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ORIGINAL ARTICLE

Predictive value of and relationship between the gamma-glutamyl transpeptidase to lymphocyte ratio and CT features in hepatocellular carcinoma patients with postoperative adjuvant TACE

Hui Zhao[1]*, Xiaokan Liu[1]*, Ruonan Xu[2], Xiaoli Guo[3], Aiguo Shen[4]

[1]Department of Interventional Radiology, Affiliated Hospital of Nantong University, Nantong, China. [2]Department of Radiology, the Sixth People's Hospital of Nantong, Nantong, China. [3]Department of Radiology, Affiliated Hospital of Nantong University, Nantong, China. [4]Oncology Central Laboratory, Nantong Tumor Hospital, Nantong, China.

*Hui Zhao and Xiaokan Liu contributed equally to this work

Summary

Purpose: *To explore the predictive value of and the relationship between the gamma-glutamyl transpeptidase (GGT) to lymphocyte ratio (GLR) and computed tomography (CT) features in hepatocellular carcinoma (HCC) patients with postoperative adjuvant transarterial chemoembolization (PA-TACE).*

Methods: *Between January 2012 and June 2015, 150 HCC patients who underwent adjuvant TACE after hepatectomy in the Affiliated Hospital of Nantong University were selected. Baseline parameters, laboratory values, clinical variables, and CT features (including CT values, irregular rim-like arterial phase enhancement (IRE), and CT enhanced values) were evaluated in all of the patients. The Mann-Whitney U test was performed to assess the GLR values between the patients with microvascular invasion (MVI) and those without MVI. Spearman correlation analysis was performed to evaluate the relationship between IRE and GLR. A nomogram based on the multivariate analysis was constructed.*

Results: *Using multivariate analysis, GLR, MVI, a-fetoprotein levels, and IRE were found to be independent prognostic factors for overall survival (OS). In the MVI group, the GLR of patients was higher than that in the non-MVI group (z=-6.652, p<0.001). We observed a clear correlation between GLR and IRE (r=0.522, p<0.001). The nomogram was constructed and the calibration curve showed excellent predictive performance.*

Conclusions: *We observed a correlation between GLR and CT features in HCC patients. The nomogram based on clinical data, pathological data, and CT features was suggested to predict the 5-year survival of HCC patients with PA-TACE, which offers an accurate, comprehensive, and reliable evaluation for individualized treatment.*

Key words: *hepatocellular carcinoma, gamma-glutamyl transpeptidase to lymphocyte ratio, irregular rim-like arterial phase enhancement, postoperative adjuvant transarterial chemoembolization, prognosis*

Introduction

About 90% of primary liver cancer cases are hepatocellular carcinoma (HCC) [1], which is the sixth most prevalent malignant tumor worldwide and causes extremely high mortality [2]. Although treatments for HCC have improved dramatically in recent years, surgical resection is still the main curative treatment modality for HCC [3]. However, high tumor recurrence rates are a major cause of death after liver resection in HCC patients [4], which may be related to the poor perioperative management [5].

Corresponding author: Aiguo Shen, MD. Oncology Central Laboratory, Nantong Tumor Hospital, No.30, Tongyang North Rd, Pingchao Town, Tongzhou District, Nantong, Jiangsu 226001, China.
Tel: +86 018932229992; Email: aiguoshen0513@163.com
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Transarterial chemoembolization (TACE) has been considered a suitable treatment for mid-term HCC for a long time [6]. Postoperative adjuvant TACE (PA-TACE) has attracted more and more attention as adjuvant therapy after radical resection of HCC. However, whether PA-TACE is beneficial for HCC patients remains a matter of debate [7,8], mainly owing to the selection bias and the heterogeneity of tumors. In recent years, many models have been developed to predict the prognosis of HCC after TACE [9], but few have been applied to PA-TACE. Hence, the application of models to assess high-risk factors in HCC patients who underwent PA-TACE has great clinical significance to improve the outcome of HCC patients.

