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Prognostic value of inflammatory and nutritional markers for hepatocellular carcinoma

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Abstract

Many clinical studies have demonstrated that the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and Onodera's prognostic nutritional index (OPNI) are visibly involved in the prognosis of a variety of tumors. In our research, we aim to determin the prognostic impact of NLR, PLR, and OPNI for hepatocellular carcinoma (HCC).

Data of hepatocellular carcinoma patients undergoing treatment in Changzhi People's Hospital between 2011 and 2017 were reviewed. 270 patients with HCC were under inclusion criteria. The optimal cut-off points of OPNI, NLR and PLR were determined by using the X-tile program. The overall survival (OS) was analyzed by Kaplan–Meier method. Multivariate analysis was performed using Cox Proportional Hazard Regression model to determine independent prognostic indicators for HCC.

As revealed by Univariate and multivariate analysis, OPNI, Treatment, PLR, and BCLC Stage can be used as independent prognostic indicators for HCC. Comparing the *P* values and hazard ratios, we found out that the OPNI has greatest influence on prognosis in these indexes. The appropriate cut-off points of NLR, PLR, and OPNI were 2.5, 133.3, and 39.5, respectively. High score OPNI group had a better OS. In the analysis between OPNI and clinicopathological characteristics, there were differences in treatment, postoperative therapy, AST, ALBI grade, NLR and PLR between the high OPNI group and the low OPNI group, while others did not.

OPNI is a straightforward and effective independent prognostic indicator for HCC.

Abbreviations: HCC = hepatocellular carcinoma, NLR = neutrophil to lymphocyte ratio, OPNI = Onodera's prognostic nutritional index, OS = overall survival, PLR = platelet to lymphocyte ratio.

Keywords: hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, Onodera's prognostic nutritional index, platelet-to-lymphocyte ratio, prognostic indicator

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1. Introduction

Hepatocellular carcinoma is the most common type of primary liver cancer, which is originate from hepatocyte. Globally, it rank the second in the cancer-related death in men.[1] The death rate of liver cancer in the U.S. was 10.3 per 100,000 in 2016.[2] The 5-year survival rate for liver cancer was only 18%.[3] China alone accounts for 50 percent of global cases.[4] In China, the main risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus infection and aflatoxin exposure.

Preoperative assessment of HCC (such as liver function tests and imaging studies), surgical techniques, and postoperative care can improve survival in patients for HCC. However, HCC has a high local recurrence rate, so long-term survival after hepatectomy remains low. The present markers related to the prognosis of HCC include osteopontin (OPN),[5] vascular endothelial growth factor (VEGF),[6] Dickkopf-1 (DKK-1),[7] transforming growth factor-β_1 (TGF-β_1),[8] glypican-3 (GPC-3),[9] etc. However, there are some deficiencies in them, such as the mechanism has not been fully clarified yet. In addition, these markers showed poor specificity, so novel prognostic markers are urgently needed for HCC.

Tumor-associated inflammatory cells play an important role in the tumor microenvironment. They can facilitate the growth, invasion and dissemination of tumor cells, which have great significance in the occurrence and development of tumors.[10] Immunoinflammatory factors were shown to be connected with the oncogenesis, progression, and prognosis of HCCs. There is also increasing evidence that the NLR and PLR (an easily measured,

reproducible and cost-effective systemic inflammatory marker) can regard as prognostic indicators for patients with a variety of solid neoplasms, such as pancreatic cancer, colorectal cancer, and epithelial ovarian cancer.[11–13]

Onodera's prognostic nutritional index (OPNI) can be utilized to evaluate the immunonutritional status of patients undergoing liver surgery.[14] It has been reported that OPNI is a useful prognostic indicator for small cell lung cancer,[15] clear cell renal cell carcinoma,[16] colorectal cancer[17] and pancreatic cancer,[18] in addition, previous studies have evaluated the prognostic value of OPNI in HCC,[19,20] but there are few studies focus on the reasons why OPNI can be used as a prognostic indicator of HCC. In our research, we aim to analyze the impact of the OPNI for patients' outcomes of HCC from the perspective of immune, inflammation promoting tumor progression and liver function impairment.

2. Patients and methods

2.1. Patients

We examined the data of patients with HCC retrospectively who treated in Changzhi People's Hospital (Changzhi, China) between 2011 and 2017. Patients included in the analysis according to the following criterias:

1. imaging techniques and postoperative pathology confirmed HCC
2. absence of coeval tumors;
3. without signs of infection;
4. completed clinical and follow-up data.

Ultimately, 270 patients meets the inclusion criterias. This study was approved by the Ethics Committee of Changzhi People's Hospital (Changzhi, China), and written informed consent for their data to be used was obtained from all of the patients.

