ORIGINAL RESEARCH

Prognostic Significance of Preoperative Gamma-Glutamyltransferase to Alkaline Phosphatase Ratio in Hepatocellular Carcinoma Patients with Curative Liver Resection: A Retrospective Cohort Study

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Purpose: Gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were involved in the development and progression of cancers. This study aimed to evaluate the prognostic value of a preoperative GGT:ALP ratio (GAR) in hepatocellular carcinoma (HCC) patients with curative liver resection.

Patients and Methods: A total of 380 HCC patients underwent curative liver resection before December 2017 and from January to December 2018 were included and stratified into training set and validation set, respectively. Prediction accuracy was evaluated by the area under the receiver operating characteristic curve (AUC). Factors determined to be significant for overall survival (OS) and tumor-free survival (TFS) by using Cox regression analysis. The Kaplan–Meier method and Log rank test were utilized for survival analysis.

Results: The AUC of GAR was 0.70 (P < 0.001). An optimal cut-off value of 0.91 yielded a sensitivity of 78.1% and a specificity of 60.4% for GAR ($P < 0.001$), which stratified the HCC patients into high-risk (>0.91) and low-risk (≤ 0.91) groups. Time-dependent ROC revealed that the AUCs for 1-, 3-, and 5-year OS predictions for GAR were 0.60, 0.69 and 0.62, respectively. In addition, GAR was identified as an independent risk factor for OS and TFS both in training and validation cohort by univariate and multivariate Cox regression analysis, as well as a good prognostic indicator for patients with Barcelona Clinic Liver Cancer stage C or without vascular invasion. Notably, the AUC of the GAR for survival was better than several potential prognostic indices ($P < 0.05$).

Conclusion: We identified the GAR as a prognostic indicator in two independent cohorts of HCC patients with curative liver resection. The patients with decreased GAR score were significantly associated with better OS and TFS.

Keywords: hepatocellular carcinoma, gamma-glutamyltransferase, alkaline phosphatase, overall survival, tumor-free survival, prognostic indicator

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of malignancy-related deaths worldwide.[1] Most HCC patients are in an advanced stage of the disease at first diagnosis because of delays in the diagnosis and limited responsiveness to systemic chemotherapy.[2] The entire treatment and management process are not implemented sufficiently early, resulting in uncontrollable disease progression and eventually patient death.[3,4] The more

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accurate estimate of the tumor burden and prognosis of patients has become an eager concern for cancer management.

There have been many different indicators used to predict the prognosis of HCC, hoping to better assist clinical diagnosis and treatment.[5–8] Systemic immune-inflammation indices[9] (neutrophil-to-lymphocyte ratio (NLR),[10] platelet-to-lymphocyte ratio (PLR)[11]), gamma-glutamyltransferase to albumin ratio index (GARI)[12] and gamma-glutamyltransferase to platelet ratio index (GPRI)[13] have been proven in many studies to effectively identify high-risk HCC patients with a poor prognosis, and CA125 and prognostic nutritional index (PNI) were associated with tumor recurrence after liver resection.[14,15] These models are constructed through blood biochemical indicators that are relatively easy to obtain in the clinic and are related to the physiological functions of the liver. Importantly, the prognosis of HCC patients depends not only on tumor burden (tumor number, size, portal vein thrombosis and extrahepatic spread) but also on underlying liver function.[16,17] Gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) are two enzymes present in the liver. Elevated GGT or ALP levels might indicate a state of liver dysfunction and have been identified as a significant prognostic factor for liver cancer,[8,18] gastric cancer[19,20] and pancreatic cancer,[21,22] suggesting that they might be indicative of tumor burden and can be used to predict cancer patient survival.

Thus, our study first developed a prognostic model for the ratio of GGT to ALP (GAR) to assess its prognostic significance in HCC patients following curative liver resection. Furthermore, we aimed to compare the discriminative ability of GAR with that of other immune-inflammation indices for predicting patient outcomes.

Methods
The present study was approved by the Ethics Committee of Liu Zhou People's hospital (2020 (KY-E-11-01)), and written informed consent was obtained from all patients. This study also complied with the guidelines outlined in the Declaration of Helsinki.

Patients
A total of 380 HCC patients who underwent curative hepatectomy at Liu Zhou People's hospital were eligible for this study. A total of 266 patients who were admitted to our hospital between December 2013 and December 2017 were identified as the training set, while 114 patients who

received surgery from January 2018 to December 2018 were identified as the validation set. In our study, the inclusion criteria followed: (1)pathological diagnosis confirmed hepatocellular carcinoma, (2) received partial hepatectomy by open or laparoscopic hepatectomy, (3) patients >18 years. Patients were excluded before first review if they had a disease that caused an increase in GGT (12 patients with alcohol addiction, 10 patients with coronary heart disease) or ALP (24 patients with bile duct disease) before surgery.

