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Serum Inflammation parameters and survival in hepatocellular carcinoma patients: importance of albumin and gamma-glutamyltranspeptidase

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Abstract

Introduction—Many single and combination blood tests that reflect local or systemic inflammation have been shown to be useful prognosticators in patients with a variety of tumor types.

To try to clarify this issue in patients with non-surgically treatable hepatocellular carcinoma, multiple serum parameters were evaluated for their relationship to survival.

Methods—A prospectively collected database was interrogated of 487 patients with known hepatocellular carcinoma and documented survival and having all the inflammation parameters of interest in this study, together with baseline tumor characteristics from CT scans. Serum parameters included NLR, PLR, CRP, ESR, albumin and GGT.

Results—All the parameters had significant Hazard Ratios on Cox regression model. Combination double parameters with Hazard Ratios >2.0 were: ESR plus GGT, albumin plus GGT, albumin plus ESR. The triplet combination of albumin plus GGT plus ESR had a Hazard Ratio of 6.33. Using Harrell's concordance index (C-index), the highest inflammation-based 2-parameter prognostic score was for albumin plus GGT.

When clinical characteristics of patients with high values for albumin plus low values for GGT were compared to low values for albumin plus high values for GGT (worse prognosis), statistically significant differences were found for tumor size, tumor focality, macroscopic portal vein invasion and serum alpha-fetoprotein levels. Addition of ESR did not provide additional tumor information.

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Author Contributions: Brian I Carr- concept, ideas and writing; Vito Gerra -biostatistics and paper proof reading.

Statement of Ethics: This work complies with the guidelines of the World Medical Association, Declaration of Helsinki. This work was approved by our institution's IRB as documented in the methods section. Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki and the need for approval for this retrospective study on de-identified and deceased HCC patients was waived by our Inonu University Institutional Ethics Committee (approval #2021/2572). Written informed consent was not required for these deceased patients, in accordance with local guidelines. This work has been reported in line with the STROCSS criteria. The clinicaltrials.gov registration number was: NCT04477720.

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Conclusion—The combination of serum albumin plus GGT levels was the most prognostically useful amongst the inflammation parameters that were tested, and reflected significant differences in tumor aggressiveness characteristics.

Keywords

HCC; survival; GGT; albumin; ESR

Introduction

The idea that chronic inflammation might be an important mechanistic aspect of the development of some cancers, was first proposed one and a half centuries ago [1] and was subsequently shown to involve the tumor microenvironment [2]. Hepatocellular carcinoma (HCC) most commonly develops on the basis of several chronic inflammatory diseases, included hepatitis B and C (HBV, HCV), non-alcoholic steatohepatitis (NASH) and chronic alcoholism [3]. Several commonly-used markers of inflammation have been used in the management of of various cancers including HCC in clinical practice, as indices of prognosis and even tumor aggressiveness [4, 5]. They include C-reactive protein (CRP), albumin, the combination of CRP and albumin (Glasgow Index), erythrocyte sedimentation rate (ESR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), as well as several indices of liver inflammation and damage, that include serum AST, ALT and GGT levels [6–13].

In order to assess their relative usefulness for HCC prognosis in clinical practice, a comparison was made between these inflammation markers. We found that the combination of serum albumin plus GGT levels was the most prognostically useful and also reflected tumor aggressiveness.

Clinical Methods

A database containing 487 adult (ages 28–88) non transplant institutional Turkish HCC patients was examined. They had both survival data and baseline tumor parameter data from CT scans on maximum tumor diameter (MTD), number of tumor nodules and presence or absence of macroscopic portal vein thrombosis (PVT); as well as baseline serum alpha-fetoprotein (AFP) levels, complete blood counts with differential white counts and platelet levels and routine serum liver function tests. Diagnosis was made either via tumor biopsy or according to AASLD/EASL guidelines. Almost all patients were Child Pugh class A or B and received locoregional therapy, bar the few who were class C, who received only best supportive care.

Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki and approval for this retrospective study on de-identified and deceased HCC patients. This work was thus approved for a waiver by the Institutional Ethics Committee. This work has been reported in line with the STROCSS criteria [35].

The clinicaltrials.gov registration number was: NCT04477720.

Statistical analysis

Patient parameters were reported as Mean ±Standard Deviation (M±SD) for continuous variables, and as frequencies and percentages (%) for categorical variables.

Normal distributions of quantitative variables were tested using the Kolmogorov-Smirnov test.