2.2. Laboratory data collection

Peripheral blood routine, liver function and AFP examination were performed in all patients within 7 days before treatment. The NLR's calculation formula as follow: NLR= neutrophil count / lymphocyte count (10^9/L). PLR can be calculated by platelet count / lymphocyte count (10^9/L). OPNI was calculated by serum albumin (g /L) + 5 lymphocyte count(10^9/L). ALBI=0.66*lg (TBIL) (μmol/L) −0.085*albumin (g/L). ALBI score ≤−2.60 defined as grade 1, −2.60 < ALBI score ≤−1.39 defined as grade 2, ALBI score ≤−1.39 defined as grade 3.

2.3. Clinicopathological characteristics

Basic features were collected, including age, treatment, postoperative treatment, tumor staging, and laboratory data (AFP, ALT, AST, TBIL, neutrophil count, lymphocyte count, platelets, serum albumin). According to the BCLC stage system, hepatocellular carcinoma was classified as 5 stages: 0, A, B, C, and D.

2.4. Follow-up

Patients were inspected by imaging techniques per 3 to 6 months postoperatively to assess tumor recurrence or metastatic dissemination. Patients' follow-up information were collected from tumor registries, hospital records or obtained from the patients and family members. In our research, we took the overall survival (OS) as the end point of the study, because OS was considered to be the most suitable event for survival analysis.

2.5. Statistical analyzes

Version 20.0 (IBM, New York), IBM SPSS Statistics has been used to perform all statistical analysis. Count data were summarized using frequencies and percentages. The appropriate cut-off points of NLR, PLR and OPNI were analyzed using X-tile version 3.6.1 (Robert L Camp, Yale University, New Haven, CT, USA). Overall survival analysis was performed by

Table 1

Demographic and clinical characteristics of the included patients with Hepatocellular carcinoma.

Characteristics	Number (%)
Age (y)	
≤60	166 (61.48%)
>60	104 (38.52%)
gender	
male	222 (82.22%)
female	48 (17.78%)
Treatment	
Surgery	162 (60.00%)
Interventional therapy	102 (37.78%)
Conservation	6 (2.22%)
Postoperative therapy	
Yes	227 (84.07%)
No	43 (15.93%)
AFP	
≤400	179 (66.30%)
>400	91 (33.70%)
ALT	
≤40	147 (54.44%)
>40	123 (45.56%)
AST	
≤40	136 (50.37%)
>40	134 (49.63%)
TBIL	
≤17.1	124 (45.93%)
>17.1	146 (54.07%)
ALBI grade	
grade 1	126 (46.67%)
grade 2	140 (51.85%)
grade 3	4 (1.48%)
NLR	
<2.5	112 (41.48%)
≥2.5	158 (58.52%)
PLR	
<133.3	179 (66.30%)
≥133.3	91 (33.70%)
OPNI	
<39.5	34 (12.59%)
≥39.5	236 (87.41%)
BCLC Stage	
0	14 (5.18%)
A	129 (47.78%)
B	70 (25.93%)
C	53 (19.63%)
D	4 (1.48%)

AFP = alpha fetoprotein, ALT = glutamic-pyruvic transaminase, AST = glutamic oxalacetic transaminase, BCLC Stage = Barcelona Clinic Liver Cancer Stage, NLR = neutrophil-to-lymphocyte ratio, OPNI = Onodera's prognostic nutritional index, PLR = platelet-to-lymphocyte ratio, TBIL = serum total bilirubin.

