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【 ORIGINAL ARTICLE 】

Impact of the Prognostic Nutritional Index on the Survival of Japanese Patients with Hepatocellular Carcinoma Treated with Sorafenib: A Multicenter Retrospective Study

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Abstract:

Objective The purpose of this multicenter retrospective study was to investigate the impact of the prognostic nutritional index (PNI) on the survival of Japanese patients with hepatocellular carcinoma (HCC) treated with sorafenib.

Methods A total of 178 HCC patients from May 2009 to December 2015 at our affiliated hospitals was included in this study. The PNI was calculated as follows: 10×serum albumin (g/dL)+0.005×total lymphocyte count (per mm^3). The patients were divided into two groups according to the cut-off value of the PNI and as calculated by a receiver operating characteristic curve analysis.

Results The optimum cut-off value of the PNI was set at 46.8. We defined the 33 patients with a PNI≥46.8 as the PNI-high group and the 145 patients with a PNI<46.8 as the PNI-low group. The response rate was 20.0% in the PNI-high group and 8.1% in the PNI-low group, without any statistically significance (p=0.09). The duration of sorafenib therapy and the overall survival in the PNI-high group were significantly better than those in the PNI-low group. The PNI-high group was thus found to be a predictive factor associated with the duration of sorafenib therapy [hazard ratio (HR) 0.58; 95% confidence interval (CI) 0.39-0.87, p=0.008] and overall survival (HR 0.62; 95% CI 0.39-0.99, p=0.046) in a multivariate analysis.

Conclusion The PNI is a simple and useful marker for predicting the survival of patients with HCC treated with sorafenib.

Key words: hepatocellular carcinoma, sorafenib, prognostic nutritional index

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Introduction

Liver cancer is the sixth-most common cancer and is the second leading cause of cancer-related deaths worldwide, with approximately 745,000 deaths reported in 2012 (1), and hepatocellular carcinoma (HCC) accounts for about 80% of all liver cancers (2). When the disease is diagnosed at an early stage, curative treatments, such as hepatic resection, liver transplantation and radiofrequency ablation (RFA), are recommended, resulting in a relatively good survival (3-6). However, many patients present at an advanced stage when

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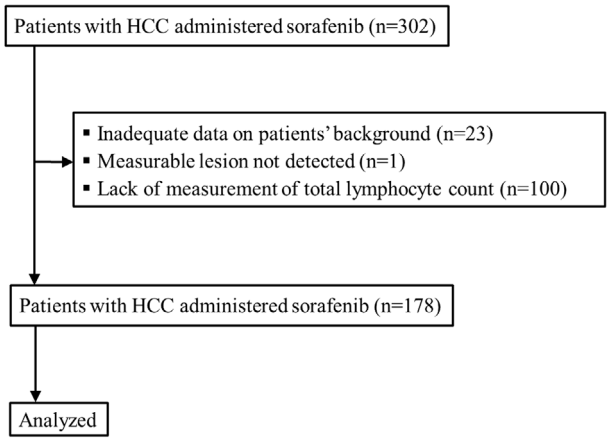

Figure 1. The flow chart of patient selection. HCC: hepatocellular carcinoma

they can no longer benefit from these curative treatments. Under the Barcelona Clinic Liver Cancer (BCLC) guideline (3, 6), transcatheter arterial chemoembolization (TACE) and sorafenib treatment are recommended for patients at intermediate and advanced stages of disease, respectively. Furthermore, sorafenib treatment can be considered even for patients with intermediate-stage disease when the definition of TACE failure/refractoriness proposed by the Liver Cancer Study Group of Japan is met or TACE is deemed to be either not feasible or has failed (5, 7).

Sorafenib is a multikinase inhibitor that blocks the Raf-MEK-ERK signaling pathway to inhibit tumor cell proliferation and blocks VEGF receptors to prevent neoangiogenesis (8, 9). Two randomized, placebo-controlled phase III studies showed the survival rate of advanced HCC patients treated with sorafenib to be better than that in a control group (10, 11). Recently, the RESORCE study showed that regorafenib also provided a good survival benefit in advanced HCC patients with progressive disease on sorafenib treatment (12).

