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ORIGINAL RESEARCH

The Prognostic Value of Inflammation Factors in Hepatocellular Carcinoma Patients with Hepatic Artery Interventional Treatments: A Retrospective Study

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Background: Hepatic artery interventional therapy has been recognized as the first choice for advanced liver cancer. However, reliable prognostic markers are still lacking. In the present study, we aimed to evaluate the prognostic value of inflammation factors including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and monocyte to lymphocyte ratio (MLR) in hepatocellular carcinoma (HCC) patients with hepatic artery interventional treatments.

Methods: Patients undergoing hepatic artery interventional therapy after being diagnosed with HCC between 2007 and 2014 were enrolled. Pre-treatment NLR, PLR and MLR were calculated, and all factors including gender, age, TNM stage, BCLC staging, inflammation factors, LDH, ALP, CEA, AFP, hepatitis, liver cirrhosis, portal vein involvement, surgical history and hepatic artery interventional treatment on overall survival (OS) were evaluated by the univariate and multivariate Cox proportional hazards analyses.

Results: Overall, 407 patients were included. The optimal cutoff values determined by receiver operating characteristic (ROC) curve analyses for NLR, PLR and MLR were 3.82, 140.00 and 0.27, respectively. High NLR was associated with worse OS (median survival time: high NLR group 9 vs low NLR group 19 months, HR 1.842, 95% CI: 1.457–2.329, P<0.001). Elevated PLR was negatively correlated with OS (8 vs 18 months, HR 1.677, 95% CI: 1.302–2.161, P<0.001). Patients in high MLR group had a worse OS (10 vs 21 months, HR 1.626, 95% CI: 1.291–2.048, P<0.001). In multivariate analysis, NLR, LDH, ALP and portal vein involvement were independent prognostic factors for OS of HCC patients after hepatic artery interventional therapy. In addition, for patients in BCLC stage A and B, higher NLR, PLR and MLR were all significantly negatively correlated to median survival time (NLR: 17 vs 26 months, HR: 1.739 (95% CI: 1.279–2.365), P<0.001; PLR: 18 vs 26 months, HR: 1.681 (95% CI: 1.245–2.271), P=0.001; MLR: 20 vs 26 months, HR: 1.589 (95% CI: 1.185–2.129), P=0.002).

Conclusion: Elevated pre-treatment NLR, PLR and MLR were associated with worse survival time in HCC patients after hepatic artery interventional therapy. Among them, NLR was an independent prognostic factor for OS.

Keywords: hepatocellular carcinoma, neutrophils, platelets, lymphocytes, inflammation, prognosis

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Background

Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy with high mortality.[1] According to a report of cancer statistics in China, there were 0.365 million newly diagnosed HCC and 0.319 million patients dying from

HCC every year. Another study revealed that 50.5% of emerging HCC patients in the world were Chinese.[2] Primary hepatectomy can be a potential curative treatment for HCC patients; however, according to current practice guidelines for the management of HCC, it is limited to patients harboring early-stage tumors and patients without portal hypertension or increased bilirubin levels.[3,4] This has made hepatic artery interventional therapies including transcatheter arterial embolization (TAE), transcatheter arterial infusion (TAI) and transcatheter arterial chemoembolization (TACE) become important treatment options for patients with heavy disease burden.[5] However, since interventional therapies are accompanied by repeated ischemic injury to liver parenchyma and adverse events, post-embolization survival outcomes remain poor.[6,7] Therefore, it is urgent to establish the prognostic factors to better stratify patients who are likely to benefit from the treatments.

Currently, several clinical factors including tumor markers and portal vein involvement have been proposed for diagnostic, prognostic or monitoring use in liver cancer. Among them, α-fetoprotein (AFP) was most studied. AFP was usually used for early detection of HCC in patients with cirrhosis or chronic hepatitis.[8] Post-treatment monitoring with AFP in HCC patients is also recommended.[9] A Japanese survey showed that AFP concentration, portal and hepatic vein involvement were independent prognostic factors for HCC patients undergoing liver resection.[10] However, these factors have not been validated in HCC patients undergoing hepatic artery interventional therapy and there are few studies exploring prognostic factors for HCC patients undergoing hepatic artery interventional therapy.[11] Recent studies have reported the role of chronic inflammation in cancer progression.[12] Cancer-related inflammation affects tumor proliferation by promoting angiogenesis and secreting different growth factors.[13] HCC can develop on a background of inflammation. Previous studies have confirmed the underlying impact of repeated hepatitis virus infection on the development of HCC.[14] Therefore, the systematic inflammatory state might serve as a surrogate marker of tumor clinical pathology in HCC patients. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are calculated as the absolute count of neutrophil (platelet) divided by the absolute count of lymphocytes. As the reflection of systemic inflammatory response, NLR and PLR have been widely investigated as new prognostic indicators to evaluate the survival outcomes in many cancers, including gastric cancer and non-small cell lung cancer.[15,16] Recently, the prognostic significance of NLR and PLR as predictive biomarkers for patients affected by HCC undergoing transcatheter arterial chemoembolization (TACE) has also been reported.[17] Results of this study manifested that high PLR and NLR were correlated with poor prognosis in recurrent hepatocellular carcinoma patients treated with TACE. However, the sample size was quite small, and therefore the conclusion needs to be further tested. In addition, the monocyte-lymphocyte ratio (MLR) has been reported to be a prognostic factor for various cancers including colon cancer, lymphoma and nasopharyngeal carcinoma.[18–21] But few studies are investigating the prognostic effect of MLR on HCC patients underwent hepatic artery interventional therapy.