For testing the associations among groups, the Chi-square test for categorical variables was used and when the variables were not distributed normally, the Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables.

For studying the time between entry to a study and a subsequent event, the non-parametric Kaplan–Meier method was used to explore survival probability.

The log-rank test was applied to evaluate the equality of survival among categories.

The Cox model is a statistical technique for exploring the relationship between the survival of a patient and singular or several explanatory variables, it allows us to estimate the hazard risk (HR) of survival for an individual, given their prognostic variables (measured as continuous or categorical), was used. The Cox proportional hazard model was fitted to the data, and the proportional hazard assumption was evaluated by means of Schoenfeld residuals (SRT).

Model fitting was evaluated by means of Akaike Information Criteria (AIC) and Bayesian information criterion (BIC) [14].

Risk estimators was expressed as Hazard Ratios (HR) and 95% Confidence Interval (95% CI). Multicollinearity among parameters was assessed using the variance inflation factor (VIF), with a score of 2 leading to the exclusion of a variable.

For the final most parsimonious multiple Cox proportional hazard model, we used the stepwise method in backward and the factors significantly associated with disease's progression, (z test of the coefficients of the multiple regression statistically significant at p-value<0.10), was left in the model.

The concordance index (C-Index) was used to measure how well the parameter is a predictor of the time to an event in a survival model, so the observation with the higher survival time has the higher probability of survival predicted by the model.

The high values of C-index mean (≥ 0.50) that the model predicts higher probabilities of survival for higher observed survival times.

When testing the null hypothesis of no association, the two-tailed probability level of error was 0.05. All the statistical computations were made using STATA, StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

Results

Single inflammation parameters in relation to survival.

Commonly used indices and parameters of clinical inflammation were examined for their relationship to survival, using a Cox regression analysis on the single parameters (Table 1A). The hazard ratios (HRs) were different for differing parameters that were considered, but all were statistically significant. The highest HRs were for albumin, GGT, ESR and CRP, being 2.31, 2.02, 1.83 and 1.46, respectively.

In a final multiple Cox regression model in all the patients on all of the single parameters together in the model, using the stepwise backward method, the highest HRs were for albumin, CRP and GGT, being 2.28, 1.83 and 1.56, respectively (Table 1B).

Combinations of inflammation parameters in relation to survival.

A Cox regression model on combinations of parameters in the model was then calculated (Table 2). All abnormal values of the combinations had significantly higher HRs when compared to normal values, with highest HRs being for the combinations of ESR (> 15 mm/hr) & GGT (> 100 IU/mL), HR 3.03; Albumin (≤ 3.5 g/dL) & GGT (> 100 IU/mL), HR 3.98 and Albumin (≤ 3.5 g/dL) & ESR (> 15 mm/hr), HR 4.03. A triplicate of Albumin (≤ 3.5 g/dL) and GGT (> 100 IU/mL) and ESR (> 15 mm/hr) compared to the triplicate of Albumin (> 3.5 g/dL) and GGT (≤ 100 IU/mL) and ESR (≤ 15 mm/hr) and had an HR of 6.33 (bottom group in Table 2).

C-index for concordance for ordering survival times.

Predictive scores regarding survival were next investigated by Harrell's concordance index (C-index), shown in Table 3. The C-index is the proportion of observations that the model can correctly order for survival times. Thus, values near 1 indicate that the risk scores are good at predictors, in this case, of survival. The combination of serum albumin and GGT values had the highest C-index of 0.64 and therefore in these comparisons had the best predictive value for survival amongst the combinations that were tested.

Clinical and tumor characteristics and survival in relation to combination GGT plus albumin parameters.

The clinical and tumor parameters were then examined for patients having Albumin (> 3.5 g/dL) and GGT (≤ 100 IU/mL) versus patients with Albumin (≤ 3.5 g/dL) and GGT (> 100 IU/mL) (Table 4A). Patients in the Albumin (≤ 3.5 g/dL) and GGT (> 100 IU/mL) group had significantly worse tumor parameters in every category measured, including MTD, tumor focality, AFP levels and percent of patients with PVT, when compared to the Albumin (≤ 3.5 g/dL) and GGT (> 100 IU/mL) group. The laboratory values were also significantly different for every parameter except blood platelet levels. The addition of ESR values to those for Albumin and GGT was also examined (Table 4B), and the tumor parameters were also significantly different between the 2 groups, but the findings were quite similar to those found for only Albumin and GGT levels, as seen in Table 4A.