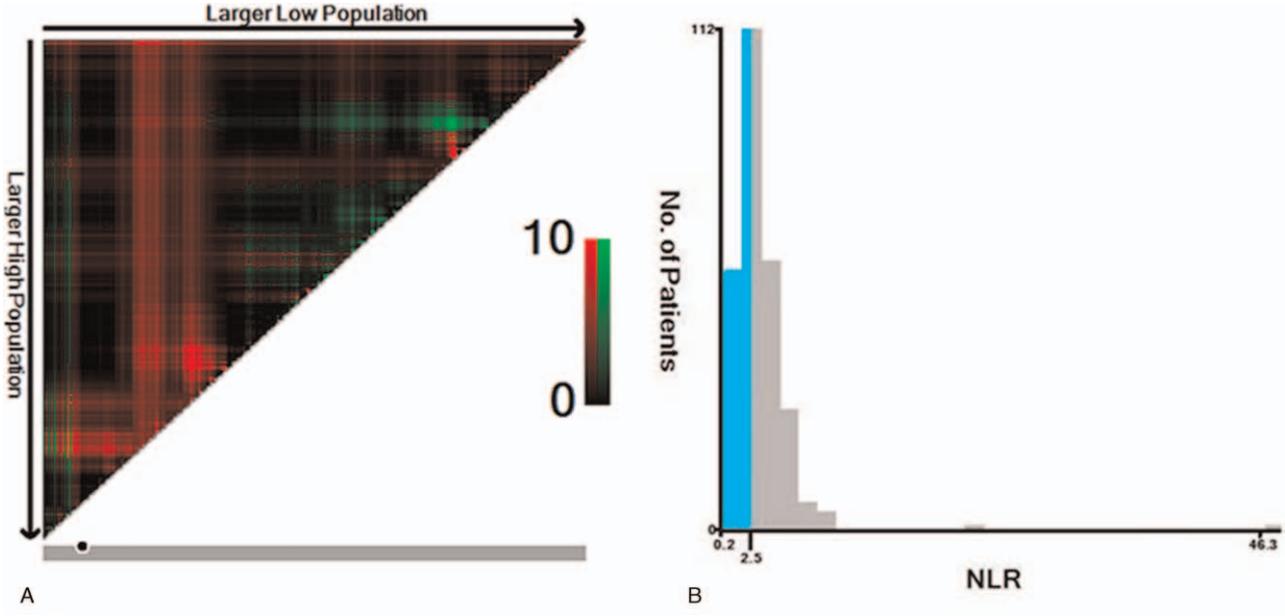

Figure 1. X-tile analysis of the NLR. The optimal cut-off values of NLR is 2.5.

Kaplan–Meier method, and log-rank test was performed to compare the differences between groups. Cox Proportional Hazards Model was utilized to carry out multivariate survival analysis. The analysis between OPNI and clinicopathological characteristics was analyzed using either the Chi-Squared test or Fisher's exact test. The hazard ratio (HR) and 95% confidence interval (95% CI) were used as measurements of correlation in our research. *P* value <.05 was considered statistically significant.

3. Results

3.1. Clinicopathological parameters

In our research, we enrolled 270 patients. There were 166 (61.48%) cases over the age of 60 and 104 (38.52%) cases under 60. The number of cases at stage 0, A, B, C, and D was 14 (5.18%), 129 (47.78%), 70 (25.93%), 53 (19.63%), and 4 (1.48%), respectively. These patients received surgical treatment (n = 162), interventional treatment (n=102) and

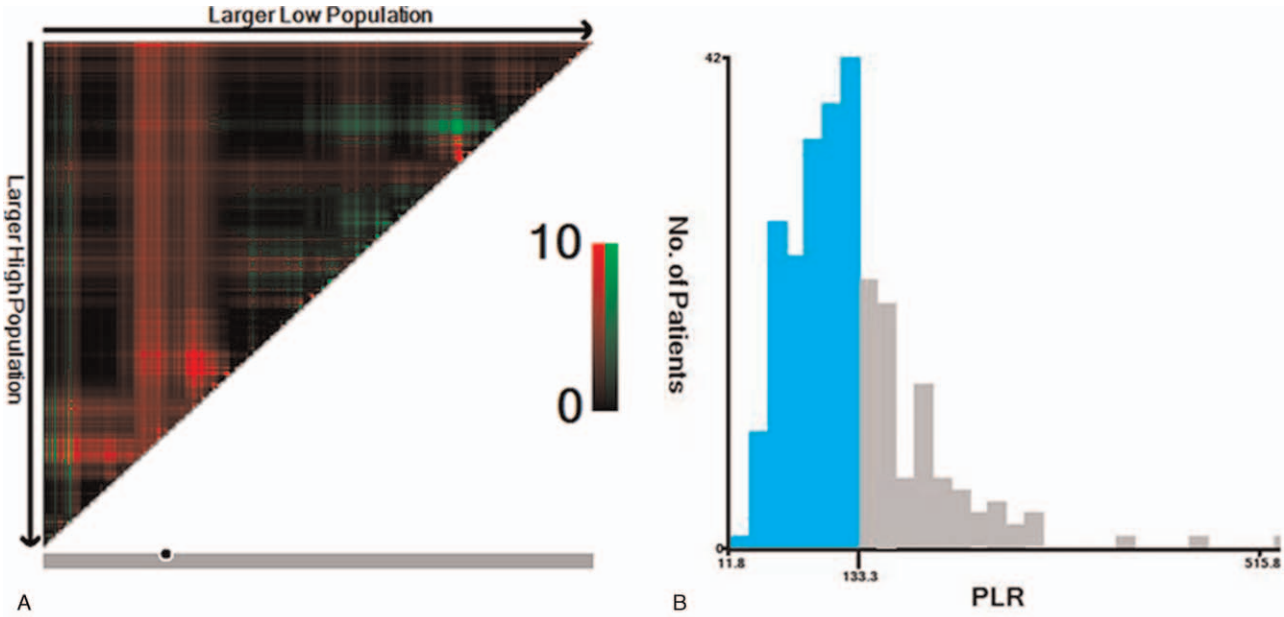

Figure 2. X-tile analysis of the PLR. The optimal cut-off values of PLR is 133.3.