In this study, we retrospectively analyzed a large sample of patients to investigate the prognostic roles of NLR, PLR, MLR and other potential prognostic factors in HCC patients who had undergone interventional treatments.

Patients and Methods

Patients and Data Recording

In this retrospective study, patients between the ages of 18 and 75 who were pathologically diagnosed with primary hepatocellular carcinoma (HCC) and underwent hepatic artery interventional therapy at West China Hospital from September 2007 to July 2014 were included. Exclusion criteria were diagnosis with cholangiocarcinoma, mixed hepatocarcinomatous or secondary HCC, active infection during the time of blood sample preparation, severe coagulation disorders, serious hemorrhage, receiving any medication that might seriously infected inflammatory markers or loss of regular follow-up. The last follow-up was on September 29, 2018. A total of 407 patients were eventually included in the study. Hepatic artery interventional therapy of enrolled patients included transcatheter arterial embolization (TAE), transcatheter arterial infusion (TAI) and transcatheter arterial chemoembolization (TACE). Our study was approved by the Medical Ethics Committee of West China Hospital, Sichuan University, and all the patients signed informed consent.

Latest clinical and laboratory data within 1 week prior to hepatic artery interventional therapy of enrolled patients were obtained from electronic medical records. Specifically, we extracted patient characteristics including age, sex, diagnoses, pathology reports, imaging result, treatment, TNM stage, Barcelona Clinic Liver Cancer

Staging (BCLC staging), infectious status of viral hepatitis B and C, liver cirrhosis, portal vein involvement, alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), AFP, neutrophil count, lymphocyte count, monocyte count and platelet count. NLR was defined as the ratio of neutrophil count to lymphocyte count. PLR was defined as the ratio of platelet count to lymphocyte count. MLR was defined as the ratio of monocyte count to lymphocyte count. The primary endpoint in our study was overall survival time.

Definition of Procedures

Transcatheter arterial chemoembolization (TACE) involves selective insertion of a catheter into the tumor's target blood supply artery, and injection of an appropriate amount of embolic particles coated with chemotherapeutic drugs, thus occluding the target artery of tumor tissues and inducing cytotoxicity.[22] It is mostly used for the treatment of liver cancer, including primary or metastatic liver cancer and postoperative recurrence of liver cancer.[23]

Transcatheter arterial infusion (TAI) involves catheter-based delivery of chemotherapeutic drugs to improve the local drug concentration and reduce the systemic reaction, suitable for the treatment of cancer patients who cannot be resected or undergo palliative resection.[24,25]

Transcatheter arterial embolization (TAE) is performed by injecting various embolization agents into the artery to block the arterial blood supply of the tumor.[23] It is mostly used for liver cancer that cannot be surgically removed and is also used for liver diseases such as hepatic hemangioma, hepatic arteriovenous fistula, etc.[23,26]

Statistical Analysis

Data analyses were performed on SPSS 21.0. The Pearson Chi-squared test was used to compare categorical variables. Receiver operating characteristic (ROC) curve analyses were conducted to determine the optimal cutoff values of NLR, PLR and MLR. Survival curves were estimated by Kaplan-Meier method and differences between groups were determined by the Log rank test. Univariate analysis and multivariate cox regression analysis were performed to assess potential prognostic factors. Multivariate cox regression analysis was performed with the forward LR (forward stepwise regression based on maximum likelihood estimation) method. To further clarify the role of NLR, PLR and MLR in HCC patients without macrovascular invasion and/or extrahepatic disease, we separately performed univariate analysis and multivariate cox regression analysis based on the BCLC classification. All tests were two-sided, and a p-value less than 0.05 was considered as statistically significant.

Results

The Optimal Cutoff Values for NLR, PLR and MLR

The optimal cutoff values of NLR, PLR and MLR were determined by ROC analysis on the basis of maximum joint sensitivity and specificity. According to ROC curves, the area under the curves (AUC) for NLR, PLR and MLR was 0.601 (95% CI: 0.546–0.656, P<0.001), 0.654 (95% CI: 0.601—0.706, P<0.001) and 0.622 (95% CI: 0.568–0.676, P<0.001). The optimal cutoff values were 3.82 for NLR, 140.00 PLR and 0.27 for MLR by ROC curves analysis (Figure 1).

Characteristics of Patients

A total of 407 patients were included with a median age of 55 (range: 18–75). Flowchart of patients' selection is shown in Figure 2. The vast majority of patients were male (85.5%, 348/407) while female patients accounted for 14.5% (59/407). Forty-six patients (11.3%) were at T1 stage, 117 patients (28.7%) were at T2 stage, 229 patients (56.3%) were at T3 stage and 15 patients (3.7%) were at T4 stage. About N staging, 294 (72.2%) patients were at N0 stage, and 113 (27.8%) patients were at N1 stage. Concerning M staging, 89.4% (364/407) of patients were in M0 stage, and 43 (10.6%) patients were in M1 stage. According to the BCLC staging, the same number of patients were at stage A (131, 32.2%) and stage B (131, 32.2%). And 143 (35.1%) patients were at stage C while only 2 (0.5%) patients were at stage D. Regarding surgical history, 177 (43.5%) patients underwent surgery before hepatic artery interventional treatment and 230 (56.5%) patients did not have surgery before. In addition, detailed information about hepatic artery interventional therapies of enrolled patients was summarized. More than half of patients underwent TACE treatment (223/407), and about forty percent of patients had TAI therapy (180/407), while only 4 patients had TAE treatment.

