Prognostic Significance of Globulin/Low-Density Lipoprotein Ratio In Patients With Hepatocellular Carcinoma After Local Ablative Therapy

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Abstract

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

Materials and methods: This study analyzed 312 HCC patients hospitalized and underwent ablative treatment in Beijing You 'an Hospital, Capital Medical University, from January 1, 2012 to January 1, 2017. Cox regression analysis was used to assess the factors independently associated with recurrence and survival. 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. Overall survival (OS) and recurrence-free survival (RFS) were calculated by Kaplan-Meier analysis, and compared between groups using the log-rank.

Result: Univariate and multivariate analysis found that the tumor number (HR: 1.676;95%CI: 1.113-2.526), tumor size (HR: 1.967;95%CI: 1.251-3.092), GLR (HR: 1.028;95%CI: 1.004-1.052) were independent risk factors of relapse; while etiology (HR: 1.328;95%CI: 1.052-1.677), tumor number (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 related to overall survival. We classified the patients into groups with high and low levels of GLR based on the optimal cut-off value of GLR identified by generating receiver operating characteristics (ROC) curve. The cumulative 1-, 3-, and 5-year RFS rates in the low GLR group were 76.4%, 53.8% and 43.4%, while those in the high GLR group were 71%, 31% and 22%, respectively (P <0.001). Concerning OS, the low GLR group showed a 1-, 3- and 5-year OS of 99.5%, 92.0% and 80.2% versus 98%, 73% and 63% 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 ≤30mm) showed better prognosis than group B (GLR≥16.54 and tumor size≤30mm or GLR<16.54 and tumor size >30mm) and group C (GLR≥16.54 and tumor size >30mm) (P <0.001).

Conclusions: Preoperative GLR ratio could serve as a biomarker to predict prognosis in HCC patients who underwent complete ablation.

Background

Hepatocellular cancer (HCC) is the sixth most common cancer in the world and the third leading cause of cancer mortality[1]. 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 and percutaneous ablation, surgical resection and liver transplantation. Ablative therapy has become the choice of more and more HCC patients and doctors, with the advantages of fewer adverse effects, shorter hospital stays, and shorter recovery time[2, 3]. However, due to the high rate of postoperative recurrence and metastasis, the

5-year relapse rate of HCC is 70%[4].In China, the 5-year survival rate is only 12.1%[5]. Therefore, we should pay attention to the evaluation of clinical indicators for the prognosis in HCC patients [6].

The liver is a crucial organ that regulates lipid metabolism. Impaired liver function is standard in HCC patients, leading to the profound dysregulation of lipid and lipoprotein metabolism[7]. One study observed that the levels of LDL-C linked to an increased risk of cancer[8]. Similar findings were suggested in another study that decreased LDL-C is an important prognostic factor in colorectal carcinoma[9].

Globulin is the main component of serum protein elevated levels of it indicate an overactive immune system that is often found in patients with chronic inflammation[10]. Previous studies demonstrated GLOB to be an independent risk factor for the incidence of colorectal and stomach cancers[11, 12].

Thus far, few articles have investigated the prognostic prediction of serum lipid ratio to serum globulin HCC patients who receive ablation therapy. Therefore, this study was designed to investigate the prognostic value of GLR for HCC patients through clinical data.

Materials And Methods

Patient Enrollment

A total of 312 HCC patients who received local ablation at Beijing You 'an Hospital affiliated to Capital Medical University from January 1, 2012 to January 1, 2017, were enrolled in this study. The diagnostic criteria for HCC is based on alpha fetoprotein (AFP), classic imaging features, and histological biopsy, which comes from the American Association for the Study of Liver Diseases (AASLD)[13]. Patients aged 18–75 years were treated with ablation to confirm complete ablation. Exclusion criteria include:1) history of other malignancies;2) Laboratory data, including globulin and LDL, were incomplete 3) Lymphocytic leukaemia, autoimmune diseases and other concomitant diseases that affected serum globulin levels;4) advanced stage of HCC;5) secondary liver cancer.

All information of the patient was kept confidential. Procedures consistent with the Declaration of Helsinki. The Ethics Committee of Beijing You 'an Hospital has granted informed consent exemptions for this study.