The relationship between (i) HCC and (ii) chronic inflammation and immune status has been demonstrated [1,10]. Liver function is an indicator of the general condition of the liver and is associated with prognosis. Previous studies have reported that elevated gamma-glutamyl transferase (GGT) levels may lead to early recurrence in HCC patients [11]. The GGT to lymphocyte ratio (GLR) is an indicator that combines liver function and immune status, which has been used to predict the prognosis of pancreatic tumors [12]. In addition, microvascular invasion (MVI) has been reported to independently predict long-term survival after liver resection in HCC patients [13].

Computed tomography (CT) plays an essential role in the diagnosis and prognosis of HCC. Irregular rim-like arterial phase enhancement (IRE) has been shown to be associated with a worse prognosis for HCC after radiofrequency ablation [14]. When researchers focused on predicting the prognosis of HCC on the basis of clinical and hematological factors, however, CT features were not taken into account. Meanwhile, the prognostic importance of CT features remains to be further improved.

Compared with a single biomarker, predictive models consisting of different biomarkers are more useful [15]. The purpose of this research was to explore the relationship between the GLR and the correlative CT features in HCC. Furthermore, we constructed a nomogram using serum, radiomic, and pathological markers to predict prognosis in HCC patients with PA-TACE.

Methods

Patient population

Between January 2012 and June 2015, 188 HCC patients who received PA-TACE after liver resection in the Affiliated Hospital of Nantong University were enrolled in this study. This retrospective study was approved by the Institutional Review Board of the Affiliated Hospital of Nantong University. Each patient signed the informed consent form before the surgery.

According to the following exclusion criteria, 38 patients were excluded. The exclusion criteria included: (1) confirmed cholangiocarcinoma after surgery (n=8); (2) received other therapies before liver resection (n=24); (3) distant metastasis (n=3); and (4) missing follow-up data (n=3). Finally, a total of 150 patients (34 females and 116 males) were successfully included in the study.

Variables

Data on clinical and pathologic characteristics were collected for each patient, including gender, age, etiology, cirrhosis, Child-Pugh class, tumor size, and MVI.

The preoperative laboratory indexes included white blood cell (WBC), lymphocyte (LYM), platelet, α-fetoprotein (AFP), total bilirubin (TBIL), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and GGT levels. Also, the GLR and the aspartate aminotransferase to lymphocyte ratio index (ALRI) of each patient were calculated.

Follow-up

All of the patients were followed-up until June 2020 by clinical medical records, telephone contact, and death

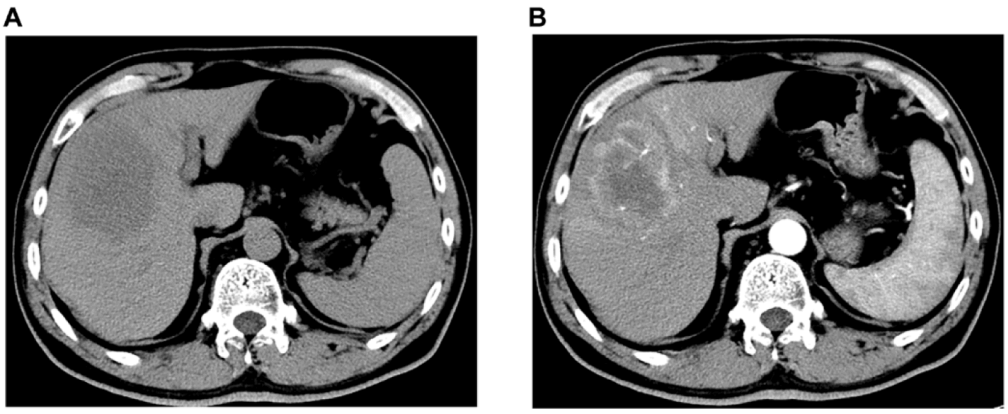

Figure 1. Hepatitis B virus carrier with hepatocellular carcinoma in a 60-year-old male. A 7-cm liver tumor shows low density on the precontrast CT scan **(A)** and IRE in the arterial phase **(B)**.

certificates. All of the patients were followed up every three months for the first two years and every six months after two years. Overall survival (OS) was determined as the interval between (i) PA-TACE and (ii) the date of death or the last follow-up.