A Kaplan-Meier Survival plot was then constructed for three 2-parameter combinations and the 3-parameter combination (Fig 1) and shows the superior and very similar survival discrimination both for GGT and albumin combination, and ESR plus albumin combination, as well as for GGT and albumin and ESR combination. These are reflected in the hazard rations in Table 2. All combinations in Fig 1 contained albumin. This is a recognized important HCC prognostic factor (Glasgow Index of albumin plus CRP). There is considerable variation in the good prognosis groups with high serum albumin levels, but the patients with low serum albumin levels all had survivals of 5, 6 or 7 months, which were very similar.

Discussion

The main findings of this comparative study, involving the inflammation markers NLR, PLR, CRP, ESR, GGT and Albumin are that while all had significant hazard ratios on Cox Regression model for survival, the highest were for GGT and albumin. The single parameters were combined and hazard ratios were highest for GGT and albumin, as well as for ESR and albumin, with an even greater hazard ration for the combination of all 3 parameters (Table 2). This was confirmed by the C-index analysis (Table 3), in which we found C-index scores of 0.64 for GGT and albumin, 0.61 for CRP and albumin, and 0.60 for combination ESR and albumin (Table 3). It was found that this could be explained in part by our finding that low albumin plus high GGT was associated with significantly worse tumor factors (MTD, number of tumor foci, PVT and AFP levels) than the opposite combination of high albumin plus low GGT levels (Table 4). Although the triple parameter combination of GGT plus albumin pus ESR showed the highest hazard ratio in Table 3, there was no increased discriminant power for tumor characteristics using 3 parameters versus 2 parameters (Table 4).

The tumor inflammatory microenvironment appears to be a bidirectional process, in which the tumor produces inflammatory cytokines, and the bodily responds to the presence of the tumor by mounting an immune inflammatory attack [15, 16]. Many effector chemokines and cytokines have been described as being involved, resulting in an enhancement of tumor growth and invasiveness. Amongst its several physiological functions in the blood, serum albumin levels have been well-described as an inflammation marker and a prognostic marker in HCC [17–30] and albumin may actively participate in HCC growth control mechanisms [12, 13, 27, 31], possibly through its ability to bind reactive oxygen species and so modulate inflammation [32, 33].

GGT has been increasingly recognized and diagnostically useful for liver inflammation, risk of HCC development and for prognosis of patients with an HCC diagnosis [34–45]. It is especially useful as a biomarker for HCC patients with low AFP levels [46]. It is a membrane-bound enzyme involved in the metabolism of the thiol antioxidant glutathione, by transferring γ-glutamyl groups and can protect cells from oxidant damage by neutralizing reactive oxygen species [47] and might thus confer a survival and a growth advantage on HCC cells [48, 49].

These 2 clinical chemistry parameters thus have multiple functions in addition to being inflammation markers. Although other parameter combinations were also prognostically useful, GGT plus albumin provided greatest survival discrimination. Furthermore, they also predicted significantly greater discrimination in all 4 measures of tumor aggressiveness that were measured here, namely, MTD, PVT, AFP and multifocality, thus providing a reasonable explanation for their prognostic usefulness.

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Data Availability Statement:

The data are available on request to the authors, as they are not publicly available on legal grounds. However, all analyzed data were included in the article. Any further enquiries should be directed to the corresponding author.

Abbreviations:

HCC	hepatocellular carcinoma
WBC	White blood count
T.Bil	Total bilirubin
AST	Aspartate amino transferase
ALT	Alanine aminotransferase
ALKP	Alkaline phosphatase
GGT	Gamma glutamyl transferase
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
NLR	neutrophil to lymphocyte ratio
PLR	platelet count to lymphocyte ratio
CT	computed axial tomography
HR	hazard ratio
se (HR)	standard error of HR
C-index	Harrell’s concordance index
AFP	alpha-fetoprotein

