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Original Article

Prognostic value of systemic inflammation response SIR parameters in unresectable hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignancies, with increasing incidence and dismal survival. Albumin, globulin, lactate dehydrogenase (LDH), and albumin to globulin ratios (AGR) have been identified as systemic inflammation response (SIR) parameters, correlated with tumor development and metastasis. The aim of this study was to investigate the predictive value of systemic inflammation-related parameters in unresectable hepatocellular carcinoma patients. A total of 101 HCC patients were recruited for this study. Patients had histologic or cytologic evidence of locally advanced stage or metastasis. Patients were divided into two groups, according to the median value of ALB, GLB, LDH, and AGR. Post-/pre-chemotherapeutic ratios were defined as the rate of pre-chemotherapeutic SIR parameters values and corresponding ones obtained after chemotherapy (≤ 1 indicates ALB, GLB, LDH, and AGR values were not increased after chemotherapy, while > 1 suggests increased ALB, GLB, LDH, and AGR values). Higher GLB levels are correlated with bone metastasis. Patients with lower baseline LDH levels had better overall survival (OS), whereas ALB, GLB, or AGR levels were not correlated with outcomes. Alterations in LDH levels were associated with therapeutic efficacy. Patients with non-increased LDH levels, following chemotherapy, exhibited improved responses, compared to those with increased LDH levels. Univariate analysis revealed that gender (female), high baseline LDH levels, and non-increased post-/pre-chemotherapy AGR ratios were risk factors affecting OS (overall survival) in patients with HCC. Multivariate analysis indicated that gender (female) and high baseline LDH levels were independent risk factors for HCC prognosis. The area under the curve of baseline LDH was 0.717 (95% CI 0.617-0.818; $P < 0.001$) and the optimum cutoff point of baseline LDH was 236.500 U/L, with a sensitivity of 73.0% and specificity of 64.6%. The current study shows that baseline LDH levels and changes in AGR levels, after chemotherapy, are correlated with outcomes of patients with HCC.

Keywords: Hepatocellular carcinoma, systemic inflammation response (SIR), prognosis

Introduction

With an estimated 42,220 new cases and 30,200 deaths, hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms. It ranks fourth among causes of cancer mortality in 2018 of United States [1]. Unfortunately, more than half of HCC patients are first diagnosed in the advanced stage, losing opportunities for surgical resection or liver transplantation [2]. To increase the survival rates of patients with unresectable HCC, alternative treatments, such as molecular targeted agents, immune therapy, and vaccines, have been widely applied in clinical treatment [3, 4]. However, disease relapse after therapy, as well as drug resistance, are critical issues giving rise to poor prognosis of HCC [5].

Systemic inflammation response (SIR) has been demonstrated to be closely correlated with outcomes of several types of cancer [6]. Coincidentally, HCC has been recognized as the best tumor model to investigate the interaction

of inflammatory response and malignancies, as a majority of HCC cases arise from chronic liver inflammation [7]. Albumin (ALB), the major component in serum protein, has been used as a predictor of malnutrition and systemic inflammation [8]. Globulin (GLB) serves as a carrier of hormones, playing an important role in inflammation [9]. Albumin to globulin ratio (AGR) represents both nutrition and inflammatory response [10]. ALB, GLB, and AGR have been used as prognostic indicators for patients with HCCs [11, 12]. Lactic dehydrogenase (LDH), a key enzyme catalyzing the conversion of pyruvate to lactate, plays a vital role in anaerobic metabolism of malignant cells, even under anaerobic conditions [13]. LDH has been demonstrated to be associated with HCC progression and prognosis [14].

The current study investigated several SIR parameters and evaluated whether these parameters could be beneficial for prognosis prediction in patients with unresectable HCC.

Materials and methods

Subjects and inclusion criteria

This study was conducted as a retrospective investigation of HCC patients that had been referred to the First Affiliated Hospital of Soochow University (Jiangsu, China), between Nov 2000 and Jul 2017. Approval for the study was granted by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University. Clinical and pathological records of all patients participating in the study were reviewed periodically.