Data Collection
Preoperative characteristics, intraoperative data, pathologic results, and medical treatment were retrospectively obtained from the medical records of each patient. The HCC diagnosis was confirmed by histopathological examination of surgical samples. Serum samples were collected and examined within one week before surgery. Laboratory measurements included GGT, ALP, total bilirubin (TBIL), albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), platelets, total peripheral neutrophils and lymphocyte count. To analyze the prognostic value of the combination of GGT with ALP levels in survival, we created a risk score named GAR, which was calculated as the strict GGT count divided by the strict ALP count. Other immune-inflammation indices, such as NLR, PLR, GARI and GPRI associated with HCC patient prognosis were calculated as previously described.[10–13] The cutoff values for preoperative GAR, PLR, NLR GAIR and GPIR were decided by applying receiver operating characteristic (ROC) curves and determining the maximum Youden index for each curve.

Follow-Up
Patients were followed up at regular intervals. The initial review included postoperative computed tomography (CT) or magnetic resonance imaging (MRI) scans performed one month after surgery. Afterwards, patients were followed up at three-month intervals for up to one year and every six months thereafter. Basic physical examination, liver function test, hepatitis B and C virus screening test, AFP level, complete blood count and abdominal ultrasound examination were performed at each visit. Overall survival (OS) was defined as the length of time from the date of surgery until death from cancer or the date of the last follow-up. Tumor-free survival (TFS) was calculated as the time from the date of surgery until the date of

detection of recurrent tumors or the date of the last follow-up without recurrence.

Statistics

All analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, United States) and R 3.15. Continuous data are presented as the medians and ranges or means ± standard deviations (SD) and were analyzed using the independent sample *t*-test or the Mann–Whitney *U*-test. Categorical variables are expressed as relative frequencies and percentages and were compared by chi-squared analysis or Fisher's exact test. The optimal cut-off value of GAR was obtained by ROC curve analysis. The "survivalROC" and "timeROC" packages in R were utilized to estimate the time-dependent ROC curves of GAR for prognosis. DeLong's test was used to compare the AUCs of the two models to determine their predictive performances. Factors determined to be significant for OS and TFS using univariate Cox regression analysis were introduced into a multivariate Cox regression model to determine adjusted hazard ratios (HR) and associated 95% confidence intervals (CI). The Kaplan–Meier method and Log rank test were utilized for survival analysis. All statistical tests were two-sided, and *P* < 0.05 was considered statistically significant.

Results

Patients' Clinicopathological Characteristics

The clinicopathological characteristics for the training set (n =266) and validation set (n =114) are provided in Table 1. Of the 380 patients analyzed, there were 320 males (84.2%) and 60 females (15.8%), who were diagnosed at a mean age of 53.6 years. The numbers of patients classified into Barcelona Clinic Liver Cancer (BCLC) stages A, B and C were 217, 61 and 102, respectively. Vascular invasion was detected in a total of 48 patients, 24 (9.0%) and 24 (21.1%) patients in the training set and validation set, respectively. There were 200 (75.2%) and 65 (57.0%) patients with tumor size > 4 cm included in the training set and validation set, respectively. During the follow-up period, a total of 66 (24.8%) patients developed recurrence and 188 (70.7%) patients died or were lost to follow-up in the training set, while 45 (39.5%) patients developed recurrence and 37 (32.2%) patients died in the validation set.

Determination of the Best Cut-off Value

Using cancer-specific death as the end point, ROC curve analysis was applied to evaluate the accuracy of GGT, ALP and GAR in predicting the prognosis of HCC patients

Table 1 Baseline Clinicopathological Characteristics of the Patients

Variables	All Patients (n = 380)	Training Set (n = 266)	Validation Set (n = 114)
Age (year)	53.6 ± 12.1	52.9 ± 12.3	55.3 ± 11.2
Gender (m/f)	320/60	223/43	97/17
BMI	23.0 ± 3.1	22.8 ± 3.2	23.3 ± 2.9
HBsAg (±)	278/102	198/68	80/34
Vascular invasion (±)	48/332	24/242	24/90
AFP (±)	260/120	191/75	69/45
Tumor size (≤4 cm/>4cm)	265/115	200/66	65/49
Tumor number (1/≥2)	252/128	100/166	28/86
Child-Pugh score (A/B)	233/147	167/99	66/48
BCLC staging (A/B/C)	217/61/102	150/42/74	67/19/28
GGT (U/L)	106.4 ± 123.8	114.6 ± 130.1	87.6 ± 105.7
ALP (U/L)	101.5 ± 70.6	103.8 ± 76.5	96.2 ± 54.1
Platelet (10^9/L)	197.0 ± 90.9	201.2 ± 92.8	187.3 ± 85.8
ALT (U/L)	39.3 ± 37.2	41.7 ± 39.0	33.9 ± 32.0
AST (U/L)	43.1 ± 39.3	45.7 ± 42.9	36.9 ± 28.1
Albumin (g/L)	38.3 ± 4.5	38.1 ± 4.4	38.9 ± 4.5
TBIL (μmol/L)	18.7 ± 36.5	20.8 ± 41.9	13.8 ± 17.9
GAR	1.1 ± 1.0	1.2 ± 1.1	0.9 ± 0.5

Abbreviations: BMI, body mass index; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; GAR, GGT:ALP ratios.