Data collection

Clinical data of all patients were collected for 7 days before treatment, which mainly includes:1) demographic data [age, gender, hypertension, diabetes and antiviral]; 2) causes of HCC[HBV, HCV, ALD and others]; 3) liver function markers [cirrhosis and Child-Pugh class];4) ablation-related factors[ablation technique (RFA, MWA, or cryoablation)and in one-session or not];5) tumor-related indicators [tumor number, tumor size and alpha-fetoprotein (AFP) level];6) laboratory data [ALT, AST, γ-GT, ALP, Fib, triglycerides, 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 = globulin/LDL.

Follow-up

The patients were followed up in the outpatient department; standard physical examination, laboratory examinations and ultrasound each quarter, then enhanced CT/MRI examination every 6 months. The last follow update was June 30, 2020. When the typical HCC imaging pattern in the liver or extrahepatic tumors was detected, with or without elevated serum AFP levels, it was determined that the tumor had recurred. The primary endpoint was recurrence-free survival (RFS), which calculated from treatment initiation to cancer recurrence, while overall survival (OS) measured from treatment initiation to death or last follow-up. After confirmed recurrence，patients were assessed and received TACE or radiofrequency ablation treatment.

Statistical analyses

Continuous data are presented as mean ±SD and categorical data as number and percentage. The comparisons of categorical data between groups were tested by Chi-square test. Using the Mann-Whitney U-test and Students t-test to analyze the comparisons of continuous variables between groups. Cox regression analysis was used to assess the factors independently associated with recurrence and survival. OS and RFS were calculated by Kaplan-Meier analysis, and compared between groups using the log-rank. 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 into groups with high and low levels of GLR. $P \leq 0.05$ denoted statistical significance. A statistical software SPSS Version 26.0 (IBM, Armonk, NY) was performed for statistical calculations.

Result

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 is 57 years (range 30–75 years). Furthermore, 99 patients（31.7%）suffered from hypertension, 69 patients （22.1%）had diabetes,182 patients（58.3%）received antiviral therapy. With regard to etiology, 247 patients (79.2%) had hepatitis B-related HCC, 36 patients (11.5%) had HCV-related HCC, 11 patients (3.5%) had alcohol-related 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, cirrhosis, γ-GT and ALP were

significantly associated with RFS. On multivariable analysis, tumor number (HR: 1.676;95%CI: 1.113-2.526), tumor size (HR: 1.967;95%CI: 1.251-3.092), GLR (HR: 1.028;95%CI: 1.004-1.052) were independent risk factors of relapse.

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, 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 (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 with high and low levels of GLR. Kaplan-Meier survival curves found that the 1-, 3-, and 5-year RFS rates of the low GLR group were 76.4%,53.8% and 43.4%, respectively, with a median RFS of 43.1 months, while 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 correlate 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 year, 3 years, and 5 years were 99.5%,92.0% and 80.2%, respectively; and the median OS of high GLR group was 51 months, with 1-year, 3-year, and 5-year OS of 98%,73% and 63%（P<0.001）, which illustrated that lower GLR values implied better survival（Figure 2）.

Previous studies have noted that high serum globulin HCC patients were independent risk factors for poor survival [14]. Kaplan-Meier survival analysis was performed on patients with globulin < 35 g/L to exclude the effect of hyperglobulinemia. The results suggest that GLR remained a significant predictor for OS and RFS（Figure 3）.

Associations between GLR and clinical data

To determine which clinical data were significantly associated with GLR, we produced a comparison of them. Eventually, we found 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 the poor liver function.

Comparing the accuracy of predictions of GLR, Globulin and LDL

It has been demonstrated that globulin can predict the prognosis of HCC patients undergoing surgical operation [14]. Meanwhile, LDL was associated with early recurrence of HCC[15]. Therefore, a ROC curve

for GLR, globulin 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 the area under the curve (AUC) for GLR was 0.600, which was superior to globulin (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 size, which determined tumor burden was the independent risk factor for HCC relapse （Table 2）. We further analyzed whether the indicator consisted of GLR and tumor size could further increase the predictive ability. Therefore, patients were classified into three groups, including group A (GLR<16.54 and tumor size ≤30mm), group B (GLR≥16.54 and tumor size ≤30mm or GLR<16.54 and tumor size >30mm) and group C (GLR≥16.54 and tumor size >30mm).The 5-year recurrence rate were 51% in group A, 73.7% in group B, 90% in group C(P <0.001（Figure 4）,while 5-year OS for patients in group A, group B, group C were 84.1%,65.4% and 60%,respectively（P <0.001（Figure 5）.