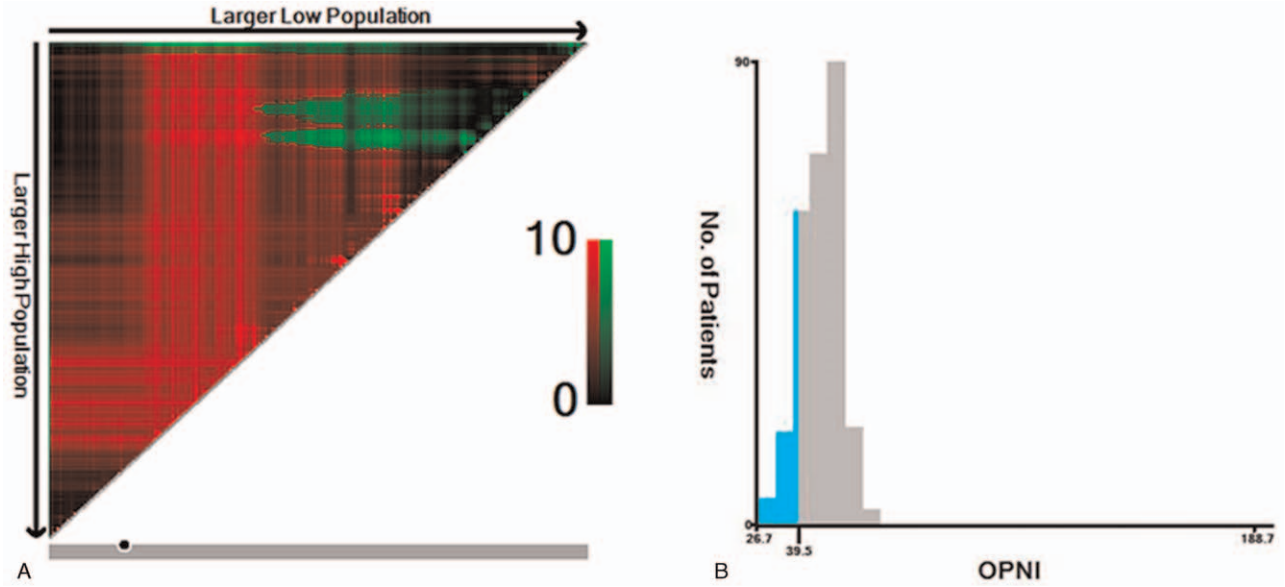

Figure 3. X-tile analysis of the OPNI. The optimal cut-off values of OPNI is 39.5.

Table 2

Univariate and multivariate analysis of hepatic carcinoma patients.

	Univariate analysis			Multivariate analysis		
variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (y)						
≤60	Reference			——		
>60	1.074	0.781–1.476	.662	——	——	——
gender						
male	Reference			——		
female	0.961	0.643–1.437	.848	——	——	——
Treatment						
Conservation	Reference			Reference		
Surgery	0.163	0.065–0.405	<.0001	0.264	0.098–0.713	.009
Interventional therapy	0.448	0.181–1.109	.082	0.372	0.139–0.996	.049
Postoperative therapy						
No	Reference			——		
Yes	0.871	0.567–1.336	.526	——	——	——
AFP						
≤400	Reference			Reference		
>400	1.454	1.056–2.002	.022	1.238	0.879–1.745	.222
ALT						
≤40	Reference			——		
>40	1.054	0.772–1.438	.741	——	——	——
AST						
≤40	Reference			Reference		
>40	1.589	1.163–2.171	.004	1.227	0.866–1.739	.251
TBIL						
≤17.1	Reference			——		
>17.1	1.089	0.795–1.491	.596	——	——	——
ALBI grade						
grade 3	Reference			Reference		
grade 2	0.517	0.163–1.634	.261	0.897	0.256–3.149	.865
grade 1	0.318	0.100–1.015	.053	0.769	0.207–2.850	.694
NLR						
<2.5	Reference			Reference		
≥2.5	1.762	1.268–2.449	.001	1.055	0.720–1.547	.782
PLR						
<133.3	Reference			Reference		
≥133.3	1.982	1.447–2.715	<.0001	1.526	1.070–2.176	.020
OPNI						
<39.5	Reference			Reference		
≥39.5	0.359	0.238–0.541	<.0001	0.513	0.320–0.822	.006
BCLC stage						
0, A	Reference			Reference		
B, C, D	3.947	2.829–5.506	<.0001	3.156	2.144–4.647	<.0001

