Original Article

DOI: 10.5582/bst.2020.03180

Are inflammation-based markers useful in patients with hepatocellular carcinoma and clinically significant portal hypertension after liver resection?

Li Qin[1], Chuan Li[1,*], Fei Xie[2], Zhenxia Wang[3], Tianfu Wen[1]

[1] Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan, China;
[2] Department of Hepato-pancreato-biliary Surgery, First People's Hospital of Neijiang, Neijiang, China;
[3] Department of Hepato-pancreato-biliary Surgery, Chengdu Second People's Hospital, Chengdu, Sichuan, China.

SUMMARY Inflammation-based markers are considered prognostic indicators for patients with hepatocellular carcinoma (HCC) after liver resection. However, there is little information concerning whether they are useful for HCC patients with clinically significant portal hypertension (CSPH). In this study, 1452 patients were enrolled. Independent risk factors for recurrence-free survival (RFS) and overall survival (OS) were analyzed for patients with and without CSPH. For HCC patients without CSPH, multivariate analysis suggested that microvascular invasion (MVI), neutrophil-to-lymphocyte ratio (NLR) ≥ 3, platelet-to-lymphocyte ratio (PLR) ≥ 150, tumor size > 5 cm, and the presence of a satellite lesion were independently associated with RFS. MVI, NLR ≥ 3, PLR ≥ 150, and advanced Barcelona clinical liver cancer (BCLC) stage contributed to mortality. However, neither NLR nor PLR showed any prognostic power in HCC patients with CSPH. For HCC patients with CSPH, tumor size > 5 cm, MVI, satellite lesion, and albumin-bilirubin (ALBI) grade were independent risk factors for RFS, whereas tumor size > 5 cm, MVI, multiple tumors, ALBI grade and advanced BCLC stage showed prognostic power for OS. Our study confirmed CSPH influences the predictive ability of inflammation-based markers. This result reminds us to pay more attention to the influence of CSPH when we apply inflammation-based markers in patients with HCC after liver resection.

Keywords hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, clinically significant portal hypertension

1. Introduction

Hepatocellular carcinoma (HCC) often arises from the cirrhotic liver, which may coexist with portal hypertension and hypersplenism manifested as thrombocytopenia and/or leukocytopenia. Liver resection is widely perceived as a curative treatment for patients with HCC, but some investigators have suggested that clinically significant portal hypertension (CSPH) is a contraindication for liver resection (*1*). On the other hand, some researchers have also argued that liver resection can be safely performed in HCC patients with CSPH (*2,3*).

Many risk factors for postoperative recurrence and mortality for HCC patients have been proposed by previously published investigations. Recently, some studies confirmed that the presence of a systemic inflammatory response, which was assessed by neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and other measurements, contributed to tumor growth, metastasis and poor therapeutic outcomes in patients with HCC (*4-6*). Both NLR and PLR can be easily calculated using laboratory tests. However, serum platelet counts and lymphocyte and neutrophil counts will be impacted by portal hypertension. Accordingly, whether NLR and PLR are suitable for HCC patients with portal hypertension is unknown. Unfortunately, few published investigations have noted the adverse impact of CSPH on inflammation-based markers. In the present study, we aimed to clarify this issue.

2. Materials and Methods

Patients with HCC who underwent liver resection between 2013 and 2019 at West China Hospital of Sichuan University were retrospectively reviewed. Patients who underwent re-resection, had ruptured HCC, received preoperative antitumor treatment, had a positive surgical margin, or had other types of

tumors were excluded. All HCCs were confirmed by postoperative pathology. The ethics committee of West China Hospital approved this study (No. 170062).

