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Changes of platelet times neutrophil to lymphocyte ratio predict BCLC stage A hepatocellular carcinoma survival

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Abstract

Platelet, neutrophil, and lymphocyte ratio (PNLR) has its own unique role in influencing postoperative recurrence for patients with hepatocellular carcinoma (HCC). Surgical stress can change systemic inflammatory response of patients. Thus the aim of this study was to identify the prognostic value of changes of platelet times neutrophil to lymphocyte ratio in hepatitis B related HCC within Barcelona clinical liver cancer (BCLC) stage A.

Data of patients with HCC within BCLC stage A were reviewed. Pre-, intra- and postoperative variables were retrospectively and statistically analyzed. The postoperative variable was calculated based on the data obtained on the first postoperative month following liver resection.

A total of 556 patients were included in present study. During the follow-up period, 257 patients experienced recurrence and 150 patients died. Multivariate analyses suggested multiple tumors (hazard ratio [HR] = 2.409; 95% confidence interval [CI] = 1.649–3.518; $P < .001$), microvascular invasion (MVI) (HR = 1.585; 95% CI = 1.219–2.061; $P = .001$), and increased postoperative PNLR (HR = 1.900; 95% CI = 1.468–2.457; $P < .001$) independently associated with postoperative recurrence, whereas MVI (HR = 1.834; 95% CI = 1.324–2.542; $P < .001$), postoperative neutrophil to lymphocyte ratio (NLR) (HR = 1.151; 95% CI = 1.025–1.294; $P = .018$) and increased postoperative PNLR (HR = 2.433; 95% CI = 1.667–3.550; $P < .001$) contributed to postoperative mortality. The 5-year recurrence-free survival and overall survival rates of patients with increased postoperative PNLR (N = 285) versus those with decreased postoperative PNLR (N = 271) were 36.8% versus 61.5% and 47.6% versus 76.4% respectively ($P < .001$).

Changes of PNLR was a powerful prognostic indicator of poor outcomes in patients with HCC within BCLC stage A. PNLR should be monitored in our postoperative follow-up.

Abbreviations: BCLC = Barcelona Clinical Liver Cancer, HCC = hepatocellular carcinoma, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, PNLR = platelet multiple neutrophil to lymphocyte ratio.

Keywords: hepatocellular carcinoma, liver resection, platelet times neutrophil to lymphocyte ratio, prognosis

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most frequent malignancy and the third most common cancer-related cause of death worldwide.[1] There are several risks that could contribute to the occurrence of HCC, which are infection of hepatitis B and C, alcoholic cirrhosis, nonalcoholic steatohepatitis, genetic hemochromatosis, primary biliary cirrhosis, among others.[2] Recently, researchers reviewed studies and summarized various risks from occupational exposure could also lead to HCC.[3,4] In China, hepatitis B infection is the most important etiologic agent of HCC. A seropidemiological survey which was performed in 2006 showed the hepatitis B surface antigen carrier rate was 7.18% in the overall Chinese population.[5] Owing to this high prevalence, China alone accounts for about 55% of the HCC cases in the world.[6] Liver resection is widely accepted as a curative treatment for patients with HCC. The Barcelona clinic liver cancer (BCLC) staging classification recommended liver resection for patients with BCLC stage A HCC (single tumor >2 cm; or up to 3 tumors, none of each >3 cm; without macrovascular invasion and extrahepatic metastasis; physical status 0–2; liver function is Child–Pugh A or B status).[7,8] However, the postoperative recurrence rate was still high, and was reported up to 50% to 70% after liver resection.[9]

The mechanism of postoperative recurrence is complex and due to multiple factors. Recently, systemic inflammatory response was considered as an important factor influencing HCC recurrence and/or overall survival for patients with HCC following liver resection, liver transplantation, radiofrequency ablation, and so on.[10–13] Some inflammation-based prognostic

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systems, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic nutritional index (PNI), and so forth, have been developed by previous investigations to predictive postoperative recurrence and/or overall survival.[12–15] However, the prognostic power of these inflammation-based prognostic systems is still under debate.[16] Platelet, neutrophil, and lymphocyte have their own unique role in influencing postoperative recurrence for patients with HCC. Moreover, patient's systemic inflammatory response can be changed by surgical stress after liver resection. Hence, we suggested the changes of an inflammation-based prognostic system combined of platelet, neutrophil, and lymphocyte counts may be better able to mirror the status of host's immune and inflammatory response, and could strengthen the predictive ability. In this study, we would like to clarify whether the changes of platelet × neutrophil to lymphocyte ratio (PNLR) could predict the postoperative outcomes of patients with BCLC stage A hepatitis B-related HCC after liver resection.