with curative liver resection. The AUC of GAR was 0.70 ($P < 0.001$), which was significantly higher than that of GGT (AUC = 0.66, $P < 0.001$) and ALP (AUC = 0.58, $P = 0.01$) (P value compared with GAR: $P = 0.044$, $P = 0.003$, respectively). An optimal cut-off value of 0.91 yielded a sensitivity of 78.1% and a specificity of 60.4% for GAR. Besides, time-dependent ROC analysis revealed that the AUCs for 1-, 3-, and 5-year OS predictions for GAR were 0.60, 0.69 and 0.62, respectively (Figure 1). To further analyze these factors, we divided the patients into high-GAR and low-GAR groups according to the cut-off value of GAR. In addition, patients were also divided into two groups according to several potential prognostic indices to compare prognostic performance with GAR [GPRI ≤ 0.36 (low) and GPRI > 0.36 (high); GARI ≤ 2.6 (low) and GARI > 2.6 (high); PLR ≤ 118.7 (low) and PLR > 118.7 (high); NLR ≤ 2.3 (low) and NLR > 2.3 (high)].

Factors Associated with OS and TFS of HCC Patients in the Training Set

Univariate and multivariate Cox regression analyses of factors affecting OS of HCC patients in the training set are shown in Table 2. Univariate analysis revealed that tumor size ($P < 0.001$), bleeding ($P = 0.002$), BCLC stage ($P = 0.006$), surgery time ($P < 0.001$), AST ($P < 0.001$), ALT ($P = 0.005$), GAR ($P < 0.001$) were prognostic factors associated with OS, while only tumor size (HR: 2.374, 95% CI 1.57–3.58, $P < 0.001$), BCLC stage (HR: 0.539, 95% CI 0.38–0.77, $P = 0.001$), and GAR (HR: 1.612, 95% CI 1.16–2.24, $P = 0.005$) were independent prognostic factors in the

training set after conducting multivariate Cox regression analysis. For TFS, univariate and multivariate Cox regression analysis identified vascular invasion (HR: 2.989, 95% CI 1.55–5.76, $P = 0.001$), BCLC stage (HR: 2.453, 95% CI 1.38–4.38, $P = 0.002$), and GAR (HR: 1.699, 95% CI 1.01–2.87, $P = 0.048$) as independent prognostic factors associated with TFS (Table 3). The Kaplan–Meier survival curves revealed that compared with patients in the high-GAR group, patients in the low-GAR group were significantly associated with better OS ($P < 0.0001$) and better TFS ($P = 0.004$) (Figure 2A and B).

Factors Associated with OS and TFS of HCC Patients in the Validation Set

In the validation set, univariate and multivariate Cox regression analysis identified age (HR: 0.468, 95% CI 0.23–097, $P = 0.042$), tumor size (HR: 2.092, 95% CI 1.03–4.27, $P = 0.043$), and GAR (HR: 2.349, 95% CI 1.21–4.56, $P = 0.012$) as independent prognostic factors of OS for HCC patients with curative liver resection (Supplementary Table 1). In addition, vascular invasion (HR: 9.993, 95% CI 1.07–93.6, $P = 0.044$), GAR (HR: 2.220, 95% CI 1.15–4.27, $P = 0.017$) and AST (HR: 2.823, 95% CI 1.17–6.80, $P = 0.021$) were identified as independent prognostic factors of TFS after performing univariate and multivariate analyses (Supplementary Table 2). The Kaplan–Meier survival curves also revealed significantly favorable OS and DFS in the low-GAR groups in the validation set ($P = 0.002$, $P = 0.006$, respectively) (Figure 2C and D).
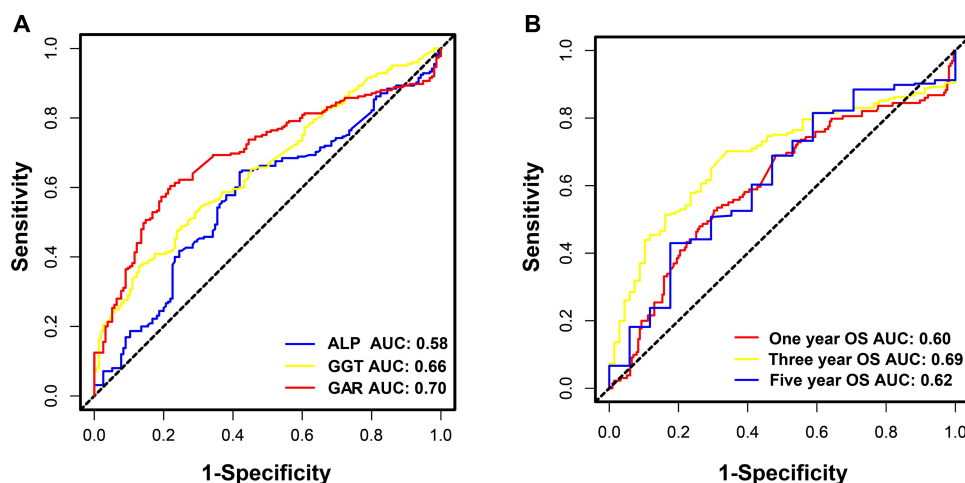

Figure 1 ROC curve analysis. Comparison of AUCs for ALP, GGT and GAR (**A**). Time-dependent ROC curve of GAR for 1-, 3-, and 5-year overall survival predictions (**B**).