High NLR group consisted of 133 (32.7%) patients while 274 (67.3%) patients were in NLR<3.82 group. Our study revealed that NLR was significantly associated with T stage (P=0.002), M stage (P=0.017), BCLC staging (P=0.005), LDH (<0.001), ALP (<0.001), CEA (0.036) and hepatic artery interventional treatment (p=0.019).

Ninety-eight (24.1%) patients were in PLR $\geq$ 140.00 group and 309 (75.9%) patients were in PLR<140.00

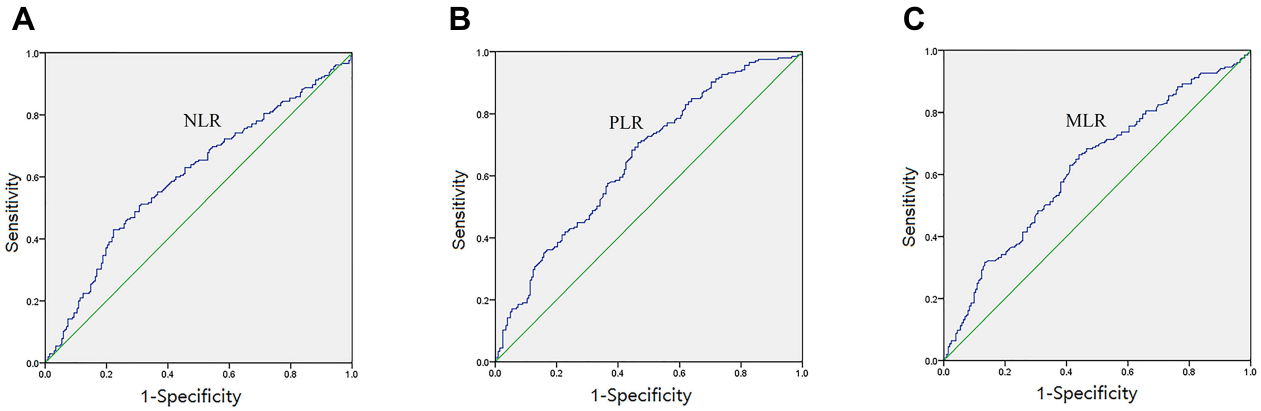

Figure 1 Receiver operating characteristic (ROC) curves for pretreatment NLR, PLR, and MLR for predicting prognosis in HCC patients after interventional treatments. (**A**) Receiver operating characteristic (ROC) curves for pretreatment NLR. (**B**) Receiver operating characteristic (ROC) curves for pretreatment PLR. (**C**) Receiver operating characteristic (ROC) curves for pretreatment MLR.

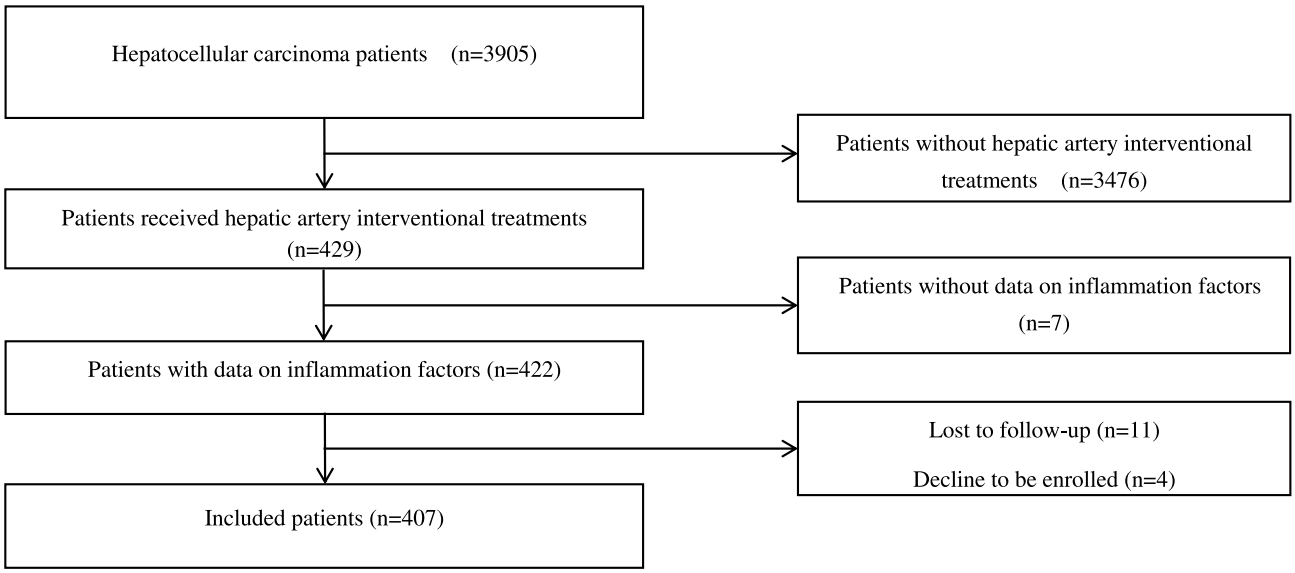

Figure 2 Flowchart of patients' inclusion and exclusion.

group. PLR was associated with T stage (P=0.012), BCLC staging (P=0.045), LDH (P<0.001) and ALP (P<0.001).

There were 225 patients (55.3%) in MLR $\geq$ 0.27 group and 182 (44.7%) patients were in MLR<0.27 group. MLR had a close connection with N stage (P=0.019), M stage (P=0.019), BCLC staging (P=0.002), LDH (P<0.001), ALP (P<0.001) and CEA (P=0.007).