Discussion

To date, it is a great challenge to prolong the long-term survival in HCC patients. Despite recent advances in combination treatment, HCC, as the sixth most common cancer worldwide, has a limited survival benefit after the operation. Therefore, we must predict the risk of postoperative early-relapse in HCC patients to conduct early re-interventions in patients at high risk of relapse. While there are many prognostic markers for liver cancer, lack of some index scores with high sensitivity and high specificity recently to predict prognosis in HCC patients. Hence, we need to search for some robust predictive biomarkers to assess the risk of recurrence in HCC patients after ablation and guide individualized therapy.

Globulin, 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[16]. Elevated globulin levels are involved in several inflammatory diseases that occur at specific times during tumor progression, including initiation, promotion, malignant transformation, invasion, and metastasis[17]. The reason for those may is that cytokines released by inflammatory cells form an inflammation-associated tumor microenvironment that promotes the growth of tumor[18, 19]. Meanwhile, inflammation could alter the biological characteristics of tumor cells and disrupt immune function, leading to poor prognosis of patients with malignant tumors[20]. Previous studies found that a high globulin level was associated with a poor prognosis in patients with colorectal cancer, non-small cell lung cancer, prostate cancer, ovarian cancer, and breast cancer [21-25].

Abnormal lipid metabolism plays an important role in the development of tumor by altering lipid metabolism pathways to sustain growth and proliferation, which would cause the change of relevant indicators[26]. Some studies have found that low LDL levels increase the risk of liver cancer in people infected HBV[27]. Lately, lots of studies, with the progression of tumor biology, have suggested that LDL

are involved in various tumors development, including breast cancer, lung cancer and liver cancer[28-30]. A explanation is that the increased activity of LDL receptors accelerates LDL clearance from circulation, which reduces the risk of cancer[31]. Another interpretation is that hepatic lipase activity is inversely correlated with LDL[32]. Meanwhile, polymorphisms of hepatic lipase gene promoters were associated with HCC[33].

As the ratio between globulin and LDL, GLR has better predicting power through the proof of this study. Moreover, our study suggests that a high GLR level may represent a poor liver function by exploring the correlation between GLR and clinical data. Most importantly, our study demonstrates, for the first time, the significance of the prognosis of GLR in HCC patients of various etiologies. Finally, multivariate Cox regression analysis proved GLR could predict OS and RFS outcomes in HCC patients undergoing complete ablation.

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. Some studies have found that the survival time of HCC patients with tumor size < 3 cm was significantly increased than other types of patients[34]. Our study found that the significance of the combination of GLR and tumor size on evaluating patient outcomes. By using combined indicators, patients will be divided into groups through preoperative evaluation. Patients, with higher recurrence risk and lower OS, should adjust the follow-up time to monitor the development of tumor and select appropriate treatment strategies, thus effectively prolonging the long-term survival of patients.

However, our study has some limitations. First of all, this was a retrospective, single-center study. Second, our sample size was limited. Therefore, it is necessary to validate these results by further large-scale multicenter randomized trials. 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 study of patients with HCC of various etiologies followed up to 8 years, we identified the prognostic value of GLR. As a cheap, readily available, non-invasive biomarker, the globulin/low-density lipoprotein ratio can predict the prognosis of HCC patients who underwent complete ablation.

Declarations

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Authors' contributions

Conceived and designed the protocol: W.W. and Z.Y.H; Collected data: Z.C.R and L.B.Y.; Analyzed data: Q.W.Y.; Wrote the manuscript: W.Q. and Q.W.Y.; Critically revised and approved the final version of manuscript: L.J.J and Y.C.W.; Treated and observed the patients: Z.T and G.D.D; All authors read and approved the final manuscript.

