Original Article

Prognostic significance of globulin/low-density lipoprotein ratio in patients with hepatocellular carcinoma after local ablative therapy: a retrospective cohort study

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Background: Low-density lipoprotein (LDL) and globulin (GLOB) have been found to be predictors for some malignant tumors, but their predictive value in hepatocellular carcinoma (HCC) has hardly been elucidated. This study assessed the prognostic significance of GLOB to LDL ratio (GLR) in HCC patients before ablation.

Methods: This study analyzed 312 early-stage HCC patients who were hospitalized and underwent ablative treatment in Beijing You'an Hospital, Capital Medical University, from 1 January 2014 to 1 January 2019. The primary endpoint was the recurrence-free survival (RFS), calculated from treatment initiation to cancer recurrence, whereas the overall survival (OS) was measured from treatment initiation to death or last follow-up. Cox regression analysis was used to assess the GLR independently associated with recurrence and survival. OS and RFS were calculated by Kaplan-Meier analysis and compared between groups using the log rank test. The optimal cut-off value and prognostic role of GLR and other markers were evaluated via the receiver operating characteristic (ROC) curves and the Youden index.

Results: Univariate and multivariate analysis found that the tumor number, tumor size, and GLR were independent risk factors of relapse, whereas etiology, tumor number, tumor size, fibrinogen (Fib), and GLR were related to OS. We classified the patients into groups with high and low levels of GLR based on the optimal cut-off value of GLR identified by ROC curve. The cumulative 1-, 3-, and 5-year RFS rates in the low GLR group were 76.4%, 53.8%, and 43.4% respectively, whereas those in the high GLR group were 71%, 31%, and 22%, respectively (P<0.001). In terms of OS, the low GLR group showed a 1-, 3-, and 5-year OS of 99.5%, 92.0%, and 80.2% respectively, and 98%, 73%, and 63% respectively for the high GLR group (P<0.001). Finally, patients were stratified by GLR and tumor size. The outcomes revealed that patients in group A (GLR <16.54 and tumor size ≤30 mm) showed better prognosis than those in group B (GLR ≥16.54 and tumor size ≤30 mm or GLR <16.54 and tumor size >30 mm) and group C (GLR ≥16.54 and tumor size >30 mm) (P<0.001).

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Conclusions: Preoperative GLR ratio has predictive value for patients with HCC who have undergone complete ablation.

Keywords: Globulin (GLOB); low-density lipoprotein (LDL); hepatocellular carcinoma (HCC); ablation

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Introduction

Hepatocellular cancer (HCC) is the sixth most common cancer in the world and the third leading cause of cancer mortality. China reported 410,000 newly diagnosed cases of HCC and 390,000 deaths in 2020 (1). First-line treatments for patients with early-stage HCC include percutaneous ablation, surgical resection, and liver transplantation (2). Ablative therapy has become the choice of mounting HCC patients and doctors, with the advantages of fewer adverse effects, shorter hospital stays, and shorter recovery time (3,4). However, due to the high rate of postoperative recurrence and metastasis, the 5-year relapse rate of HCC is 70% (5). In China, the 5-year survival rate of HCC is only 12.1% (6). Therefore, attention should be paid to the evaluation of clinical indicators for the prognosis in HCC patients.

Highlight box

Key findings

- This study found that preoperative globulin (GLOB) to low-density lipoprotein (LDL) ratio has predictive value for hepatocellular carcinoma (HCC) patients who underwent complete ablation.

What is known and what is new?

- Treatment of HCC is evolving rapidly, but the high rate of postoperative recurrence needs to be addressed. Hence, attention should be paid to the evaluation of clinical indicators for the prognosis in HCC patients.
- In this study, the pre-treatment lipid level marker LDL and the immune level indicator GLOB were combined for HCC patient prognosis prediction.

What is the implication, and what should change now?

- By using combined indicators, the follow-up time for patients with higher recurrence risk should be adjusted to monitor the development of a tumor and select appropriate treatment strategies, thus effectively prolonging the long-term survival of patients.

The liver is a common organ that regulates lipid metabolism. Impaired liver function is standard in HCC patients, leading to the profound dysregulation of lipid and lipoprotein metabolism (7,8). Low-density lipoprotein (LDL), an important apolipoprotein assessed in patients with hypertension (9), could regulate the cell cycle, activate proteinase C, and induce oxidative stress response, affecting the growth and proliferation of HCC cells (10,11). A study observed that the levels of low-density lipoprotein cholesterol (LDL-C) are linked to an increased risk of cancer (12). Similarly, another study reported that decreased LDL-C is an important prognostic factor in colorectal carcinoma (13). Globulin (GLOB) is the main component of serum protein, elevated levels of which indicate an overactive immune system that is often found in patients with chronic inflammation (14). Previous studies have demonstrated GLOB to be an independent risk factor for the incidence of colorectal and stomach cancers (15,16). It has also been documented that high preoperative serum GLOB in HCC patients is a risk factor for poor survival (17).