PA-TACE procedure

The first TACE was performed 4-6 weeks after surgery, when the patient's liver function had recovered. We inserted the catheter retrogradely into the femoral artery. Then under the guidance of angiography, the catheter reached the hepatic artery. We then infused lipiodol and chemotherapeutic agents, such as epirubicin and oxaliplatin, into the arteries near the resection margin. The dosage of chemotherapeutic agents and lipiodol was determined based on liver function and physical status.

CT scan protocol and image analysis

All 150 HCC patients underwent a 64-slice CT scan (Siemens, Germany) one week before operation. Patients were scanned in supine position. After inspiration, a breath-hold scan was performed from the diaphragm to the lower margin of the liver. The abdominal dynamic enhanced CT scan was performed using iodixanol at a dosage of 1.5-2 mL/kg and a rate of 3-4 mL/s through the cubital vein. The arterial phase, portal phase, and delay phase scans were performed at 25-30 s, 60-70 s, and 100-120 s after contrast agent injection. The analysis of all the data after scanning was completed on a Symbia workstation (Siemens, Germany).

We observed and analyzed the images with the mediastinal (width: 150-180 Hu; level: 45-85 Hu) window settings. IRE was defined as irregular rim-like peripheral hyperenhancement in the arterial phase with central hypoenhancement (Figure 1). Two radiologists with 8 and 5 years of abdominal radiology experience retrospectively analyzed the preoperative CT images of liver tumors without knowledge of pretreated serum data.

Statistics

A new nomogram was established to evaluate the 5-year OS of HCC patients with PA-TACE after liver resection. We drew a calibration plot to assess the consistency between the predictions of the nomogram and the observed actual results. Statistical analysis was performed in R (http://www.r-project.or). The received operating characteristic (ROC) curve was used to assess the predictive value of serum levels and CT features. Kaplan-Meier method and stepwise Cox regression were performed for univariate and multivariate analyses of survival. The Mann-Whitney U test was used to evaluate the difference of GLR between the HCC+MVI group and the HCC+ Normal group. Spearman correlation analysis was conducted to assess the relationship between the IRE and GLR. All of the data analysis was performed using SPSS (version 26, IBM, New York, NY, USA), and $p<0.05$ was considered to indicate statistical significance.

Table 1. Clinical characteristics and CT features

Characteristics	*Number (%)/Mean±SD*
Gender: male/female (n)	116 (77.3)/34 (22.7)
Age (years)	55.2±9.6
Etiology: HBV/non-HBV (n)	89 (59.3)/61 (40.7)
Cirrhosis: present/absent (n)	102 (68.0)/48 (32.0)
Child-Pugh class: A/B (n)	131 (87.3)/19 (12.7)
Tumor size (cm)	4.7±3.0
MVI: present/absent (n)	73 (48.7)/77 (51.3)
AFP (ng/mL): median (range)	159.2 (1.1-20000)
WBC ($\times10^9$/L)	5.0±1.6
LYM ($\times10^9$/L)	1.6±0.5
Platelets ($\times10^9$/L)	145.2±60.9
TBIL (μmol/L)	18.8±35.4
AST (U/L)	40.9±29.9
ALP (U/L)	96.2±47.8
GGT (U/L)	56.44±31.56
GLR: median (range)	32.2 (6.9-116.3)
ALRI: median (range)	21.1 (6.45-148.9)
PTC: present/absent (n)	65 (43.3)/85 (56.7)
IRE: present/absent (n)	63 (42.0)/87 (58.0)
CT value (Hu)	37.11±5.74
CT enhanced value (Hu)	61.15±10.42