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Availability of data and materials

Data to support the study findings are available on request from the corresponding author.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Capital Medical University affiliated Beijing You'an Hospital (No.LL-2019-004-K)

Consent for publication

Not applicable.

Competing interests

The authors claim that they have no competing interests.

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Tables

Table 1 Demographic and clinicopathological data in HCC patients

Variables	Mean±SD/n(%)
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,≤30mm/＞30mm(%)	237(76.0%)/73(23.4%)
AFP,<7ng/mL/7-400ng/mL/≥400ng/mL(%)	131(42.0%)/162(51.9%)/16(5.1%)
Viral load,<100IU/mL/≥100IU/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
ApolipoproteinA1(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

Abbreviations: 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; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio.

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

variables	Univariate		Multivariate	
	HR(95%)	*P*-value	HR(95%)	*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,≤30mm/>30mm(%)	1.934（1.421-2.631）	**<0.001**	1.967(1.251-3.092)	**0.003**
AFP,<7ng/mL/7-400ng/mL/≥400ng/mL(%)	1.057（0.840-1.330）	0.637		
Viral load,<100IU/mL/≥100IU/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（1.001-1.006）	**0.003**		
ALP(U/L)	1.003（1.000-1.006）	**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		
ApolipoproteinA1(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**

Abbreviations: 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; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio.

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

variables	Univariate		Multivariate	
	HR(95%)	*P-value*	HR(95%)	*P-value*
Age (year sold)	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(≤30mm/>30mm)	1.671(1.086-2.571)	**0.02**	2.061(1.243-3.418)	**0.005**
AFP(<7ng/mL/7-400ng/mL/≥400ng/mL)	1.236(0.888-1.722)	0.21		
Viral load(<100IU/mL/≥100IU/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		
ApolipoproteinA1(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**

Abbreviations: 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; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio.

Table 4 The GLR-based comparison of baseline clinical data

Variables	Total	GLR<16.54	GLR≥16.54	*P-value*
		n=212	n=100	
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(≤30mm/>30mm)	237/73	157/53	80/20	0.31
AFP(<7ng/mL/7-400ng/mL/ ≥400ng/mL)	131/162/16	93/107/11	38/55/5	0.664
Viral load(<100IU/mL/≥100IU/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
ApolipoproteinA1(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

Abbreviations: 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; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HDL, high-density lipoprotein; GLR, the globulin to LDL ratio.

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

Rank	variable	The AUC values	95% CI	*P-value*
1	GLR	0.600	0.535-0.665	0.033
2	Globulin	0.585	0.516-0.653	0.035
3	LDL	0.416	0.348-0.483	0.034