Currently, a number of prognostic markers have been proposed for HCC, including monocyte-to-lymphocyte ratio (MLR) (18), neutrophil-lymphocyte ratio (NLR) (19), platelet-lymphocyte ratio (PLR) (20), albumin-bilirubin (ALBI) grade (21), and platelets-albumin-bilirubin (PALBI) grade (22), among others. Although the pretreatment level of lipid and immunological status plays an indispensable role in predicting the prognosis of many patients with malignant tumors, few articles have linked the two indicators for the prognosis prediction of HCC patients. Also, the combination of two biomarkers is better than the use of 1 biomarker alone in tumor diagnosis and prognosis prediction (23,24). Therefore, this study was designed to investigate the prognostic value of the GLOB to LDL ratio (GLR) for HCC patients. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-161/rc).

Methods

Research design and patients

This study was a retrospective study conducted in a single hospital. A total of 312 early-stage HCC patients who received local ablation at Beijing You'an Hospital affiliated to Capital Medical University from 1 January 2014 to 1 January 2019 were enrolled in this study. The diagnostic criteria for HCC were based on alpha-fetoprotein (AFP), classic imaging features, and histological biopsy, which were drawn from the American Association for the Study of Liver Diseases (AASLD) (25).

The inclusion criteria for this study were as follows: (I) age ≥18 and <75 years; (II) patients treated with ablation to achieve complete ablation; (III) Barcelona Clinic Liver Cancer (BCLC) stage 0 and A; (IV) no concomitant serious medical disease; (V) complete clinical data. The exclusion criteria were as follows: (I) history of other malignancies; (II) laboratory data, including GLOB and LDL, were incomplete; (III) lymphocytic leukemia, autoimmune diseases, and other concomitant diseases that affected serum GLOB levels; (IV) advanced stage of HCC; (V) secondary liver cancer.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing You'an Hospital, Capital Medical University [(2019) No.023]. As a minimum-risk study that was in accordance with the Helsinki protocol, the requirement for patients' informed consent was waived by the same ethics committee that approved the study. All methods were performed in accordance with the relevant guidelines and regulations.

Data collection

Clinical data of all patients were collected for 7 days before treatment, mainly including the following: (I) demographic data (age, gender, hypertension, diabetes, and antiviral medication); (II) causes of HCC [hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), and others]; (III) liver function markers (cirrhosis and Child-Pugh class); (IV) ablation-related factors {ablation technique [radiofrequency ablation (RFA), microwave ablation (MWA), or cryoablation] and whether it was completed in 1 session or not}; (V) tumor-related indicators (tumor number, tumor size, and AFP level); (VI) laboratory data [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (γ-GT), alkaline phosphatase (ALP), fibrinogen (Fib), triglycerides, high-density lipoprotein (HDL), LDL, apolipoprotein A1, apolipoprotein B, free fatty acids, and apolipoprotein A1/B and viral load]. The GLR was calculated using the following formula: GLR = GLOB/LDL.

Treatment procedures

All patients enrolled were treated with ablation, which was performed by two interventional radiologists with at least 5 years of experience. For the procedure, the skin was first thoroughly disinfected and covered with a sterile cloth, after which a local anesthetic was injected and the ablation needle was inserted into the skin. Blood pressure, pulse, respiratory rate, and oxygen saturation were monitored during the procedure. After complete ablation was confirmed, coagulation was performed along the needle tract before the probe was removed to prevent needle tract bleeding. Most importantly, the safe ablation range of 0.5–1.0 cm was reserved to ensure complete coverage of the tumor and complete ablation.

Follow-up

The patients were followed up in the outpatient department; standard physical examination, laboratory examinations, and ultrasound were performed every 3 months, then enhanced computed tomography (CT)/magnetic resonance imaging (MRI) examination were performed every 6 months. The last follow-up date was on 30 June 2022. When the typical HCC imaging pattern in the liver or extrahepatic tumors were detected, regardless of whether the AFP levels were elevated, it was deemed as tumor recurrence. The primary endpoint was recurrence-free survival (RFS), which was calculated from treatment initiation to cancer recurrence, whereas overall survival (OS) was measured from treatment initiation to death or last follow-up. Patients with confirmed recurrence were re-assessed and given ablation treatment again.

