European Review for Medical and Pharmacological Sciences 2016; 20: 2302-2309

Platelet-to-lymphocyte ratio acts as an independent risk factor for patients with hepatitis B virus-related hepatocellular carcinoma who received transarterial chemoembolization

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Abstract. – OBJECTIVE: Hepatocellular carcinoma (HCC) is a common cause of tumor-related deaths worldwide. Previous studies have shown that increased systemic inflammation and platelet-to-lymphocyte ratio (PLR) are associated with poor prognosis of various cancers. The objective of the present study was to investigate the effects of pretreatment PLR on survival in patients with hepatitis B virus (HBV)-related HCC who underwent repeated transarterial chemoembolization (TACE).

PATIENTS AND METHODS: A total of 122 patients with HBV-related HCC who underwent TACE from two centers in the central China were analyzed retrospectively and were separated into two groups based on the median value of neutrophil-to-lymphocyte ratio (NLR; low: < 2.61 or high: ≥ 2.61) and PLR (low: < 96.13 or high: ≥ 96.13).

RESULTS: Patients with low pretreatment PLR and NLR had a higher rate of overall survival compared with patients with a high PLR and NLR (log-rank test). Univariate analyses indicated that a high PLR was a significant risk factor for poor survival (p = 0.022), and multivariate analyses further showed that a high PLR was an independent factor that predicted worse survival (p = 0.001).

CONCLUSIONS: We suggest that a high pretreatment PLR is a useful prognosticator for poor survival in patients with HBV-related HCC undergoing TACE.

Key Words:
Platelet-to-lymphocyte ratio, Hepatocellular carcinoma, Chemoembolization, Inflammation.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of tumor-related deaths in China and the fifth most common cause worldwide[1]. The rate of survival of patients with HCC is typically poor due to rapid proliferation, deterioration of liver function, increased intrahepatic spread, and metastasis. In developing countries such as China, many patients with HCC lose the opportunity for resection due to diagnosis later in the disease course, or because they cannot afford the expense for liver transplantation. Transarterial chemoembolization (TACE) remains the primary treatment for unresectable HCC[2]. It is generally accepted that a combined treatment strategy utilizing TACE and the multiple tyrosine kinase inhibitor sorafenib appears to be promising for improving survival[3]. Additionally, systemic chemotherapy such as 5-fluorouracil, oxaliplatin, and interferon[4], as well as immunotherapy[5], is a potential choice. In these patients, evaluation of potential prognostic factors is helpful in deciding on an optimal treatment strategy to increase survival benefits.

Recently, systemic inflammation is proven to be related to poor prognosis and increased tumor progression. Inflammation triggered by tumor necrosis or local antitumor immunological responses within the tumor has been confirmed to be unfavorable with regard to survival of patients with cancer[6,7]. Accumulating evidence[8-12] has shown that increased systemic inflammation is related to poor prognosis of many types of cancers including lung cancer, colorectal cancer, pancreatic cancer, and prostate cancer.

Platelet-to-lymphocyte ratio (PLR) has been used as a marker to evaluate systemic inflammatory responses. PLR is associated with poor

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prognosis in gastric cancer, epithelial ovarian cancer, and lung cancer, among others[13,14]. In addition, the neutrophil-to-lymphocyte ratio (NLR), an index of systemic inflammation, has been associated with worse survival in many types of cancer[8-12].

Many clinical investigations have shown that elevated PLR is associated with prognosis in advanced HCC[15], huge HCC[16], unresectable HCC[17], recurrent HCC undergoing TACE[18], and HCC treated by transplantation[19,20]. Most patients included in these studies had advanced or terminal stage HCC. However, the prognostic value of these two factors in the case of early or middle stage HCC has been unclear. Furthermore, the prognostic value of PLR and NLR has not been extensively evaluated in patients with hepatitis B virus (HBV)-related HCC. The objective of the present work was to assess the role of the PLR as a risk factor for the overall survival (OS) of patients with HBV-related HCC who underwent repeated TACE in two centers. Most patients were diagnosed with stage II or III (American Joint Committee on Cancer/Union for International Cancer Control tumor, node, metastasis [AJCC/UICC TNM staging system]) before TACE. To our knowledge, this was the first study to evaluate the ability of NLR and PLR to predict the risk of OS exclusively in patients with HBV-related HCC.

Patients and Methods

Ethics Statement

This study was approved by the Ethics Committee of the Hunan Province Geriatric Hospital and Second Xiangya Hospital, Central South University, China. All the enrolled patients signed the informed consent forms, and the information was stored in the hospital database and used for research.

