvant chemoradiotherapy was not performed before surgery. The exclusion criteria were as follows: 1. patients with a history of

surgery 2 mo before admission; 2. patients with a history of blood transfusion; 3. patients using hemostatic and anticoagulant drugs; 3. patients with bleeding, thrombotic disease, or splenectomy; and 4. patients with pregnancy, chronic disease, acute infection, relapse, or other distant organ metastases and those who were lost to follow-up or had incomplete information.

### Statistical analysis

Prognostic analysis was performed using Kaplan-Meier and Cox regression analyses. The Mann-Whitney U test was used for comparisons between two groups. The relationships between HAR and clinicopathological characteristics were determined by logistic regression. The receiver operating characteristic (ROC) curve was used to evaluate the ability of a single factor or combined factors to predict the short-term survival of GC patients. The rms package of R software was used to construct a prognostic nomogram model for the short-term survival of GC patients, and the scores of various indicators were obtained. In addition, Harrell's concordance index (C-index) was calculated to evaluate the performance of the model's prediction results [22]. A p-value less than 0.05 was considered to indicate a statistically significant result. Analyses were performed by SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and R (version x64 3.6.1)

## RESULTS

### Prognostic analysis of GC patients with D2 radical resection

The factors associated with prognosis were as follows: age, CEA, CA19-9, CA125, HAR, PHR, PLR, PAR, FLR, HFR, tumor size, vascular infiltration, nerve infiltration and stage (all  $P < 0.05$ ). Multivariate Cox regression analysis found that age, HAR, and stage were independent risk factors affecting prognosis (all  $P < 0.05$ ) (Table 1). Kaplan-Meier analysis found that the difference in the survival time of GC patients with a low HAR and high HAR was statistically significant ( $P = 0.003$ ), indicating that GC patients with low HAR had a poor prognosis (Figure 1).



### Association between HAR and clinicopathological characteristics

To analyze the association between HAR and clinicopathological characteristics, we performed logistic regression analysis. HAR was associated with stage, T classification, and large tumor size (all  $P < 0.05$ ) (**Figure 2**). Logistic regression analysis showed that a low HAR was effectively related to high stage (OR = 0.45 for II vs. I; OR = 0.48 for III vs. I), T classification (OR = 0.52 for T4 vs. T1), and large tumor size (OR = 0.51 for  $\geq 4$  cm vs.  $< 4$  cm) (all  $P < 0.05$ ) in GC patients (**Table 2**). These results indicate that GC patients with a low HAR were more likely to have advanced GC.

### Comparison between the low HAR group and the high HAR group

To further analyze the relationships between HAR and prognostic factors, we divided the GC patients into a low HAR group and a high HAR group according to the median HAR value. The factors with statistically significant differences between the two groups were sex, CA125, PHR, PLR, PAR, FLR, HFR, PFR, NLR, ALR, large tumor size, stage, and T classification (all  $P < 0.05$ ), suggesting that patients with a low HAR had high stage, T classification, CA125, FLR, PAR, and PLR, large tumor sizes, and low HFR (**Table 3 and Figure 3**).

### ROC curve analysis

To evaluate the ability of HAR or combined factors to predict the short-term survival of GC patients, we performed ROC curve analysis. The area under the curve (AUC) of HAR alone in predicting the 1-year survival of GC patients was 0.656, the sensitivity was 78.19%, and the specificity was 52.94%, while the AUC of predicting the 2.5-year survival was 0.804, the sensitivity was 85.29%, and the specificity was 74.95%. The AUC of HAR combined with age, CA19-9, CA125 and stage to predict the 1-year survival of GC patients was 0.833, the sensitivity was 86.83%, and the specificity was 84.77%, while the AUC of predicting the 2.5-year survival was 0.832, the sensitivity was 87.87% and the specificity was 72.18% (**Figure 4**). These results indicate that HAR



combined with prognostic factors can accurately predict the short-term survival of patients with GC.

### Construction of the prognostic nomogram

To predict the short-term survival probability of GC patients after surgery, we used the rms package to construct a logistic regression model of HAR combined with age, CA19-9, CA125 and stage, and the C-index evaluated by this model was 0.820, indicating that this prediction model had certain accuracy. Then, the plotting function was employed, and the nomogram was plotted (Figure 5). A score of HAR  $\geq 3.18$  was 0 points, while a score of HAR  $< 3.18$  was 37 points; a score of age  $\geq 62$  years was 13 points, while a score of age  $< 62$  years was 0 points; a score of CA19-9  $\geq 13.255$  U/mL was 26 points, while a score of CA19-9  $< 13.255$  U/mL was 0 points; a score of CA125  $\geq 8.5$  U/mL was 18 points, while a score of CA125  $< 8.5$  U/mL was 0 points; a score of stage I was 0 points; a score of stage II was 63 points; and a score of stage III was 100 points. The highest score was 194 points, indicating that the 1-year survival probability of GC patients was 60%-65% and that the 5-year survival probability was  $< 10\%$ . According to the total points, the probability of the short-term survival of GC patients can be predicted.