Statistical analyses

No sample size calculation was performed as this was a retrospective study.

Continuous data were presented as mean ± standard deviation (SD) and categorical data as numbers and percentages. The comparisons of categorical data between groups were tested by the chi-square test. The Mann-

Table 1 Demographic and clinicopathological data in HCC patients

Variables	Value
Age (years old)	56.63±8.63
Gender, male/female	248 (79.5)/64 (20.5)
Hypertension	99 (31.7)
Diabetes	69 (22.1)
Antiviral	182 (58.3)
Etiology (HBV/HCV/ALD/others)	247 (79.2)/36 (11.5)/ 11 (3.5)/18 (5.8)
Cirrhosis	268 (85.9)
Child-Pugh class (A/B)	217 (69.6)/94 (30.1)
Fractional ablation (yes/no)	280 (89.7)/31 (9.9)
Ablative modality (RFA/MWA/AHC)	158 (50.6)/60 (19.2)/94 (30.1)
Tumor number (single/multiple)	216 (69.2)/96 (30.8)
Tumor size (≤20/>20 mm)	237 (76.0)/73 (23.4)
AFP (<7/7–400/>400 ng/mL)	131 (42.0)/162 (51.9)/16 (5.1)
BCLC stages (0/A)	214 (68.6)/98 (31.4)
Viral load (<100/≥100 IU/mL)	165 (52.9)/121 (38.8)
ALT (U/L)	37.02±27.25
AST (U/L)	37.19±20.81
γ-GT (U/L)	73.59±58.06
ALP (U/L)	95.99±44.72
Fibrinogen (mg/dL)	2.63±0.87
Triglyceride (mmol/L)	1.09±1.04
HDL (mmol/L)	1.13±0.35
Apolipoprotein A1 (g/L)	40.85±54.09
Apolipoprotein B (g/L)	24.67±32.49
A1/B	1.76±0.53
Free fatty acid (mmol/L)	0.51±0.26
GLR	16.18±7.90

Values are presented as mean ± SD or n (%). HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; RFA, radiofrequency ablation; MWA, microwave ablation; AHC, argon-helium cryoablation; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

Whitney *U*-test and Student's *t*-test were used to analyze the comparisons of continuous variables between groups. Cox regression analysis was used to assess the GLR independently associated with recurrence and survival. OS and RFS were calculated by Kaplan-Meier analysis and compared between groups using the log rank test. The optimal cut-off value and prognostic role of GLR and other markers were evaluated via the receiver operating characteristic (ROC) curves and the Youden index. The patients were classified with high and low levels of GLR. A 2-sided P≤0.05 denoted statistical significance. The statistical software SPSS 26.0 (IBM Corp., Armonk, NY, USA) was performed for statistical calculations.

Results

Baseline characteristics

Table 1 summarizes the preoperative clinicopathological data of 312 HCC patients after ablation. There were 64 (20.5%) women and 248 (79.5%) men included in this study, and the average age of patients was 57 years (range, 30–75 years). Furthermore, 99 patients (31.7%) had hypertension, 69 patients (22.1%) had diabetes, and 182 patients (58.3%) had received antiviral therapy. With regard to etiology, 247 patients (79.2%) had HBV-related HCC, 36 patients (11.5%) had HCV-related HCC, 11 patients (3.5%) had ALD-HCC, and 18 patients (5.8%) had other etiologies of liver disease.

The median follow-up was 56.8 months (range, 44.1–78.9 months). By the last follow-up, 210 patients (67.3%) had disease relapses, and 99 patients (31.7%) passed away. The 1-, 3-, and 5-year RFS rates were 25.3% (79/312), 53.5% (167/312), and 63.5% (198/312), and the OS rates of 1-, 3-, and 5-year were 99.0% (309/312), 85.9% (268/312), and 74.7% (233/312), respectively.

Prognostic factors related to RFS

Univariate survival tests were conducted to identify risk factors associated with RFS (*Table 2*). The results indicated that GLR, gender, tumor number, tumor size, Child-Pugh class, BCLC stages, cirrhosis, γ-GT, and ALP were significantly associated with RFS. On multivariable analysis, tumor number [hazard ratio (HR): 1.676; 95% confidence interval (CI): 1.113–2.526], tumor size (HR: 1.967; 95% CI: 1.251–3.092), and GLR (HR: 1.028; 95% CI: 1.004–1.052) were independent risk factors of relapse.