2. Methods

2.1. Study group

Data on patients with BCLC stage A HBV-related HCC who underwent liver resection at our center between January 2007 and December 2013 were reviewed. All patients had Child A liver function and positive hepatitis B surface antigen. HCC was confirmed by postoperative pathology. Patients who fit any one of the following criteria were excluded from this study: co-infection with hepatitis C virus; experienced simultaneous splenectomy; ruptured HCC; infections during the perioperative period; re-resection; or received preoperative antitumor treatments. This study was approved by the ethics committee of West China Hospital.

2.2. Follow-up and definitions

All preoperative blood cell counts and differential counts were taken 2 days before liver resection. After operation, all patients were regularly followed up in the first postoperative month and then every 3 months in the subsequent years. Liver function, blood cell tests, serum alpha-fetoprotein (AFP), HBV-DNA, visceral ultrasonography or CT or MR imaging and chest radiography were monitored for all patients. Bone scintigraphy was performed whenever HCC recurrence was suspected. Entecavir or lamivudine was administrated to patients with positive HBV-DNA load. Postoperative recurrence was defined as positive imaging findings compared with preoperative examination values and newly rising tumor marker (AFP) values or confirmation by biopsy or resection. The NLR was defined as absolute neutrophil count divided by the lymphocyte count (10^9 cells/L).[16] The PLR was estimated as the absolute platelet count divided by the lymphocyte count (10^9 cells /L).[14] The PNI was calculated as following formula: serum albumin (gram per liter) $+5\times$ lymphocyte count (10^9 cells/L).[12] PNLR was calculated as follows: platelet × neutrophil divided by lymphocyte count (10^9/L). Postoperative NLR, PLR, PNI, and PNLR were calculated based on the data obtained on the first postoperative month after operation. Change of PNLR was calculated by postoperative PNLR minus preoperative PNLR. If the postoperative PNLR minus preoperative PNLR was >0, the change of PNLR was considered as increased, if not, it was considered as decreased. An HBV-DNA $>10^4$ copies/mL was considered high.[17] An AFP >400 ng/mL was considered high AFP level.[18]

Table 1

Demographic data of this study.

Variables	No./mean ± SD
Age, y	50.3 ± 11.8
Female/male	95/461
Differentiation (well/moderate/poor)	131/331/94
Multiple tumors	48
Tumor size, cm	5.6 ± 2.2
MVI	147
High preoperative AFP	219
High preoperative HBV-DNA	180
TB, μmol/L	14.2 ± 6.3
Intraoperative transfusion	79
Platelet, 10^9 cells/L	119 ± 52
Preoperative NLR	1.7 ± 1.3
Preoperative PLR	82.2 ± 48.8
Preoperative PNI	64.5 ± 26.7
Preoperative PNLR	203.8 ± 18.7
Postoperative NLR	1.7 ± 1.3
Postoperative PLR	78.0 ± 42.8
Postoperative PNI	65.7 ± 27.5
Postoperative PNLR	221.4 ± 164.5
Change of PNLR (increase vs. decrease)	285/271

AFP = alpha fetoprotein, HBV = hepatitis B virus, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, PNLR = platelet multiple neutrophil to lymphocyte ratio, SD = standard deviation, TB = total bilirubin.

2.3. Statistical analysis

All statistical analyses were performed by SPSS 21.0 (SPSS Inc, Chicago, IL) for windows. All continuous variables are presented as the mean ± SD and compared by using *t* test for normal distributions and Mann-Whitney *U* test for abnormal distributions. Categorical variables were compared using the χ^2 test or Fisher exact test. The independent risk factors for recurrence-free survival (RFS) and overall survival (OS) were identified by Cox regression. The Kaplan-Meier method was used to compare the postoperative RFS and OS for different groups. The difference of RFS and OS curves was compared using a log-rank test. A *P* value of <.05 was considered statistically significant.

