Prognostic Value of Inflammatory and Nutritional Markers for Hepatocellular Carcinoma

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Research

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Abstract

Background: It is well known that the prognosis of cancer patients after tumor resection is closely related to the patient's autoimmune ability and nutritional status. A large number of studies have shown that the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and Onodera's prognostic nutritional index (OPNI) are significantly correlated with the prognosis of various tumors. In this study, we analyzed the prognostic value of NLR, PLR and OPNI for hepatocellular carcinoma (HCC) for the first time.

Patients and Methods: Data of hepatocellular carcinoma patients undergoing hepatectomy in Changzhi People's Hospital (Changzhi, China) from 2011 to 2017 were retrospectively analyzed. A total of 286 patients with hepatocellular carcinoma were included in the analysis. The Optimum cut-off values of OPNI, NLR and PLR were determined by using the X-tile program. The overall survival (OS) was analyzed by Kaplan-Meier method and verified by log-rank test. Multivariate analysis was performed using Cox Proportional Hazard Regression model to determine independent prognostic indicators for HCC.

Results: Univariate and multivariate analysis showed that OPNI ($p<0.001$), Treatment (Surgery, $p=0.04$; Interventional therapy, $p=0.002$), Postoperative treatment (YES, $p=0.004$) and Stage can be used as independent prognostic maker for HCC. Comparing the P values and hazard ratios, we found out that the OPNI has greatest influence on prognosis in these preoperative indexes. The optimal cut-off values of NLR, PLR and OPNI were 2.5, 133.3 and 39.5, respectively. Compared with the low OPNI group, the high OPNI group had a better prognosis. In the correlation analysis between OPNI and clinicopathological features, only Age and NLR showed statistical differences, while others did not.

Conclusions: OPNI can be used as a simple and effective independent prognostic marker for hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) are the most common carcinomas of the liver cells or hepatocytes. The incidence of HCC is higher in men than in women. Globally, it is the second leading cause of cancer death in men. In the United States, the death rate from liver cancer increased from 7.2 to 10.3 per 100,000 between 2000 and 2016 (1). The 5-year survival rate for liver cancer was only 18% (2). China alone accounts for 50 percent of global cases (3). Numerous studies have shown that the key mutated genes associated with HCC include *TERT*, *TP53*, *CTNNB1*, *ARID1A* and *AXIN1* (4–6). Specifically, The most common types of mutations are the driver mutations of *TERT*, *TP53* and *CTNNB1* (7). Surgery remains the standard treatment for primary HCC, and it has been the only potentially curative therapy.

Preoperative assessment of HCC (such as liver function tests and imaging studies), surgical techniques, and postoperative care can improve survival in patients undergoing hepatectomy for HCC. 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) (8),vascular endothelial growth factor (VEGF)

(9)Dickkopf-1 (DKK-1) (10)transforming growth factor-β_1 (TGF-β_1) (11)glypican-3 (GPC-3) (12), 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 are an important factor affecting the tumor microenvironment. These cells can promote the proliferation, invasion and metastasis of tumor cells ,which play an important role in the occurrence and development of tumors (13). Immunoinflammatory factors were shown to be associated with the oncogenesis, progression, and prognosis of HCCs. Studies have shown that peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (the PLR; an easily measured, reproducible and cost-effective systemic inflammatory marker) can serve as prognostic markers for patients with a variety of solid tumors, such as non-small cell lung cancer, colorectal cancer, and gastric cancer (14–16).

Onodera's Prognostic Nutritional Index (OPNI) can be used to evaluate the immunonutritional status of patients undergoing liver surgery. It has been reported that OPNI can be used as a useful prognostic marker for esophageal cancer (17), gastric cancer (18), colorectal cancer (19) and pancreatic cancer (20),but the prognostic value of the OPNI for HCC has not been determined. In this study, we try to evaluate the prognostic value of the OPNI for HCC.

Patients And Methods

Patients

We conducted a retrospective analysis of the data of patients with hepatocellular carcinoma who treated in Changzhi People’s Hospital (Changzhi, China) from 2011 to 2017. The criteria for inclusion in the analysis were as follows:1) HCC was confirmed; 2) absence of coeval tumors; 3) without signs of infection; 4) Completed Clinical and follow-up data. Ultimately, 286 patients with hepatocellular carcinoma were included in the analysis. 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.

