

Preoperative lymphocyte-to-monocyte ratio predicts survival in primary hepatitis B virus-positive hepatocellular carcinoma after curative resection

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Background: Both inflammation and immunity are associated with the development of malignancy. The lymphocyte-to-monocyte ratio (LMR) has been confirmed as a prognostic factor for several malignant diseases. The purpose of our study was to analyze prognostic significance of preoperative LMR in hepatitis B virus (HBV)-related hepatocellular carcinoma after curative resection.

Patients and methods: A total of 253 patients with primary HBV-positive hepatocellular carcinoma who underwent a curative operation were enrolled in this retrospective study. The relationship between preoperative LMR and survival outcomes was analyzed through Kaplan–Meier curves and multivariate Cox regression analyses.

Results: Patients with a high LMR had a significantly higher mean overall survival than those with a low LMR (67 months vs 55 months, $P=0.023$), and high LMR remained significant for longer survival in the multivariate analysis (hazard ratio, 0.147; 95% confidence interval [CI]: 0.085–0.253; $P=0.021$). Furthermore, patients with a high LMR also had a higher median recurrence-free survival than those with a low LMR in univariate analyses (60 months vs 48 months, $P=0.026$) and multivariate analyses (hazard ratio, 0.317; 95% CI: 0.042–1.023; $P=0.032$). However, the survival benefit was limited to patients with advanced cancer.

Conclusion: LMR was confirmed as an independent prognostic biomarker for primary HBV-positive hepatocellular carcinoma after curative resection.

Keywords: lymphocyte-to-monocyte ratio, survival, HBV, hepatocellular carcinoma

Introduction

In the People's Republic of China, recent health statistics data have revealed the increasing trend of morbidity and mortality of people with liver cancer in a setting of an estimated 100 million carriers of hepatitis B virus (HBV), accounting for the most common cancer and the second leading cause of cancer-related death.¹ Although the development of comprehensive treatment and advances in surgery have benefited liver cancer patients, the prognosis remains poor mainly due to high recurrence and metastasis rates after surgical resection, especially for HBV-positive hepatocellular carcinoma.^{2,3} Classification of patients facilitates predicting survival, thus helping to provide individualized therapies and improve clinical survival outcomes; therefore, the importance of prognostic and predictive biomarkers has been increasingly recognized.⁴ However, biomarkers definitely associated with prognosis are currently limited to clinicopathological characteristics which can only be assessed through postoperative histological studies and findings during surgery, such as histological stage, the pathological type, or TNM stage.^{5–9} So novel pretreatment biomarkers characterized by affordability and technical feasibility are required.

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Inflammation plays an important role in the development of various malignant tumors.¹⁰ Inflammatory cells can secrete various proangiogenic factors and inflammatory mediators, thus prompting a favorable cancer-related inflammatory microenvironment, which can further promote vascular invasion and suppress the host immune system.^{11–13} Otherwise, various cytokines secreted by tumors can influence the blood cells associated with host inflammatory and immunity, such as the neutrophilic, lymphocytic, and monocyte cells and blood platelets.^{14,15}

It has been confirmed that several inflammatory response-related biomarkers can potentially predict prognosis of various types of malignancies, such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio (LMR).^{16–20} Otherwise, we have analyzed the prognostic significance of LMR in 144 patients with pancreatic adenocarcinoma, and found higher preoperative LMR was significantly associated with better survival.²¹ However, there was still no report on the association of preoperative LMR with survival of resected HBV-positive hepatocellular carcinoma. In this study, we try to evaluate the prognostic significance of preoperative LMR in HBV-positive hepatocellular carcinoma patients who underwent curative surgery.

Patients and methods

Patients

Two hundred and fifty-three patients with primary hepatocellular carcinoma who underwent curative resection at the First Department of General Surgery in The First Affiliated Hospital of Xin-Xiang Medical University were enrolled in this study between July 1, 2008 and July 1, 2014. Inclusion criteria included histologically confirmed hepatocellular carcinoma and positive HBsAg, age more than 18 years, and life expectancy more than 6 months. The exclusion criteria included acute and severe preoperative lymphatic system or malignant hematologic conditions or adjuvant treatments. The standard of curative resection was consistent with the National Comprehensive Cancer Network guidelines for hepatobiliary cancer. Clinicopathologic characteristics of all patients were collected from the medical records by one surgeon and checked by another surgeon, including sex, age, tumor size, liver cirrhosis, Child-Pugh stage, HBsAg, AFP level, Barcelona Clinic Liver Cancer (BCLC) stage, TNM stage, tumor site and size, pathological differentiation, and operation type. Histopathological and TNM staging were assessed through postoperative histopathological examination and clinical assessment, respectively. Absolute lymphocyte count and monocyte count were obtained from a routine

blood test on the day before surgery. LMR was calculated using the following equation:

$$\text{LMR} = \frac{\text{absolute lymphocyte count}}{\text{absolute monocyte ratio}}$$