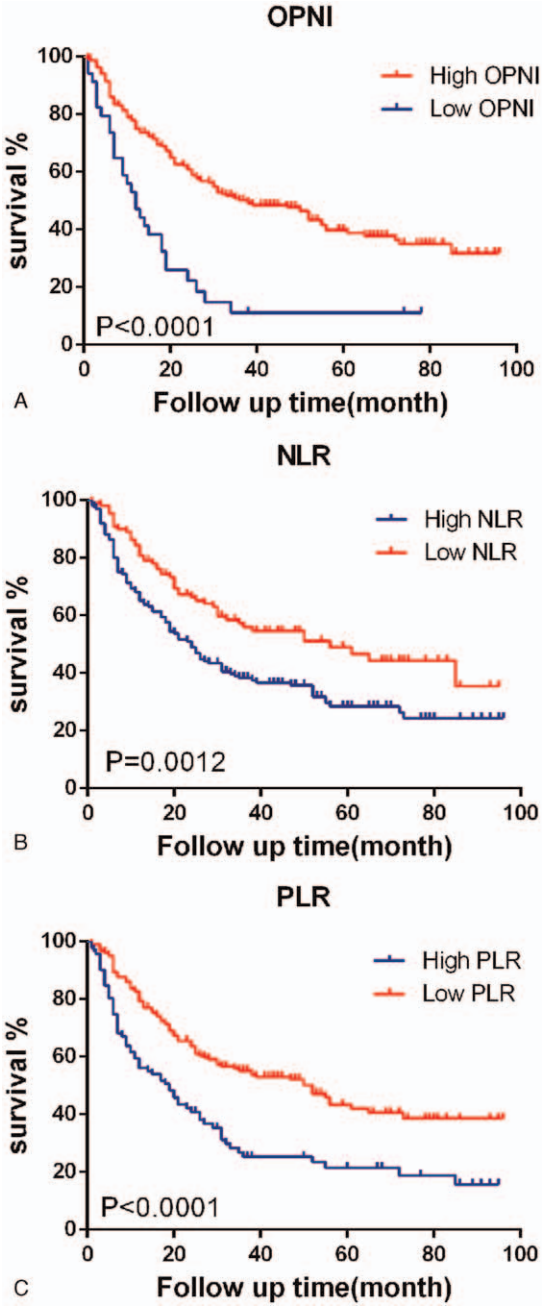

Figure 4. The overall survival analysis of patients with HCCs. The Kaplan–Meier curve analysis demonstrated high overall survival rates for the patients presenting with a higher OPNI (A) but lower NLR (B) and PLR (C).

conservation (n = 6). 227 (84.07%) patients received postoperative treatment, while the other 43 cases (15.93%) did not. The distribution of AFP, ALT, AST, TBIL, ALBI grade, NLR, PLR, OPNI, and more relevant information were summarized in Table 1.

3.2. X-tile analysis

NLR, PLR, and OPNI were used as test variables and OS as state variables, the X-tile program determined the optimal cut-off values of NLR, PLR and OPNI. The analysis results showed that the appropriate cut-off points of NLR, PLR, and OPNI were 2.5, 133.3, and 39.5, respectively (Figs. 1–3).

3.3. Follow-up

The median follow-up time was 24 months (range 1–96 months). The 231 (85.6%) patients performed well without recurrence or metastasis. Recurrence and metastasis occurred in 39 (14.4%) patients. Among them, there were 4 (1.5%) cases of bone metastasis, 4 (1.5%) cases of lung metastasis, 2 (0.7%) cases of posterior brain metastasis, and 1 (0.4%) case each of retroperitoneal, hepatic and adrenal metastasis.

3.4. Univariate survival analysis

Results of univariate survival analysis elucidated that the Treatment (Surgery vs Conservation, $P < .0001$), AFP ($P = .022$), AST ($P = .004$), ALBI grade (grade 1 vs grade 3, $P = .053$), NLR ($P = .001$), PLR ($P < .0001$), OPNI ($P < .0001$), and Stage (0, A vs B, C, D, $P < .0001$) were obviously correlated with the OS of HCC. The correlations between clinicopathological parameters and the OS of HCC were shown in Table 2.

3.5. Multivariate survival analysis

These significant factors in the univariate survival analysis were selected for further analysis in the multivariate survival analysis. The multivariate survival analysis elucidated that OPNI ($P = .006$), Treatment (Surgery vs Conservation, $P = .009$; Interventional therapy vs Conservation, $P = .049$), PLR ($P = .020$), and BCLC Stage (0, A vs B, C, D, $P < .0001$) can be utilized as independent prognostic makers for HCC (Table 2). Comparing the P values and hazard ratios, we found out that the OPNI has greatest influence on prognosis in these indexes.