Table 2 Univariate and Multivariate Cox Regression Analyses of Overall Survival in Training Set

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
≤ 60	1					
> 60	0.770	0.56–1.06	0.113			
Gender						
Female	1					
Male	0.864	0.59–1.26	0.448			
Tumor size (cm)						
≤ 4	1					
> 4	2.770	1.88–4.08	< 0.001	2.374	1.57–3.58	**< 0.001**
Vascular invasion						
No	1					
Yes	1.264	0.79–2.01	0.324			
Bleeding (mL)						
≤ 300	1					
> 300	1.683	1.21–2.34	0.002	–	–	0.400
BCLC stage						
A+B	1					
C	0.618	0.44–0.87	0.006	0.539	0.38–0.77	**0.001**
Surgery time (min)						
≤ 240	1					
> 240	1.814	1.29–2.56	< 0.001	–	–	0.670
Platelet (10^9/L)						
≤ 100						
> 100	0.797	0.48–1.32	0.375			
AST (U/L)						
≤ 40						
> 40	1.709	1.27–2.29	< 0.001	–	–	0.159
ALT (U/L)						
≤ 40						
> 40	1.525	1.14–2.05	0.005	–	–	0.532
Albumin (g/L)						
≤ 40						
> 40	1.34	0.99–1.83	0.057			
GAR						
≤ 0.91						
> 0.91	2.140	1.59–2.90	< 0.001	1.612	1.16–2.24	**0.005**

Note: $P < 0.05$, marked in bold font, shows statistical significance.
Abbreviations: OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GAR, gamma-glutamyltransferase to alkaline phosphatase ratio.

Prognostic Values of Preoperative GAR in Different HCC Subgroups

Cox regression analysis identified that tumor size, BCLC stage and vascular invasion were associated with prognosis in HCC patients with curative liver resection. We next investigated the prognostic value of the preoperative GAR in different subgroups of HCC patients to analyze these factors. The results showed that GAR was a prognostic indicator for

Table 3 Univariate and Multivariate Cox Regression Analyses of Tumor-Free Survival in Training Set

Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)						
≤ 60	I					
> 60	0.702	0.41–1.21	0.202			
Gender						
Female	I					
Male	1.345	0.63–2.85	0.440			
Tumor size (cm)						
≤ 4	I					
> 4	1.356	0.79–2.32	0.269			
Vascular invasion						
No	I			I		
Yes	5.093	2.90–8.94	< 0.001	2.989	1.55–5.76	**0.001**
Bleeding (mL)						
≤ 300	I					
> 300	1.323	0.78–2.25	0.299			
BCLC stage						
A+B	I			I		
C	3.566	2.14–5.93	< 0.001	2.453	1.38–4.38	**0.002**
Surgery time (min)						
≤ 240	I					
> 240	0.724	0.34–1.53	0.396			
Platelet (10^9/L)						
≤ 100	I					
> 100	1.067	0.49–2.34	0.8711			
AST (U/L)						
≤ 40	I					
> 40	1.820	1.11–2.99	0.018	–	–	0.952
ALT (U/L)						
≤ 40	I					
> 40	2.020	1.24–3.30	0.005	–	–	0.059
Albumin (g/L)						
≤ 40	I					
> 40	1.624	0.96–2.75	0.071			
GAR						
≤ 0.91	I			I		
> 0.91	2.040	1.24–3.37	0.005	1.699	1.01–2.87	**0.048**

Note: *P* < 0.05, marked in bold font, shows statistical significance.
Abbreviations: OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GAR, gamma-glutamyltransferase to alkaline phosphatase ratio.