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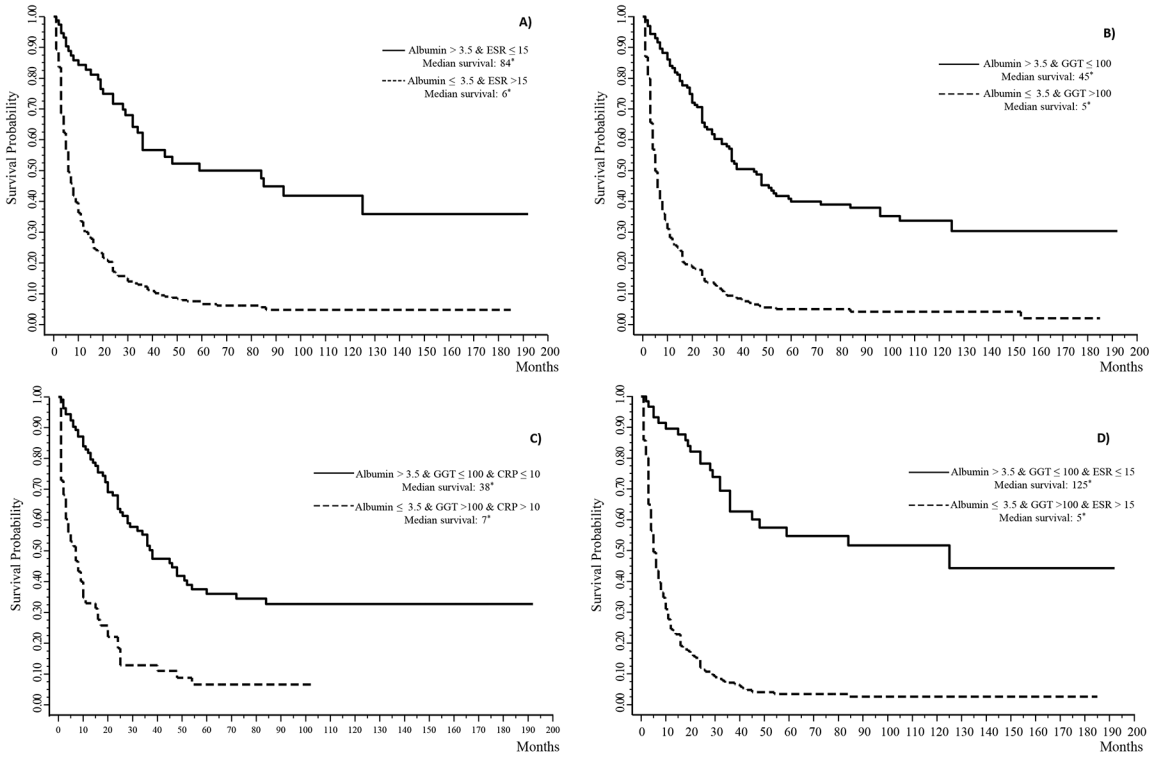

Fig 1.

Kaplan-Meier survival plots for 4 combinations of parameters.

Kaplan-Meier Survival plots, according to combined categories of:

A) Albumin (> 3.5/≤ 3.5,g/dL) and ESR (≤15/>15,mm/hour), log-rank test p<0.0001

B) Albumin (> 3.5/≤ 3.5,g/dL) and GGT (≤100/>100,IU/mL), log-rank test p<0.0001

C) Albumin (> 3.5/≤ 3.5,g/dL), GGT (≤100/>100,IU/mL), and CRP (≤10/>10,mg/L) log-rank test p<0.0001

D) Albumin (> 3.5/≤ 3.5,g/dL), GGT (≤100/>100,IU/mL), and ESR (≤15/>15,mm/hour) log-rank test p<0.0001

* Median survival in months.

Abbreviations: ESR, erythrocyte sedimentation rate; GGTP, gamma glutamyl transpeptidase; CRP, C-Reactive Protein.

Table 1A.

Cox regression model on single parameters in the model.

Parameter	HR	se (HR)	p	95% C.I.
NLR				
≤ 3.0 (*Ref. category*)	1			
> 3.0	1.44	0.13	<0.001	1.21 to 1.72
PLR				
≤ 0.15 (*Ref. category*)	1			
> 0.15	1.25	0.12	0.02	1.04 to 1.50
CRP (mg/dL)				
≤ 10 (*Ref. category*)	1			
> 10	1.46	0.12	<0.001	1.24 to 1.72
ESR (mm/hour)				
≤ 15 (*Ref. category*)	1			
> 15	1.83	0.20	<0.001	1.48 to 2.26
GGT (IU/mL)				
≤ 100 (*Ref. category*)	1			
> 100	2.02	0.16	<0.001	1.72 to 2.37
Albumin (g/dL)				
> 3.5 (*Ref. category*)	1			
≤ 3.5	2.31	0.20	<0.001	1.95 to 2.74

Abbreviations: HR, Hazard-Ratio; se (HR), standard error of Hazard-Ratio; NLR, Neutrophils to Lymphocytes Ratio; PLR, Platelet count to Lymphocytes Ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase.