The correlations between NLR, PLR, MLR and clinical features of HCC patients are shown in Table 1.

Prognostic Factors of HCC Patients

The univariate cox proportional hazards analysis showed that age, TNM stages, BCLC staging, NLR, PLR, MLR, LDH, ALP, CEA, AFP and portal vein involvement had a strong connection with the survival outcomes of HCC patients who had undergone hepatic artery interventional therapy (Table 2). The median survival time of patients in NLR $\geq$ 3.82 group was 9 months, while the patients in NLR < 3.82 group had a median survival time of 19 months (HR 1.842, 95% CI: 1.457–2.329, P<0.001) (Figure 3A). Comparing with patients in low PLR group, patients in PLR $\geq$ 140.00 group appeared to have shorter median survival time (8 months vs 18 months) with hazard ratio being 1.677 (95% CI: 1.302–2.161, P<0.001) (Figure 3B). Patients in MLR $\geq$ 0.27 group had a median survival time of 10 months compared to 21 months of patients in MLR < 0.27 group (HR 1.626, 95% CI: 1.291–2.048, P<0.001) (Figure 3C). Our multivariate analysis showed that NLR

Table 1 Correlation Between Peripheral NLR, PLR, MLR, and Clinical Variables of HCC Patients

Variables	Cases	NLR		P	PLR		P	MLR		P
		<3.82	≥3.82		<140.00	≥140.00		<0.27	≥0.27	
Gender										
Male	348	237	111		265	83		158	190	
Female	59	37	22	0.414	44	15	0.794	24	35	0.500
Age										
<60	236	162	74		184	52		114	122	
≥60	171	112	59	0.504	125	46	0.257	68	103	0.087
T stage										
I	46	37	9		37	9		24	22	
II	117	90	27		100	17		61	56	
III	229	139	90		161	68		90	139	
IV	15	8	7	**0.002**	11	4	**0.012**	7	8	0.091
N stage										
0	294	203	91		228	66		142	152	
I	113	71	42	0.231	81	32	0.215	40	73	**0.019**
M stage										
0	364	252	112		281	83		170	194	
I	43	22	21	**0.017**	28	15	0.080	12	31	**0.019**
BCLC staging										
A	131	101	30		109	22		69	62	
B	131	83	48		99	32		65	66	
C	143	90	53		99	44		48	95	
D	2	0	2	**0.005**	2	0	**0.045**	0	2	**0.002**
LDH										
<199.00	160	127	33		137	23		90	70	
≥199.00	247	147	100	**<0.001**	172	75	**<0.001**	92	155	**<0.001**
ALP										
<134.50	239	178	61		204	35		130	109	
≥134.50	168	96	72	**<0.001**	105	63	**<0.001**	52	116	**<0.001**
CEA										
<7.93	372	256	116		281	91		174	198	
≥7.93	35	18	17	**0.036**	28	7	0.555	8	27	**0.007**
Hepatitis										
Without hepatitis	181	120	61		135	46		83	98	
Hepatitis B	209	142	67		160	49		93	116	
Hepatitis C	6	4	2	0.916	5	1	0.899	1	5	0.403
Liver cirrhosis										
No	183	123	60		131	52		85	98	
Yes	209	144	65	0.721	169	40	**0.031**	93	116	0.699
Portal vein involvement										
Yes	68	48	20		49	19		26	42	
No	310	208	102	0.577	237	73	0.445	142	168	0.255
Surgical history										
Yes	177	122	55	0.545	138	39	0.397	88	89	

(*Continued*)

Table 1 (Continued).

Variables	Cases	NLR		P	PLR		P	MLR		P
		<3.82	≥3.82		<140.00	≥140.00		<0.27	≥0.27	
No	230	152	78		171	59		95	135	**0.091**
Interventional Treatment										
TACE	223	141	82		168	55		93	130	
TAI	180	132	48	**0.019**	138	42	0.952	89	91	
TAE	4	1	3		3	1		1	3	0.216
AFP										
<400	241	166	75	0.615	200	41	<0.001	114	127	
≥400	152	101	51		101	51		65	87	0.379

Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; BCLC staging, Barcelona Clinic Liver Cancer staging; LDH, lactate dehydrogenase; ALP,alkaline phosphatase; CEA, carcinoembryonic antigen; AFP, α-fetoprotein. P-values in bold were found to be significant.

(P=0.013), LDH (P=0.001), ALP (p=0.017) and portal vein involvement (P<0.001) were independent prognostic factors for survival of HCC patients, while PLR and MLR were revealed not to have independent prognostic values for those patients' survival (Table 3).

Analysis of Patients Without Macrovascular Invasion and/or Extrahepatic Disease

A total of 262 HCC patients in BCLC stages A or B were included for the analysis (Table 4). The univariate cox proportional hazards analysis showed that age, NLR, PLR, MLR, LDH, and ALP were significantly associated with the survival outcomes (Table 5). Patients with higher NLR, PLR and MLR were all significantly negatively correlated to median survival time (NLR: 17 vs 26 months, HR: 1.739 (95% CI: 1.279–2.365), P<0.001; PLR: 18 vs 26 months, HR: 1.681 (95% CI: 1.245–2.271), P=0.001; MLR: 20 vs 26 months, HR: 1.589 (95% CI: 1.185–2.129), P=0.002). Multivariate analysis revealed that PLR and LDH were significant prognostic factors for overall survival (Table 6).