Patients

Inclusion criteria included age between 18 and 80 years, diagnosis of HCC using biopsy or two imaging techniques showing typical features of HCC, confirmed HBV infection, Eastern Cooperative Oncology Group performance status of 0-2, Child-Pugh class of A or B, and no extrahepatic metastases. Patients were excluded if they were < 18 years of age, had severe disease such as heart failure or hepatic failure, a medical history of any other cancer, presence of tumor thrombi in the first portal branch or main portal vein, hepatic decompensation (including ascites), esophageal or gastric variceal bleeding or hepatic encephalopathy, severe underlying cardiac or renal diseases, severe coagulation disorders, or active infection at the time of blood sampling to establish NLR and PLR.

Between March 2007 and January 2015, 485 patients with HBV-related HCC from two centers (Second Xiangya Hospital, Central South University, Changsha, Hunan and Hunan Province Geriatric Hospital, Changsha, Hunan, central China) underwent serial TACE. In total, 122 patients with complete laboratory data were included retrospectively in the study.

In these patients, TACE was the sole first-line anticancer treatment because the opportunity for operative treatment was lost or waived. The last follow-up date for this study was in April 2015.

The diagnosis of HCC was confirmed based on the pathological analysis or radiological criteria of the American Association for the Study of Liver Diseases using either computed tomography or magnetic resonance imaging. HBV infection was diagnosed using laboratory detection of the hepatitis B surface antigen. All patients were infected with HBV and none was hepatitis C virus positive.

NLR and PLR were calculated as the ratios of the neutrophils and platelets to lymphocytes, respectively, from blood samples taken before the first TACE. If more than one set of measurements were available for a given patient, only the lowest PLR value was used. For each ratio, the patients were separated into two groups based on the median value of NLR and PLR (low: < 2.61 or high: ≥ 2.61, and low: < 96.13 or high ≥ 96.13, respectively).

TACE Procedure

Superior mesenteric and celiac arteriography was initially performed to assess anatomy, tumor burden, and the tumor-feeding artery. The catheter was selectively inserted into the tumor-feeding artery as close as possible to the tumor. Chemotherapeutic agents including 5-fluorouracil and oxaliplatin or pirarubicin were infused. Next, an emulsion of 10 mg mitomycin C and 5 mL to 30 mL of lipiodol was administered (the dose of lipiodol was selected depending on the size of the tumor and vasculature). Chemotherapeutic agents and doses were adjusted based on the liver function and white blood cell count. If there was insufficient embolization

with lipiodol in hypervascular tumors, gelatin sponge particles were used for further embolization. To prevent some complications, patients generally received hydration and premedications (including antiemetic agents) before chemoembolization.

Follow-up

The primary endpoint of the present study was overall survival (OS). Survival was defined as the time interval between the diagnosis of HCC and death or the last follow-up.

Statistical Analysis

SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables with normal distribution were presented as mean ± standard error. The median value was used where normal distribution was absent. When two groups were compared, Student's *t*-tests were performed.

Qualitative variables were presented as percentages, and the correlation between categorical variables was investigated using the Chi-square test. OS was estimated using the Kaplan-Meier method and the log-rank test was used for comparison of outcomes. Mortality risks were analyzed using the multivariate Cox regression model in which (in a backward-Wald manner) all the significant variables from the univariate analysis were included. A *p*-value of < 0.05 was considered significant.

Results

Demographic Data

All 122 patients were ethnic Chinese; 107 (87.7%) of 122 patients were men and 12.3% were women. The median age was 56 years (range, 26 to 77 years). Forty patients (32.7%) remained alive. The median OS was 22 months (range, three to 118 months). The liver functional reserve was assessed to be Child-Pugh grade A in 108 (88.5%) patients and grade B in 14 (11.5%) patients before TACE. None of the patients received systemic chemotherapy or sorafenib.

The median count of white blood cells, neutrophil granulocytes, lymphocytes, and platelets was 5.20×10^9/L (range, 2.4×10^9/L to 11.59×10^9/L), 3.19×10^9/L (range,1.01×10^9/L to 9.69×10^9/L), 1.19×10^9/L (range, 0.37×10^9/L to 2.97×10^9/L), and 120×10^9/L (range, 20×10^9/L to 553×10^9/L), respectively. The median PLR and NLR were 96.13 (range, 18.66 to 547.52) and 2.61 (range, 0.75 to 15.06) (Table I). Accordingly, patients with NLR < 2.61 were assigned to the low NLR group, while patients with NLR ≥ 2.61 were assigned to the high NLR group. Patients with PLR < 96.13 were assigned to the low PLR group, while patients with PLR ≥ 96.13 were assigned to the high PLR group. No significant differences in demographic and clinicopathological features were noted between the low and high PLR groups.