Preoperative peripheral blood routine tests and OPNI evaluation

Preoperative peripheral blood routine examination was performed in all patients within 7 days before surgery. The NLR was calculated by dividing the neutrophil count (10^9/L) by the lymphocyte count (10^9/L). Platelet to lymphocyte ratio (PLR) was calculated using the same method as NLR. OPNI's calculation formula was: OPNI = serum albumin (g /L) + 5 lymphocyte count(10^9/L).

Clinicopathological features

Basic features were collected, including age, treatment, postoperative treatment, tumor staging, and laboratory data (neutrophil count, lymphocyte count, platelets, serum albumin). According to the BCLC stage system, hepatocellular carcinoma was divided into four stages: 0, A, B, C and D.

Follow-up

Patients were examined by endoscopy and computed tomography every 3 to 6 months postoperatively to assess tumor recurrence or distant metastasis. Patient follow-up information was obtained from tumor registries, hospital records or direct contact with the patient and family members. In this study, we took the overall survival (OS) as the end point of the study, because the OS of all patients receiving the same chemotherapy regimen and course of treatment may be biased, and OS was considered to be the most suitable event for survival analysis. OS was defined as the time from randomization to death due to any cause.

Statistical analyses

IBM SPSS Statistics, version 20.0 (IBM, New York, USA) has been used to calculate all statistical analysis. count data were summarized using frequencies and percentages.The optimal cut-off values of NLR, PLR and OPNI were analyzed using X-tile version 3.6.1(Robert L Camp, Yale University, New Haven, CT, USA). Univariate survival analysis was performed by Kaplan-Meier method, and log-rank test was performed to compare the differences between groups. Cox Proportional Hazards Model was used to carry out multivariate survival analysis. The hazard ratio (HR) and 95% confidence interval (95% CI) were used as measurements of correlation in this study. P-value < 0.05 was considered statistically significant.

Results

Clinicopathological parameters

In this study, we enrolled 286 patients. There were 175 (61.19%) cases over the age of 60 and 111 (38.81%) cases under 60. The number of cases at stage 0, A, B, C and D was 14 (4.89%), 136 (47.55%), 70 (24.47%), 62 (21.67%) and 4 (1.39%), respectively. These patients received surgical treatment (n = 186), interventional treatment (n = 93) and conservation (n = 7). Postoperative treatment was performed in 241 (84.26%) patients, not in 43 (15.03%), and unknown in 2 (0.71%) patients. The distribution of NLR, PLR, OPNI, and more detailed clinicopathological variables were shown in Table 1.

Table 1
Demographic and clinical characteristics of the included patients with Hepatocellular carcinoma.

Characteristics	Number (%)
Age (year)	
≤ 60	175 (61.19%)
> 60	111 (38.81%)
Treatment	
Surgery	186 (65.03%)
Interventional therapy	93 (32.52%)
Conservation	7 (2.45%)
Postoperative therapy	
Yes	241 (84.26%)
No	43 (15.03%)
Unknow	2 (0.71%)
NLR	
2.5	42(14.69%)
≥ 2.5	244 (85.31%)
PLR	
133.3	126 (44.06%)
≥ 133.3	160 (55.94%)
OPNI	
< 39.5	198 (69.23%)
≥ 39.5	88 (30.77%)
Stage	
0	14 (4.89%)
A	136 (47.55%)
B	70 (24.47%)
C	62 (21.67%)
D	4 (1.39%)

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 optimal cut-off values of NLR, PLR and OPNI were 2.5, 133.3 and 39.5, respectively (Fig. 1–3).

Follow-up

The median follow-up time was 30.5 months (range 0.5–96 months). The 236 (82.5%) patients performed well without recurrence or metastasis. Recurrence and metastasis occurred in 50 (17.5%) patients. Among them, there were 5 (1.7%) cases of bone metastasis, 4 (1.4%) cases of lung metastasis, 2 (0.7%) cases of posterior brain metastasis, and 1 (0.3%) case each of retroperitoneal, hepatic and adrenal metastasis.

Univariate survival analysis

Results of univariate survival analysis showed that the Age ($p = 0.03$), Treatment (Surgery, $p < 0.0001$;Interventional therapy, $p = 0.02$), Postoperative treatment(YES, $p = 0.001$), NLR ($p = 0.003$), PLR ($p = 0.01$), OPNI ($p = 0.008$) and Stage were significantly correlated with the OS of HCC. The correlations between clinicopathological features and the OS of HCC were shown in Table 2.