Table 1B.

Final multiple Cox regression model in HCC patients on all parameters together in the model by the stepwise backward method.

Parameters *	HR	se (HR)	p	95% C.I.
GGT (IU/mL)				
≤ 100 (*Ref. category*)	1			
> 100	1.56	0.21	0.001	1.20 to 2.02
CRP (mg/dL)				
≤ 10 (*Ref. category*)	1			
> 10	1.83	0.26	<0.001	1.38 to 2.43
Albumin (g/dL)				
> 3.5 (*Ref. category*)	1			
≤ 3.5	2.28	0.40	<0.001	1.62 to 3.22

Abbreviations: HR, Hazard-Ratio; se (HR), standard error of HR; CRP, C-Reactive Protein; GGTP, gamma glutamyl transpeptidase.

Table 2.

Cox regression model on parameter combinations in the model.

Parameter	HR	se (HR)	p	95% C.I.
Combinations				
ESR and CRP				
ESR (≤ 15) & CRP (≤ 10) (*Ref category*)	1			
ESR (> 15) & CRP (> 10)	2.69	0.46	<0.001	1.93 to 3.75
ESR and GGT				
ESR (≤ 15) & GGT (≤ 100) (*Ref. category*)	1			
ESR (> 15) & GGT (> 100)	3.03	0.44	<0.001	2.27 to 4.04
Albumin and CRP				
Albumin (> 3.5) & CRP (≤ 10) (*Ref. category*)	1			
Albumin (≤ 3.5) & CRP (> 10)	1.42	0.06	<0.001	1.31 to 1.54
Albumin and GGT				
Albumin (> 3.5) & GGT (≤ 100) (*Ref. category*)	1			
Albumin (≤ 3.5) & GGT (> 100)	3.98	0.51	<0.001	3.10 to 5.12
Albumin and ESR				
Albumin (> 3.5) & ESR (≤ 15) (*Ref. category*)	1			
Albumin (≤ 3.5) & ESR (> 15)	4.03	0.74	<0.001	2.81 to 5.79
Albumin, GGT, and ESR				
Albumin (> 3.5) & GGT (≤ 100) & ESR (≤ 15) (*Ref. category*)	1			
Albumin (≤ 3.5) & GGT (> 100) & ESR (> 15)	6.33	1.43	<0.001	4.07 to 9.85

Abbreviations: HR, Hazard-Ratio; se (HR), standard error of Hazard-Ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase. Units given in Table 1.

Table 3.

Predictive single and combination scores for survival using Harrell's concordance index (C-index).