A total of 101 HCC patients were recruited for this study. Patients had histologic or cytologic evidence of locally advanced or metastasis. Patient characteristics are detailed in **Table 1**. The median age of the 101 patients was 58 years (range, 28-83 years), while 81 patients were male and 20 were female. The median BMI (kg/m^2) of the 101 patients was 22.8 kg/m^2 (range, 18.2-31.8 kg/m^2) and 33 patients had bone metastasis. Prognostic analyses were performed regarding overall survival (OS).

Blood samples

Peripheral venous blood (5-7 mL) was collected into sterile ethylenediaminetetraacetic acid (EDTA) tubes. Blood samples were analyzed using a hematology analyzer (Sysmex XE-2100; Sysmex, Kobe, Japan) or biochemical analyzer (Olympus AU5421+ISE, Olympus, Japan). ALB, GLB, LDH, and AGR levels are recorded in **Table 1**. The patients were divided into two groups, according to the median values of ALB (low ALB, < 38.70 or high ALB, ≥ 38.70), GLB (low GLB, < 29.10 or high GLB, ≥ 29.10), LDH (low LDH, < 215.00 or high LDH, ≥ 215.00), and AGR (low AGR, < 1.29 or high AGR, ≥ 1.29). Post/pre-chemotherapeutic ratios are defined as the rate of pre-chemotherapeutic SIR-related indicator values and corresponding ones obtained after chemotherapy.

Evaluations

Computed tomography (CT) scans were performed for assessment of response, every 2 months, and evaluated according to the criteria of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Follow-ups

This study recorded responses to chemotherapy, including partial response (PR), stable disease (SD), and progressive disease (PD). After first line chemotherapy, disease progression was defined as a lack of response to chemotherapy. In contrast, stable disease or partial response after chemotherapy was defined as a response to chemotherapy. Survival time was measured from the date of chemotherapy until death or last clinical evaluation. Prognostic analyses were performed regarding overall survival (OS). OS was defined as the time from diagnosis date to death from any cause.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (Chicago, USA). Association between blood parameter status and clinic pathologic features or chemotherapeutic efficacy was explored and assessed using χ^2 tests. For analysis of survival data, Kaplan-Meier curves were constructed. Statistical analysis was carried out using the log-rank test. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of SIR-related indicators for HCC and to determine the best cutoff value of SIR-related indicators. Multivariate logistic regression was employed

Table 1. Clinicopathologic features

Clinicopathologic features	n	ALB				GLB				LDH				AGR			
		Low (n)	High (n)	χ^2	*P* value	Low (n)	High (n)	χ^2	*P* value	Low (n)	High (n)	χ^2	*P* value	Low (n)	High (n)	χ^2	*P* value
Gender	101																
Male	81	42	39	0.033	0.856	38	43	1.099	0.295	41	40	0.002	0.961	41	40	0.002	0.961
Female	20	9	11			12	8			10	10			10	10		
Age (years)																	
≤ 58	52	25	27	0.251	0.617	30	22	2.874	0.090	29	23	1.193	0.275	22	30	2.539	0.111
> 58	49	26	23			20	29			22	27			29	20		
BMI (kg/m^2)																	
≤ 22.8	29	12	17	0.010	0.919	15	14	< 0.001	0.976	19	10	1.365	0.243	14	15	0.288	0.592
> 22.8	72	29	43			37	35			38	34			39	33		
Bone metastasis																	
Yes	33	18	15	2.525	0.112	10	23	5.829	0.016*	16	17	1.603	0.206	15	18	0.498	0.480
No	68	48	20			38	30			42	26			36	32		

*: $P < 0.05$.