both OS and TFS in patients with BCLC stage C (*P* = 0.008, *P* = 0.025, respectively), while statistically significant differences were obtained in the OS of patients with BCLC stage A or B but not the TFS (*P* < 0.001, *P* = 0.14, respectively) (Figure 3). Furthermore, among the patients with tumor size > 4 cm, the high-GAR group also appeared to experience
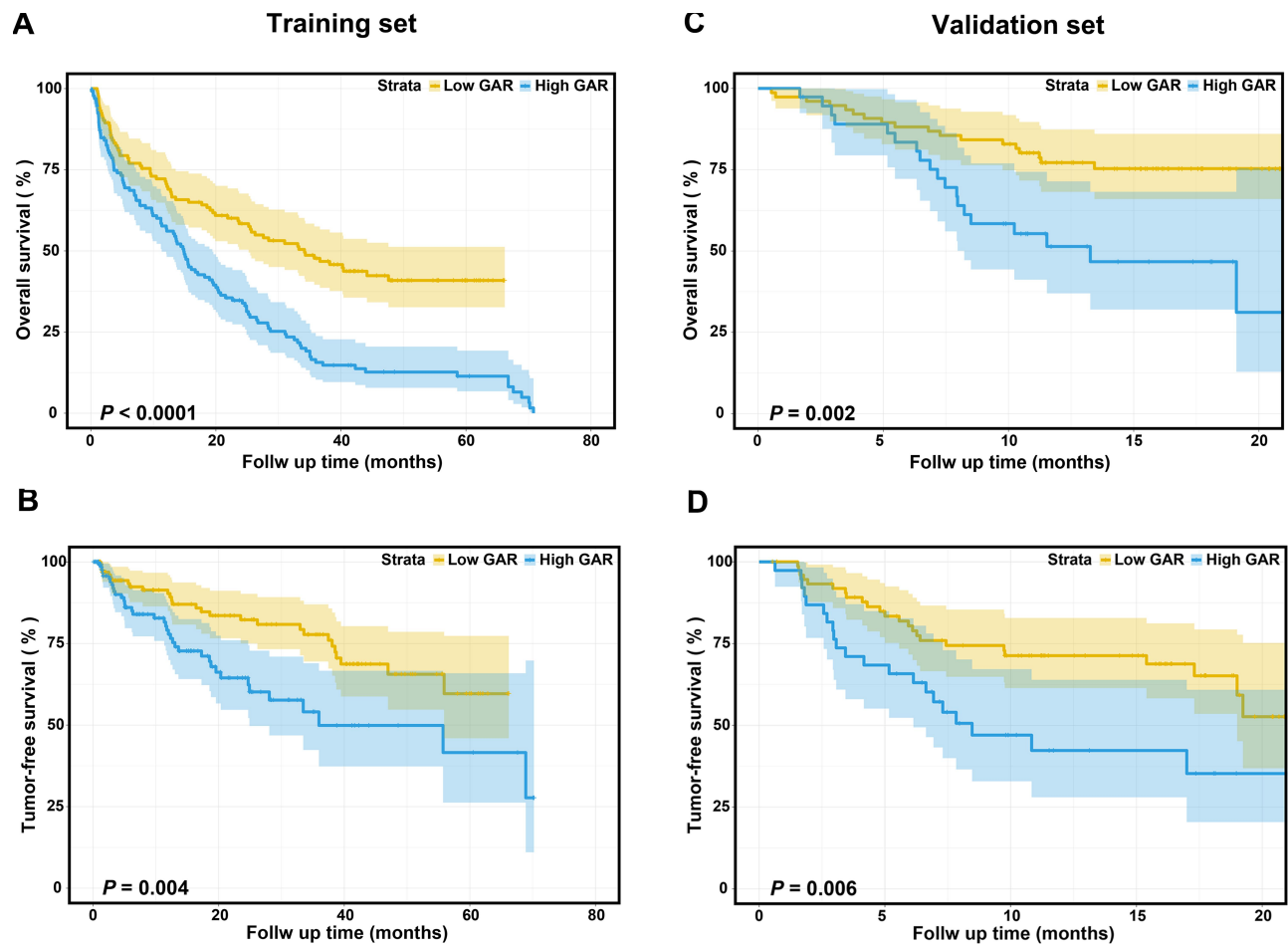
Figure 2 Kaplan–Meier survival curves for HCC patients in the training set and validation set. Preoperative GAR was significantly correlated with shorter OS and TFS both in the training set (**A** and **B**) and validation set (**C** and **D**).

poorer OS and TFS ($P < 0.001$, $P = 0.031$, respectively), while among patients without vascular invasion, a similar observation was made for OS but not TFS ($P < 0.001$, $P = 0.072$, respectively) (Figure 4).

Comparative Performance of GAR and Other Predictive Models

To further compare the prognostic performance between GAR and other potential prognostic indices identified by previous studies, we applied ROC curve analysis by using cancer-specific death as the end point. The GAR showed a higher AUC value (0.69, $P < 0.001$) than the GPRI (0.58 VS 0.69, $P < 0.001$), GARI (0.61 VS 0.69, $P < 0.001$), PLR (0.64 VS 0.69, $P = 0.122$) and NLR (0.60 VS 0.69, $P < 0.001$) (Figure 5). The results indicated that GAR seems to be a better prognostic marker in predicting OS for HCC patients with curative liver resection.

Discussion

This is the first study to establish a correlation between the GAR and postoperative survival and recurrence in HCC patients with curative liver resection. According to the cut-off value of GAR, a higher GAR indicates worse OS and TFS for HCC patients. With univariate and multivariate Cox regression analysis, we found that GAR was an independent risk factor for OS and TFS in the training and validation cohorts. In addition, after grouping by BCLC stage, vascular invasion and tumor size, GAR still maintained good prognostic performance. Notably, GAR was a superior prognostic factor for survival outcome than several potential prognostic indices. All of these data provided further evidence that preoperative GAR could act as a potential prognostic marker to predict survival in HCC patients undergoing curative liver resection.