Follow-up

All patients were followed-up through regular outpatient visits; physical examination and laboratory examinations including AFP every 3 months for the first 2 years, every 6 months for the next 3 years, and once annually thereafter. Enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scans were obtained generally every year. Clinical follow-up lasted from surgery to either death or the endpoint of study (ie, June 2015). This study had been approved by the Ethics Committee of The First Affiliated Hospital of Xin-Xiang Medical University. Written informed consent was obtained from all patients.

Statistical analysis

Statistical analyses were performed by SPSS 20.0 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ (two sided) was considered as statistically significant. The optimal cutoff values for the LMR were confirmed through receiver operating characteristic (ROC) curve analysis. Overall survival (OS) was accurately defined as the duration from surgery to death, whereas recurrence-free survival (RFS) was calculated as the duration from surgery to tumor recurrence. Qualitative variables were analyzed through the χ^2 test or Fisher's exact test, while quantitative values were evaluated by independent Student's *t*-test. The OS and RFS curves were studied in Kaplan–Meier analyses through the log-rank test. The Cox regression model was used to evaluate the hazard ratio (HR) and multivariate analysis.

Results

A total of 253 patients with primary localized hepatocellular carcinoma in our study consisted of 165 males and 88 females, with an average age of 60 ± 1.8 years. According to the TNM staging, there were 122 patients with stage I or II tumors, 131 patients with stage III or IV tumors. In view of pathology, 128 patients had well/moderately differentiated adenocarcinoma, while 125 patients with poor differentiation. Moreover, there was no statistically significant association between LMR and clinicopathologic characteristics, except TNM stage. Baseline clinicopathologic characteristics are shown in Table 1.

Table 1 Correlation between the percentage of LMR and clinico-pathologic characteristics

Characteristics	LMR		P-value
	<3.0 (n=181)	≥3.0 (n=72)	
Age (years)			0.965
≥60	81	32	
<60	100	40	
Sex			0.237
Male	114	51	
Female	67	21	
Liver cirrhosis			0.695
Yes	152	59	
No	29	13	
Child-Pugh stage			0.110
A	128	58	
B	53	14	
AFP (ng/mL)			0.147
≤20	73	22	
>20	108	50	
BCLC stage			0.377
A	131	56	
B	50	16	
Tumor size (cm)			0.330
≥5.0	80	27	
<5.0	101	45	
Tumor site			0.826
Left	56	25	
Right	102	39	
Left and right	23	8	
TNM stage			0.003
I-II	83	48	
III	98	24	
Pathological differentiation			0.905
Well/moderate	92	36	
Poor	89	36	
Operation type			0.613
Laparoscopic	52	23	
Open	129	49	

Abbreviations: LMR, lymphocyte-to-monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

Prognostic significance of LMR for hepatocellular carcinoma

In the ROC curve analysis, we confirmed that the optimal cutoff levels for the LMR was 3.0 for OS and 3.2 for RFS. The area under the curve was 0.566 for OS and 0.652 for RFS (Figure 1). The median follow-up duration was 33 months (range: 6–85 months). There were significant associations between BCLC stage, TNM stage, pathological differentiation, and LMR with OS and RFS (Table 2).

At the end of this study, 79 (31.2%) out of the 253 patients studied had died, including 18 (25.0%) out of 72 patients with an LMR ≥3.0 and 61 (33.7%) out of 181 patients with an LMR <3.0. Tumor recurrence occurred in 85 (48.6%) out of 175 patients with an LMR <3.2, and 27 (34.7%) out of 78 patients with an LMR ≥3.2. Kaplan–Meier survival analysis showed that LMR ≥3.0 was related to a shorter OS. The mean OS of patients with an LMR ≥3.0 in peripheral blood was 67 months, which is statistically significantly higher than those with an LMR <3.0 (55 months) (67 months vs 55 months, $P=0.023$), (Table 2; Figure 2). Otherwise, this result remained statistically significant in the multivariate analysis for OS (HR, 0.147; 95% confidence interval [CI]: 0.085–0.253; $P=0.021$) (Table 2).