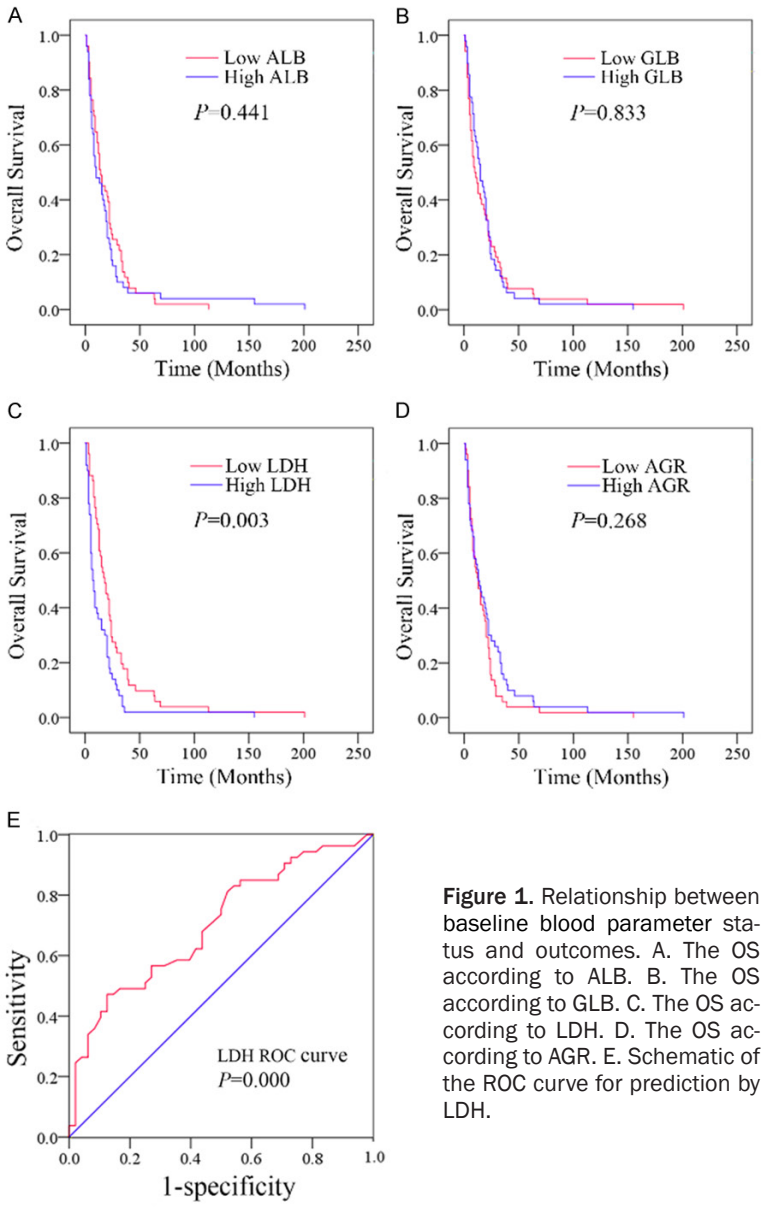

Figure 1. Relationship between baseline blood parameter status and outcomes. A. The OS according to ALB. B. The OS according to GLB. C. The OS according to LDH. D. The OS according to AGR. E. Schematic of the ROC curve for prediction by LDH.

to identify independent risk factors associated with HCC. Values of $P < 0.05$ indicate statistical significance.

Results

Baseline LDH levels correlated with outcomes of HCC patients

Kaplan-Meier plots were used to determine the effects of baseline ALB, GLB, LDH, and AGR status on OS (**Figure 1A-D**). The patients were divided into two groups, according to the median values of ALB, GLB, LDH, or AGR. The median OS of the higher ALB group was 14 (95% confidence interval [CI] 8.002-19.998) months, while that of the lower ALB group was 10 (95% CI 3.076-16.924) months (P = 0.441). The median OS of the higher GLB group was 15 (95% CI 9.522-20.478) months, while that of the lower GLB group was 10 (95% CI 4.952-15.048) months (P = 0.898). The median OS of the higher LDH group was 7 (95% CI 4.229-9.772) months, while that of the lower LDH group was 18 (95% CI 11.877-24.123) months (P = 0.003). The median OS of the higher AGR group was 13 (95% CI 7.225-18.775) months, while that of the lower AGR group was 13 (95% CI 8.342-17.658) months (P = 0.268). Therefore, patients with lower baseline LDH levels showed a better prognosis. However, baseline levels of GLB, LDH, or AGR showed no effects on OS.

ROC curve analysis was then performed to evaluate the predictive value of baseline LDH for HCC and to determine the best cutoff value. As shown in **Figure 1E**, the area under the curve of baseline LDH was 0.717 (95% CI 0.617-0.818; $P < 0.001$) and the optimum cut-off point of baseline LDH was 236.500 U/L, with a sensitivity of 73.0% and specificity of 64.6%.