GAR is an integrated indicator based on GGT and ALP. As a membrane-bound enzyme, GGT plays a key role in
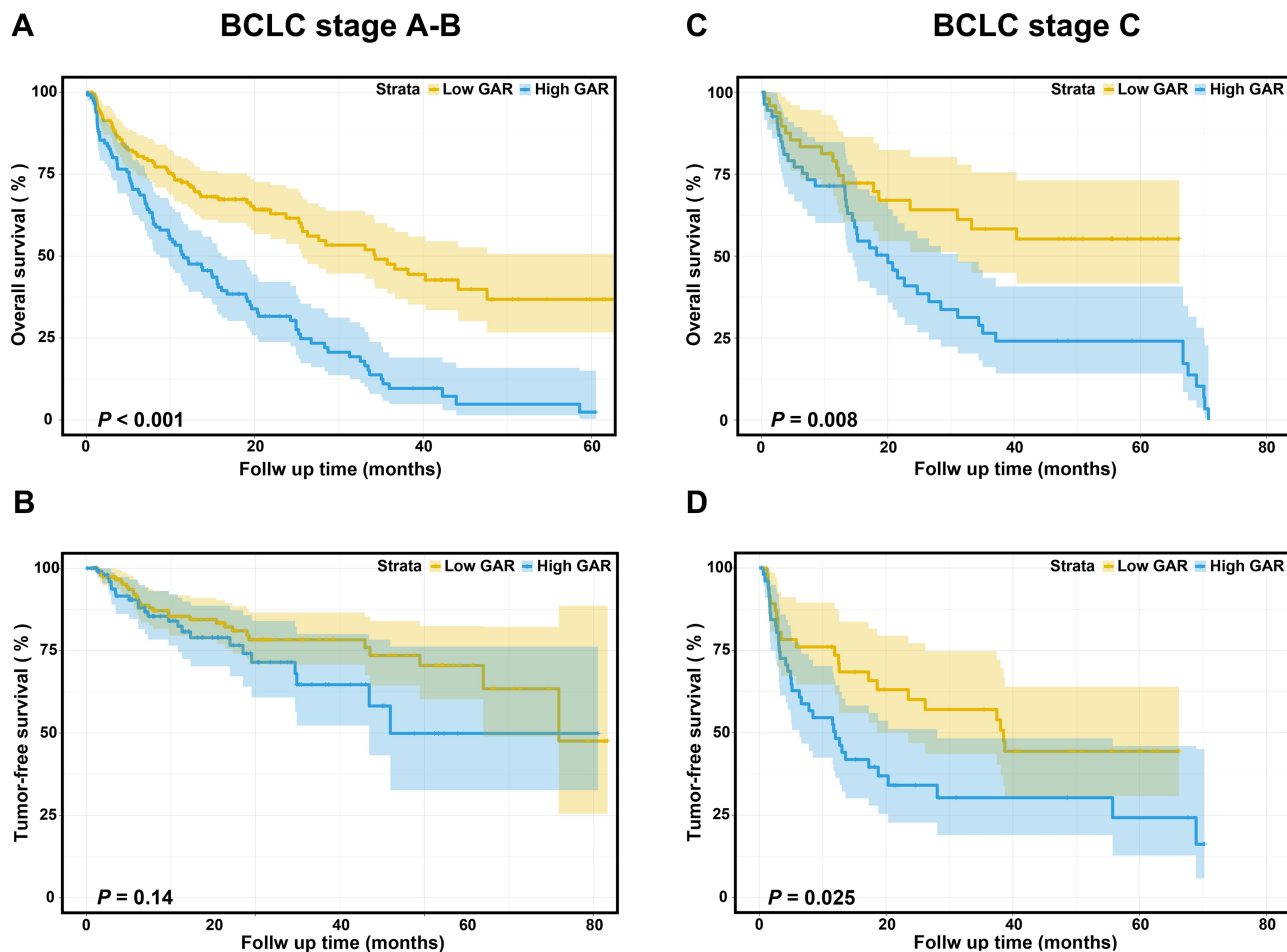
Figure 3 Kaplan–Meier survival curves for the different HCC subgroups. Preoperative GAR was a significant prognostic indicator of OS (**A**), while high-GAR was not a prognostic factor for poor TFS in patients with BCLC stage A-B (**B**). In addition, high-GAR was significantly correlated with worse OS and TFS in subgroups with BCLC stage C (**C** and **D**).

glutathione (GSH) metabolism. Since GSH is the main water-soluble antioxidant within the cell, GGT is involved in a defensive mechanism against oxidative stress.[23] However, stimulated by overactivated oxidative stress, especially induced by specific inflammatory factors, intracellular GGT may play a pro-oxidative role.[24] The pro-oxidant activity of GGT may contribute to the persistent oxidative stress described in cancer and modulate processes involved in tumor progression, such as cell proliferation and apoptosis.[24] Increased serum GGT has been inversely associated with survival in many cancers;[21,25,26] this negative correlation is strongest for liver cancer.[23] ALP can be secreted by normal tissues, including the liver, bone and small intestine, and increases under the influences of inflammation, metabolic disorders, and tumors.[18,27] Several studies have indicated that ALP plays important roles in strengthening cancer cell proliferation, vascular invasion and distant metastasis, cell cycle

regulation and tumor formation.[28–30] Additionally, increased serum ALP levels always occur in liver disease and may reflect liver injury, which suggested that higher preoperative serum ALP level may associated with poorer survival of HCC patients. Importantly, GGT and ALP are both participate in the development of inflammation, which exerts an enormous function on tumor formation.[8] Thus, serum GGT and ALP may be diagnostic or prognostic markers of liver cancer.