TBIL: total bilirubin; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; GLR: gamma-glutamyl transpeptidase to lymphocyte ratio; ALRI: aspartate aminotransferase to lymphocyte ratio index; IRE: irregular rim-like arterial phase enhancement; PTC: peritumor capsule

Results

Patient data

Baseline characteristics are shown in Table 1. We enrolled 150 pathologically confirmed HCC patients. The average age was 55.2±9.6 years. Thirty-four females (22.7%) and 116 males (77.3%) underwent surgery and PA-TACE. Eighty-nine patients had a history of hepatitis virus infection, and 102 patients were complicated with cirrhosis. According to the Child-Pugh classification, 131 patients were classified as A (87.3%) and 19 as B (12.7%). Seventy-three patients (48.7%) had MVI, as confirmed by postoperative pathology. The mean±SD of LYM, GGT, and AST was 1.6±0.5, 56.44±31.56, and 40.9±29.9, respectively. The median GLR and ALRI was 32.2 (range, 6.9-116.3) and 21.1 (range, 6.45-148.9), respectively. All patients underwent dynamic enhanced CT scanning, and 63 HCC patients (42.0%) were observed to have IRE. A peritumor capsule (PTC) was observed on CT images in 65 HCC patients (43.3%).

Survival analyses

The median survival time was 60 months (range, 4-96 months), and the 5-year OS rate was 54.0%. To evaluate the risk of OS in HCC patients,

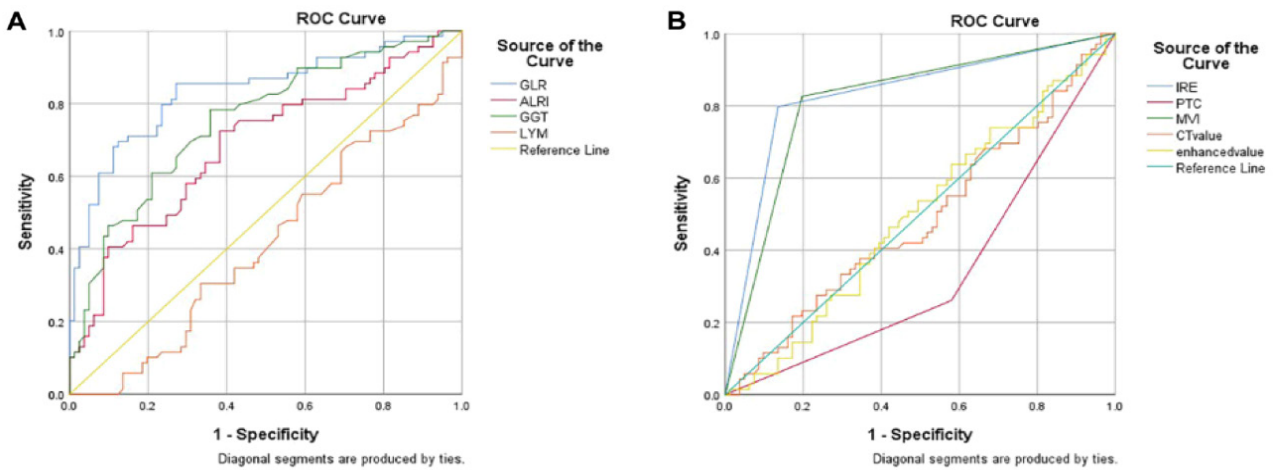

Figure 2. A: The ROC curves of serum parameters for HCC patients. **B:** The ROC curves of CT parameters and MVI for HCC patients.