Discussion

Inflammation is a protective process from further tissue damage caused by physical, biological or chemical factors.[27] It is a complicated reaction which involves many different kinds of immune cells and chemicals released by them.[28] But once the acute protective procedure cannot get rid of the etiology, it will develop into chronic inflammation which might develop into cancer.[29] Many studies have reported the possible connection, which could predict the prognosis of cancer, between chronic inflammation and oncogenesis.[30,31] HCC is also regarded as developing from chronically damaged liver tissue which contains a lot of inflammation cells, and those cells promote the tumorigenesis and tolerance to therapy.[32]

Recently, an increasing number of studies have focused on the role of NLR and PLR in predicting prognosis of HCC patients after interventional treatment.[33,34] However, their study involved a small number of patients and usually included only a single type of hepatic artery interventional therapy.[35] In addition, few studies have investigated the prognostic value of MLR in HCC patients. To the best of our knowledge, the present retrospective analysis is the first study to systematically evaluate the prognostic value of NLR, PLR and MLR based on 407 HCC patients after hepatic artery interventional therapy.

Neutrophils, the first cells to assemble at the site of inflammation, not only work as protector of our body, but also play an important role in tumorigenesis.[36] Previous studies showed that neutrophils in the tumor microenvironment produce MMP9 (gelatinase B), and this molecule has been proved to promote the angiogenesis, progression, and metastasis of tumor in mouse transplantation models.[37–39] Reactive oxygen species (ROS) derived from neutrophil participates in cell death pathway during inflammation. However, once ROS fails to destroy cells, it causes direct gene damage which contributes to tumor initiation.[40] In addition, neutrophils release neutrophil elastase (NE) by cell degranulation to stimulate inflammation reaction and attack invading organisms.[41] NE has

Table 2 Univariate Analysis Estimating the Prognostic Factors for HCC

Variables	Univariate Analysis					
	N	Median Survival Time (Months)	P[a]	HR	95% CI	P[b]
Gender						
Male	348	15				
Female	59	13	0.382	1.147	0.838–1.571	0.392
Age						
≥60	171	14				
<60	236	18	**0.026**	1.288	1.026–1.617	**0.029**
T stage						
I	46	14				
II	117	23				
III	229	13				
IV	15	10	**<0.001**	1.341	1.138–1.580	**<0.001**
N stage						
0	294	16				
1	113	12	**0.015**	1.346	1.054–1.719	**0.017**
M stage						
0	364	16				
1	43	10	**0.016**	1.508	1.071–2.123	**0.019**
BCLC staging						
A	131	23				
B	131	15				
C	143	11				
D	2	3	**<0.001**	1.320	1.151–1.514	**<0.001**
NLR						
≥3.82	133	9				
<3.82	274	19	**<0.001**	1.842	1.457–2.329	**<0.001**
PLR						
≥140.00	98	8				
<140.00	309	18	**<0.001**	1.677	1.302–2.161	**<0.001**
MLR						
≥0.27	225	10				
<0.27	182	21	**<0.001**	1.626	1.291–2.048	**<0.001**
LDH						
≥199.00	247	10				
<199.00	160	24	**<0.001**	1.980	1.554–2.523	**<0.001**
ALP						
≥134.50	168	7				
<134.50	239	21	**<0.001**	1.835	1.461–2.304	**<0.001**
CEA						
≥7.93	35	5				
<7.93	372	16	**0.001**	1.842	1.276–2.660	**0.001**
Hepatitis						
Without hepatitis	181	16				
Hepatitis B	209	15				

(*Continued*)

Table 2 (Continued).

Variables	Univariate Analysis					
	N	Median Survival Time (Months)	P[a]	HR	95% CI	P[b]
Hepatitis C	6	8	0.794	0.972	0.782–1.208	0.798
Liver cirrhosis						
No	183	16				
Yes	209	15	0.388	0.905	0.719–1.140	0.397
Portal vein involvement						
Yes	68	4				
No	310	18	**<0.001**	2.142	1.607–2.857	**<0.001**
Surgical history						
Yes	177	23				
No	230	29	0.646	1.055	0.835–1.333	0.653
Interventional treatment						
TACE	223	30				
TAI	180	25				
TAE	4	26	0.949	1.008	0.812–1.253	0.940
AFP						
<400	241	31				
≥400	152	17	**<0.001**	1.686	1.334–2.131	**<0.001**

Notes: P[a] is the P value for Log Rank test, P[b] is the P value for HR in the univariate analysis. P-values in bold were found to be significant.
Abbreviations: BCLC staging, Barcelona Clinic Liver Cancer staging; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; HR, hazard ratio; CI, confidential interval.

been reported to have many protumor effects.[42,43] A recent study proved that NE stimulates tumor cell proliferation through phosphatidylinositol 3-kinase (PI-3K) pathway.[44] Neutrophils also contribute to tumor cell migration by reducing the expression of cell surface E-cadherin.[45] Chen et al demonstrated that neutrophils could be chemotactically confined by IL-8 and substances secreted by tumor cells, which leads to spatially localized tumor cell