Changes in LDH levels, after chemotherapy, associated with chemotherapeutic efficacy in HCC patients

To determine the association between changes in ALB, GLB, LDH, or AGR status and chemotherapeutic efficacy, blood samples were obtained and CT evaluations were performed, simultaneously, after first-line chemotherapy for 2 mouths. Relationships between changes

Table 2. Relationship between changes in the blood parameter status and chemotherapeutic efficacy

	Post-/pre-chemotherapy ratio	PR+SD (n = 38)	PD (n = 63)	χ^2	*P* value
ALB	≤ 1 (n = 54)	19	35	0.294	0.588
	> 1 (n = 47)	19	28		
GLB	≤ 1 (n = 41)	18	23	1.159	0.282
	> 1 (n = 60)	20	40		
LDH	≤ 1 (n = 44)	22	22	5.089	0.024*
	> 1 (n = 57)	16	41		
AGR	≤ 1 (n = 59)	21	38	0.249	0.618
	> 1 (n = 42)	17	25		

*: $P < 0.05$.

in blood parameter levels after chemotherapy and chemotherapeutic efficacy are presented in **Table 2**, respectively.

A total of 54 patients had non-increased ALB levels, following chemotherapy, of which 19 patients were PR (partial response) or SD (stable disease) and 35 patients were PD (progressive disease). A total of 47 patients had increased ALB levels, following chemotherapy, of which 19 patients were PR or SD and 28 patients were PD ($P = 0.588$).

A total of 41 patients had non-increased GLB levels, following chemotherapy, of which 18 patients were PR or SD and 23 patients were PD. Moreover, 60 patients had increased GLB levels, following chemotherapy, of which 20 patients were PR or SD and 40 patients were PD ($P = 0.282$).

A total of 44 patients had non-increased LDH levels, following chemotherapy, of which 22 patients were PR or SD and 22 patients were PD. A total of 57 patients had increased LDH levels, following chemotherapy, of which 16 patients were PR or SD and 41 patients were PD ($P = 0.024$).

A total of 42 patients had non-increased AGR levels, following chemotherapy, of which 17 patients were PR or SD and 25 patients were PD. A total of 59 patients had increased AGR levels, following chemotherapy, of which 21 patients were PR or SD and 38 patients were PD ($P = 0.618$).

Thus, changes in LDH levels, after chemotherapy, were associated with chemotherapeutic efficacy of HCC patients. However, ALB, GLB, or AGR had no significant effects on chemotherapeutic efficacy.

Changes in AGR levels, after chemotherapy, correlated with outcomes of HCC patients

Kaplan-Meier plots were used to determine the effects of individual changes of ALB, GLB, LDH, and AGR status on OS (**Figure 2A-D**). The median OS of patients with increased ALB levels, following chemotherapy, was 18 (95% CI 12.253-23.747) months, while that of the non-increased group was 9 (95% CI 5.399-12.601) months ($P = 0.061$). The median OS of patients with increased GLB levels, following chemotherapy, was 10 (95% CI 5.662-14.338) months, while that of the non-increased group was 16 (95% CI 9.727-22.273) months ($P = 0.954$). The median OS of patients with increased LDH levels, following chemotherapy, was 11 (95% CI 7.301-14.699) months, while that of the non-increased group was 18 (95% CI 12.312-23.688) months ($P = 0.288$). The median OS of patients with increased AGR levels, following chemotherapy, was 21 (95% CI 16.463-25.537) months, while that of the non-increased group was 8 (95% CI 6.118-9.882) months ($P = 0.025$). Thus, patients with increased AGR levels, after chemotherapy, had increased survival rates. However, changes in GLB, LDH, or AGR levels had no effect on OS.

Prognostic factors for HCC

Univariate analyses demonstrated that gender (female) (hazard ratio [HR] 1.759; 95% CI 1.054-2.934; $P = 0.031$), high baseline LDH levels (HR 1.796; 95% CI 1.204-2.680; $P = 0.004$), and a decreased post-/pre-chemotherapeutic AGR ratio (HR 1.562; 95% CI 1.043-2.338; $P = 0.030$) were significant risk factors for a poor prognosis (**Table 3**). According to multivariate analysis, gender (female) (HR 1.704; 95% CI 1.021-2.841; $P = 0.041$) and high baseline LDH levels ratios (HR 1.638; 95% CI 1.085-2.471; $P = 0.019$) were found to be independently associated with poor survival.