Table 2 Prognostic factors associated with RFS by Cox proportional hazards regression model

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years old)	1.008 (0.992–1.024)	0.327		
Gender (male/female)	0.637 (0.443–0.917)	0.015		
Hypertension	1.118 (0.837–1.494)	0.451		
Diabetes	1.183 (0.855–1.637)	0.31		
Antiviral	1.003 (0.760–1.324)	0.981		
Etiology (HBV/HCV/ALD/others)	0.962 (0.834–1.110)	0.595		
Cirrhosis	1.912 (1.217–3.002)	0.005		
Child-Pugh class (A/B)	1.373 (1.025–1.840)	0.034		
Fractional ablation (yes/no)	1.388 (0.892–2.160)	0.146		
Ablative modality (RFA/MWA/AHC)	0.949 (0.814–1.106)	0.503		
Tumor number (single/multiple)	1.873 (1.411–2.486)	<0.001	1.676 (1.113–2.526)	0.013
Tumor size (≤20/>20 mm)	1.934 (1.421–2.631)	<0.001	1.967 (1.251–3.092)	0.003
AFP (<7/7–400/>400 ng/mL)	1.057 (0.840–1.330)	0.637		
BCLC stages (0/A)	0.522 (0.381–0.734)	0.025		
Viral load (<100/≥100 IU/mL)	1.065 (0.898–1.265)	0.468		
ALT (U/L)	0.999 (0.994–1.003)	0.555		
AST (U/L)	1.005 (0.999–1.012)	0.102		
γ-GT (U/L)	1.003 (1.011–1.016)	0.003		
ALP (U/L)	1.004 (1.000–1.008)	0.041		
Fibrinogen (mg/dL)	0.930 (0.788–1.098)	0.393		
Triglyceride (mmol/L)	0.880 (0.703–1.102)	0.266		
HDL (mmol/L)	0.949 (0.643–1.401)	0.794		
Apolipoprotein A1 (g/L)	0.999 (0.997–1.002)	0.446		
Apolipoprotein B (g/L)	0.998 (0.994–1.002)	0.343		
A1/B	0.896 (0.694–1.155)	0.396		
Free fatty acid (mmol/L)	0.973 (0.583–1.624)	0.917		
GLR	1.018 (1.003–1.034)	0.017	1.028 (1.004–1.052)	0.02

RFS, recurrence-free survival; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; RFA, radiofrequency ablation; MWA, microwave ablation; AHC, argon-helium cryoablation; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

Prognostic factors related to OS

To further explore whether GLR was a predictive factor of OS, we used univariate analyses to evaluate the relationship between data and OS. Our results revealed that GLR, gender, antiviral, etiology, Child-Pugh classification, fractional ablation, tumor number, tumor size, BCLC stages, viral load, AST, γ-GT, and Fib were dramatically associated with OS. Multivariate analysis showed that that etiology (HR: 1.328; 95% CI: 1.052–1.677), tumor number

Table 3 Prognostic factors associated with OS by Cox proportional hazards regression model

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years old)	1.019 (0.996–1.043)	0.103		
Gender (male/female)	0.499 (0.278–0.895)	0.02		
Hypertension (yes/no)	0.758 (0.484–1.186)	0.225		
Diabetes (yes/no)	1.128 (0.708–1.799)	0.612		
Antiviral (yes/no)	0.516 (0.346–0.768)	0.001		
Etiology (HBV/HCV/ALD/others)	1.260 (1.075–1.477)	0.004	1.328 (1.052–1.677)	0.017
Cirrhosis (yes/no)	1.571 (0.791–3.120)	0.197		
Child-Pugh class (A/B)	1.984 (1.320–2.981)	0.001		
Fractional ablation (yes/no)	2.044 (1.160–3.603)	0.013		
Ablative modality (RFA/MWA/AHC)	0.971 (0.776–1.214)	0.794		
Tumor number (single/multiple)	1.778 (1.190–2.658)	0.005	1.615 (1.015–2.570)	0.043
Tumor size (≤20/>20 mm)	1.671 (1.086–2.571)	0.02	2.061 (1.243–3.418)	0.005
AFP (<7/7–400/>400 ng/mL)	1.236 (0.888–1.722)	0.21		
BCLC stages, 0/A (%)	0.714 (0.453–0.968)	0.012		
Viral load (<100/≥100 IU/mL)	1.422 (1.114–1.814)	0.005		
ALT (U/L)	1.000 (0.993–1.007)	0.997		
AST (U/L)	1.010 (1.002–1.018)	0.014		
γ-GT (U/L)	1.004 (1.001–1.007)	0.017		
ALP (U/L)	1.003 (0.999–1.007)	0.16		
Fibrinogen (mg/dL)	0.730 (0.559–0.951)	0.02	0.73 (0.535–0.996)	0.047
Triglyceride (mmol/L)	1.016 (0.827–1.249)	0.879		
HDL (mmol/L)	0.977 (0.560–1.702)	0.934		
Apolipoprotein A1 (g/L)	0.998 (0.994–1.002)	0.279		
Apolipoprotein B (g/L)	0.995 (0.989–1.002)	0.162		
A1/B	1.180 (0.819–1.700)	0.373		
Free fatty acid (mmol/L)	1.208 (0.602–2.427)	0.595		
GLR	1.034 (1.014–1.055)	0.001	1.031 (1.003–1.06)	0.032