Table 2
Univariate and multivariate analysis of hepatic carcinoma patients.

variable	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Age (year)			0.03			
≤ 60	Reference			——		
> 60	1.18	0.79–1.57		——	——	——
Treatment						
Conservation	Reference			Reference		
Surgery	1.33	1.06–1.65	< 0.0001	1.08	0.76–1.55	0.04
Interventional therapy	1.27	1.05–1.87	0.02	2.11	1.56–2.62	0.002
Postoperative therapy						
Unknow	Reference			Reference		
No	0.44	0.27–1.30	0.76	0.57	0.36–1.03	0.77
Yes	1.43	1.19–2.16	0.001	1.82	1.06–2.23	0.004
NLR			0.003			0.07
2.5	Reference			Reference		
≥ 2.5	1.34	1.09–1.67		0.65	0.56–1.12	
PLR			0.01			0.09
133.3	Reference			Reference		
≥ 133.3	1.16	1.01–1.74		0.78	0.70–1.38	
OPNI			0.008			< 0.0001
< 39.5	Reference			Reference		
≥ 39.5	1.519	1.181–1.955		1.21	1.12–2.08	
Stage						

variable	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
0	Reference			Reference		
A	1.04	0.78–1.60	0.002	1.00	0.88–1.67	< 0.0001
B	1.22	1.06–1.85	0.04	1.19	1.05–1.87	< 0.0001
C	2.17	1.59–2.67	< 0.0001	2.06	1.69–3.15	< 0.0001
D	2.68	2.35–3.74	< 0.0001	3.12	2.75–4.03	< 0.0001

Multivariate survival analysis

These significant factors in the univariate survival analysis were selected for further analysis in the Cox proportional hazards mode. The multivariate survival analysis showed that OPNI ($p < 0.001$), Treatment (Surgery, $p = 0.04$; Interventional therapy, $p = 0.002$), Postoperative treatment (YES, $p = 0.004$) and Stage can be used as independent prognostic maker for HCC (Table 2). Comparing the P values and hazard ratios, we found out that the OPNI has greatest influence on prognosis in these preoperative indexes. The survival curves of OPNI, PLR and NLR, as well as the associated P values, were shown in Fig. 4.

The relationships between the Onodera's prognostic nutritional index and the Clinicopathological factors

According to clinicopathological characteristics, all patients were divided into high OPNI group and low OPNI group by the optimal OPNI cut-off value. Statistical analysis showed that there were differences in Age ($p = 0.007$) and NLR ($p = 0.04$) between the two groups(Table 3). Compared with the low OPNI group, patients in the high OPNI group were younger and had lower NLR.

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 (year)			0.007
≤ 60	113 (68.07%)	75 (62.50%)	
> 60	53 (31.93%)	45 (37.50%)	
Treatment			0.777
Conservation	2 (1.05%)	5 (5.21%)	
Surgery	115 (60.52%)	71 (73.96%)	
Interventional therapy	73 (38.43%)	20 (20.83%)	
Postoperative therapy			0.59
Yes	165 (85.49%)	76 (81.72%)	
No	27 (13.99%)	16 (17.20%)	
Unknow	1 (0.51%)	1 (1.08%)	
III/IV	194 (34.155%)	28 (31.461%)	
NLR			0.04
□2.5	36 (17.39%)	6 (7.41%)	
≥ 2.5	171 (82.61%)	75 (92.59%)	
PLR			0.69
□133.3	77 (45.83%)	49 (41.53%)	
≥ 133.3	91 (54.17%)	69 (58.47%)	
Stage			0.177
0	12 (6.09%)	2 (2.25%)	
A	108 (54.82%)	28 (31.46%)	
B	54 (27.41%)	16 (17.98%)	
C	22 (11.17%)	40 (44.94%)	
D	1 (0.51%)	3 (3.37%)	

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.

Cancer is a deeline 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. OPNI is an indicator related to nutritional and immune status (24). Hideo Matsumoto et al. showed that OPNI may be a useful indicator of postoperative complications and length of hospital stay in patients with pancreatic cancer, and may affect overall survival 6 months after surgery (25). 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 significantly worse than that of patients with OPNI higher than cut-off value (26–27). Yakup Bozkaya et al. 's analysis of NSCLC showed that there were significant differences in clinical characteristics distribution, overall survival and progression free survival between the high-OPNI group and the low-OPNI group (28).

In the present study, we divided the patients into the high OPNI group and the low OPNI group according to the optimal OPNI cut-off value (39.5). Overall survival was significantly higher in the high OPNI group than in the low OPNI group. Univariate and multivariate survival analyses indicated that OPNI was an independent prognostic maker for HCC. In addition, treatment, postoperative treatment, and stage were also associated with the prognosis of HCC. Further analysis of the relationship between OPNI and clinicopathological features showed that patients with high OPNI were younger and had lower NLR.