Discussion

HCC has been well accepted as the best tumor type to study the interaction of inflammatory

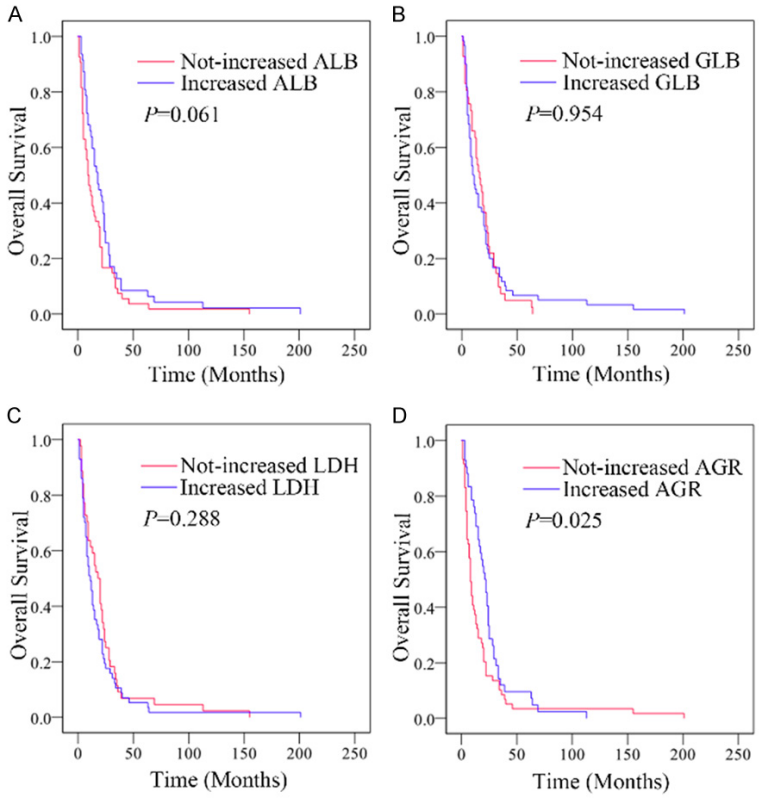

Figure 2. Relationship between changes in blood parameter status after chemotherapy and outcomes. A. The OS according to changes in ALB. B. The OS according to changes in GLB. C. The OS according to changes in LDH. D. The OS according to changes in AGR.

response and malignancies because of chronic liver inflammation, especially hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, leading to a majority of HCC occurrence [7, 15, 16]. Possible mechanisms involved in SIR-induced carcinogenesis are listed as follows. First, as a major etiology for HCC, HBV infections may contribute to fibrosis and cirrhosis, a preneoplastic condition for HCC [17]. Moreover, prophylactic HBV vaccinations have already been proven to prevent the development of hepatomas in children and young adults [18]. Second, SIR may lead to oxidative stress and release of oxygen-free radicals, which provokes DNA damage, epigenetic modifications, and telomerase reactivation [19]. Third, inflammatory cytokines, such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α (TNF-α), have been proven to be vital lynchpins in inflammation-mediated carcinogenesis. Activation of phosphoinositide 3-kinase-protein kinase B (PI3K-Akt) pathways by inflammatory cytokines may induce cell proliferation, malignant survival, angiogenesis, and metastasis [20]. Considering that SIR is tightly associated with tumor progression and outcomes, nu-merous studies have obtained an in-depth look at the role systemic inflammation plays in cancer progression and outcome prediction. Thus, for a more accurate and comprehensive prognostic analysis of HCC, the current study investigated the predictive value of ALB, GLB, LDH, and AGR in patients with HCC.