3. Results

A total of 556 patients were involved in present study, including 95 females and 461 males. As shown in Table 1, the mean age was 50.3 ± 11.8 years. The mean tumor size was 5.6 ± 2.2 cm. A total of 48 patients had multiple tumors (tumor number ≥2). Microvascular invasion (MVI) was detected in 147 patients. One hundred eighty patients had high preoperative HBV-DNA load, whereas 219 patients suffered from high preoperative AFP level. Seventy-nine patients received intraoperative transfusion. The mean follow-up was 40.2 ± 20.0 months. After operation, the PNLR increased in 285 patients whereas decreased in 271 patients. During the follow-up period, 257 patients experienced recurrence, whereas 150 patients died. Among patients with postoperative recurrence, 17 patients received liver transplantation, 23 patients received radiofrequency ablation, 45 patients underwent reresection, and 172 patients underwent transcatheter arterial chemoembolization. The 1-, 3-, 5-year RFS rates were 83.3%, 55.1%, and 48.5% respectively, whereas the 1-, 3-, and 5-year OS rates were 97.5%, 78.7%, and 60.7%, respectively (Fig. 1A and B).

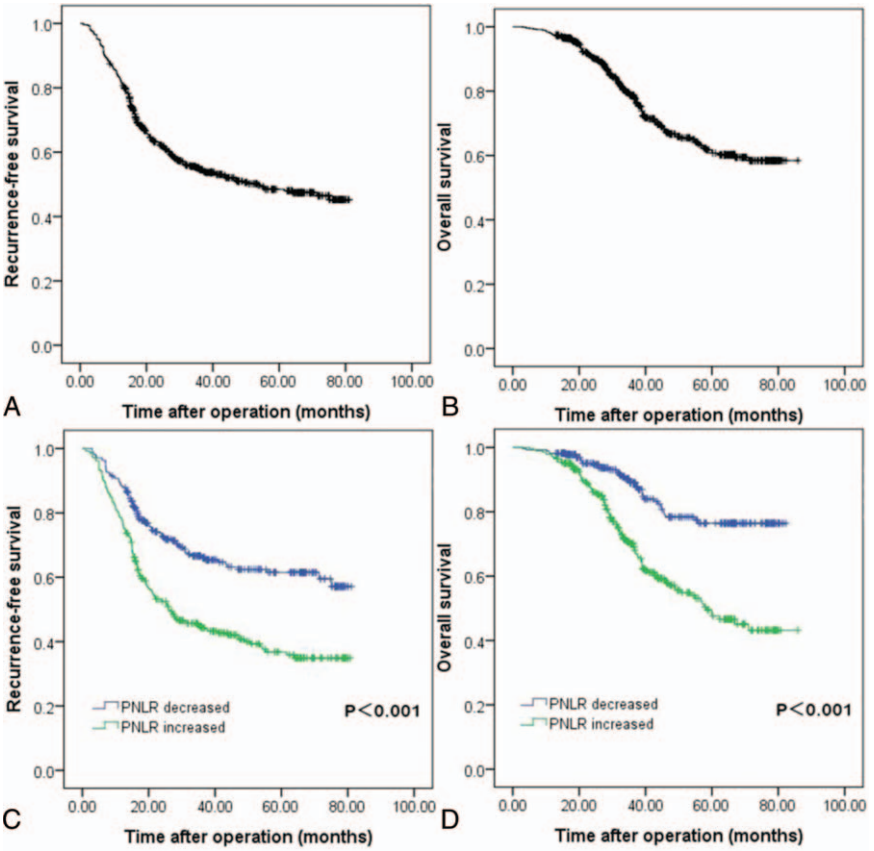

Figure 1. RFS (A) and OS (B) rates of HCC patients after liver resection. RFS (C) and OS (D) curves of patients with increased postoperative PNLR versus those with decreased postoperative PNLR. HCC = hepatocellular carcinoma, PNLR = platelet multiple neutrophil to lymphocyte ratio, RFS = recurrence-free survival, OS = overall survival.

Table 2

Factors associated with postoperative recurrence in the univariate analyses.

Variables	Recurrence	Nonrecurrence	*P*
Age, y	50.3 ± 12.0	50.3 ± 11.6	.969
Male/female	214/43	247/52	.837
Tumour size, cm	5.4 ± 2.2	5.6 ± 2.3	.277
Multiple tumors (yes/no)	32/225	16/283	.003
MVI (yes/no)	88/169	59/240	<.001
Differentiation (well/moderate/poor)	60/146/51	71/185/43	.218
AFP >400 ng/mL (yes/no)	104/153	115/184	.629
High HBV-DNA load (yes/no)	87/170	93/206	.490
Transfusion (yes/no)	42/215	35/264	.115
Platelet, 10^9 cells/L	117.6 ± 53.4	119.6 ± 52.2	.965
Total bilirubin, μmol/L	15.2 ± 6.5	14.7 ± 6.0	.356
Preoperative NLR	1.75 ± 1.15	1.69 ± 1.35	.566
Preoperative PLR	79.4 ± 44.1	84.7 ± 52.5	.209
Preoperative PNI	65.0 ± 26.8	64.1 ± 26.7	.711
Preoperative PNLR	205.8 ± 167.3	202.2 ± 193.6	.818
Postoperative NLR	1.9 ± 1.3	1.5 ± 1.2	<.001
Postoperative PLR	78.6 ± 45.6	77.6 ± 40.4	.792
Postoperative PNI	65.3 ± 27.5	66.0 ± 27.6	.776
Postoperative PNLR	233.7 ± 143.6	210.9 ± 146.2	.102
Change of PNLR (increase vs. decrease)	166/91	119/180	<.001