OS, overall survival; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; RFA, radiofrequency ablation; MWA, microwave ablation; AHC, argon-helium cryoablation; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

(HR: 1.615; 95% CI: 1.015–2.570), tumor size (HR: 2.061; 95% CI: 1.243–3.418), Fib (HR: 0.73; 95% CI: 0.535–0.996), and GLR (HR: 1.031; 95% CI: 1.003–1.06) were prognostic factors of patients' survival in HCC (*Table 3*).

The prognostic value of GLR

According to the GLR cut-off value, all patients were divided into groups of high and low levels of GLR. Kaplan-Meier survival curves found that the 1-, 3-, and 5-year

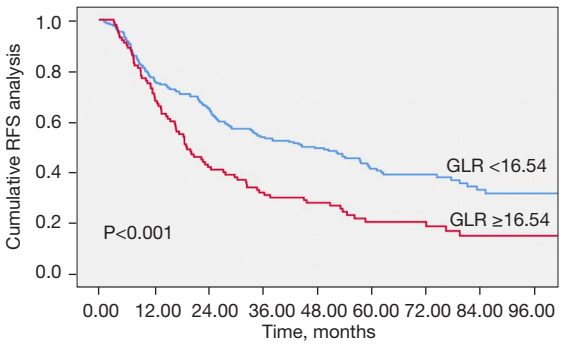

Figure 1 The Kaplan-Meier analysis of RFS for patients with high GLR group (GLR ≥16.54) and low GLR group (GLR <16.54). GLR, the globulin to LDL ratio; RFS, recurrence-free survival; LDL, low-density lipoprotein.

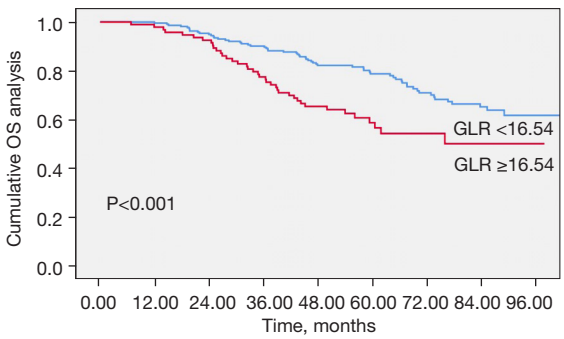

Figure 2 The Kaplan-Meier analysis of OS for patients with high GLR group (GLR ≥16.54) and low GLR group (GLR <16.54). GLR, the globulin to LDL ratio; OS, overall survival; LDL, low-density lipoprotein.

RFS rates of the low GLR group were 76.4%, 53.8%, and 43.4%, respectively, with a median RFS of 43.1 months, whereas the 1-, 3-, and 5-year RFS rates of high GLR group were 71%, 31%, and 22%, respectively, with a median RFS of 19.3 months (P<0.001), which indicated that higher GLR values were correlated with shorter recurrence time (*Figure 1*).

As for OS, the median OS of patients in the low GLR group was 59 months, and the OS rates at 1-, 3-, and 5-year were 99.5%, 92.0%, and 80.2%, respectively; and the median OS of high GLR group was 51 months, with 1-, 3-, and 5-year OS of 98%, 73%, and 63% (P<0.001), which illustrated that lower GLR values implied better survival (*Figure 2*).