Figures

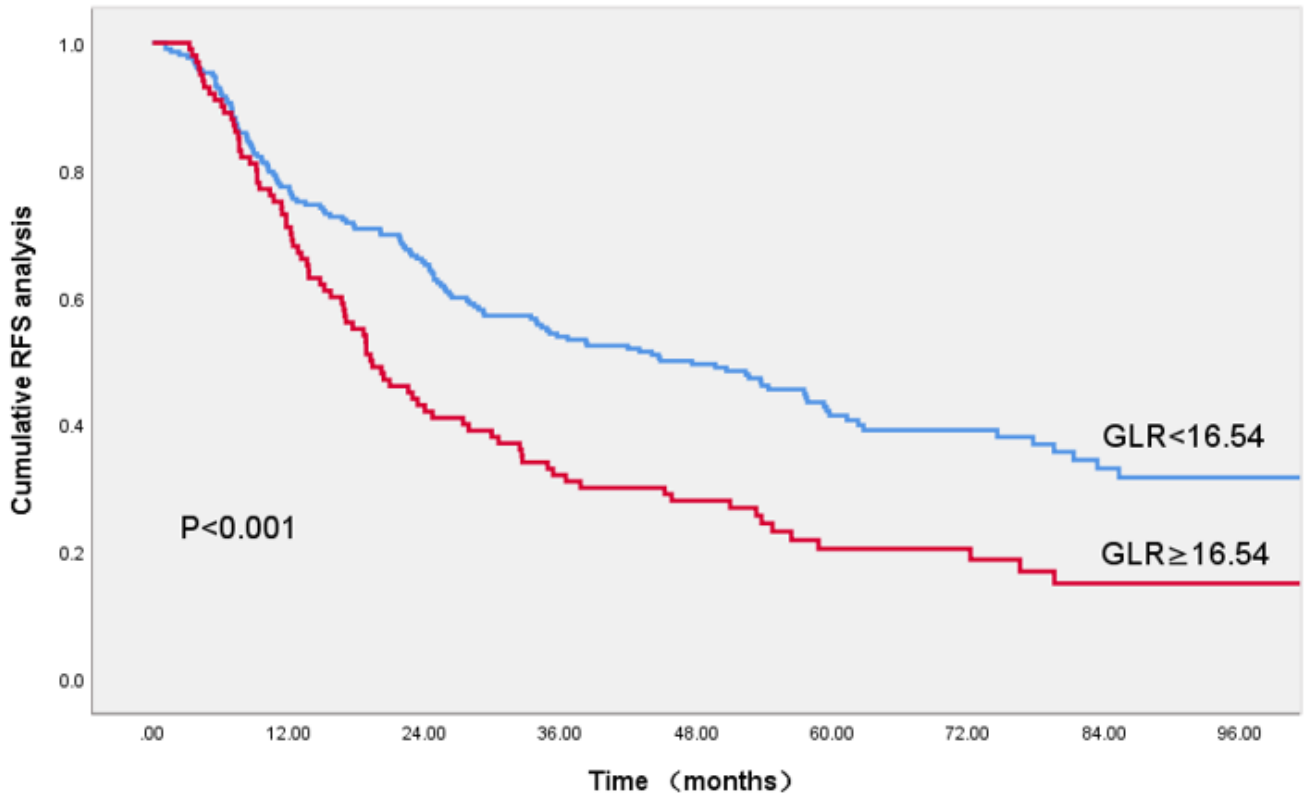

Figure 1

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