Overall Survival

The rates of OS according to patient characteristics are presented in Table II. PLR, T status, lymph node metastasis, and Child-Pugh grade were the characteristics that significantly influenced the OS ($p = 0.015$, $p = 0.011$, $p = 0.003$, and $p = 0.000$, respectively). The patients with higher PLR and NLR had decreased survival ratios ($p = 0.002$ and $p = 0.005$, respectively) (Figure 1).

Table III shows a comparison of demographic and clinical parameters of patients categorized according to the PLR. T status was significant ($p = 0.006$). No significant difference was noted between the two groups in terms of age, sex, -fetoprotein group, size of major lesion, white blood cell count, number of TACE procedures, lymph node metastasis and Child-Pugh grade ($p > 0.05$).

Table I. Counts of total white blood cells, neutrophils, lymphocytes, and platelets; platelet-to-lymphocyte ratios; and neutrophil-to-lymphocyte ratios in patients with hepatocellular carcinoma (n=122).

Blood components	Mean	Median	Minimum	Maximum	Normal values
Total white blood cells ($\times10^9$/L)	5.60 ± 0.19	5.20	2.40	11.59	4-10
Absolute neutrophil count ($\times10^9$/L)	3.63 ± 0.16	3.19	1.01	9.69	1.80-6.40
Absolute lymphocyte count ($\times10^9$/L)	1.28 ± 0.05	1.19	0.37	2.97	1.00-3.30
Total platelets ($\times10^9$/L)	134.76 ± 7.21	120	20	553	100-300
Neutrophil-to-lymphocyte ratio	3.38 ± 0.21	2.61	0.75	15.06	
Platelet-to-lymphocyte ratio	113.02 ± 5.97	96.13	18.66	547.52	

Table II. Overall survival and p-value according to the characteristics of patients.

		No. of patients	Duration of survival, months (95% confidence interval)	*p*-value
Age (years)	< 60	76	27.55 (22.21-33.34)	0.670
	≥ 60	46	29.28 (23.59-34.87)	
Gender	Men	107	29.16 (24.97-33.33)	0.194
	Women	15	21.40 (13.81-29.86)	
NLR	Low	61	31.80 (26.98-36.90)	0.066
	High	61	24.61 (19.23-30.07)	
PLR	Low	61	32.95 (28.15-38.25)	0.015
	High	61	23.46 (18.26-29.29)	
T status	T0-2	60	33.32 (28.22-38.40)	0.011
	T3-4	62	23.35 (18.69-29.00)	
Lymph node metastasis	N0	94	31.32 (26.99-35.99)	0.003
	N1	28	17.75 (11.79-25.06)	
Child-Pugh grade	A	108	30.39 (26.17-34.72)	0.000
	B	14	11.36 (7.57-15.71)	

NLR=neutrophil-to-lymphocyte ratio; PLR=platelet-to lymphocyte ratio.

Correlations

Univariate analysis identified the following factors as affecting the OS: Child-Pugh grade (A versus B; hazard ratio [HR]: 3.429, 95% confidence interval [CI]: 1.586-7.415, p = 0.002), PLR (low versus high; HR: 1.776, 95% CI: 1.099 to 3.126, p = 0.046), the number of TACE procedures (HR: 0.816, 95% CI: 0.693 to 0.961, p = 0.015). The multivariate Cox regression analysis identified that the rates of OS were significantly associated with PLR (low versus high; HR: 1.971, 95% CI: 1.206 to 3.221, p = 0.007), Child-Pugh grade (A versus B; HR: 3.652, 95% CI: 1.704-7.824, p = 0.001), and the number of TACE procedures (HR: 0.813, 95% CI: 0.696 to 0.950, p = 0.009). The results of univariate and multivariate analyses are presented in Table IV.

Discussion

Evidence suggests that the inflammatory tumor microenvironment may play a critical role in tumor occurrence and progression[21]. PLR, as a marker to evaluate the systemic inflammatory responses, is shown to be a prognostic factor in various tumors[9,11,22].