2.1. Follow-up

All laboratory tests were performed one week before the operation. After liver resection, patients were regularly followed up every 3 months during the first two postoperative years and then very 6 months after 2 years. Antiviral drugs (entecavir, lamivudine or tenofovir) were conventionally administered to patients with positive hepatitis B virus (HBV)-DNA load before and after resection. The routine follow-up included blood cell tests, liver function tests, serum alpha-fetoprotein (AFP) measurement, HBV-DNA tests, visceral ultrasonography, computed tomography or magnetic resonance imaging and chest radiography. Bone scintigraphy was performed whenever HCC recurrence was suspected. Postoperative recurrence was defined as positive imaging findings compared with the preoperative examination values or as confirmed by biopsy or resection.(*7*)

2.2. Definitions

High AFP was defined as > 400 ng/mL (*7*). Preoperative HBV DNA load > 10^4 copies/mL was considered to be a high preoperative HBV DNA load (*8*). Clinically significant portal hypertension (CSPH) was defined by the presence of esophagogastric varices and/or a platelet count < 100 × 10^9/L in association with splenomegaly (*9*). The definitions of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI), systemic immune-inflammation index (SII), aspartate aminotransferase-to-platelet count ratio index (APRI) and albumin-bilirubin (ALBI) grade are listed in Table 1(*10-15*). NLR ≥ 3 was defined as being high (*10*). PLR ≥ 150 was considered high (*10*). The cut-off value of PNI was 45, as reported in the literature (*11*). SII ≥ 330 was considered high (*12*). PRI ≥ 0.5 was considered high (*13,14*). ALBI values were divided into 3 grades: grade 1 (less than -2.60), grade 2 (between -2.60 and -1.39) and grade 3 (above -1.39) (*15*).

2.3. Statistical analysis

All statistical analyses were performed in SPSS 26.0 (SPSS Company, Chicago, IL) for Windows. All continuous variables were analyzed using one-way analysis of variance. Binary variables were compared by using the χ^2 test or Fisher's exact test. The Kaplan-Meier method was applied to determine the recurrence-free survival (RFS) and overall survival, and the log-rank test was performed to test the survival differences. Multivariable analysis was carried out using Cox regression analysis to identify independent risk factors for OS and RFS. All variables with a P value < 0.1 in the univariate analysis were taken into the multivariate analysis. A P value of < 0.05 was considered statistically significant.

3. Results

A total of 1,452 patients were included in this study. The clinical and demographic data of this study are shown in Table 2. Patients were followed up regularly until death or the termination of this study (April 2020). The minimum follow-up period of this study was 3 months. During a mean of 33.7 ± 18.5 months of follow-up, 1,027 patients suffered from recurrence, and 810 patients died.

3.1. Independent prognostic factors for RFS and OS in patients without CSPH

In patients without CSPH, multivariate analysis revealed that the presence of microvascular invasion (MVI) (HR = 1.681, 95% CI = 1.372-2.060, P < 0.001), NLR ≥ 3 (HR = 1.222, 95% CI = 1.015-1.472, P = 0.035), PLR ≥ 150 (HR = 1.272, 95% CI = 1.058-1.529, P = 0.011), tumor size larger than 5 cm (HR = 1.693, 95% CI = 1.306-2.195, P < 0.001) and the presence of a satellite lesion (HR1.263, 95% CI = 1.026-1.554, P = 0.028) were independently associated with postoperative recurrence (Table 3). As shown in Table 4, presence of MVI (HR = 1.756, 95% CI = 1.335-2.309, P < 0.001), NLR ≥ 3 (HR = 1.274, 95% CI = 1.032-1.571, P = 0.024), PLR ≥ 150 (HR = 1.428, 95% CI = 1.161-1.756, P = 0.001), and Barcelona Clinic Liver Cancer (BCLC) stage (HR = 2.100, 95% CI = 1.614-2.732, P < 0.001) were independent risk factors for OS.