Table 2. Univariate analysis and multivariate analysis for 5-year overall survival

Variables	*Overall survival Univariate*			*Multivariate*		
	HR	*95%CI*	*p value*	*HR*	*95%CI*	*p value*
Gender		0.768-2.253	0.317			
Male	1					
Female	1.316					
Age, years		0.683-1.828	0.657			
≥60	1					
<60	1.118					
Etiology		0.515-1.492	0.626			
Yes	1					
No	0.876					
Cirrhosis		0.397-1.405	0.366			
Yes	1					
No	0.747					
Child-Pugh class		0.650-2.619	0.453			
A	1					
B	1.305					
Tumor size, cm		0.427-1.259	0.260			
≥5	1					
<5	0.733					
MVI		4.559-16.006	<0.001		1.958-8.170	<0.001
Yes	8.542			4.000		
No	1			1		
AFP		0.179-0.467	<0.001		0.310-0.837	0.008
≥400	1			1		
<400	0.289			0.510		
GLR		0.065-0.250	<0.001		0.135-0.599	0.001
≥30.39	1			1		
<30.39	0.127			0.284		
IRE		4.772-15.693	<0.001		2.071-7.951	<0.001
Yes	8.654			4.058		
No	1			1		
PTC		0.940-3.034	0.080			
Yes	1					
No	1.689					

we analyzed the commonly used indexes of laboratory parameters, including GGT, lymphocyte count, and AST levels, and CT features, such as IRE, CT values, PTC, and CT enhanced values, by ROC curve analysis (Figure 2). The areas under the curve (AUCs) for GGT, LYM, GLR, ALRI, MVI, CT values, IRE, CT enhanced values, and PTC were 0.755, 0.415, 0.835, 0.686, 0.814, 0.487, 0.831, 0.495, and 0.340, respectively. The AUCs of GGT, GLR, MVI, and IRE were>0.70. The optimum cut-off value for GLR was 30.39, the sensitivity was 85.6%, and the specificity was 72.8%.

Predictors associated with OS

Univariate analysis (Table 2) yielded the following p values for associations with OS: age (p=0.657), gender (p=0.317), etiology (p=0.626), cirrhosis (p=0.366), Child-Pugh class (p=0.453), tumor size (p=0.260), MVI (p<0.001), AFP (p<0.001), GLR (p<0.001), PTC (p=0.08), and IRE (p<0.001). Thus, GLR, AFP, MVI, and IRE were significantly associated with OS. The statistically significant factors were analyzed by multivariate Cox regression analysis. The results indicated that AFP (95% confidence interval [95%CI], 0.31-0.84, p=0.008), MVI (95%CI, 1.96-8.17, p<0.001), GLR (95%CI, 0.14-0.60, p=0.001), and the presence of IRE (95%CI, 2.071-7.951, p<0.001) were independent predictors of OS.

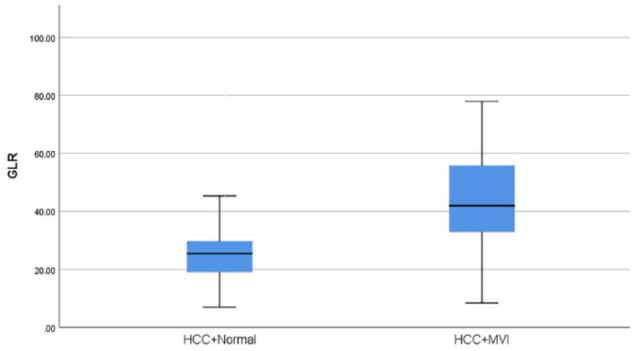

Figure 3. Box plot of the gamma-glutamyl transpeptidase to lymphocyte ratio (GLR) in the HCC+ Normal group and the HCC+MVI group. The GLR in the HCC+MVI group was significantly higher (z=-6.652, p<0.001).