In Kaplan–Meier univariate analysis of RFS, patients with high LMR (≥3.2) had higher mean RFS than patients with low LMR (<3.2) (60 months vs 48 months, $P=0.026$). In Cox multivariate analysis, high LMR was also confirmed as a significant predictor for RFS (HR, 0.317; 95% CI: 0.042–1.023; $P=0.032$) (Table 3).

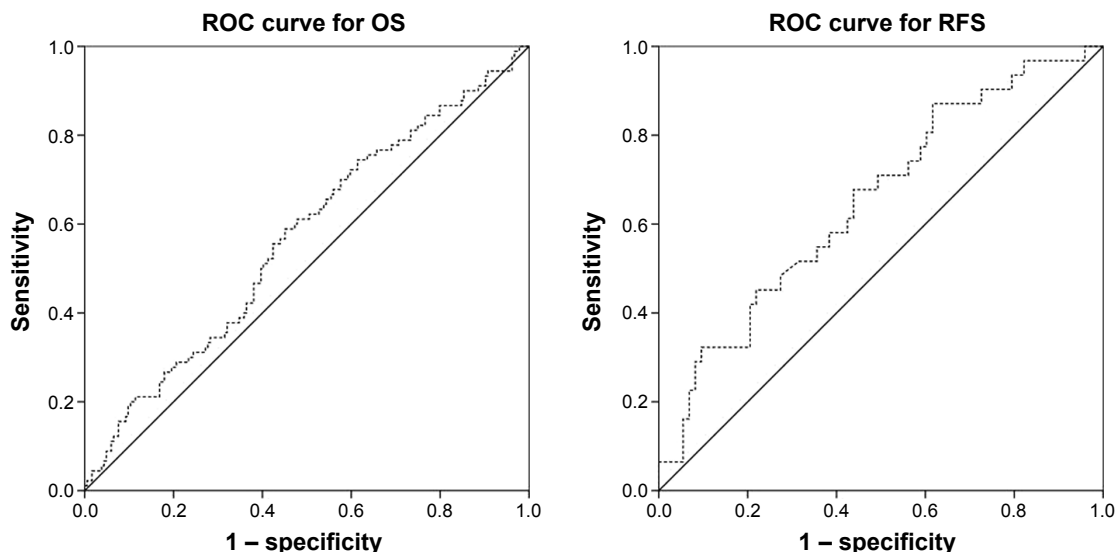


Figure 1 Left panel shows receiver-operator characteristic (ROC) curve for overall survival (OS), the area under the curve was 0.566 for lymphocyte-to-monocyte ratio (LMR). Right panel showed ROC curve for recurrence-free survival (RFS), the area under the curve was 0.652 for LMR.

Table 2 Univariate and multivariate analyses of the association of the prognostic factors with OS

Characteristics	Univariate			Multivariate		
	n	MS (months)	P-value	HR	95% CI	P-value
Age (years)			0.092			
≥60	113	57				
<60	140	56				
Sex			0.534			
Male	165	54				
Female	88	63				
Liver cirrhosis			0.518			
Yes	211	58				
No	42	58				
Child-Pugh stage			0.204			
A	186	53				
B	67	57				
AFP (ng/mL)			0.765			
≤20	95	64				
>20	158	66				
BCLC stage			0.031	6.532	3.874–11.562	0.022
A	187	65				
B	66	53				
Tumor size (cm)			0.001			
≥5.0	107	63				
<5.0	146	42				
Tumor site			0.632			
Left	81	63				
Right	141	61				
Left and right	31	58				
Tumor stage			0.000	5.432	3.168–9.283	0.000
I-II	131	78				
III	122	48				
Pathological differentiation			0.045	0.626	0.412–0.952	0.028
Well/moderate	128	68				
Poor	125	43				
Operation type			0.105			
Laparoscopic	75	58				
Open	178	57				
LMR			0.023	0.147	0.085–0.253	0.021
≥3.0	72	67				
<3.0	181	55				

Abbreviations: OS, overall survival; MS, mean survival; CI, confidence interval; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