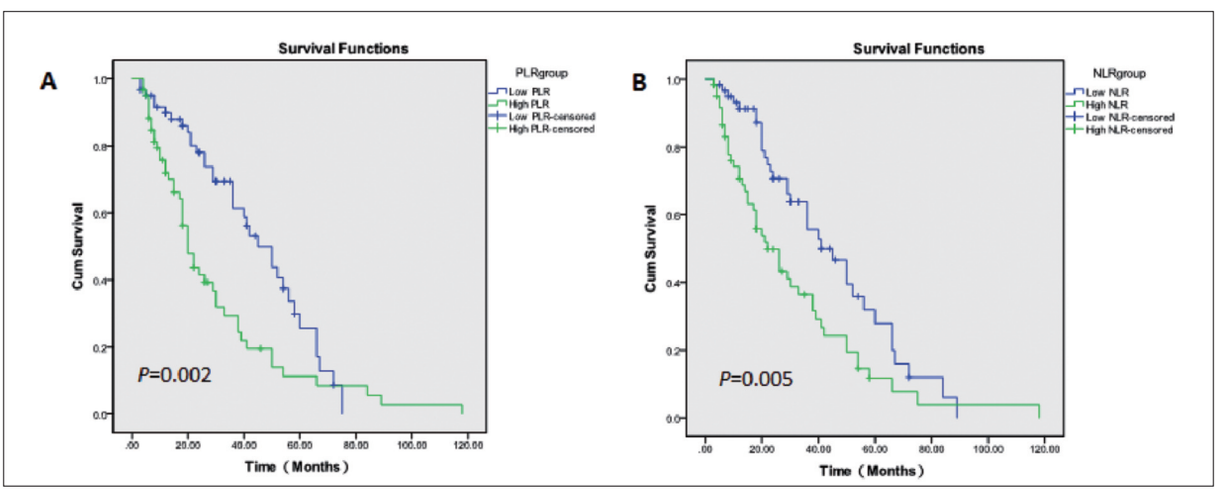

Figure 1. The overall survival according to platelet-to lymphocyte ratio (PLR) ***(A)*** and neutrophil-to-lymphocyte ratio (NLR) ***(B)***. The difference between groups were statistically significant (p = 0.002, p= 0.005).

Table III. Parameters of patients categorized according to the platelet-lymphocyte ratio.

Parameters		Platelet-Lymphocyte ratio		p-value
		Low	High	
Age (years)	< 60	38	38	1.000
	≥ 60	23	23	
Sex	Male	56	51	0.270
	Female	5	10	
AFP (ng/mL)	≤ 400	30	28	0.856
	> 400	31	33	
Size of major lesion (cm)	< 3	13	7	0.221
	≥ 3	48	54	
WBC ($\times 10^9$/L)		5.38 ± 0.29	5.82 ± 0.25	0.251
PLT ($\times 10^9$/L)		96.88 ± 6.13	172.65 ± 11.15	0.000
tTACE (times)		2.51 ± 0.20	2.86 ± 0.28	0.295
T status	T0-2	38	22	0.006
	T3-4	23	39	
N status	N0	50	44	0.282
	N1	11	17	
Child-Pugh grade	A	56	52	0.395
	B	5	9	

AFP=α-fetoprotein, PLT=platelet, TACE=transarterial chemoembolization, tTACE (times)=the number of TACE procedures, WBC=white blood cells.

Our objective was to investigate the effects of the blood NLR and PLR on survival in patients with HBV-related HCC who were undergoing TACE. As a predictor, PLR values are relatively simple and easy to detect from the serum of patients. A high PLR is an independent prognostic factor that is related to poor survival in patients with HBV-related HCC who are undergoing TACE. PLR (low *versus* high; HR: 1.971, 95% CI: 1.206 to 3.221, $p = 0.007$), Child-Pugh grade (A *versus* B; HR: 3.652, 95% CI: 1.704 to 7.824, $p = 0.001$), and the number of TACE procedures (HR: 0.813, 95% CI: 0.696-0.950, $p = 0.009$) are the independent risk factors of poor survival.

The molecular mechanisms by which high PLR predicts worse survival of patients with cancer still remain unclear; one explanation is that patients with elevated PLR have a high percentage of platelets and a low percentage of lymphocytes. A recent study described a lymphocyte-dependent host tumor-immune response[23]. Inflam-

Table IV. Univariate and multivariate analysis of risk factors for the overall survival.