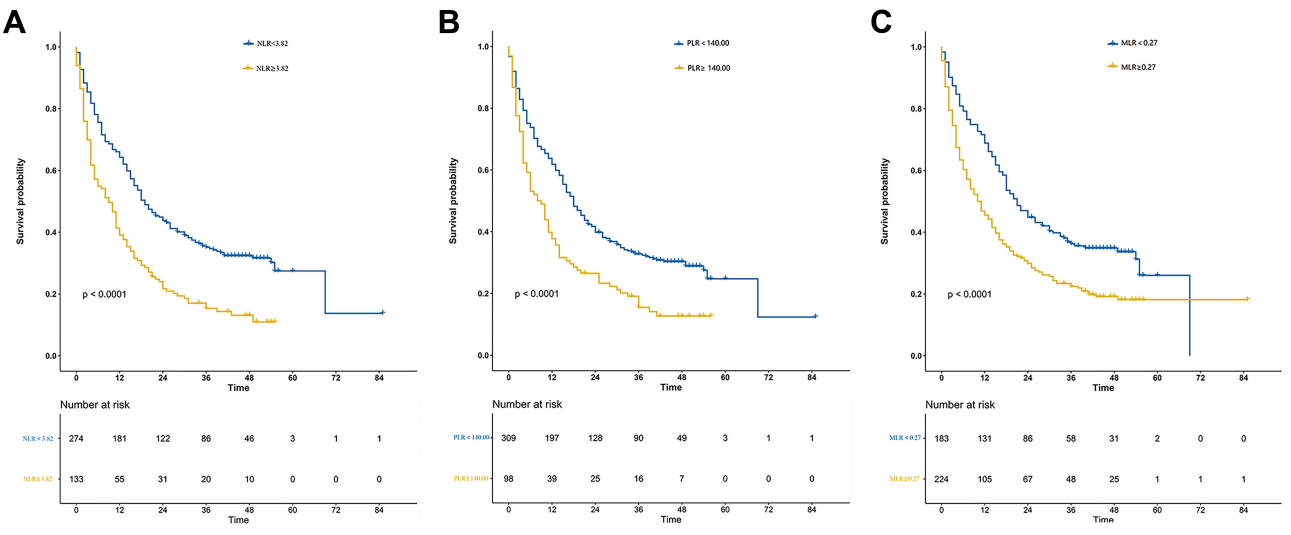

Figure 3 Kaplan–Meier survival curves for overall survival (OS) in HCC patients after interventional treatments. (**A**) OS of patients with NLR ≥ 3.82 was shorter than those with NLR < 3.82 (p < 0.001, log-rank). (**B**) OS of patients with PLR ≥ 140.00 was shorter than those with PLR < 140.00 (p < 0.001, log-rank). (**C**) OS of patients with MLR ≥ Table 1 Correlation between peripheral NLR, PLR, MLR, and clinical variables of hepatic cancer patients.

Table 3 Prognostic Factors for OS as Determined by Multivariate Analysis

Variables	Standard Error	Wald	P value	HR	95.0% CI for HR	
					Lower	Upper
Age	0.130	2.571	0.109	0.812	0.630	1.047
Gender	0.180	0.001	0.976	0.995	0.699	1.415
T stage	0.119	0.204	0.652	1.055	0.835	1.334
T0		6.965	0.138			
T1	0.815	0.208	0.648	1.451	0.293	7.170
T2	0.412	0.129	0.719	0.862	0.384	1.935
T3	0.346	1.192	0.275	0.686	0.348	1.350
T4	0.302	4.452	0.035	0.529	0.293	0.956
N stage	0.149	0.063	0.802	0.963	0.720	1.289
M stage	0.213	0.087	0.768	0.939	0.619	1.425
BCLC staging	0.109	0.007	0.934	0.991	0.800	1.227
A		3.517	0.319			
B	1.031	0.703	0.402	2.374	0.315	17.913
C	1.036	1.414	0.234	3.427	0.450	26.097
D	1.045	1.426	0.232	3.484	0.449	27.025
NLR	0.158	6.171	**0.013**	0.675	0.496	0.921
PLR	0.161	0.244	0.621	1.083	0.790	1.485
MLR	0.149	1.418	0.234	0.837	0.625	1.122
LDH	0.148	10.455	**0.001**	0.619	0.463	0.828
ALP	0.146	5.673	**0.017**	0.707	0.532	0.940
CEA	0.174	2.345	0.126	0.766	0.544	1.078
Portal vein involvement	0.176	14.561	**<0.001**	0.511	0.362	0.721
AFP	0.134	3.721	0.054	0.773	0.595	1.004

Notes: P-values in bold were found to be significant.
Abbreviations: BCLC staging, Barcelona Clinic Liver Cancer staging; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; HR, hazard ratio; CI, confidential interval.

arrest. However, this process helps adjacent tumor cells extravasate and migrate.[46] In HCC, hepatocyte growth factor (HGF) secreted by neutrophils in the liver stimulates cancer cells proliferation through the c-Met pathway.[47] In contrast to the pro-tumor effect of neutrophil, lymphocyte work by attacking tumors through differentiating into tumor-specific CD8+ cytotoxic T cell.[48] Schumacher K et al also found that the intratumor CD8+ T cell infiltration was an independent positive prognostic factor of esophageal carcinomas.[49] Therefore, high NLR might reflect the imbalance in immune response to tumor cells and suggest a relatively worse prognosis as compared with low NLR. In our study, we found patients in high NLR group (NLR $\geq$ 3.82) had worse median survival time than those in low NLR group (9 months vs 19 months, $P < 0.001$). Furthermore, our multivariate analysis showed NLR $\geq$ 3.82 was an independent prognostic factor of worse OS (Table 3). Recently, Zhou et al found high NLR value was a predictor of poor prognosis for patients undergoing TACE with unresectable HBV-related HCC,[50] which is consistent with our result.