AFP = alpha fetoprotein, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, PNLR = platelet multiple neutrophil to lymphocyte ratio, TB = total bilirubin.

3.1. Risk factors associated with postoperative recurrence

As shown in Table 2, univariate analyses suggested that multiple tumors, MVI, postoperative NLR, and change of PNLR were all potential impacts on RFS. However, only multiple tumors (hazard ratio [HR] = 2.409; 95% confidence interval [CI] = 1.649–3.518; $P < .001$), MVI (HR = 1.585; 95% CI = 1.219–2.061; $P = .001$), and change of PNLR (HR = 1.900; 95% CI = 1.468–2.457; $P < .001$) increased the incidence of postoperative recurrence in the multivariate analysis (Table 3). The 1-, 3-, and 5-year RFS rates of patients with increased PNLR were 77.5%, 44.3%, and 36.8%, respectively, whereas of patients with decreased postoperative PNLR were 88.2%, 66.1% %, and 61.5%, respectively (Fig. 1C, $P < .001$)

3.2. Risk factors associated with overall survival

As shown in Table 4 and Table 5, additional analyses were also performed to identify risk factors associated with postoperative

Table 3

Factors associated with postoperative recurrence in the multivariate analyses.

Variables	HR	95% CI	*P*
MVI	1.585	1.219–2.061	.001
Change of PNLR	1.900	1.468–2.457	<.001
Multiple tumors	2.409	1.649–3.518	<.001

CI = confidence interval, HR = hazard ratio, MVI = microvascular invasion, PNLR = platelet multiple neutrophil to lymphocyte ratio.

Table 4

Factors associated with postoperative survival in the univariate analyses.

Variables	Survival	Died	*P*
Age, y	50.5±11.8	49.7±11.6	.474
Male/female	337/69	124/26	.925
Tumour size, cm	5.4±2.2	6.0±2.2	.002
Multiple tumors (yes/no)	35/371	13/137	.986
MVI (yes/no)	84/322	63/87	<.001
Differentiation (well/moderate/poor)	85/253/68	46/78/26	.041
AFP >400 ng/mL (yes/no)	148/258	71/79	.020
High HBV-DNA load (yes/no)	129/277	51/99	.618
Transfusion (yes/no)	48/358	29/121	.023
Platelet, 10^9 cells/L	117.8±50.9	120.3±57.3	.958
Total bilirubin, μmol/L	14.9±6.3	15.0±6.1	.911
Preoperative NLR	1.7±1.3	1.9±1.2	.065
Preoperative PLR	84.0±51.3	77.4±41.2	.156
Preoperative PNI	64.9±26.9	63.5±26.1	.590
Preoperative PNLR	195.6±181.2	226.1±182.0	.079
Postoperative NLR	1.5±1.2	2.1±1.5	<.001
Postoperative PLR	78.1±41.9	77.8±45.4	.936
Postoperative PNI	65.8±27.2	65.3±28.5	.839
Postoperative PNLR	204.7±168.5	266.7±144.3	<.001
Change of PNLR (increase vs. decrease)	174/232	111/39	<.001

AFP = alpha fetoprotein, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, PNLR = platelet multiple neutrophil to lymphocyte ratio, TB = total bilirubin.

survival by univariate and multivariate Cox regression analyses. In the univariate analyses, multiple tumors, MVI, high preoperative AFP level, differentiation, intraoperative transfusion, tumor size, postoperative NLR, and change of PNLR were associated with mortality after liver resection for patients with HCC within the BCLC stage A. However, only MVI (HR = 1.834; 95% CI = 1.324–2.542; $P < .001$), postoperative NLR (HR = 1.151; 95% CI = 1.025–1.294; $P = .018$), and change of PNLR (HR = 2.433; 95% CI = 1.667–3.550; $P < .001$) were demonstrated as independent prognostic factors for poor OS in the multivariate Cox regression analysis. The OS rate of patients with increased PNLR was significantly poor than those with decreased postoperative PNLR. The 1-, 3-, 5-year OS rates were 97.2%, 70.1%, 47.6%, respectively, in patients with increased postoperative PNLR, and 98.2%, 89.0%, 76.4%, respectively, in patients with decreased postoperative PNLR (Fig. 1D, $P < .001$).