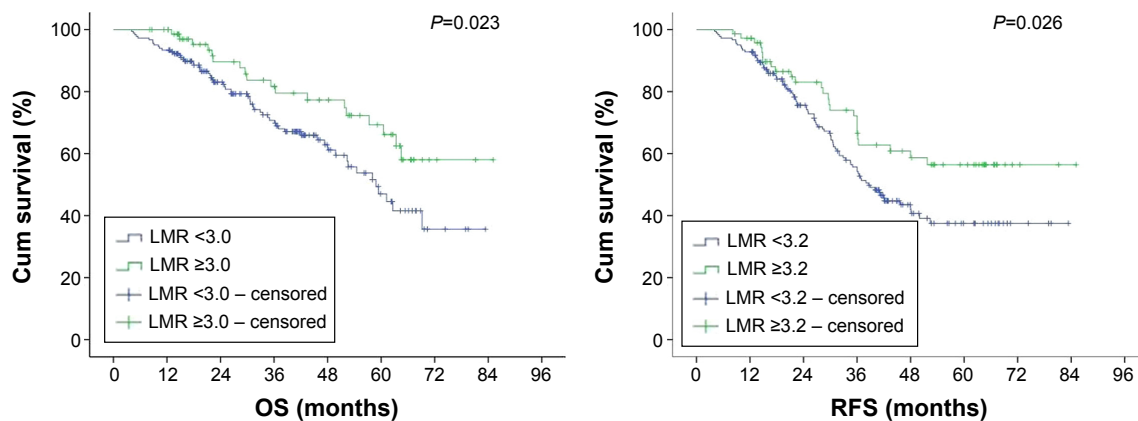


Figure 2 Kaplan-Meier estimates of survival. Left panel showed the association between lymphocyte-to-monocyte ratio (LMR) and overall survival (OS) (mean survival in LMR ≥3.0, 67 months; in LMR <3.0, 55 months, $P=0.023$). Right panel showed the association between LMR and recurrence-free survival (RFS) (mean survival in LMR ≥3.2, 60 months; in LMR <3.4, 48 months, $P=0.026$).

Abbreviation: Cum, cumulative.

Table 3 Univariate and multivariate analyses of the association of the prognostic factors with RFS

Characteristics	Univariate			Multivariate		
	n	MS (months)	P-value	HR	95% CI	P-value
Age (years)			0.132			
≥60	113	52				
<60	140	51				
Sex			0.331			
Male	165	50				
Female	88	58				
Liver cirrhosis			0.612			
Yes	161	52				
No	92	54				
Child-Pugh stage			0.213			
A	186	53				
B	67	51				
AFP (ng/mL)			0.565			
≤20	95	58				
>20	158	52				
BCLC stage			0.025	3.622	1.374–6.542	0.026
A	187	60				
B	66	52				
Tumor size (cm)			0.512			
≥5.0	107	59				
<5.0	146	52				
Tumor site			0.821			
Left	81	59				
Right	141	57				
Left and right	31	54				
Tumor stage			0.000	6.513	3.167–8.522	0.000
I+II	131	64				
III	122	45				
Pathological differentiation			0.042			
Well/moderate	128	60				
Poor	125	40				
Operation type			0.261			
Laparoscopic	75	52				
Open	178	53				
LMR			0.026	0.317	0.042–1.023	0.032
≥3.2	72	60				
<3.2	181	48				

Abbreviations: RFS, recurrence-free survival; MS, mean survival; CI, confidence interval; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

For advanced hepatocellular carcinoma (TNM stage III), patients with high LMR (≥ 3.0) had significantly longer overall mean survival than those with an LMR < 3.0 (60 months vs 45 months, $P=0.029$). Furthermore, this result remained significant for RFS (56 months vs 38 months, $P=0.029$). However, there was no statistically significant association between LMR and OS and RFS of patients with stage I and stage II cancer (for OS, 75 months vs 71 months, $P=0.579$; for RFS, 63 months vs 62 months, $P=0.816$) (see Figure 3).

In subgroup analysis of age, we found that the high LMR provided an OS (70 months vs 56 months, $P=0.036$) and RFS (64 months vs 50 months, $P=0.041$) benefit for patients aged < 60 years. In patients ≥ 60 years, there was no significant difference between high LMR and low LMR, for

OS (52 months vs 49 months, $P=0.280$) and RFS (45 months vs 41 months, $P=0.279$) (see Figure 4).