Platelets have already been reported to take part in various stages of cancer progression and using antiplatelet doses of aspirin has been confirmed to prevent cancer migration and poor prognosis.[51] One theory is that platelets help tumor cells avoid immune elimination in many ways including secreting TGF-β and platelet-derived growth factor (PDGF) to inhibit NK cell from killing tumor cells, conjugating with fibrinogen and forming a network to prevent tumor cells from interacting with NK cells, and upregulating glucocorticoid-induced TNF-related ligand (GITRL) to suppress cytotoxicity function of NK cells.[52,53] Another opinion is that platelets have a significant effect on angiogenesis in the cancer development process by releasing VEGF and other angiogenic cytokines.[54] In a word, high PLR might be associated with severe tumor progression and represent poor prognosis for cancer patients. Our results revealed a manifest

Table 4 Correlation Between Peripheral NLR, PLR, MLR, and Clinical Variables of HCC Patients in BCLC Stages A and B

Variables	Cases	NLR		P	PLR		P	MLR		P
		<3.74	≥3.74		<106.79	≥106.79		<0.30	≥0.30	
Gender										
Male	222	158	64		150	72		134	88	
Female	40	26	14	0.432	26	14	0.750	20	20	0.220
Age										
<60	145	100	45		101	44		87	58	
≥60	117	84	33	0.619	75	42	0.341	67	50	0.655
LDH										
<205.50	131	105	26		94	37		92	39	
≥205.50	131	79	52	**<0.001**	82	49	0.114	62	69	**<0.001**
ALP										
<109.50	131	105	26		97	34		91	40	
≥109.50	131	79	52	**<0.001**	79	52	**0.018**	63	68	**<0.001**
CEA										
<2.48	104	72	32		66	38		62	42	
≥2.48	104	74	30	0.762	73	31	0.303	61	43	0.888
Hepatitis										
Without hepatitis	118	81	37		79	39		71	47	
Hepatitis B	135	95	40		89	46		79	56	
Hepatitis C	2	2	0	0.896	2	0	0.906	0	2	0.281
Liver cirrhosis										
No	119	81	38		68	51		69	50	
Yes	136	100	36	0.338	105	31	**0.001**	83	53	0.621
Portal vein involvement										
Yes	15	8	7		8	7		6	9	
No	228	162	66	0.147	154	74	0.258	136	92	0.135

Notes: P-values in bold were found to be significant.
Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen.

worse median OS time in high PLR group (≥140) than that in low PLR group (8 months vs 18 months, p<0.001). The multivariate analysis showed that PLR ≥ 140 was not an independent prognostic indicator of worse OS in HCC patients.

After being recruited into inflammation tissue, monocytes differentiate into two macrophage phenotypes including M1 macrophages and M2 macrophages. Among them, M2 has been reported to stimulate tumor progression.[48] Chitinase 3-like protein 1 (*CHI3L 1*), secreted by M2 macrophage, upregulates the expression of matrix metalloproteinase genes and promotes the metastasis of gastric and breast cancer by activating interleukin-13 receptor α2 (*IL-13Rα2*).[49] In cervical cancer, macrophages were shown to be associated with cancer invasion progress by secreting vascular endothelial growth factor (VEGF) to stimulate angiogenesis.[55] In prostate cancer, Soki, Fabiana N. et al demonstrated a decreased bone marrow tumor growth by inducing macrophage apoptosis.[56] In addition to pro-tumor functions, macrophages also suppress the anti-tumor function of CD4+ T cell by direct cell–cell interaction. Meanwhile, they can secrete some molecules such as TGF-β and Arg-1, which inhibit the proliferation of T cell.[57] Thus, it has been speculated that MLR which represents the relative counts of monocytes and lymphocytes can be a potential negatively correlated prognostic marker for tumors. In the present study, patients with elevated MLR (≥0.27) had significant worse median OS time than patients in low MLR group (10 months vs 21 months, p <0.001), which

Table 5 Univariate Analysis Estimating the Prognostic Factors for HCC Patients in BCLC Stages A and B

A						
Variables	**Univariate Analysis**					
	N	**Median Survival Time (Months)**	**P[a]**	**HR**	**95% CI**	**P[b]**
Gender						
Male	222	24				
Female	40	21	0.307	0.818	0.553–1.211	0.315
Age						
≥60	117	20				
<60	145	26	**0.014**	1.435	1.069–1.925	**0.016**
NLR						
≥3.74	78	17				
<3.74	184	26	**<0.001**	1.739	1.279–2.365	**<0.001**
PLR						
≥106.79	86	18				
<106.79	176	26	**0.001**	1.681	1.245–2.271	**0.001**
MLR						
≥0.30	108	20				
<0.30	154	26	**0.001**	1.589	1.185–2.129	**0.002**
LDH						
≥205.50	131	20				
<205.50	131	27	**0.001**	1.605	1.197–2.152	**0.002**
ALP						
≥109.50	131	19				
<109.50	131	27	**0.001**	1.646	1.227–2.209	**0.001**
CEA						
≥2.48	104	24				
<2.48	104	24	0.723	1.061	0.760–1.483	0.727
Hepatitis						
Without hepatitis	118	23				
Hepatitis B	135	23				
Hepatitis C	2	24	0.696	0.887	0.665–1.182	0.411
Liver cirrhosis						
No	119	22				
Yes	136	24	0.082	0.773	0.576–1.039	0.088
Portal vein involvement						
Yes	15	8				
No	228	24	**<0.001**	3.687	2.099–6.476	**<0.001**
B						
Variables	**Univariate Analysis**					
	N	**Median Survival Time (Months)**	**P[a]**	**HR**	**95% CI**	**P[b]**
Gender						
Male	222	24				
Female	40	21	0.307	0.818	0.553–1.211	0.315

(*Continued*)

Table 5 (Continued).