Risk factor	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender:men/women	1.788	0.883-3.621	0.106			
Age (years): < 60/≥ 60	0.699	0.408-1.199	0.194			
AFP: ≤ 400/> 400 ng/mL	0.992	0.628-1.566	0.972			
T status: T0-2/T3-4	1.571	0.955-2.585	0.075			
N status	1.689	0.969-2.943	0.065			
Diameter of major lesion	0.940	0.475-1.858	0.858			
tTACE (times)	0.816	0.693-0.961	0.015	0.813	0.696-0.950	0.009
Child-Pugh grade: A/B	3.429	1.586-7.415	0.002	3.652	1.704-7.824	0.001
NLR (low or high)	1.111	0.658-1.875	0.695			
PLR (low or high)	1.776	1.009-3.126	0.046	1.971	1.206-3.221	0.007

AFP=α-fetoprotein, CI=confidence interval, HR=hazard ratio, NLR=neutrophil-to-lymphocyte ratio, PLR=platelet-to-lymphocyte ratio, TACE=transarterial chemoembolization, tTACE (times)=the number of TACE procedures.

mation promotes tumor angiogenesis, invasion, and metastasis through a subset of regulatory T lymphocytes and chemokines. Therefore, patients with subset-specific lymphocytopenia may have a higher risk of tumor recurrence and a worse prognosis. Platelets secrete certain growth factors including tumor growth factor-beta, platelet-derived growth factor, PF4, vascular endothelial growth factor, and thrombospondin-1[24,25]. These growth factors can stimulate the proliferation of tumor cells and adhesion to other cells leading to tumor growth and metastases, respectively[26]. Divella et al[27] found that high levels of tumor growth factor-beta were related to a poor prognosis in metastatic breast cancer. Platelet-derived transforming growth factor-beta, as well as the direct contact between platelets and tumor cells, synergistically promote the transition of cancer cells into an invasive mesenchymal-like phenotype, thus enhancing metastasis[28]. Vascular endothelial growth factor has been shown to be an important mediator of tumor angiogenesis[29]. Platelet-derived nucleotides can promote tumor cell transendothelial migration and metastasis via the P2Y2 receptor[30]. Finally, direct signaling between platelets and tumor cells can induce an epithelial-mesenchymal-like transition and promote metastasis.

HCC has been shown to be an inflammation-induced cancer[31]. Many clinical studies have demonstrated that elevated levels of neutrophils, platelets, lymphocytes, NLR, or PLR are associated with prognosis in HCC treated by surgical resection[32], transplantation[19], ablation[33], or TACE[16,18]. Huang et al[17] demonstrated that a high NLR independently predicted poor survival in patients with unresectable HCC who undergo TACE, while an increased postoperative NLR indicated a better outcome for patients following TACE. Kinoshita et al[34] calculated the PLR in 150 patients with HCC without treatment limitations and reported that an elevated PLR was associated with worse OS. In addition, a recent study found that both high NLR and PLR were associated with poor prognosis and metastasis in patients with recurrent HCC treated with TACE, while high PLR was a better predictor of one-year OS as an independent prognostic factor[18]. The host's immune status may be different in patients with HCC who are infected with hepatitis B compared with those with HCC who are not infected with hepatitis B. To our knowledge, no previous studies have reported hepatitis B-associated changes in the NLR or PLR of patients with the first occurrence of HCC undergoing TACE. These results demonstrate that PLR is a strong and independent risk factor for HBV-related HCC. The patients with higher NLR had decreased survival ratios, but NLR was not an independent risk factor of OS in the present study.

There are some limitations to the present work. First, 363 patients were excluded from the study, which may influence the generalizability of our results. Second, the PLR or NLR value in the present study was lower than other previous reports, because most patients underwent TACE after being diagnosed with stage II or III HCC (AJCC/UICC TNM staging system), rather than the advanced stage. The blood samples were obtained before the first TACE, and the physical examination results of a majority of the patients were good, rather than after the recurrence or during the progress of HCC. More studies are needed to investigate whether the level of PLR or NLR is associated with the TNM staging. Third, this paper was limited by the retrospective nature of the analysis and the relatively limited number of patients included. Clearly, further prospective studies are needed to confirm and update the preoperative prognostic score model for the prediction of OS in HBV-related HCC.

Conclusions

A high pretreatment baseline PLR is a useful prognosticator of poor survival in patients with HBV-related HCC undergoing TACE. Further investigations in larger and more homogeneous populations are needed to validate the prognostic ability of PLR in patients with HBV-related HCC undergoing TACE.

Acknowledgements

We thank Prof. Xinjian Chen (University of Utah, USA) for the reviews on this manuscript.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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