ALB, one of the major components of plasma proteins, is synthesized in the liver and mirrors individual nutrition status, chronic inflammatory response, disease regression, and prognosis [21-23]. Weight loss, chronic malnutrition status, and cachexia have been recognized as typical characteristics of patients suffering from malignant tumors, notably manifesting as a lower serum ALB level and increased tumor mortality [24]. Since serum ALB levels reflect not only nutrition status but also chronic inflammation, recent studies have revealed that a higher serum ALB level is a favorable prognostic predictor in several types of malignant tumors [25]. However, few studies have shown ALB alone as a significant prognostic indicator in patients with advanced HCC. In view of the role ALB plays in biological metabolism and chronic inflammation, this study suggests ALB as a promising prognosis predictor for advanced HCC. Possible mechanisms are listed as follows. First, as a major protein synthesized by hepatocytes, levels of serum ALB partially reflect the proportion of normal hepatocytes and their metabolic activity. Thus, in advanced HCC, a sharpened decrease of serum ALB levels may indicate a decrease in the quantity of normal hepatocytes, suggesting an exhausting status and malignant progression. Second, ALB has been demonstrated to play a crucial anticancer role by stabilizing cell growth and DNA replication, as well as maintaining

Table 3. Univariate and multivariate logistic regression analysis of HCC risk factors

Risk Factors	Overall Survival (OS)			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender (Female or Male)	1.759 (1.054-2.934)	0.031*	1.704 (1.021-2.841)	0.041*
Age (> 58 years or ≤ 58 years)	0.815 (0.547-1.214)	0.314	-	-
BMI (> 22.8 kg/m^2 or ≤ 22.8 kg/m^2)	0.717 (0.462-1.115)	0.140	-	-
Bone metastasis (Yes or No)	1.049 (0.689-1.598)	0.824	-	-
Baseline ALB (> 38.700 g/L or ≤ 38.700 g/L)	0.859 (0.577-1.278)	0.454	-	-
Baseline GLB (> 29.100 g/L or ≤ 29.100 g/L)	0.975 (0.658-1.446)	0.901	-	-
Baseline LDH (> 215.000 U/L or ≤ 215.000 U/L)	1.796 (1.204-2.680)	0.004**	1.638 (1.085-2.471)	0.019*
Baseline AGR (> 1.290 or ≤ 1.290)	0.804 (0.540-1.196)	0.282	-	-
Post-/pre-chemotherapeutic ALB ratio (> 1 or ≤ 1)	0.693 (0.467-1.029)	0.069	-	-
Post-/pre-chemotherapeutic GLB ratio (> 1 or ≤ 1)	0.988 (0.659-1.483)	0.955	-	-
Post-/pre-chemotherapeutic LDH ratio (> 1 or ≤ 1)	1.233 (0.829-1.835)	0.301	-	-
Post-/pre-chemotherapeutic AGR ratio (≤ 1 or > 1)	1.562 (1.043-2.338)	0.030*	1.376 (0.907-2.087)	0.133

*: $P < 0.05$; **: $P < 0.01$.

homeostasis of sex hormones to protect against sex hormone-induced cancers [26, 27]. Moreover, in patients with HCC, a lower recurrence rate and better OS has been proven to be tightly correlated with higher serum ALB levels [28, 29]. Thus, increased ALB levels might lead to relieved tumor loads, improved nutrition status, and recovery of liver function, suggesting a better prognosis in HCC. However, in the present study, post-/pre-chemotherapy ALB ratio had no effect on OS. It was speculated that serum ALB levels could be influenced by multiple factors, such as infection, exogenous infusion, underlying liver disease, and other accompanied chronic diseases.

Serum GLB contains acute-phase proteins, such as immunoglobulins, C-reactive protein (CRP), and complements C3 [30]. As a representative SIR parameter, GLB arises in response to various pro-inflammatory cytokines and chemokines, particularly IL-6, IL-1β, and TNF-α [31, 32]. Therefore, as a parameter which partly mirrors the intensity of SIR, high serum GLB levels have been demonstrated to be significantly associated with tumor angiogenesis and recurrence in patients with malignant tumors [31, 33]. Actually, previous studies have revealed that an increased serum GLB level significantly contributes to poor prognosis in several types of malignant tumors [9, 30, 34, 35]. Unfortunately, previous studies have focusing on the prognostic value of GLB in patients with advanced HCC are scarce. Considering serum GLB levels reflect the inflammatory status, it is reasonable to classify low GLB levels as a favorable prognostic indicator in advanced HCC. In the present study, higher GLB levels were correlated with more possible bone metastasis. However, neither baseline GLB levels nor post-/pre-chemotherapy GLB ratios were correlated with OS in advanced HCC.