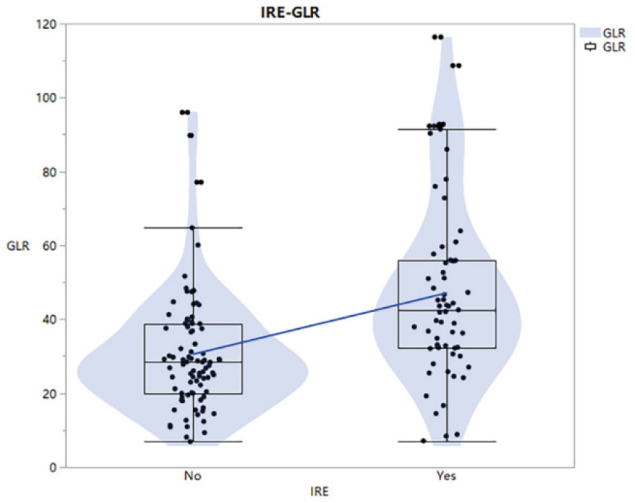

Figure 4. Box plot showing the GLR was significantly higher in HCC patients with IRE than in patients without IRE (z=-6.185, p<0.001). Spearman correlation analysis indicated a positive relationship between IRE and GLR (r=0.522, p<0.001).

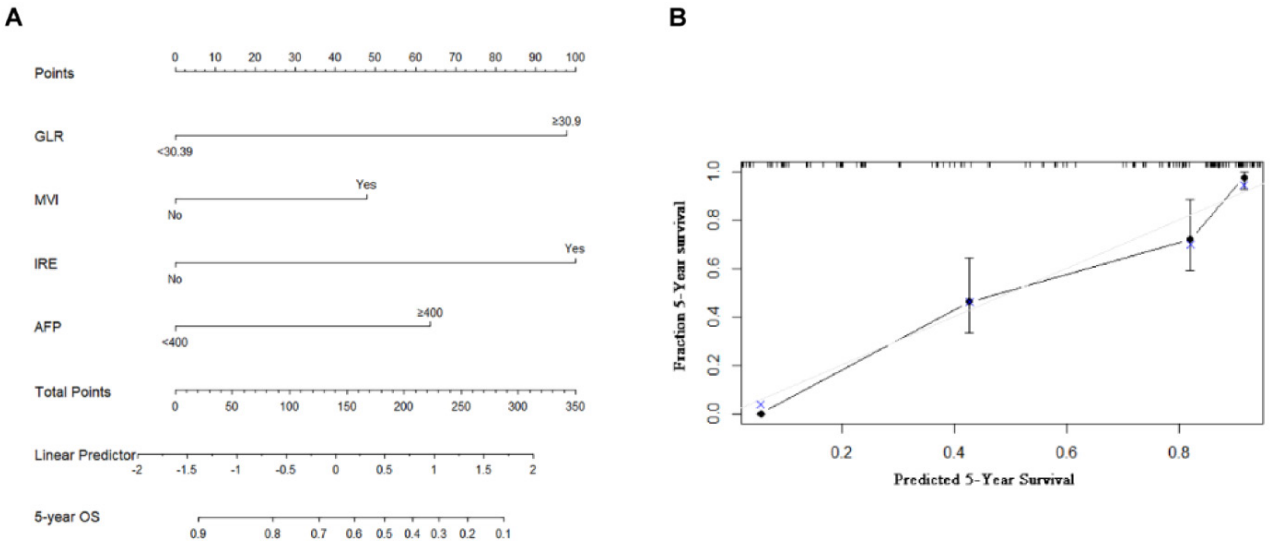

Figure 5. Establishment and evaluation of the nomogram. **A:** Prognostic nomogram showing the assessment of 5-year survival in HCC patients with PA-TACE. **B:** The calibration curve of the nomogram at 5 years showed good correlation between the prediction and actual observation.

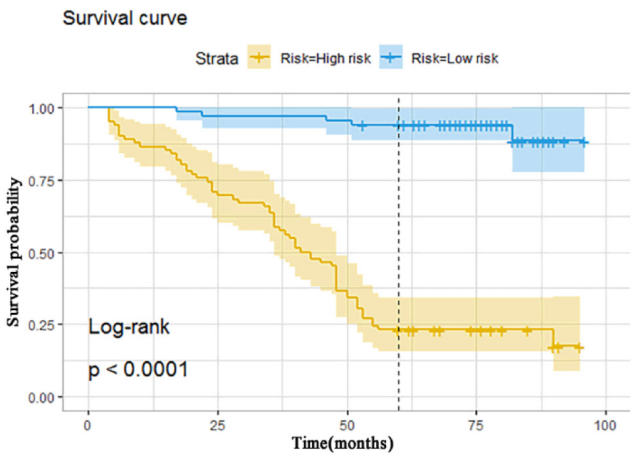

Figure 6. Kaplan-Meier survival curve showing a significant survival difference between the high-risk group and the low-risk group.