A multivariate analysis entering variables such as gender, tumor size, histological differentiation type, Child-Pugh stage, LMR, TNM stage and BCLC stage, into the Cox regression model to determine independent prognostic predictors for operable hepatocellular carcinoma was performed. The result showed that LMR (HR, 0.147; 95% CI: 0.085–0.253; $P<0.05$), TNM (HR, 5.432; 95% CI: 3.168–9.283; $P<0.05$), pathological differentiation (HR, 0.626; 95% CI: 0.412–0.952; $P<0.05$), and BCLC stage (HR, 6.532; 95% CI: 3.874–11.562; $P<0.05$) were the independent prognostic factors for OS (Table 2). Otherwise, LMR (HR, 0.317; 95% CI: 0.042–1.023; $P<0.05$), TNM (HR, 6.513; 95%

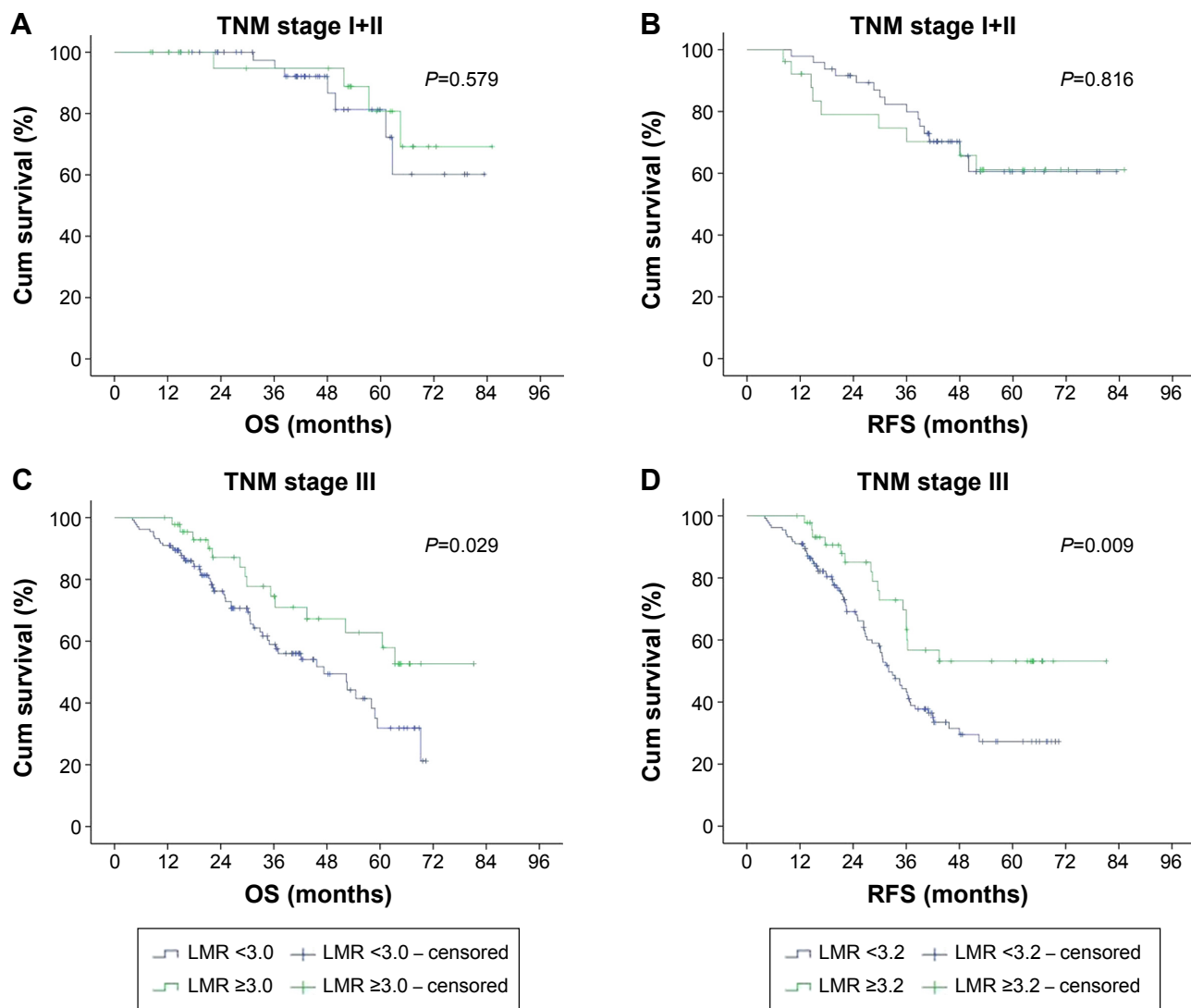


Figure 3 TNM stage-wise survivability. Panel (A and B) showed that there was no statistically significant correlation between lymphocyte-to-monocyte ratio (LMR) and overall survival (OS) and recurrence-free survival (RFS) of patients with early stage cancer, while panel (C and D) showed there was a significant association between LMR and OS and RFS of advanced cancer patients.