AGR, calculated as the ratio of serum ALB and GLB, has been reported to be an independent and significant predictor of long-term mortality in several types of cancer, including HCC [12, 36-38]. The mechanisms by which low serum AGR values impact recurrence and survival have not been fully elucidated. However, favorable prognosis with a high AGR value can partly explained by the functions of ALB and GLB. Since HCC has been regarded as a typical malignant tumor derived from chronic inflammation, both increased ALB levels and decreased serum GLB levels indicate low intensity of SIR, suggesting a higher AGR value and better OS. The present study observed a significant improvement of OS in patients with increased AGR values after first-line chemotherapy. Additionally, non-increased post-/pre-chemotherapy AGR ratios have been proven to be a risk factor affecting OS of unresectable HCC by univariate analysis. This study defined AGR as a prognostic indicator in unresectable HCC for the first time. Considering that AGR is

the combination of ALB and GLB, this study suggests that it could be less affected by conditions like dehydration and fluid retention, further enhancing its predictive value.

Unlike normal cells, the phenomenon by which malignant cells preferentially conduct anaerobic glycolysis to produce most of the energy instead of mitochondrial oxidative phosphorylation, even in the presence of oxygen, has been widely accepted as the Warburg effect [39, 40]. LDH, a key enzyme that plays a crucial role in anaerobic glycolysis, is an indicator for tumor hypoxia, neo-angiogenesis, and worse prognosis in several types of malignant tumors, including HCC [41-43]. The mechanisms of high serum LDH levels and poor prognosis involve the following respects. First, malignant cells manifest a high rate of glucose uptake and lactate production, presenting a hypermetabolic status and a high serum LDH level [44]. Second, hypoxia, a prominent characteristic of solid tumors, facilitates the process of anaerobic glycolysis and promotes cancer proliferation [45]. Third, hypoxia-mediated hypoxia inducible factor (HIF) has been demonstrated to upregulate LDH activity, as well as further activation of vascular endothelial growth factors (VEGFs) and promotion of tumor angiogenesis [46, 47]. Thus, high serum LDH levels mirror a hypermetabolic status, suggesting a high proliferation rate and aggressiveness of malignant tumors. Few studies have obtained an in-depth study of the predictive value of LDH in advanced HCC. For instance, in the retrospective study of Scartozzi M et al., patients with a low pre-treatment LDH level (< 450 U/L) had better OS, compared with those with a pre-treatment LDH level above 450 U/L. Patients with a decreased LDH value after transarterial-chemoembolization (TACE) exhibited better OS, compared with those with an increased LDH level [43].

In the present study, patients with non-increased LDH levels, following first-line chemotherapy, exhibited improved responses, compared to those with increased LDH levels. Multivariate analysis revealed that a high baseline LDH level was an independent risk factor affecting OS in patients with advanced HCC. ROC curve analysis showed that pre-treatment LDH values of 236.50 U/L were considered to be the optimal cutoff value for prognosis, with a sensitivity of 73.0% and specificity of 64.6%. In summary, since LDH is an inexpensive and convenient parameter routinely detected in clinical laboratories, this study suggests low pre-treatment LDH as a favorable predictive parameter for HCC prognosis. Additionally, given the correlation between LDH and tumor angiogenesis, serum LDH levels may be used to screen out patients suitable for anti-VEGF inhibitor treatment.

In conclusion, the current study investigated the predictive value of ALB, GLB, AGR, and LDH, demonstrating that gender (female), pre-treatment LDH levels, and post-/pre-chemotherapy AGR ratios are closely correlated with outcomes of unresectable HCC patients. Moreover, this study defined high pre-treatment LDH levels as an independent risk factor affecting OS of patients with unresectable HCC. Considering the high rates of HBV infection and HCC morbidity in china, these non-invasive, inexpensive, and convenient parameters may be beneficial to treatment of HCC. However, the current study had some limitations, including insufficient samples, data coming from a single center, and the retrospective design.

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Disclosure of conflict of interest

None.

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