The relationship between MVI, IRE, and GLR

In HCC patients with MVI, GLR was significantly increased (z=-6.652, p<0.001; Figure 3). By the Mann-Whitney U test, we found significant differences in GLR levels between the IRE group and the non-IRE group (z=-6.185, p<0.001; Figure 4). A positive relationship between IRE and GLR was also observed (r=-0.522, p<0.001).

Construction of the nomogram

According to the results of our multivariate analysis, we established a nomogram to predict 5-year survival for HCC patients with PA-TACE (Figure 5A). The calibration curve was also constructed (Figure 5B). To verify the nomogram's performance, patients were divided into a low-risk group and a high-risk group according to the risk ratio. The Kaplan-Meier survival curves (Figure 6) based on the risk ratio showed that patients had a significantly poorer 5-year OS rate at high risk.

Discussion

PA-TACE has been shown to be beneficial for HCC patients after hepatectomy [16]. Many factors may influence the efficacy of PA-TACE in HCC patients, such as tumor stage, liver function, and the general conditions [17]. Therefore, it is crucial to identify which HCC patients could benefit most from PA-TACE. Traditionally, the Child-Pugh score has been widely used in liver function assessment before hepatectomy [18], but the evaluation of ascites and encephalopathy lacks objectivity. The BCLC stage determines the treatment strategy only by pretreatment parameters [19]. Both of these staging systems have some limitations in clinical application. More importantly, there are few models to predict OS in HCC patients with PA-TACE at present.

In this study we evaluated each HCC patient's survival with incorporated CT features and hematologic and clinical factors. The MVI, AFP, IRE, and GLR were observed to be independent prognostic predictors for HCC patients with PA-TACE. Moreover, MVI and IRE were associated with GLR, which suggests that liver function and inflammatory status can affect the prognosis of HCC patients with such CT feature. The establishment of models based on liquid biopsy to predict HCC patients' prognosis has become a hot research area in recent years [20]. To the best of our knowledge, this is the first study concerning the correlation between MVI, IRE, and GLR of HCC patients with PA-TACE.

In the present study, the GLR was significantly increased in HCC patients with MVI (z=-6.652, p<0.001), which suggests that the liver function and immune status of HCC patients combined with MVI are at a low level, leading to a higher GLR and a poorer prognosis. As is well known, the portal vein/hepatic vein's local branches are usually invaded by HCC, which can cause tumor thrombosis at a relatively early stage. But the importance of MVI has long been underestimated, in part because it is considered a mild form of tumor invasion [21]. With the deepening of research, the significance of MVI for HCC patients has gradually emerged. Yamamoto et al [22] reported that MVI plays an essential role in recurrence and intrahepatic metastasis of HCC. In recent years, many studies have shown that MVI is associated with poorer prognosis of HCC patients [23,24]. Besides, the presence or absence of MVI in HCC has guiding significance for selecting surgical strategies. Han et al [25] indicated that wide surgical margins are more suitable for HCC patients with MVI. The above shows that HCC with MVI is more malignant. In the present study, multivariate analysis showed that MVI is an independent predictor of the prognosis in HCC patients who underwent PA-TACE. GGT is an essential enzyme in liver glutathione metabolism, mainly in the hepatocyte membrane and microsomes [26]. After transhepatic tumor resection, radiofrequency ablation, and TACE, the overall survival rate was not satisfactory in HCC patients due to the increased GGT count [27,28]. Also, GGT plays a vital role in the occurrence, vascular invasion, and metastasis of HCC [29,30]. Lymphocytes are essential for the body's tumor immunity. T lymphocytes can directly kill tumor cells after being activated by antigens presented by dendritic cells and in-