The 1-, 3-, and 5-year RFS were 74.4%, 41.2 and 32.9% respectively for patients with low NLR, and 64.0%, 26.2% and 14.6% respectively for patients

Table 1. Definitions of inflammation-based markers in this study

Variables	Definitions
Neutrophil-to-lymphocyte ratio	Absolute neutrophil count divided by the lymphocyte count
Platelet-to-lymphocyte ratio	Platelet count divided by lymphocyte count
Prognostic nutrition index	Serum albumin (g/L) + 5 × lymphocyte count (10^9/L).
Systemic immune-inflammation index	Platelet counts × neutrophil counts/lymphocyte counts
Aspartate aminotransferase-to-platelet count ratio index	[(Aspartate aminotransferase/upper limit of normal)/platelet count (10^9/L)] × 100
Albumin-bilirubin grade	($\log_{10}$ bilirubin (μmol/L) × 0.66) + (albumin (g/L) × -0.085)

Table 2. Clinical and demographic data of current study

Variables	N/mean ± SD
Male/female	1229/223
Age (years)	51.1 ± 12.0
Tumor size (cm)	7.1 ± 3.7
Multiple tumors	351
Presence of MVI	836
The number of patients with high AFP	609 (ranged from 401 to 256360 ng/mL)
The number of patients with high HBV-DNA	648 (ranged from 1.01×10^4 copies/mL to 7.65×10^7 copies/mL)
The number of patients with high NLR	387 (ranged from 3.0 to 14.2)
The number of patients with high PLR	260 (ranged from 150 to 903)
The number of patients with high SII	577 (ranged from 330 to 5501)
The number of patients with low PNI	326 (ranged from 32.95 to 44.98)
ALBI grade 1/2/3	981/471/0
BCLC stage 0 and A/B/C	672/162/618
Presence of CSPH	527

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SD, standard deviation; SII, Systemic immune-inflammation index.

Table 3. Univariate and multivariate analyses of predictors for postoperative recurrence in patients without clinically significant portal hypertension

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Age > 60 years	0.868			
Male	0.729			
Tumor size > 5 cm	< 0.001	1.693	1.306-2.195	< 0.001
Multiple tumors	0.018			0.982
Poor tumor differentiation	0.002			0.529
AFP > 400 ng/mL	< 0.001			0.112
High HBV-DNA load	0.886			
Presence of MVI	< 0.001	1.681	1.372-2.060	< 0.001
Satellite lesion	0.001	1.263	1.026-1.554	0.028
NLR ≥ 3	< 0.001	1.222	1.015-1.472	0.035
PNI < 45	0.001			0.322
PLR ≥ 150	< 0.001	1.272	1.058-1.529	0.011
SII ≥ 330	0.002			0.439
APRI ≥ 0.5	0.039			0.785
ALBI grade	0.001			0.073
BCLC stage	< 0.001			0.586

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SII, Systemic immune-inflammation index.

Table 4. Univariate and multivariate analyses of predictors for postoperative mortality in patients without clinically significant portal hypertension

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Age > 60 years	0.983			
Male	0.657			
Tumor size > 5 cm	< 0.001			0.242
Multiple tumors	0.008			0.271
Poor tumor differentiation	< 0.001			0.999
AFP > 400 ng/mL	< 0.001			0.101
High HBV-DNA load	0.426			
Presence of MVI	< 0.001	1.756	1.335-2.309	< 0.001
Satellite lesion	0.032			0.624
NLR ≥ 3	< 0.001	1.274	1.032-1.571	0.024
PNI < 45	0.003			0.785
PLR ≥ 150	< 0.001	1.428	1.161-1.756	0.001
SII ≥ 330	0.001			0.593
APRI ≥ 0.5	0.021			0.394
ALBI grade	0.002			0.239
BCLC stage	< 0.001	2.100	1.614-2.732	< 0.001

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SII, Systemic immune-inflammation index.

with high NLR ($P < 0.001$, Figure 1A). The 1-, 3-, and 5-year OS were 91.5%, 61.2 and 39.6% respectively for patients with low NLR, and 88.5%, 43.7% and 26.3% respectively for patients with high NLR ($P < 0.001$, Figure 1B). The 1-, 3-, and 5-year RFS of patients with low and high PLR were 75.4%, 41.9%, 32.5% and 62.8%, 25.0%, 15.5% respectively. A significant difference was observed ($P < 0.001$, Figure 1C). The 1-, 3-, and 5-year OS of patients with low PLR were 92.6%, 62.7%, and 40.9% respectively, which were significantly better than those with low PLR (85.8%, 40.5%, 23.2% respectively, $P < 0.001$, Figure 1D)