Although the elevated levels of GGT and ALP are both associated with poor prognostic of HCC patient, the diagnostic performance evaluated by ROC analysis was not satisfactory. By calculating the ratio of GGT to ALP, we found that the diagnostic performance can be improved. At the same time, based on the respective cut-off values by ROC analysis, the data indicated that patients with high levels of GGT (GGT > 120 U/L) were almost accompanied with ALP elevation (ALP > 80 U/L). Therefore, the
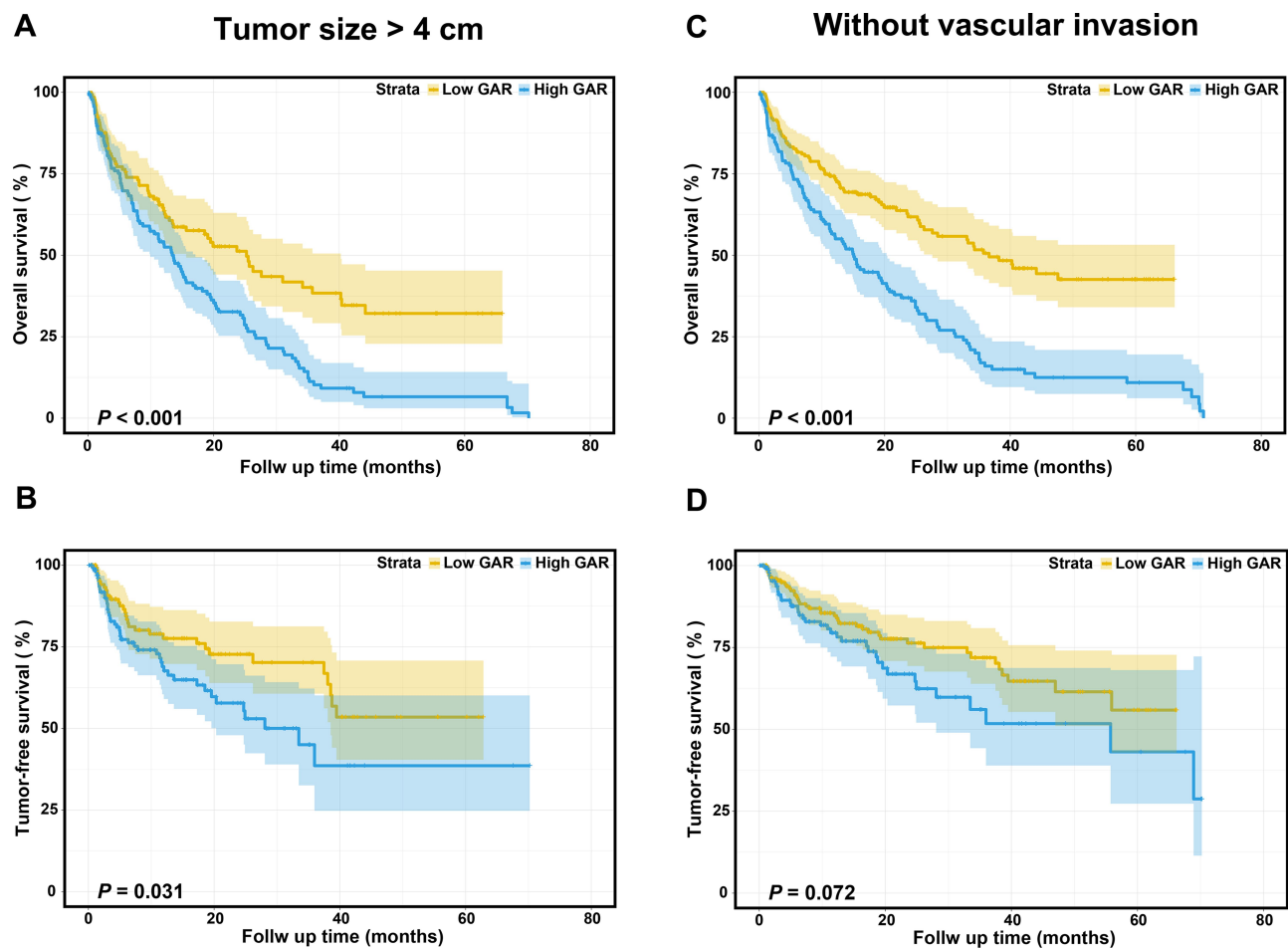
A   **Tumor size > 4 cm**

C   **Without vascular invasion**

B

D

Figure 4 Kaplan–Meier survival curves for the different HCC subgroups. High-GAR was significantly correlated with worse OS and TFS in subgroups with tumor size > 4 cm (**A** and **B**). In addition, preoperative GAR was a significant prognostic indicator of OS (**C**), while high-GAR was not a prognostic factor for poor TFS in patients without vascular invasion (**D**).

increase in GAR suggests a poor prognosis, not caused by the deviation of GGT and ALP, but the greater change amplitude in GGT, suggesting that GGT may be more sensitive than ALP in HCC progression. Previous studies have found that inflammation is a key driving factor leading to tumorigenesis and progression, and GGT is closely related to inflammation, which can be induced by various inflammatory factors that significantly increased during the acute inflammation phase.[24]