4. Discussion

Liver resection is one of the curative managements for patients with HCC. However, postoperative recurrence remains the predominant obstacle to long-term survival for patients with HCC following liver resection. Researchers in this field have established several prediction model to help clinical practice.[19–22] In the present study, we determined increased postoperative PNLR was an independent and useful prognostic predictor of postoperative prognosis for patients with BCLC stage A HCC after liver resection. Both RFS and OS in increased postoperative PNLR group were significantly lower compared with the rates in decreased postoperative PNLR group.

Inflammation plays an important role in the development and progression of malignancy.[23] Some inflammation-based prognostic systems, such as NLR and PLR, were confirmed to influence the prognosis of HCC after liver resection by previous investigations.[11,14,24] However, the mechanisms of these

Table 5

Factors associated with postoperative survival in the multivariate analyses.

Variables	HR	95% CI	*P*
MVI	1.834	1.324–2.542	<.001
Change of PNLR	2.433	1.667–3.550	<.001
Postoperative NLR	1.151	1.025–1.294	.018

CI = confidence interval, HR = hazard ratio, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PNLR = platelet multiple neutrophil to lymphocyte ratio.

inflammation-based prognostic systems in predicting postoperative recurrence were not identical. Previous studies suggested platelet can shield tumor cells from immune responses by providing a procoagulant surface facilitating amplification of cancer-related coagulation, thus facilitating HCC growth and metastasis.[25,26] Experimental study also confirmed platelet could enhance the progress and invasion of several HCC cell lines.[27] Moreover, platelets contain many angiogenesis-regulating proteins. More than 80% vascular endothelial growth factor (a proangiogenic protein) was compromised in the platelet pool.[28] Sitia et al's experimental study even suggested antiplatelet therapy could prevent HCC and improve survival in a mouse model of chronic hepatitis B.[29] A large cohort study which was performed by Wu et al[30] confirmed aspirin use contributes to a reduced risk of HCC recurrence after liver resection. Different to platelet, Wang et al's study[31] showed the intratumoral expression of PD-L1, which is expressed in HCC and associated with local tumor antigen-specific tolerance for HCC, correlated with NLR, but not PLR and PNI. Motomura et al[32] reported that higher IL-17 levels and higher CD163-expressing tumor-associated macrophages were found in the peritumoral regions for patients with high NLR for patients with HCC after liver transplantation. Different to platelet and neutrophil, lymphocyte did not promote HCC progression and invasion, but play a key role in overcoming HCC recurrence. Accordingly, different inflammation-related variables have different role in influencing HCC recurrence after liver resection. Some investigators also suggested combination of inflammation-based prognostic systems may predict the outcomes of patients with other malignancies.[33] Recently, Wu et al[34] confirmed combination of PLR and NLR was a useful prognostic factor in advanced non-small cell lung cancer patients. Cummings et al[35] also reported PLR and NLR predict endometrial cancer survival. Combination of PLR and NLR can be better to patient's stratification.[35]

A number of investigations suggested preoperative inflammation-based prognostic system could indicate the outcomes of HCC.[12,13] However, liver resection is a stress to patients. We believe the stress which was proposed by operation may influence the balance of immune and inflammation for patients with HCC. Accordingly, we thought change of inflammation-based prognostic system after liver resection may be better than preoperative inflammation-based prognostic system. Our study also confirmed the prognostic power of change of PNLR was better than NLR, PLR, and PNI. Dan et al[10] also suggested the NLR change at the first month after radiofrequency ablation could predict the OS of patients with small HCC.

There are some limitations in the present study. Firstly, this is a single center's respective study. Secondly, our study only involved patients with hepatitis B virus infection. In China, up to 80% HCC patients had a history of hepatitis B virus infection.[36] Whether this conclusion is suitable to other causes related HCC needs a further study.

5. Conclusion

In conclusion, our study suggested change of postoperative PNLR, a simple and easily calculated inflammatory marker, can independently predict postoperative OS and RFS for patients with BCLC A stage HCC after liver resection. Change of postoperative PNLR helps us to identify patients at high risk of postoperative recurrence, should be clinical monitored in our postoperative follow-up.

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