Abbreviation: Cum, cumulative.

CI: 3.167–8.522; $P < 0.05$), and BCLC stage (HR, 3.622; 95% CI: 1.374–6.542; $P < 0.05$) were the independent prognostic factors for RFS (Table 3).

Discussion

Both experimental and clinical data indicate that inflammation plays an important role in progression and metastasis of malignancies, which are also associated with host immunity.²² Lymphocytes were considered as the main components of the antitumor immune system, which were also the cellular basis of immunoeediting and immunosurveillance, which can reflect antitumor immune response.²³ Patients with advanced malignancy present with significant lymphocytopenia, suggesting local and systemic immunosuppression, which has

been confirmed as an independent prognostic factor for OS in malignancy.^{24–26}

Tumor-infiltrating leukocytes also have an important role in the development and progression of tumor, such as neutrophils and monocytes.²⁷ The monocytes in peripheral blood includes the dendritic cells and macrophages.²⁸ Dendritic cells have an immune regulatory function, which can cause immunosuppression of patients with malignant tumors through activating Treg cells, while macrophages can kill tumor cells.^{29,30} Otherwise, the role of macrophages/monocytes in the development and progression of cancer is controversial, presenting as inhibiting as well as enhancing potential of monocytes in human cancer.³¹ However, there is increasing evidence that the tumor-associated macrophages can prompt tumor

