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

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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 every 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 esophageal 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. 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 χ² 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 (10^7/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 (10^7/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

| Variable                        | 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 1.01×10⁶ copies/mL to 7.65 ×10⁷ 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       | 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; SD, standard deviation; 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       | 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  | 1.61-2.732 | < 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; SD, standard deviation; 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
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, \( P = 0.002 \)).
Second, both NLR and PLR could predict the postoperative outcomes of HCC patients without CSPH. Many studies have suggested that those with CSPH. Many studies have suggested that both NLR and PLR could predict the postoperative prognosis of patients with HCC after liver resection. 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. Second, lymphocytes are very important anticancer cells. 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. 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. However, some investigations confirmed that SII is a good predictor for patients with HCC, but they proposed other optimal cut-off values. For example, Wang et al. used 305 as the best cut-off value of SII, whereas Fu et al. 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

### 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
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.

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