3.2. Independent prognostic factors for RFS and OS in patients with CSPH

Among patients with CSPH, as presented in Table 5, the multivariate analysis confirmed that tumor size

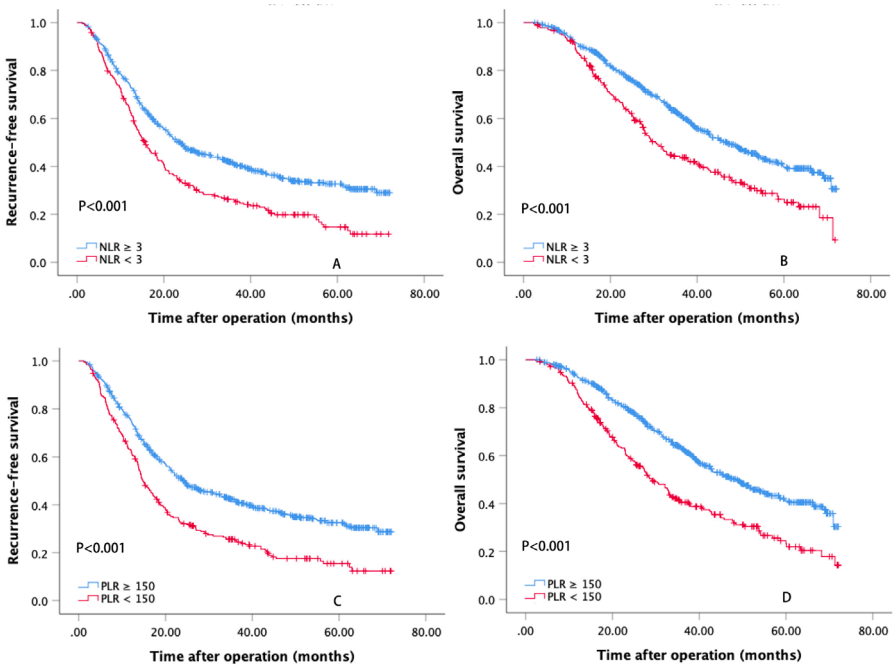

Figure 1. The recurrence-free (A) and overall (B) survival curves of patients with high and low neutrophil to lymphocyte ratios. The recurrence-free (C) and overall (D) survival curves of patients with high and low platelet to lymphocyte ratios.

Table 5. Univariate and multivariate analyses of predictors for postoperative recurrence in patients with clinically significant portal hypertension

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Age > 60 years	0.529			
Male	0.432			
Tumor size > 5 cm	< 0.001	1.485	1.173-1.879	0.001
Multiple tumors	0.007			0.743
Poor tumor differentiation	0.011			0.998
AFP ≥ 400 ng/mL	0.188			
High HBV-DNA load	0.824			
Presence of MVI	< 0.001	1.875	1.495-2.351	< 0.001
Satellite lesion	< 0.001	1.532	1.187-1.976	0.001
NLR ≥ 3	0.078			0.294
PNI < 45	0.179			
PLR ≥ 150	0.836			
SII ≥ 330	0.263			
APRI ≥ 0.5	0.166			
ALBI grade	0.006	1.333	1.098-1.619	0.004
BCLC stage	< 0.001			0.140

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SII, Systemic immune-inflammation index.

Table 6. Univariate and multivariate analyses of predictors for postoperative mortality in patients with clinically significant portal hypertension

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Age > 60 years	0.785			
Male	0.721			
Tumor size > 5 cm	< 0.001	1.398	1.003-1.948	0.048
Multiple tumors	0.063	0.656	0.489-0.882	0.005
Poor tumor differentiation	0.005			0.214
AFP > 400 ng/mL	0.142			
High HBV-DNA load	0.367			
Presence of MVI	< 0.001	1.598	1.188-2.150	0.002
Satellite lesion	0.007			0.051
NLR ≥ 3	0.097			0.572
PNI < 45	0.012			0.287
PLR ≥ 150	0.543			
SII ≥ 330	0.052			0.466
APRI ≥ 0.5	0.320			
ALBI grade	0.002	1.389	1.117-1.726	0.003
BCLC stage	< 0.001	2.209	1.490-3.276	< 0.001