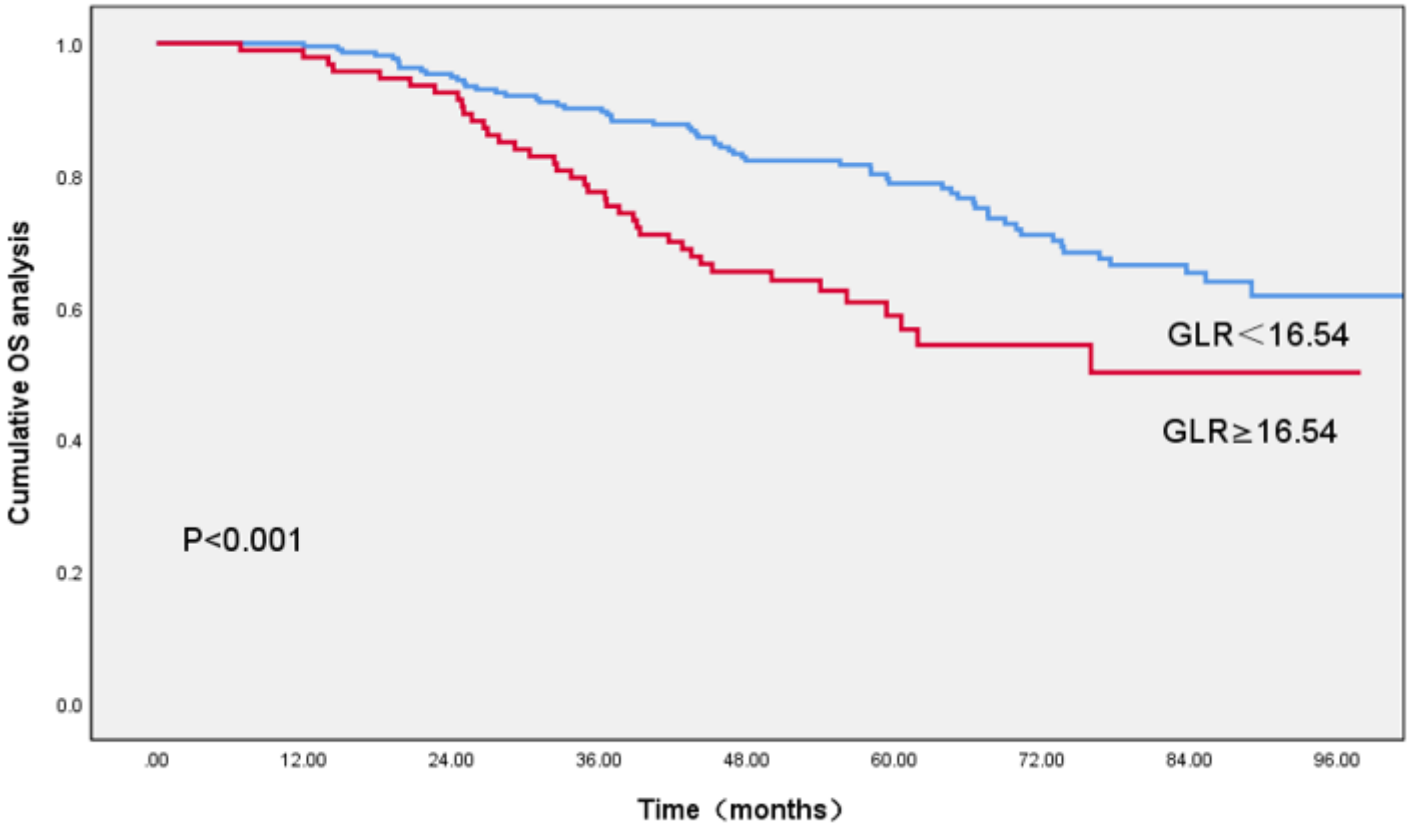

Figure 2

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

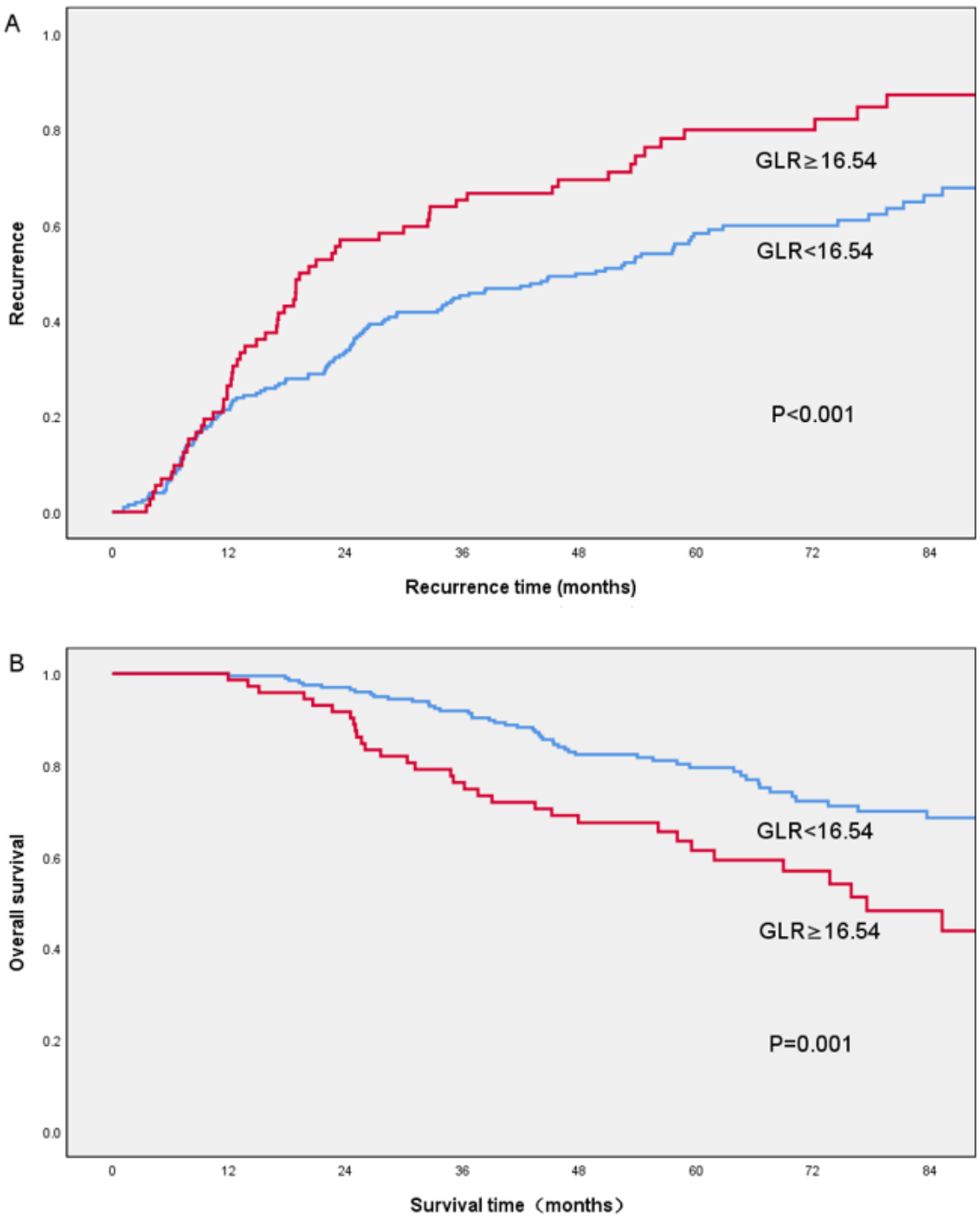

Figure 3

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. Abbreviations: OS, overall survival; GLR, the globulin to LDL ratio.