Previous research noted that high serum GLOB in patients with HCC patients was an independent risk factor

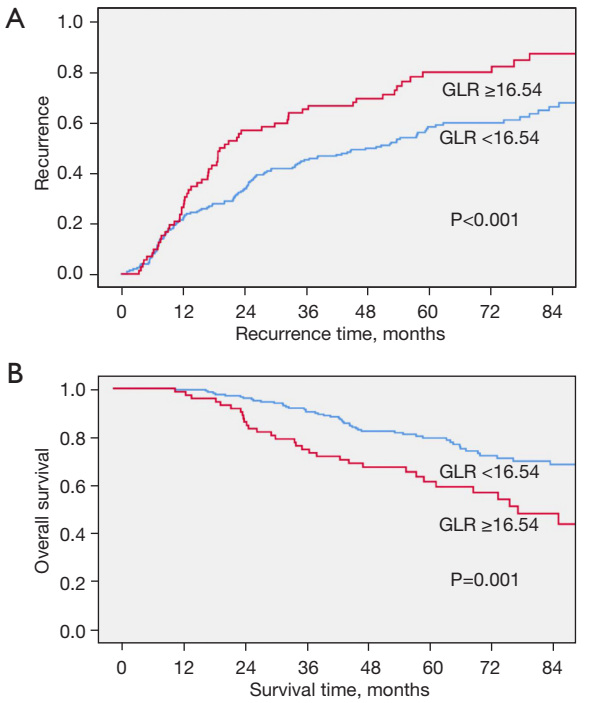

Figure 3 The Kaplan-Meier analysis of recurrence (A) and OS (B) for patients with high GLR group (GLR ≥16.54) and low GLR group (GLR <16.54) among patients with normal globulin. GLR, the globulin to LDL ratio; OS, overall survival; LDL, low-density lipoprotein.

for poor survival (17). Kaplan-Meier survival analysis was performed on patients with GLOB <35 g/L to exclude the effect of hyperglobulinemia. The results suggested that GLR remained a significant predictor for OS and RFS (*Figure 3*).

Associations between GLR and clinical data

A comparison was conducted to determine the clinical factors that were significantly associated with GLR. Eventually, we found that etiology, Child-Pugh B, high AST levels, high ALP levels, low Fib levels, and high apolipoprotein A1/B ratio were significantly associated with high GLR levels (*Table 4*), which demonstrated that high GLR levels represent poor liver function.

Comparing the accuracy of predictions of GLR, GLOB, and LDL

It has been demonstrated that GLOB can predict

Table 4 The GLR-based comparison of baseline clinical data

Variables	Total	GLR <16.54, n=212	GLR ≥16.54, n=100	P value
Age (years old)	56.63±8.63	56.15±8.93	57.66±7.92	0.149
Gender (male/female)	248/64	167/45	81/19	0.649
Hypertension (yes/no)	213/99	147/65	66/34	0.554
Diabetes (yes/no)	243/69	168/44	75/25	0.399
Antiviral (yes/no)	128/182	83/129	45/53	0.26
Etiology (HBV/HCV/ALD/others)	247/36/11/18	180/15/7/10	67/21/4/8	<0.001
Cirrhosis (yes/no)	44/268	35/177	9/91	0.075
Child-Pugh class (A/B)	217/94	161/50	56/44	<0.001
Fractional ablation (yes/no)	280/31	190/22	90/9	0.724
Ablative modality (RFA/MWA/AHC)	158/60/94	100/43/69	58/17/25	0.198
Tumor number (single/multiple)	216/96	151/61	65/35	0.266
Tumor size (≤20/>20 mm)	237/73	157/53	80/20	0.31
AFP (<7/7–400/>400 ng/mL)	131/162/16	93/107/11	38/55/5	0.664
BCLC stages (0/A)	214/98	150/62	64/36	0.086
Viral load (<100/≥100 IU/mL)	165/121	119/80	46/41	0.159
ALT (U/L)	37.02±27.25	38.74±29.89	33.38±20.19	0.064
AST (U/L)	37.19±20.81	33.95±16.94	44.06±26.04	0.001
γ-GT (U/L)	73.59±58.06	75.96±60.73	68.56±51.88	0.294
ALP (U/L)	95.99±44.72	91.74±40.17	105.01±52.17	0.014
Fibrinogen (mg/dL)	2.63±0.87	2.79±0.89	2.29±0.69	<0.001
Triglyceride (mmol/L)	1.09±1.04	1.13±0.52	1.02±1.67	0.418
HDL (mmol/L)	1.13±0.35	1.14±0.33	1.10±0.40	0.33
Apolipoprotein A1 (g/L)	40.85±54.09	41.57±55.79	39.33±50.54	0.734
Apolipoprotein B (g/L)	24.67±32.49	26.44±34.66	20.93±27.10	0.128
A1/B	1.76±0.53	1.63±0.45	2.04±0.58	<0.001
Free fatty acid (mmol/L)	0.51±0.26	0.50±0.24	0.54±0.31	0.234