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SII, Systemic immune-inflammation index.

greater than 5 cm (HR = 1.484, 95% CI = 1.173-1.879, $P = 0.001$), MVI (HR = 1.875, 95% CI = 1.495-2.351, $P < 0.001$), satellite lesion (HR = 1.532, 95% CI = 1.187-1.976, $P = 0.001$) and ALBI grade (HR = 1.333, 95% CI = 1.098-1.619, $P = 0.004$) independently predicted postoperative recurrence.

As shown in Table 6, tumor size greater than 5 cm (HR = 1.398, 95% CI = 1.003-1.948, $P = 0.048$), multiple tumors (HR = 0.656, 95% CI = 0.489-0.882, $P = 0.005$), MVI (HR = 1.598, 95% CI = 1.188-2.150,

Table 7. Comparison of clinicopathological characteristics of patients with or without clinically significant portal hypertension

Variable	Patients without CSPH	Patients with CSPH	*P* values
Age	50.5 ± 12.2	52.2 ± 11.6	< 0.001
Female/male	150/775	73/454	0.230
Tumor size (cm)	7.7 ± 3.9	6.0 ± 3.1	< 0.001
MVI (yes/no)	564/361	272/255	0.001
Multiple tumors (yes/no)	217/708	134/393	0.400
Poor tumor differentiation	195/730	71/456	< 0.001
AFP > 400 ng/mL	408/516	200/327	0.020
High HBV-DNA load	397/528	251/276	0.083
Satellite lesion	149/776	80/447	0.641
NLR	2.6 ± 2.2	2.7 ± 1.7	0.519
PLR	130.9 ± 87.8	64.9 ± 30.2	< 0.001
PNI	49.5 ± 5.6	47.6 ± 5.2	< 0.001
SII	489.1 ± 591.4	198.5 ± 126.9	< 0.001
APRI	0.82 ± 0.72	1.09 ± 1.83	< 0.001
Neutrophil	3.6 ± 1.6	3.1 ± 1.5	< 0.001
Lymphocyte	1.6 ± 0.6	1.3 ± 0.5	< 0.001
Albumin	41.4 ± 4.4	40.9 ± 4.3	0.059
AST	47.5 ± 31.3	49.2 ± 36.3	0.350
ALBI grade (grade 1/2)	663/262	318/209	< 0.001
BCLC stage (0/A *vs.* B/C)	393/532	279/248	< 0.001

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; APRI, Aspartate aminotransferase-to-platelet count ratio index; BCLC stage, Barcelona Clinic Liver Cancer stage; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; MVI, microvascular invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio, PNI, Prognostic nutrition index; SII, Systemic immune-inflammation index.

P = 0.002), ALBI grade (HR = 1.389, 95% CI = 1.117-1.726, *P* = 0.003) and BCLC stage (HR = 2.209, 95% CI = 1.490-3.276, *P* < 0.001) were independent risk factors in the multivariate analysis (Table 6).

3.3. Comparison of clinicopathological characteristics of patients with versus without CSPH

As listed in Table 7, large tumors, MVI, poor tumor differentiation, high preoperative AFP, high PLR, high SII, low APRI and advanced tumors were more often observed in patients without CSPH, whereas older patients, lower PNI, low preoperative lymphocyte count, low preoperative neutrophil count and ALBI grade 2 were more often found in those with CSPH.

4. Discussion

In this study, we confirmed that NLR and PLR may be prognostic predictors for HCC patients without CSPH, but not for those with CSPH. Moreover, ALBI grade may be a surrogate predictive marker for those with CSPH.