3.6. Survival curve analysis of patients with HCC

The results of survival curve analysis elucidated that high OS for the patients presenting with a higher OPNI (High OPNI vs Low OPNI, $P < .0001$) (Fig. 4A) but lower NLR (High NLR vs Low NLR, $P = .0012$) (Fig. 4B) and PLR (High PLR vs Low PLR, $P < .0001$) (Fig. 4C). Patients with advanced BCLC stage had poor OS ($P < .0001$) (Fig. 5A). Similarly, patients with higher ALBI grade had poor OS ($P = .0036$) (Fig. 5B).

3.7. Analysis of the relationship between BCLC stage, ALBI grade, and OPNI

The prognosis of HCC is closely related to liver function, so we further analyzed the correlation between BCLC stage, ALBI grade and OPNI. The results of our analysis confirmd that patients with BCLC stage C and D had significantly lower OPNI than patients with stage 0 (stage 0 vs stage A: 49.05 ± 1.263 vs 48.94 ± 1.231, $P = .9758$, stage 0 vs stage B: 49.05 ± 1.263 vs 46.01 ± 0.730, $P = .0827$, stage 0 vs stage C: 49.05 ± 1.263 vs 45.05 ± 0.7012, $P = .0102$, stage 0 vs stage D: 49.05 ± 1.263 vs 39.04 ± 3.447, $P = .0037$) (Fig. 6A). Similarly, patients with ALBI grade 2 and 3 had lower OPNI than patients with ALBI grade 1 (grade 1 vs grade 2: 51.39 ± 0.3174 vs 44.02 ± 1.122, $P < .0001$, grade 1 vs grade 3: 51.39 ± 0.3174 vs 32.03 ± 3.077, $P < .0001$) (Fig. 6B).

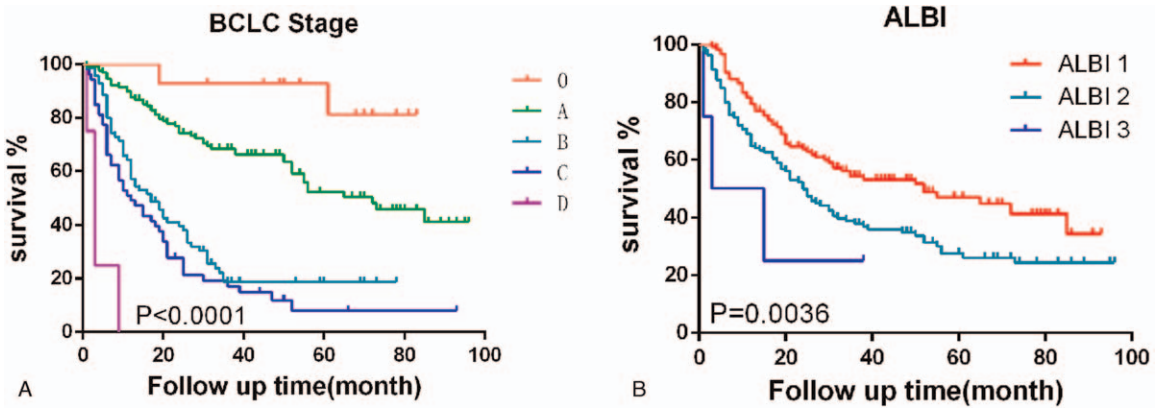

Figure 5. The overall survival analysis of patients with HCCs. Patients with advanced BCLC stage had poor overall survival. Similarly, patients with higher ALBI grades had poor overall survival.

3.8. The relationship between the OPNI and clinicopathological parameters

According to the optimal OPNI cut-off point, all patients were selected into high score OPNI group and low score OPNI group. Statistical analysis elucidated that there were differences in Treatment ($P=.006$), Postoperative therapy ($P=.005$), AST ($P=.001$) ALBI grade ($P<.0001$), NLR ($P<.0001$), and PLR ($P=.001$) between the 2 groups (Table 3).

4. Discussion

HCC is the sixth most common cancer in the world and the fouth leading cause of death among cancer patients.[21] Even after hepatectomy, because of low postoperative survival rate and high recurrence rate, the prognosis of HCC patients is still poor.[22,23] The severity and prognosis of HCC are determined by multiple factors, such as infection of viral hepatitis, metastasis, and treatment methods. Therefore, it is particularly important to use a simple and easily measured indicator to determine the prognosis of HCC.