B						
Variables	**Univariate Analysis**					
	N	**Median Survival Time (Months)**	**P[a]**	**HR**	**95% CI**	**P[b]**
Age						
≥60	117	20				
<60	145	26	**0.014**	1.435	1.069–1.925	**0.016**
NLR						
≥3.74	78	17				
<3.74	184	26	**<0.001**	1.739	1.279–2.365	**<0.001**
PLR						
≥106.79	86	18				
<106.79	176	26	**0.001**	1.681	1.245–2.271	**0.001**
MLR						
≥0.30	108	20				
<0.30	154	26	**0.001**	1.589	1.185–2.129	**0.002**
LDH						
≥205.50	131	20				
<205.50	131	27	**0.001**	1.605	1.197–2.152	**0.002**
ALP						
≥109.50	131	19				
<109.50	131	27	**0.001**	1.646	1.227–2.209	**0.001**
CEA						
≥2.48	104	24				
<2.48	104	24	0.723	1.061	0.760–1.483	0.727
Hepatitis						
Without hepatitis	118	23				
Hepatitis B	135	23				
Hepatitis C	2	24	0.696	0.887	0.665–1.182	0.411
Liver cirrhosis						
No	119	22				
Yes	136	24	0.082	0.773	0.576–1.039	0.088
Portal vein involvement						
Yes	15	8				
No	228	24	**<0.001**	3.687	2.099–6.476	**<0.001**

Notes: Confidential Interval. P[a] is the P value for Log Rank test, P[b] is the P value for HR in the univariate analysis. P-values in bold were found to be significant.
Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidential interval.

was in consistence with the finding in the previous study that MLR had a negative correlation with OS of HCC patients after radical resection.[58] Notably, our result revealed that MLR was not an independent prognostic factor of survival in HCC patients after hepatic artery interventional therapy.

Several studies have reported that increased circulating inflammatory cell counts, including neutrophil and monocyte, were associated with advanced tumor stage, while lymphocyte counts being inversely related.[59] As indicators of systematic inflammation status, neutrophil and monocyte were reported to have participated in tumor cell proliferation and migration, tumor progression and metastasis.[60] However, lymphocyte plays a key role in anti-tumor reaction, and lymphocyte cell counts reflect immune response status. Therefore, the levels of NLR, PLR and MLR could indicate the severity of aggressive

Table 6 Prognostic Factors for OS in HCC Patients with BCLC Stages A and B as Determined by Multivariate Analysis

Variables	Standard Error	Wald	P value	HR	95.0% CI for HR	
					Lower	Upper
Age	0.191	2.814	0.093	1.378	0.947	2.003
Gender	0.230	0.273	0.602	0.887	0.565	1.393
NLR	0.246	0.196	0.658	1.115	0.688	1.806
PLR	0.210	4.050	**0.044**	1.525	1.011	2.300
MLR	0.240	0.028	0.867	1.041	0.650	1.667
LDH	0.203	6.121	**0.013**	1.651	1.110	2.457
ALP	0.197	0.906	0.341	1.206	0.820	1.772
CEA	0.197	1.952	0.162	0.760	0.516	1.117
Portal vein involvement	0.323	14.939	**<0.001**	3.489	1.851	6.575

Note: P-values in bold were found to be significant.
Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; HR, hazard Ratio; CI, confidential interval.

tumor at certain degree. In our study, patients with higher NLR, PLR, MLR values tend to be diagnosed with more advanced tumor stages and BCLC stages, which were consistent with the results of previous studies.[61]

A great challenge for the future and also a limitation of our study is to explore recognized demarcation standards of inflammation indexes for clinical use. Moreover, the AUC values for ROC curves were relatively low (between 0.6 and 0.7). However, the predictive models constructed in our study were based on a relatively large sample size, which made our results more reliable. In addition, it is not of great clinical significance to explain the role of a model solely by its AUC value. Therefore, our univariate and multivariate COX regression analysis further identified the significant predictive role of NLR, PLR and MLR. Furthermore, more studies are needed to further investigate the prognostic role of MLR in HCC patients after hepatic artery interventional therapy. Finally, our study was restricted to Chinese Han population, which may not be a good representative for other ethnic groups.

Conclusion

In conclusion, our research was conducted based on a large sample of HCC patients who had undergone hepatic artery interventional therapy and investigated the prognostic roles of pretreatment NLR, PLR, and MLR. The present study confirmed the results of previous studies that high NLR and PLR were associated with poor survival. In addition, MLR was negatively correlated with survival in HCC patients after hepatic artery interventional therapy. Among them, only NLR was an independent index for predicting the prognosis. These inflammation markers are readily available and may help in making clinical decisions. On the basis of the results of our study and previous researches, clinicians can use inflammatory indicators to predict the prognosis of patients before treatment and combine other conditions to determine the best scheme for patients.

Abbreviations

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; HCC, hepatocellular carcinoma; OS, overall survival; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization; TAI, transcatheter arterial infusion; AFP, α-fetoprotein; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; ROC, receiver operating characteristic; AUC, the area under the curves; ROS, reactive oxygen species; NE, neutrophil elastase; PI-3K, phosphatidylinositol 3-kinase; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; GITRL, glucocorticoid-induced TNF-related ligand; CHI3L, chitinase 3-like protein; IL-13Rα2, interleukin-13 receptor α2; VEGF, vascular endothelial growth factor.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent

The study protocol has been approved by the Medical Ethics Committee of West China Hospital, Sichuan University, and all the patients signed informed consent.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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