In this study, both NLR and PLR predicted the outcomes of HCC patients without CSPH, but not in those with CSPH. Many studies have suggested that both NLR and PLR could predict the postoperative prognosis of patients with HCC after liver resection (*6,10*). There are some potential mechanisms by which high NLR and PLR could contribute to poor prognosis. First, both neutrophils and platelets could secrete some factors that could promote angiogenesis, tumor progression and metastasis (*16,17*). Second, lymphocytes are very important anticancer cells (*18,19*). However, many previous investigations ignored the adverse influence of CSPH on neutrophils, platelets and lymphocytes. CSPH results in low platelet counts and even low white blood cell counts. As shown in Table 7, high PLR was rare in those with CSPH due to a low preoperative platelet count. Moreover, both neutrophils and lymphocytes were reduced in patients with CSPH, though it seems that lymphocytes decreased slightly more than neutrophils. The discrepancy in the magnitudes of the lymphocyte and neutrophil declines may explain why the NLR was not a prognostic predictor for patients with CSPH. However, few previous studies ignored the impact of CSPH on markers of the systemic inflammatory response. Our results could also explain why the predictive ability of NLR and PLR was controversial among previous investigators. In this study, larger tumor size, more MVI and higher AFP level were observed in HCC patients without CSPH. The tolerance for surgical procedures of patients with CSPH may be worse than those without CSPH due to thrombocytopenia. Accordingly, some HCC patients with CSPH cannot tolerate liver resection, such as those with very large tumors or advanced BCLC stage. Because, in this situation, we need to remove a lot of liver parenchyma, and the surgical procedure is more complicated.

It was interesting that SII was not a prognostic predictor, even in patients without CSPH, although this marker was calculated using neutrophils, lymphocytes and platelets. Hu *et al.* (*12*) reported that circulating tumor cell levels were significantly higher and the prognosis was poorer in HCC patients with a high SII. They divided HCC patients into high- and low-SII groups by using a cut-off of 330, which was also used in the current study (*12*). However, some investigations confirmed that SII is a good predictor for patients with HCC, but they proposed other optimal cut-off values (*20,21*). For example, Wang *et al.* (*21*) used 305 as the best cut-off value of SII, whereas Fu *et al.* (*20*) used 226 as the optimal cut-off value of SII. Further study is needed to determine the best cut-off level of SII from the view of predicting the outcome of patients who underwent liver resection for HCC.

There are some limitations in this study. This is a retrospective study and lacks validation. Moreover, there are many biomarkers of the systemic inflammatory response, only some of which we measured. Different from previous studies, we assessed the influence of inflammation-based markers on prognosis of HCC patients with or without CSPH respectively. Our study

confirmed that these biomarkers can be impacted by CSPH, especially those calculated from platelets, neutrophils, lymphocytes and albumin.

In conclusion, CSPH could influence the predictive capacity of biomarkers of the systemic inflammatory response. NLR and PLR only showed prognostic power in HCC patients without CSPH, whereas poor liver function assessed by ALBI grade contributed to a poor prognosis for HCC patients with CSPH following liver resection. In clinical practice, we should not ignore the adverse influence of CSPH on inflammation-based biomarkers in predicting the outcomes of patients with HCC after liver resection.

Acknowledgements

This study was supported by grants from the State Key Scientific and Technological Research Programs (2017ZX10203207-003-0020), the National Natural Science Foundation of China (81900576), and the Science and Technological Supports Project of Sichuan Province (2019YJ0149).