HCC is one kind of consumptive disease with a high incidence of malnutrition. When the organism cannot provide sufficient nutrition for tumor cell proliferation, the destruction of tumor cells to the organism will be accelerated. Therefore, the nutritional status of patients also affects the disease and prognosis. Moreover, P.A. Thompson et al verified that the immune responses involved in the tumor microenvironment as well as systemic inflammatory responses may accelerate progression of tumor.[24] OPNI was proposed by Onodera in 1984, it was originally used to assess the risk of postoperative complications and mortality in patients with gastrointestinal tumors. Since then, it has been widely used to predict the prognosis of multiple tumors. OPNI is calculated by lymphocytes and serum albumin. Albumin is mainly synthesized from liver parenchymal cells, and patients with HCC often accompany with chronic inflammation and fibrosis, which may impairs the liver's ability to synthesize albumin. Therefore, patients with low OPNI have lower albumin levels, which reflect impaired liver function

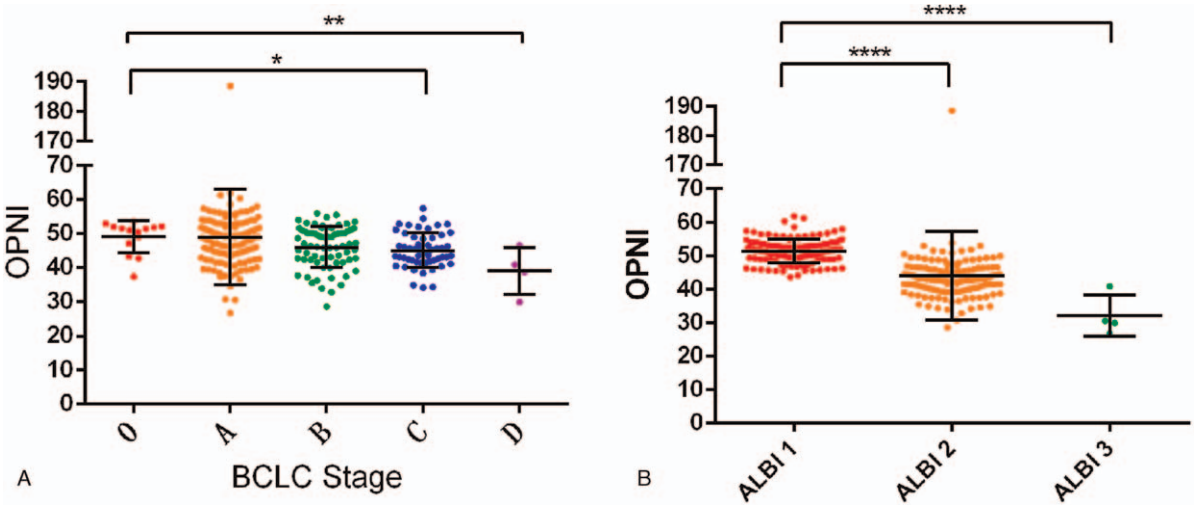

Figure 6. Analysis of the relationship between BCLC stage, ALBI grade and OPNI. Patients with BCLC stage C and D had significantly lower OPNI than patients with stage 0 (stageC vs 0, $P=.0102$, stage D vs 0, $P=.0037$). Patients with ALBI grade 2 and 3 had lower OPNI than patients with ALBI grade 1 (grade 2 vs 1, $P<.0001$, grade 3 vs 1, $P<.0001$). * means $P<.05$, ** means $P<.01$, **** means $P<.0001$.

Table 3

The relationships between the Onodera's prognostic nutritional index and the clinicopathological factors in the patients of hepatic carcinoma.

Characteristics	OPNI		*P* value
	HIGH (≥39.5)	LOW (<39.5)	
Age (y)			.274
≤60	148 (62.70%)	18 (52.90%)	
>60	88 (37.30%)	16 (47.10%)	
gender			.616
male	193 (81.80%)	29 (85.30%)	
female	43 (18.20)	5 (14.7%)	
Treatment			.006
Conservation	5 (2.10%)	1 (2.90%)	
Surgery	150 (63.60%)	12 (35.30%)	
Interventional therapy	81 (34.30%)	21 (61.80%)	
Postoperative therapy			.005
Yes	204 (86.40%)	23 (67.60%)	
No	32 (13.60%)	11 (32.40%)	
AFP			.078
≤400	161 (68.20%)	18 (52.90%)	
>400	75 (31.80%)	16 (47.10%)	
ALT			.355
≤40	131 (55.50%)	16 (47.10%)	
>40	105 (44.50%)	18 (52.90%)	
AST			.001
≤40	128 (54.20%)	8 (23.50%)	
>40	108 (45.80%)	26 (76.50%)	
TBIL			.552
≤17.1	110 (46.60%)	14 (41.20%)	
>17.1	126 (53.40%)	20 (58.80%)	
ALBI grade			<.0001
grade 1	126 (53.40%)	0 (0.00%)	
grade 2	109 (46.20%)	31 (91.20%)	
grade 3	1 (0.40%)	3 (8.80%)	
NLR			<.0001
<2.5	109 (46.20%)	3 (8.80%)	
≥2.5	127 (53.80%)	31 (91.20%)	
PLR			.001
<133.3	165 (69.9%)	14 (41.20%)	
≥133.3	71 (30.10%)	20 (58.80%)	
BCLC Stage			.218
0	13 (5.50%)	1 (2.90%)	
A	115 (48.70%)	14 (41.20%)	
B	59 (25.00%)	11 (32.40%)	
C	47 (19.90%)	6 (17.60%)	
D	2 (0.80%)	2 (5.90%)	