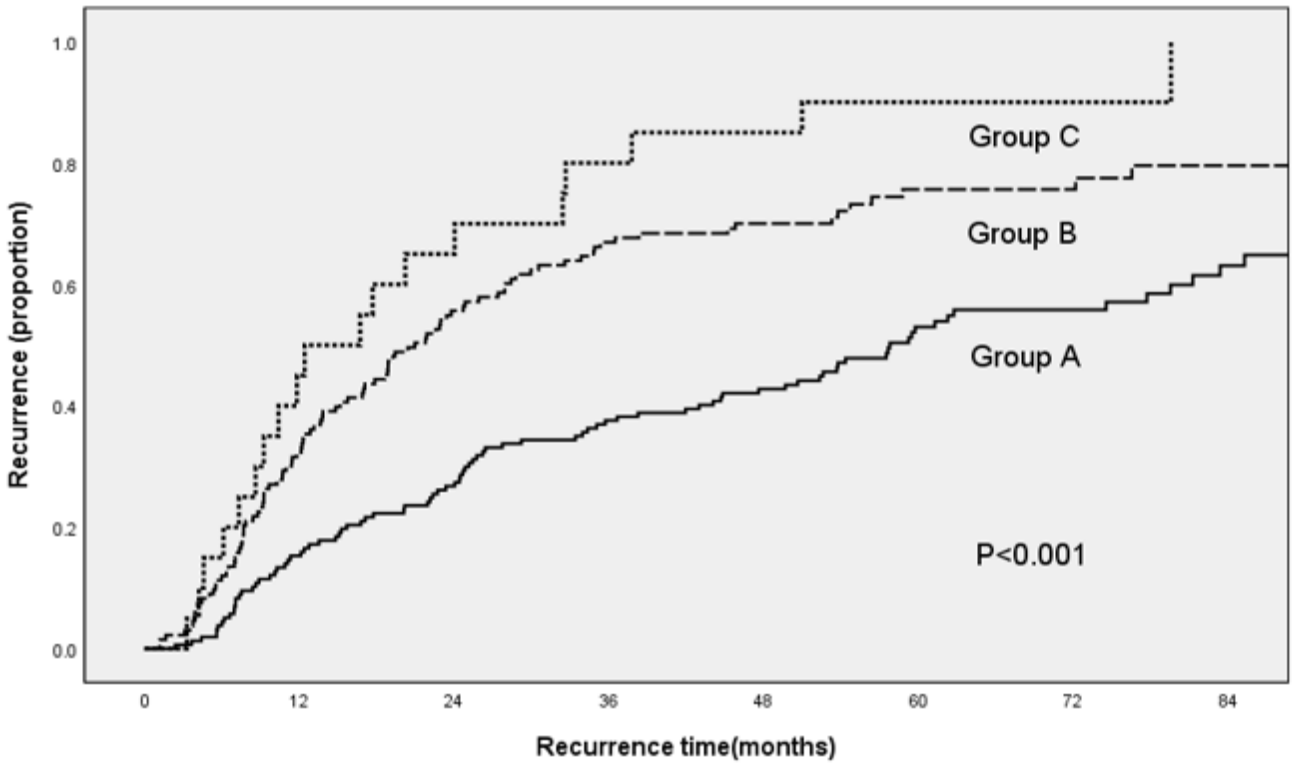

Figure 4

The Kaplan-Meier analysis of recurrence (A) of the subgroup study stratification of patients according to GLR and tumor size. Abbreviations: GLR, the globulin to LDL ratio.

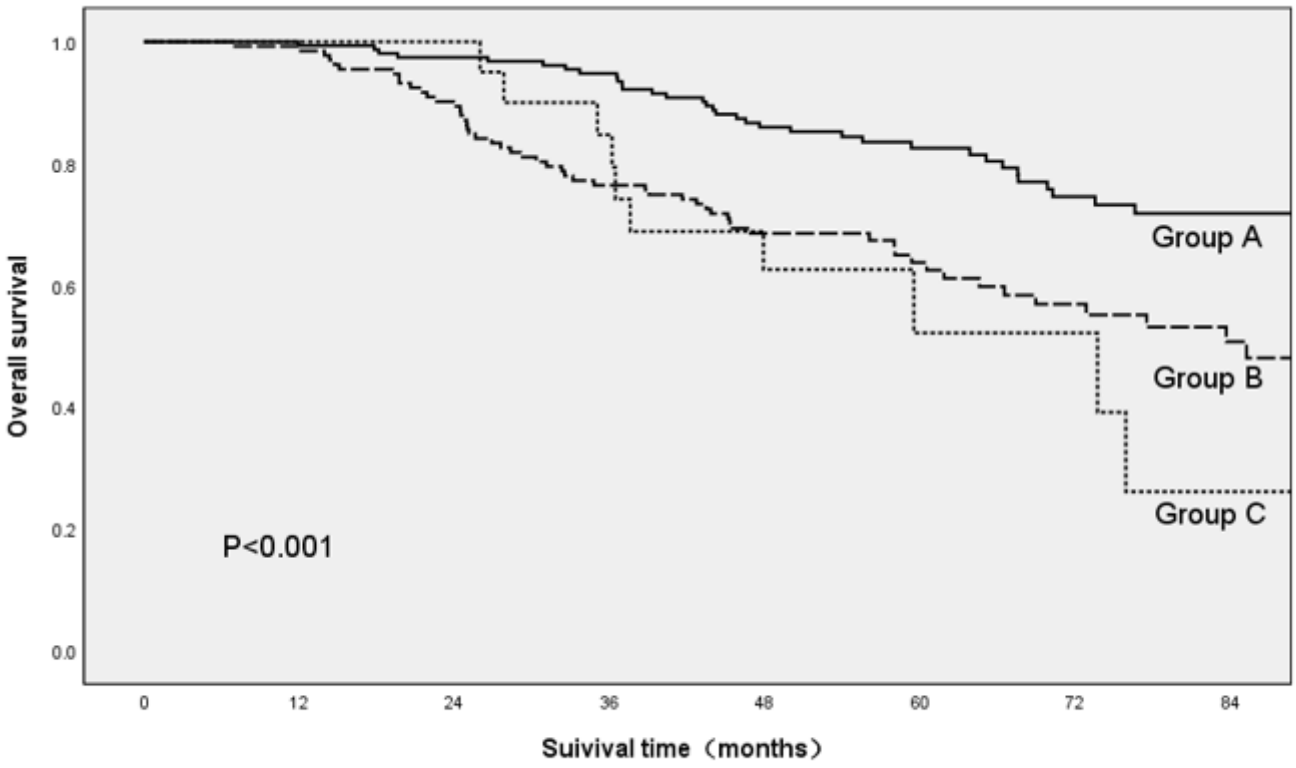

Figure 5

The Kaplan-Meier analysis of recurrence (A) of the subgroup study stratification of patients according to GLR and tumor size. Abbreviations: OS, overall survival; GLR, the globulin to LDL ratio.