As simple, convenient, inexpensive and noninvasive markers, GGT and ALP have been involved in building different models in many studies and have been proven to be powerful prognostic predictors for HCC patients. Wang et al indicated that elevated GGT levels were significantly associated with poor OS and RFS in HCC patients and established a preoperative prognostic scoring model combining four risk factors with an AUC of 0.696 by ROC analysis.[5] Wu et al suggested that HCC

patients with low levels of ALP, GGT and LDH have favorable OS and RFS, even those with cirrhosis.[8] Xu et al found that HCC patients with preoperative GGT ≥ 115 U/L and ALP > 120 U/L had aggressive liver disease and significantly shorter overall survival.[18] The above research results are consistent with our study, which proves that GGT and ALP are closely related to the prognosis of liver cancer. Owing to the difficulties in diagnosing the TNM stage and tumor size before surgery, clinicians can use preoperative GAR to assess the tumor burden of HCC patients and determine the next treatment. Early treatment can be performed on patients with high preoperative GAR levels; for example, we can use TACE to minimize the increase in tumor size before surgery to improve the prognosis of these patients, which may help prevent dangerous situations such as recurrence and metastasis.[6]
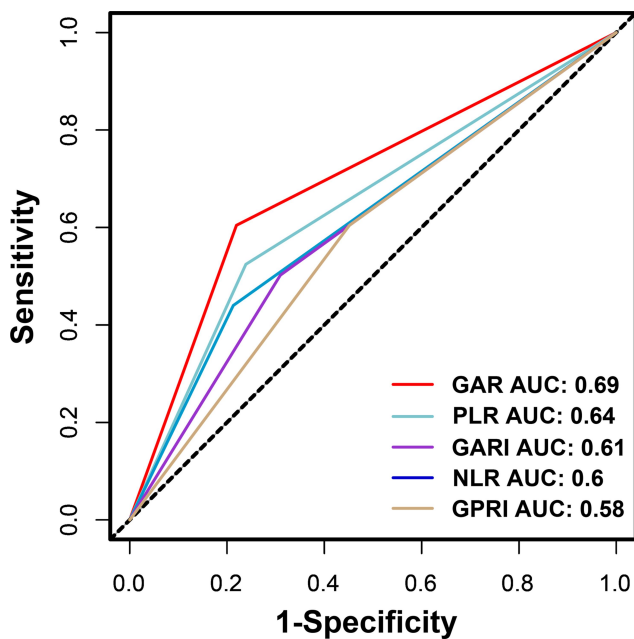
Figure 5 Predictive ability of the GAR was compared with other potential prognostic indicators by ROC curves. The discriminatory capability of GAR was superior to that of other potential prognostic indicators in overall survival prediction.

Overall prognosis and treatment decision-making in HCC patients are based on appropriate patient stratification.[31] Vascular invasion is a significant but poor prognostic factor of survival in HCC patients and a better predictor of tumor recurrence than the commonly used Milan criteria.[32–34] When we further explored the predictive prognostic potential of the GAR in the group without vascular invasion, we found that patients can be divided according to the GAR into two groups with significantly different OS ($P < 0.001$). In addition, tumor size is strongly associated with vascular invasion, with a larger tumor size indicating a higher possibility of vascular invasion.[35] Notably, GAR maintains its good prognostic performance in HCC patients with large tumor sizes. In clinical practice, it is difficult to predict the OS of patients after receiving curative liver resection for advanced HCC, such as BCLC stage C patients. After stratifying the patient cohort according to BCLC stage, we found that the prognostic performance of GAR in OS or TFS was still strong in BCLC stage C patients with HCC.[9] Taken together, our results suggest that GAR might be a powerful prognostic indicator for HCC patients, whether for patients with advanced disease or without vascular invasion. The predictive significance of GAR in those subgroups should help clinicians identify patients at high risk of recurrence and enable targeted, rational, adjuvant therapy after surgery.

Limitation

Although our study was the first to identify the prognostic value of the GAR in HCC patients with curative liver resection, it has several limitations. First, since the present study was a retrospective study, selection bias, withdrawal bias and other clinical bias were inevitable. Some potential confounders, such as alcohol consumption, hepatitis C and neoadjuvant chemotherapy, were not documented, which may have resulted in some meaningful clinical parameters being ignored. Second, we enrolled HCC patients only from a single medical center, and the sample size was small. Third, most HCC patients included in our study had a hepatitis B virus–positive background (278/380,73.2% HBV positive), which differs greatly from the patient populations in previous studies in the United States, Europe and Japan. In the future, prospective and multicenter studies with large sample sizes will be required to further validate our findings and promote the clinical application of the GAR.

Conclusion

We first identified the GAR as a prognostic marker in two independent cohorts of HCC patients with curative liver resection. The patients with decreased GAR were significantly associated with better OS and TFS. As a low-cost routine laboratory test, the GAR could be viewed as a novel prognostic predictor in the clinical management of HCC.

Abbreviations

HCC, hepatocellular carcinoma; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; GAR, GGT:ALP ratio; AUC, area under the receiver operating characteristic curve; OS, overall survival; TFS, tumor-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; GAIR, gamma-glutamyltransferase to albumin ratio index; GPIR, gamma-glutamyltransferase to platelet ratio index; TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; SD, standard deviation; HR, hazard ratios; CI, confidence intervals; BCLC, Barcelona Clinic Liver Cancer.

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Disclosure

The authors declare no conflicts of interest for this work.

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