and are associated with poorer prognosis. Albumin has been included in various HCC staging systems and liver function scoring systems to assess the prognosis of HCC, such as BCLC staging, CLIP classification, Child-Pugh Class and ALBI score. In addition, lymphocytes are a core component of the immune system, it plays an important role in the anti-tumor immune response. Lymphocytes are usually the largest component of the immune-infiltrating site, therefore it's also called "tumor-infiltrating lymphocytes" or TILs. TILs mainly include T lymphocytes, B lymphocytes, natural killer (NK) cells and other immune cells. The phenotype of these immune lymphocytes can promote or inhibit the occurrence and development of tumors, which is of great significance in the prediction and prognosis of tumors.[25,26] In a meta-analysis of tumor-infiltrating lymphocytes and prognosis of HCC, T lymphocytes infiltration (CD8+, FOXP3+, CD3+, and Granzyme B+ lymphocytes) is associated with a better prognosis for HCC.[27] OPNI is an indicator related to nutritional and immune status.[28] It can reflect the levels of albumin and lymphocytes in patients with HCC, and may have potential prognostic value.

Hideo Matsumoto et al showed that OPNI may be a useful indicator of postoperative complications and length of hospital stay in patients with esophageal cancer, and may affect OS 6 months after surgery.[29] In the analysis of OPNI in patients with colorectal cancer and malignant pleural mesothelioma, some scholars found that the prognosis of patients with OPNI lower than cut-off value was distinctly worse than that OPNI higher than cut-off value.[17,30] This is consistent with our research. In present research, we selected the patients into the high score OPNI group and the low score OPNI group according to the optimal OPNI cut-off point (39.5). Overall survival was distinctly higher in the high OPNI group. Further, univariate and multivariate survival analyses indicated that OPNI can be utilized as an independent prognostic indicator for HCC.

HCC is different from other cancers, in addition to the factors of the tumor itself, liver function has a great influence on the prognosis of patients. In routine clinical practice, BCLC stage and ALBI grade have been used to evaluate the prognosis of HCC. Higher BCLC stage and ALBI grade generally predict a poor prognosis for HCC. Therefore, in our research, we analyzed the correlation between BCLC stage, ALBI grade and OPNI. The results elucidated that patients with higher BCLC stage and ALBI grade had lower OPNI. OPNI was in good agreement with BCLC stage and ALBI grade in evaluating the prognosis of HCC, which further confirmd the prognostic value of OPNI in HCC.

Yakup et al analysis of NSCLC showed that there were marked distinction in clinical characteristics distribution, overall survival and progression free survival between the high-OPNI group and the low-OPNI group.[31] Similarly, in our further analysis of the relationship between OPNI and clinicopathological features, there were differences in treatment, postoperative therapy, AST, ALBI grade, NLR and PLR between 2 groups.

Perioperative malnutrition is closely related to the incidence and mortality of postoperative complications in cancer patients.[32] Reasonable enteral or parenteral nutrition treatment for patients with nutritional risk can effectively improve the prognosis.[33] In the future clinical work, OPNI can be calculated routinely before surgery in patients with hepatocellular carcinoma. When OPNI is low, it often indicates that the patients are in a state of malnutrition and poor immune function. Therefore, enteral or parenteral nutrition treatment can be given before surgery to improve the overall prognosis of the patients.

There are several limitations of this study. A small sample size from a single-center limit us to make a more precise conclusion. In addition, since our study was retrospective observational, the results may be influenced by undetected clinical features. In future studies, we will combine multi-center studies to make up for this shortcoming.

In summary, OPNI, as a simple index to evaluate the nutritional and immune status of patients, has good feasibility and practical value in clinical practice. It can be used as an auxiliary indicator to help assess the severity and prognosis of HCC patients.

Author contributions

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