hibit tumor growth and proliferation by secreting various cytokines. Therefore, the high level of lymphocyte infiltration around the tumor is often considered a sign of a better prognosis [31]. GLR is calculated by two established predictors, which can comprehensively assess the patient's liver function and immune level. Hence, higher GLR (high GGT levels and low lymphocyte count) indicates severe liver function damage and low immune status, which may be related to MVI. According to our multivariate analysis results, the GLR was an independent factor associated with OS in HCC patients with PA-TACE.

Previous studies showed that IRE and an irregular (or non-smooth) tumor margin were reliable indicators of aggressive behavior and poor survival for HCC [32-34]. Kawamura et al [14] reported that a rim-like enhancement pattern was related to early recurrence after radiofrequency ablation. Our research was in agreement with these studies. HCC patients with IRE had a poorer prognosis than those without IRE after PA-TACE in our study. Box plots indicated significant differences in GLR levels between the IRE group and the non-IRE group. Furthermore, Spearman correlation analysis showed that GLR was also associated with IRE ($r=0.522$, $p<0.001$). The relationship between GLR and IRE in HCC patients may be due to the following reasons. First, both of these indicators are associated with the malignancy degree of the tumor. Liao et al [35] suggested that higher GLR levels are related to poor tumor staging, MVI, early recurrence, and low OS rates. In our study, most patients had a history of chronic HBV infection. As is well known, the tumor microenvironment is affected by chronic inflammation, resulting in lower lymphocyte levels, which is a factor that may cause vascular invasion [36]. Second, IRE is related to tumor hypoxia and stem cell features such as CK19 and carbonic anhydrase [37,38]. CK19-positive HCC patients had higher invasiveness, which reduces liver function [39]. These may be the reasons for the elevated GLR in HCC patients with IRE. In this situation, we have reasons to propose that the presence of IRE contributes to a higher GLR, more aggressive tumors, and a worse prognosis.

Unfortunately, the prognostic significance of PTC was not proven in our research. Theoretically, the existence of a fibrous capsule may act as a barrier to slow down or prevent the invasion of HCC. Still, such a barrier may simply be considered as a marker of an effective host response to the tumor [34]. AFP is a commonly used index in the detection and follow-up of HCC. Lower AFP levels are associated with less advanced tumor stage, a lower risk of mortality, and microscopic vascular involvement [40]. In our multivariate Cox analysis, we found that AFP≥400 was an independent factor associated with OS in HCC patients with PA-TACE, which is consistent with a previous study [8].

Using CT features to predict HCC patients' prognosis is very promising because it is a non-invasive and simple method during diagnosis. GLR is calculated from the GGT and LYM ratio, which can be easily obtained from the clinic. Our study's most significant result was the establishment of a comprehensive nomogram with strong predictive power by using different types of biomarkers. Patients were stratified into low-risk and high-risk groups on the basis of the nomogram. A Kaplan-Meier curve based on the risk ratio showed that HCC patients in the low-risk group had a significantly higher 5-year OS rate than patients in the high-risk group, which reminds us that high-risk HCC patients need more active treatment after receiving PA-TACE, so that they could benefit more from treatment and prolong their survival.

Several limitations should be acknowledged in this study. First, our study population was recruited from one single hospital, which may cause a selection bias. Second, this was a retrospective study, and the sample size was relatively small. Third, various factors may influence GLR before surgery, such as medication history.

Conclusions

To sum up, our findings indicate that a higher GLR level was associated with the presence of IRE and MVI. The GLR, IRE, MVI, and AFP were used to build a simple nomogram. Given its low cost and strong predictive power, it can act as a practical tool to guide individualized treatment for HCC patients after PA-TACE.

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Conflict of interests

The authors declare no conflict of interests.

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