Data were presented as n or mean ± SD. GLR, the globulin to LDL ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; RFA, radiofrequency ablation; MWA, microwave ablation; AHC, argon-helium cryoablation; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the prognosis of HCC patients undergoing surgical operation (26). Meanwhile, LDL has been associated with early recurrence of HCC (27). Therefore, an ROC curve for GLR, GLOB, and LDL was plotted to determine whether the prediction efficiency of the composite indicator was better than that of the single indicator. Eventually, we found that the area under the curve (AUC) for GLR was 0.698, which was superior to GLOB (0.585) and LDL (0.416) levels alone (*Table 5*).

Stratify patients based on GLR and tumor size

We have previously demonstrated that high GLR levels reflect impaired hepatic functions in HCC patients, and the tumor

Table 5 Ranking of the prognostic ability of the variable based on AUC

Rank	Variable	AUC	95% CI	P value
1	GLR	0.698	0.633–0.763	0.033
2	Globulin	0.585	0.516–0.653	0.035
3	LDL	0.416	0.348–0.483	0.034

AUC, area under the curve; CI, confidence interval; GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

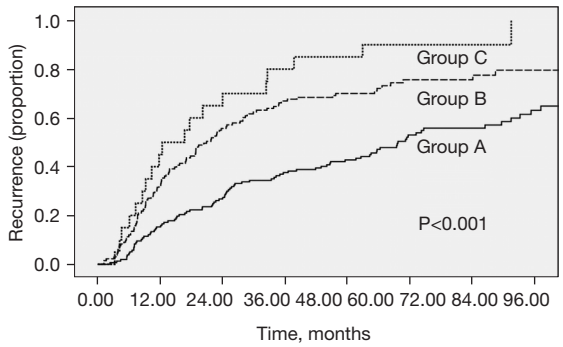

Figure 4 The Kaplan-Meier analysis of recurrence of the subgroup study stratification of patients according to GLR and tumor size. Group A: patients with GLR <16.54 and tumor size ≤20 mm; Group B: patients with GLR ≥16.54 and tumor size ≤20 mm or patients with GLR <16.54 and tumor size >20 mm; Group C: patients with GLR ≥16.54 and tumor size >20 mm. GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

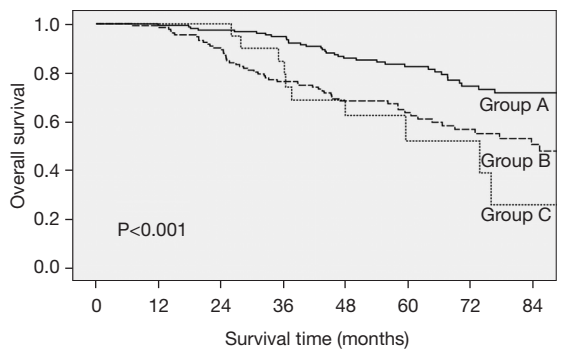

Figure 5 The Kaplan-Meier analysis of OS of the subgroup study stratification of patients according to GLR and tumor size. Group A: patients with GLR <16.54 and tumor size ≤20 mm; Group B: patients with GLR ≥16.54 and tumor size ≤20 mm or patients with GLR <16.54 and tumor size >20 mm; Group C: patients with GLR ≥16.54 and tumor size >20 mm. OS, overall survival; GLR, the globulin to LDL ratio; LDL, low-density lipoprotein.

size, which determined tumor burden, was the independent risk factor for HCC relapse (*Table 2*). We further analyzed whether the indicator consisting of GLR and tumor size could further increase the predictive ability. Therefore, patients were classified into 3 groups, including group A (GLR <16.54 and tumor size ≤20 mm), group B (GLR ≥16.54 and tumor size ≤20 mm or GLR <16.54 and tumor size >20 mm), and group C (GLR ≥16.54 and tumor size >20 mm). The 5-year recurrence rate was 51% in group A, 73.7% in group B, and 90% in group C (P<0.001; *Figure 4*), whereas the 5 - year OS for patients in group A, group B, and group C was 84.1%, 65.4%, and 60%, respectively (P<0.001; *Figure 5*).