Perioperative malnutrition is closely related to the incidence and mortality of postoperative complications in cancer patients (29). Reasonable enteral or parenteral nutrition treatment for patients with nutritional risk can effectively improve the prognosis (30–31). 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.

Declarations

Acknowledgments

Not applicable

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YX, XY: acquisition, analysis and interpretation of data, manuscript drafting; XZ: manuscript revising; LY: drafting and critical appraisal of manuscript; LZ: study design, data interpretation, final approval of the manuscript. All authors have given final approval to this version of the manuscript to be published.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

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Figures

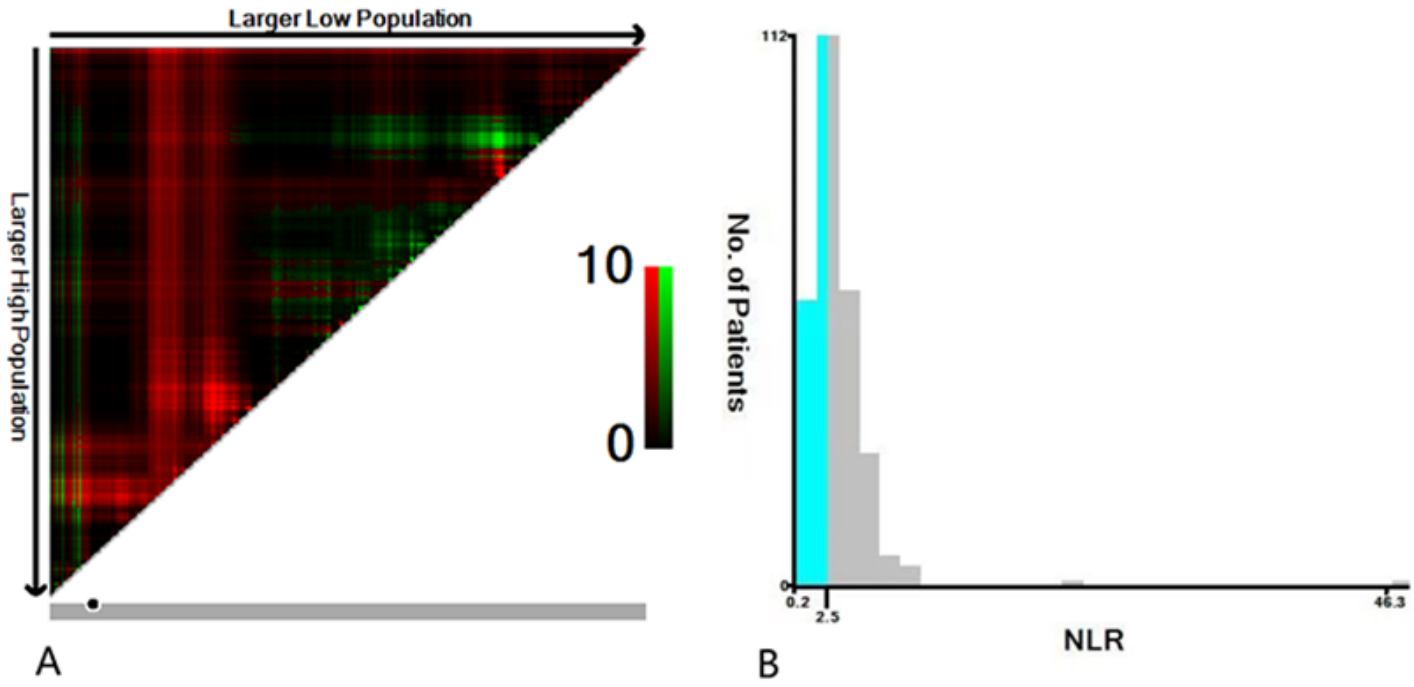

Figure 1

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