### DISCUSSION

The systemic inflammatory response and malnutrition are markedly related to the prognosis of cancer [10-11,13]. Neutrophils, lymphocytes, platelets, and fibrinogen may play important roles in tumor-induced systemic inflammatory responses [23-24]. Hemoglobin and albumin are the two most common indicators of nutritional status. At the same time, serum albumin can also reflect the inflammation of patients. Various scores and indicators based on inflammation and nutritional status have been produced to predict the prognosis of cancer, such as the controlling nutritional status score, C-reactive protein to albumin ratio, NLR, PLR, prognostic nutrition index, and systemic immune inflammation index. [25-27]. Deng *et al* [28] showed that the preoperative PLR was significantly associated with poor prognosis in GC patients with surgical

resection. Gu *et al* [29] also found that GC patients with elevated PLRs had poor overall survival. Sun *et al* [30] indicated that the combination of NLR and PLR was an independent risk factor for the overall survival of stage III GC patients undergoing radical resection. In addition, Suzuki *et al* [31] found that high plasma fibrinogen was related to tumor progression and poor overall survival in GC patients. Huang *et al*. [32] showed that elevated FLRs are a high risk factor for peritoneal metastasis in patients with GC. This study also showed that PLR and FLR were significantly related to the prognosis of GC patients.

Hemoglobin is used to determine anemia. Hypoxia caused by anemia, on the one hand, may accelerate tumor angiogenesis to promote tumor progression; on the other hand, it may make tumor cells resistant to radiotherapy and chemotherapy through proteomics and genomic changes [13, 33-34]. Moreover, it is well known that hypoxia-inducing factor 1 (HIF-1) can regulate gene products that promote tumor progression, and hypoxia increases its expression [35]. However, the molecular mechanisms of hypoxia need to be further elucidated. Previous studies have found that anemia was an independent risk factor for poor prognosis in patients with malignant tumors [36-37]. Huang *et al* [38] found that GC patients with low hemoglobin levels before surgery had poor survival. Liu *et al* [39] demonstrated that preoperative low hemoglobin concentrations were significantly related to not only large tumor sizes but also poor 5-year overall survival and high postoperative complication rates in advanced GC patients. Shen *et al* [40] suggested that preoperative anemia was markedly related to large tumor sizes, deep invasion depths and high stages and showed that stage I and II GC patients with anemia before surgery had a low long-term survival rate compared with patients without anemia before surgery.

Malnutrition and inflammation can inhibit albumin synthesis. Serum albumin was an independent prognostic indicator of malignant tumors [14, 41]. Lien *et al* [42] showed that serum albumin was effectively associated with the 5-year survival of GC patients. Moreover, relevant studies have indicated that low albumin levels are related to poor prognosis in GC [14, 43]. However, Crumley *et al* [14] demonstrated

that GC patients with low albumin levels had a poor prognosis compared with those with high albumin levels, but this factor was not an independent predictor of prognosis. Moreover, Toyokawa *et al* [44] believed that CAR is an independent prognostic factor for overall survival in patients who underwent R0 resection for stage III gastric cancer. This study indicated that HAR, stage and age were independent risk factors for the short-term survival of GC patients. Logistic regression analysis showed that a low HAR was markedly correlated with high stage, T classification, and large tumor size in GC patients. To further analyze the relationships between HAR and prognostic factors, we divided GC patients into a low HAR group and a high HAR group according to the median HAR value, and the results found that patients with low HAR had high stage, T classification, CA125, and large tumor size. In addition, Kaplan-Meier analysis indicated that low HAR was related to short survival in GC patients.

Serum tumor markers can be used to predict the prognosis of cancer. Previous studies have found that elevated CEA, CA19-9, and CA125 Levels were related to the prognosis of GC [45-47]. Related studies have also indicated that preoperative CEA and CA19-9 Levels are related to tumor invasion depth and stage, and can be used to predict prognosis [48-49]. Kochi *et al* [50] indicated that serum CA125 and CA19-9 were independent predictors of GC prognosis. This study also showed that CEA, CA19-9 and CA125 were associated with the prognosis of GC patients. The prognosis of patients with GC was evaluated mainly according to the AJCC TNM classification system [3-4]. However, this system has some limitations in clinical application. Currently, nomograms combining prognostic factors have been developed, and it has been found that nomograms including inflammation and tumor markers can predict the prognosis of cancer more accurately than the traditional TNM classification system [51-53]. In this study, HAR, stage, age, CA19-9 and CA125 were used to construct a nomogram model for the short-term survival of GC patients, and the C-index for model evaluation was 0.820. The accuracy, sensitivity and specificity of this model for predicting the 1-year survival of GC patients were 83.30%, 86.83% and 84.77% respectively, and the accuracy, sensitivity and specificity of the model for predicting the 2.5-year survival of GC

patients were 83.20%, 87.87% and 72.18%, indicating that the model had a certain validity in predicting the short-term survival of patients with GC. This study has some limitations. First, this was a single-center, small-sample retrospective study. Second, several other inflammatory markers correlated with prognosis were not included. <sup>2</sup> Therefore, multicenter large-scale prospective randomized controlled trials are necessary. In conclusions, this is the first study to apply HAR to predict the prognosis of GC patients with D2 radical resection and to construct a short-term survival prognostic nomogram for GC patients. Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model based on HAR, stage, age, CA19-9 and CA125 can correctly predict the short-term survival of GC patients with D2 radical resection, thus providing a reference for the development of personalized postoperative treatment and follow-up plans.

## **CONCLUSION**

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

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