References

1. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J, HCC EPoEo. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001; 35:421-430.
2. Giannini EG, Savarino V, Farinati F, Ciccarese F, Rapaccini G, Marco MD, Benvegnu L, Zoli M, Borzio F, Caturelli E, Chiaramonte M, Trevisani F, Italian Liver Cancer g. Influence of clinically significant portal hypertension on survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. Liver Int. 2013; 33:1594-1600.
3. Jang CW, Kwon HJ, Kong H, Ha H, Han YS, Chun JM, Kim SG, Hwang YJ. Impact of clinically significant portal hypertension on surgical outcomes for hepatocellular carcinoma in patients with compensated liver cirrhosis: a propensity score matching analysis. Ann Hepatobiliary Pancreat Surg. 2016; 20:159-166.
4. Sanghera C, Teh JJ, Pinato DJ. The systemic inflammatory response as a source of biomarkers and therapeutic targets in hepatocellular carcinoma. Liver Int. 2019; 39:2008-2023.
5. Zheng J, Seier K, Gonen M, Balachandran VP, Kingham TP, D'Angelica MI, Allen PJ, Jarnagin WR, DeMatteo RP. Utility of Serum Inflammatory Markers for Predicting Microvascular Invasion and Survival for Patients with Hepatocellular Carcinoma. Ann Surg Oncol. 2017; 24:3706-3714.
6. Goh BK, Kam JH, Lee SY, Chan CY, Allen JC, Jeyaraj P, Cheow PC, Chow PK, Ooi LL, Chung AY. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and prognostic nutrition index as preoperative predictors of early mortality after liver resection for huge (>/=10 cm) hepatocellular carcinoma. J Surg Oncol. 2016; 113:621-627.
7. Li C, Shen JY, Zhang XY, Peng W, Wen TF, Yang JY, Yan LN. Predictors of Futile Liver Resection for Patients with Barcelona Clinic Liver Cancer Stage B/C Hepatocellular Carcinoma. J Gastrointest Surg. 2018; 22:496-502.
8. Huang G, Li PP, Lau WY, Pan ZY, Zhao LH, Wang ZG, Wang MC, Zhou WP. Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels: A Randomized Controlled Trial. Ann Surg. 2018; 268:943-954.
9. Takemura N, Aoki T, Hasegawa K, Kaneko J, Arita J, Akamatsu N, Makuuchi M, Kokudo N. Hepatectomy for hepatocellular carcinoma after perioperative management of portal hypertension. Br J Surg. 2019; 106:1066-1074.
10. Yamamura K, Sugimoto H, Kanda M, Yamada S, Nomoto S, Nakayama G, Fujii T, Koike M, Fujiwara M, Kodera Y. Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci. 2014; 21:682-688.
11. Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, Chan HL, To KF. Prognostic Nutritional Index (PNI) Predicts Tumor Recurrence of Very Early/Early Stage Hepatocellular Carcinoma After Surgical Resection. Ann Surg Oncol. 2015; 22:4138-4148.
12. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, Fan J. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014; 20:6212-6222.
13. Wang H, Xue L, Yan R, Zhou Y, Wang MS, Cheng MJ, Huang HJ. Comparison of FIB-4 and APRI in Chinese HBV-infected patients with persistently normal ALT and mildly elevated ALT. J Viral Hepat. 2013; 20:e3-10.
14. Luo H, Li C, Chen L. Preoperative albumin-bilirubin grade combined with aspartate aminotransferase-to-platelet count ratio index predict outcomes of patients with hepatocellular carcinoma within Milan criteria after liver resection. Biosci Trends. 2019; 13:176-181.
15. Johnson PJ, Berhane S, Kagebayashi C, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015; 33:550-558.
16. Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol. 2011; 54:948-955.
17. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, Jirouskova M, Degen JL. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood. 2005; 105:178-185.
18. Wang M, Li C, Wen TF, Peng W, Chen LP. Postoperative Low Absolute Lymphocyte Counts may Predict Poor Outcomes of Hepatocellular Carcinoma After Liver Resection. Chin Med J (Engl). 2016; 129:536-541.
19. Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, Xu MQ. Postoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio predicts the outcomes of hepatocellular carcinoma. J Surg Res. 2015; 198:73-79.

20. Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, Li H, Zhang J, Zhang Y, Zhao H, Yang Y. Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria. Cell Physiol Biochem. 2018; 47:293-301.
21. Wang C, He W, Yuan Y, Zhang Y, Li K, Zou R, Liao Y, Liu W, Yang Z, Zuo D, Qiu J, Zheng Y, Li B, Yuan Y. Comparison of the prognostic value of inflammation-based scores in early recurrent hepatocellular carcinoma after hepatectomy. Liver Int. 2020; 40:229-239.

Received May 25, 2020; Revised June 26, 2020; Accepted July 5, 2020.

*Address correspondence to:
Chuan Li, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China.
E-mail: lichuan@scu.edu.cn

Released online in J-STAGE as advance publication July 8, 2020.