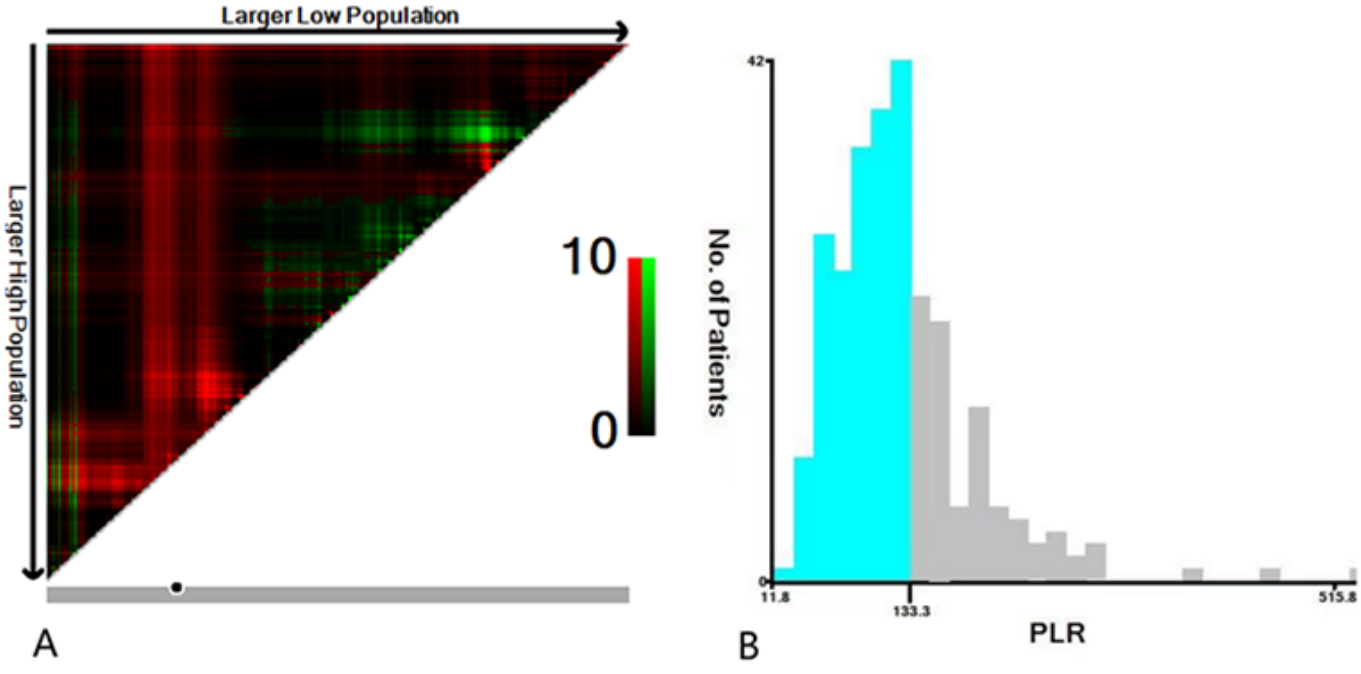

Figure 2

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

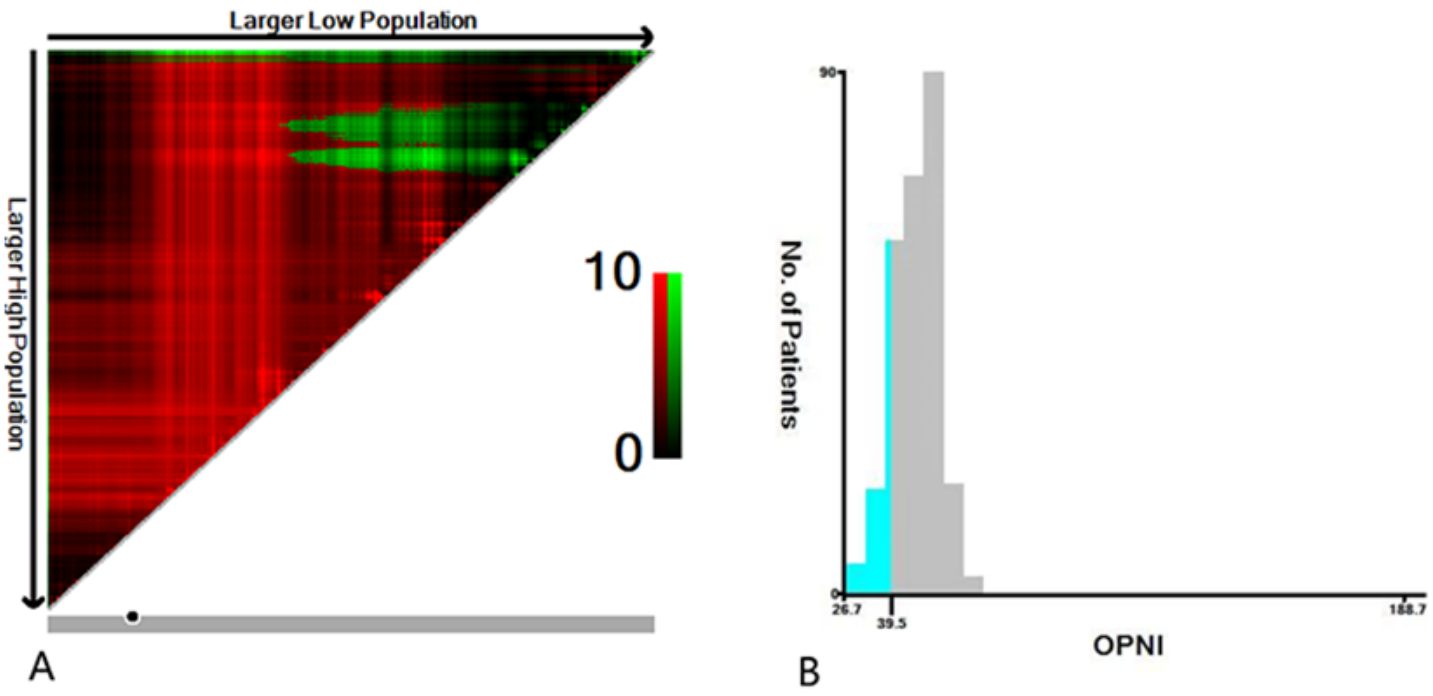

Figure 3

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

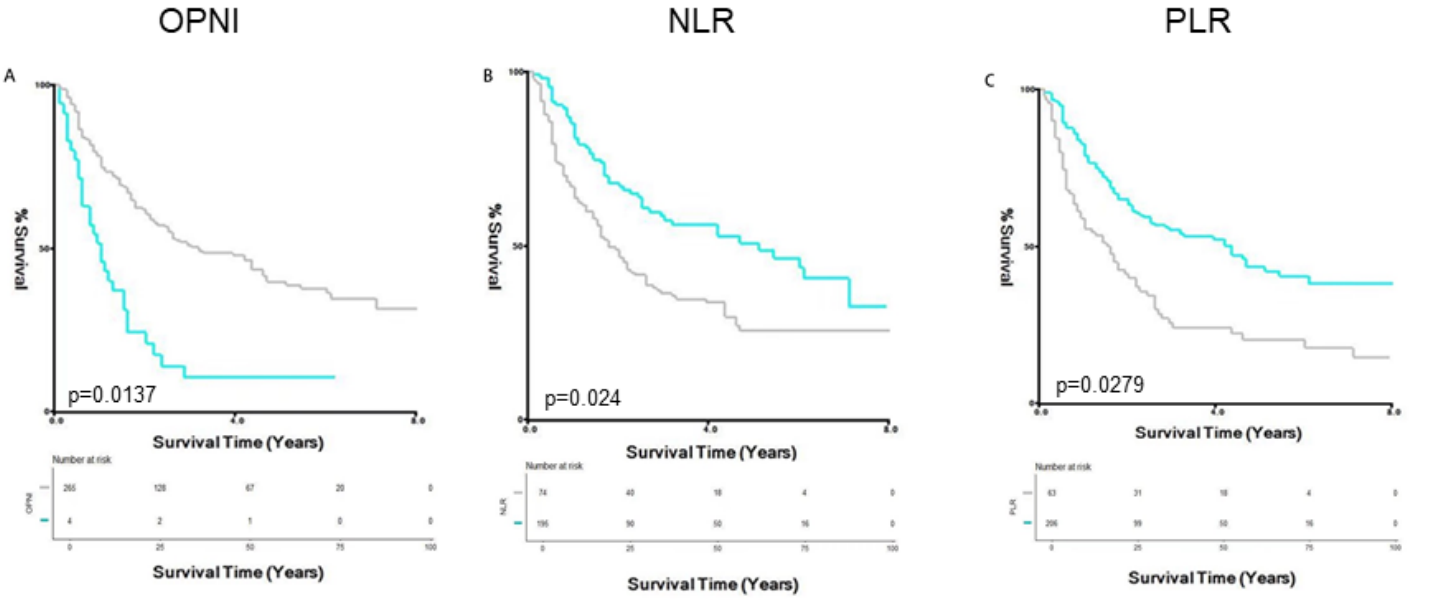

Figure 4

The overall survival analysis of 286 patients with HCCs. The Kaplan-Meier curve analysis demonstrated high overall survival rates for the patients presenting with (A) a higher OPNI, (B) a lower NLR, or (C) a lower PLR.