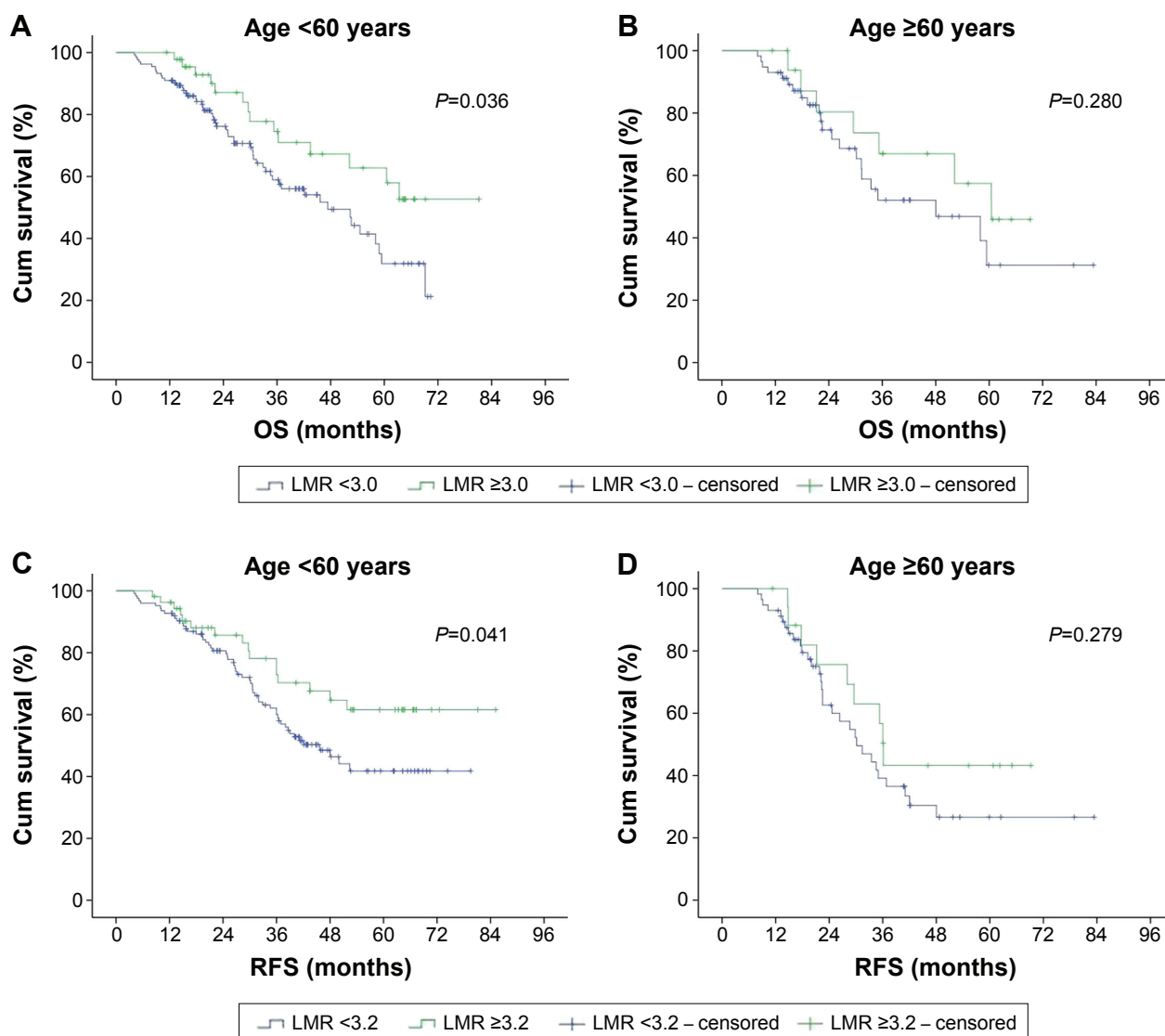


Figure 4 Age-wise survivability. Panel (A and C) showed high lymphocyte-to-monocyte ratio (LMR) provided overall survival (OS) (70 months vs 56 months, $P=0.036$) and recurrence-free survival (RFS) (64 months vs 50 months, $P=0.041$) benefit for patients aged <60 years. In panel (B and D), for patients aged ≥ 60 years, there was no significant difference between high LMR and low LMR, for OS (52 months vs 49 months, $P=0.280$) and RFS (45 months vs 41 months, $P=0.279$).

Abbreviation: Cum, cumulative.

progression.^{32,33} Furthermore, several published studies showed that increased preoperative peripheral blood monocyte count was related to poor survival in patients with cancer.^{34,35}

LMR, a biomarker related to both inflammation and immunity, can reflect the unbalanced status of inflammation and immunity, and has also been confirmed as a significant prognostic factor for several malignancies.^{36–38} In the present study, we respectively analyzed 253 patients who underwent a curative operation for primary HBV-positive hepatocellular carcinoma, and found LMR was not only an independent prognostic factor of primary hepatocellular carcinoma, but also significantly related to TNM stage. However, the association was limited to patients with advanced hepatocellular

carcinoma in subgroup analyses. It has been confirmed that advanced cancer patients who were characterized by severe inflammatory status can present as having a lower LMR.³⁹ Otherwise, LMR was highly correlated with TNM stage, thus the prognosis.

Otherwise, we found that high LMR did not represent better prognosis for patients aged less than 60 years, but for patients aged ≥ 60 years. It has been confirmed that the immune system deteriorates in the elderly, a phenomenon known as immunosenescence. In the setting of aging, the quality and quantity of lymphocytes decline.⁴⁰ Furthermore, the LMR of the elderly may be influenced, therefore not inflecting actual inflammatory status. Therefore, this study

confirmed that preoperative LMR can be applied to enable pretreatment risk stratification for individual patients, and to predict post-curative resection survival for HBV-positive hepatocellular carcinoma patients. Otherwise, LMR, as a preoperative prognostic predictive marker, can be used to plan individual treatment through patient classification. In other words, patients with a high LMR need be more aggressively treated and more frequently followed-up.

Limitations

There were several limitations in this study. The outcome of the retrospective design of the study cannot fully confirm the significance of LMR. It will take a larger scale multicenter prospective study to confirm the role of LMR. Furthermore, we estimated the cutoff LMR values for OS and RFS through ROC curves, which may not be applied to other studies. We are doing a meta-analysis including various LMR validation studies to confirm the optimal cutoff value for LMR.

Conclusion

In conclusion, LMR, characterized as easy to perform, with general availability and affordability, could be considered as an independent prognostic predictive biomarker for operable hepatocellular carcinoma.

Disclosure

The authors report no conflicts of interest in this work.

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