Inflammation based prognostic scores		C-index	p-value	95% C.I.	Comparisons (p-value)					
					(a)	*(b)*	*(c)*	*(d)*	*(e)*	*(f)*
NLR	*(a)*	0.55	<0.001	0.51 to 0.58	--	0.88	0.02	0.01	0.96	0.04
PLR	*(b)*	0.55	<0.001	0.52 to 0.59	--	--	0.04	0.01	0.85	0.05
Albumin (g/dL)	*(c)*	0.60	<0.001	0.57 to 0.63	--	--	--	0.86	0.01	0.97
CRP (mg/dL)	*(d)*	0.60	<0.001	0.57 to 0.64	--	--	--	--	0.97	0.83
ESR (mm/hour)	*(e)*	0.55	<0.001	0.51 to 0.58	--	--	--	--	--	0.01
GGT (IU/mL)	*(f)*	0.60	<0.001	0.56 to 0.63	0.04	0.05	0.97	0.83	0.01	--
Combined					*(a_1)*	*(a_2)*	*(a_3)*			
ESR (mm/hour)	*(a_1)*	0.54	<0.001	0.52 to 0.57	--	0.02	<0.001			
CRP (mg/dL)	*(a_2)*	0.59	<0.001	0.56 to 0.61	--	--	0.02			
ESR, CRP	*(a_3)*	0.61	<0.001	0.58 to 0.64	<0.001	0.02	--			
					(b_1)	*(b_2)*	*(b_3)*			
ESR (mm/hour)	*(b_1)*	0.55	<0.001	0.52 to 0.57	--	0.001	<0.001			
GGT (IU/mL)	*(b_2)*	0.60	<0.001	0.57 to 0.62	--	--	0.003			
ESR, GGT	*(b_3)*	0.62	<0.001	0.59 to 0.64	<0.001	0.003				
					(c_1)	*(c_2)*	*(c_3)*			
Albumin (g/dL)	*(c_1)*	0.60	<0.001	0.58 to 0.62	--	0.99	<0.001			
GGT (IU/mL)	*(c_2)*	0.60	<0.001	0.58 to 0.62	--	--	<0.001			
Albumin, GGT	*(c_3)*	0.64	<0.001	0.62 to 0.66	<0.001	<0.001	--			
					(d_1)	*(d_2)*	*(d_3)*			
Albumin (g/dL)	*(d_1)*	0.59	<0.001	0.57 to 0.61	--	0.01	0.002			
CRP (mg/dL)	*(d_2)*	0.55	<0.001	0.53 to 0.58	--	--	<0.001			
Albumin, CRP	*(d_3)*	0.61	<0.001	0.59 to 0.64	0.002	<0.001	--			
					(e_1)	*(e_2)*	*(e_3)*			
Albumin (g/dL)	*(e_1)*	0.59	<0.001	0.57 to 0.61	--	0.004	0.42			
ESR (mm/hour)	*(e_2)*	0.55	<0.001	0.52 to 0.57	--	--	<0.001			
Albumin, ESR	*(e_3)*	0.60	<0.001	0.57 to 0.62	0.42	<0.001	--			

Abbreviations: C-index, Harrell's concordance index, 95% CI, 95% Confidence Interval.

NLR, Neutrophils and Lymphocytes Ratio; PLR, Platelet count and Lymphocytes Ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase.

Table 4.

Clinical and tumor parameter values in (**A**), patients dichotomized according to serum Albumin plus GGT values; (**B**), Albumin, GGT plus ESR values.

Parameter	**Albumin > 3.5 (g/dL) & GGT ≤ 100 (IU/L) (n=166)**	**Albumin ≤ 3.5 (g/dL) & GGT >100 (IU/L) (n=321)**	**p***
A)			
AFP (IU/mL)	3999.00±9039.66	20694.49±65090.39	0.002
MTD (cm)	5.63±3.55	7.55±4.25	<0.0001
PVT (%)	15.25	41.56	<0.001 ^
Nodule numbers (%)			<0.001 ^
≤ 2	69.44	50.00	
> 2	30.56	50.00	
Cirrhosis (%)	63.79	84.58	<0.001 ^
Hemoglobin (g/dL)	13.31±2.14	12.25±8.32	<0.0001
Platelet counts (10^3/μL)	217.6±71.3	316.18± 164.3	0.82
Albumin (g/dL)	4.82±5.50	2.61±0.56	<0.0001
NLR	3.21±2.75	5.60±9.62	<0.0001
PLR	23.61±118.45	35.71±113.39	0.02
CRP (mg/L)	7.41±26.08	22.97±37.38	<0.0001
ESR (mm/hr)	21.53±21.09	38.91±23.15	<0.0001
Total Bilirubin (mg/dL)	1.16±1.70	5.37± 18.55	<0.0001
ALKP (IU/L)	149.71±398.78	292.48±233.67	<0.0001
GGTP (IU/L)	50.03±25.32	269.38±208.28	<0.0001
AST (IU/L)	47.86±38.60	214.51±698.97	<0.0001
Parameter	**Albumin > 3.5 & GGT ≤ 100 & ESR ≤ 15**	**Albumin ≤ 3.5 & GGT >100 & ESR > 15**	**p***
B)			
AFP (IU/mL)	2945.96±7005.86	19285.13±66369.27	0.01
MTD (cm)	5.84±4.02	7.57±4.18	0.001
PVT (%)	8.16	37.24	<0.001 ^
Nodule numbers (%)			0.003 ^
≤ 2	71.19	49.46	
> 2	28.81	50.54	

Abbreviations: MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis; AFP, Alpha-fetoprotein; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate (mm/hour); ALKP, Alkaline phosphatase; GGTP, gamma glutamyltranspeptidase; AST, Aspartate Aminotransaminase; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; AFP, Alpha-fetoprotein.

*Wilcoxon rank-sum (Mann-Whitney) test;

^Chi-square test.