Discussion

To date, it is still a great challenge to prolong long-term survival in HCC patients. Despite recent advances in combination treatment, HCC, the sixth most common cancer worldwide, shows limited survival benefits after the surgical treatment. Therefore, it is worthwhile to predict the risk of postoperative early relapse in HCC patients and for early reinterventions to be conducted in patients with high risk of relapse. This study investigated the prognostic value of GLR in HCC patients treated by ablation. Finally, we found that GLR was an independent risk factor for RFS and OS with a higher AUC than separate indicators, suggesting that GLR is a superior predictor of RFS and OS.

GLOB, reflecting immune status, is a protein produced by immune organs that plays a vital role in immunity and inflammation. It can be detected as a regulator for the circulatory system to assist blood coagulation, transport proteins, and indicate antibody levels (28). Elevated GLOB levels are involved in several inflammatory diseases that occur at specific times during tumor progression, including initiation, promotion, malignant transformation, invasion, and metastasis (29). The reason for those may be that cytokines released by inflammatory cells form an

inflammation-associated tumor microenvironment that promotes tumor growth (30). Meanwhile, inflammation could alter the biological characteristics of tumor cells and disrupt immune function, leading to poor prognosis in patients with malignant tumors (31). Abnormal lipid metabolism plays an important role in the development of tumors by altering lipid metabolism pathways to sustain growth and proliferation, which would cause a change in relevant indicators (32). Some studies have found that low LDL levels increase the risk of liver cancer in people infected with HBV (33,34). Lately, several studies, with the progression of tumor biology, have suggested that LDL is involved in the development of various tumors, including breast cancer, lung cancer, and liver cancer (35-37). An explanation is that the increased activity of LDL receptors accelerates LDL clearance from circulation, which reduces the risk of cancer (38). Another interpretation is that hepatic lipase activity is inversely correlated with LDL (39). Meanwhile, polymorphisms of hepatic lipase gene promoters have been associated with HCC (40).

As the ratio between GLOB and LDL, GLR has better predictive power compared to a single indicator, as demonstrated by this study. Moreover, by exploring the correlation between GLR and clinical data, our study suggested that a high GLR level may represent poor liver function, giving good guidance value for clinical practice. Most importantly, our study shows, for the first time, the significance of the prognosis of GLR in HCC patients of various etiologies, which together with multivariate Cox regression analysis showed that GLR predicts OS and RFS outcomes in HCC patients, reflecting the generalizability of combined markers. In contrast to other predictive markers, GLR is a ratio of common and easy-to-obtain indicators in clinical practice. Also, the calculation of the ratio of the two variables is relatively straightforward, facilitating clinical utilization. In the context of the high recurrence rate, it is essential to use combined indicators to predict the prognosis of HCC patients after ablation, then to further optimize treatment strategies and guidance. A study found that the survival time of HCC patients with tumor size <2 cm was significantly longer than that of other types of patients (41). Our study found the significance of the combination of GLR and tumor size in evaluating patient outcomes. By using combined indicators, patients will be divided into groups through preoperative evaluation. For patients with higher recurrence risk and lower OS, the follow-up time should be adjusted to monitor the development of a tumor and select appropriate treatment strategies, thus effectively prolonging the long-term survival of patients.

For early-stage HCC patients, ablative therapy and surgery are equally effective and are recommended as first-line treatment by guidelines (42). In this study, all patients received ablative therapy and did not receive surgical treatment. Since the two treatment modalities may affect GLR differently, whether GLR is predictive of surgical patients will need to be demonstrated in further surgical cohorts in the future.

Our study has some limitations. First of all, this was a retrospective, single-center study with a limited sample size. Therefore, it is necessary to validate these results through further large-scale multicenter randomized trials. Second, this study was conducted to predict the prognosis of HCC patients after ablation using baseline GLR data, lacking post-ablation data. Further studies are warranted to investigate whether post-ablation GLR could also be utilized for prognostic prediction. In addition, our study did not provide evidence of the potential mechanism of GLR on tumor progression. Future studies, based on our results, will conduct further experiments to explore the mechanism.

Conclusions

In this 8-year follow-up study of various etiologies, we determined the prognostic value of GLR as an inexpensive, readily available, and noninvasive biomarker for HCC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-161/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-161/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-161/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study has been approved by the Ethics Committee of Beijing You'an Hospital, Capital Medical University [(2019) No.023]. As a minimum-risk study that was in accordance with the Helsinki protocol, the requirement for patients' informed consent was waived by the same ethics committee that approved the study. All methods were performed in accordance with the relevant guidelines and regulations.

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