The prognostic nutritional index (PNI) proposed by Onodera et al. (13) has been shown to be a useful tool for evaluating the preoperative condition and outcome of patients with malignant gastrointestinal tract tumors. It is easily calculated from the serum albumin and total lymphocyte count in the peripheral blood and it reflects the immunological and nutritional condition of cancer patients. Several studies have reported the PNI to be a useful prognostic factor for patients with gastric cancer (14, 15), colorectal cancer (16) and HCC (17, 18) after surgical treatment. However, few studies have so far evaluated the implications of the PNI in advanced HCC patients treated with sorafenib.

The purpose of this study was to investigate the impact of the PNI on the survival of Japanese patients with advanced HCC treated with sorafenib and to clarify the relationship between the PNI and the duration of sorafenib therapy.

Materials and Methods

Inclusion criteria

The inclusion criteria of this retrospective cohort study were as follows: HCC diagnosed based on early enhancement in the arterial phase and washout in the portal vein or equilibrium phase of enhanced computed tomography (CT) or enhanced magnetic resonance imaging (MRI) (19) or historically proven disease; not indicated for surgical resection, liver transplantation or local ablation therapy; Child-Pugh score 5-7 and measurable lesions detected on radiological imaging. The exclusion criteria were as follows: inadequate patient background data; no data on the total lymphocyte count in peripheral blood at baseline treatment.

Treatment

Sorafenib was administered orally, and all treatment decisions, including the dose and duration, were determined at the physician's discretion or choice. In general, sorafenib treatment was discontinued if progressive disease was identified on follow-up CT, if serious adverse events were observed or if a deterioration of the liver function was noted. Best supportive care or other palliative treatments were subsequently provided. The best radiological response was evaluated by the modified Response Evaluation Criteria in Solid Tumors (mRECIST). At follow-up visits after sorafenib administration, drug-related adverse events, such as fatigue, hand-foot skin reaction (HFSR), diarrhea, nausea, vomiting, rash/desquamation, hypertension, upper gastrointestinal (GI) hemorrhaging, were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Patient selection and data collection

A total of 302 HCC patients treated with sorafenib at the Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital, Maebashi, Japan, and its affiliated hospitals from May 2009 to December 2015 were included in the present study. Of these patients, 23 for whom background data were deemed inadequate, 1 who had no measurable lesions, and 100 missing data on the total lymphocyte count were excluded. Therefore, the remaining 178 patients were analyzed. A flow chart of the patient selection is shown in Fig. 1.

We reviewed the medical records in February 2017 and collected the data. We also collected data on the level of serum albumin and total lymphocyte count at baseline treatment. We calculated the PNI using the following formula: 10×serum albumin value (g/dL)+0.005×total lymphocyte count (per mm^3) (13).

This study was compliant with the Declaration of Helsinki and approved by the institutional review board, and the need for written informed consent was waived because of the retrospective nature of the study.

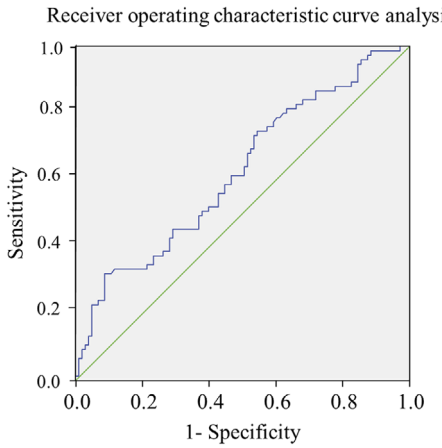

Figure 2. Result of receiver operating characteristic curve analysis, which was used to calculate optimum cut-off value of the PNI for predicting the one-year survival. PNI: prognostic nutritional index

Statistical analyses

To assess the sensitivity and specificity of the PNI for predicting the one-year survival of HCC patients treated with sorafenib, we determined the receiver operating characteristic (ROC) curve, and the Youden index was estimated to determine the optimum cut-off value for the PNI. We divided all patients into two groups according to the cut-off value of the PNI. Continuous variables were represented as the median [interquartile range (IQR)] and compared with a Mann-Whitney U test. Categorical variables were represented as the count (percentage) and compared with a chi-squared test or Fisher exact test when appropriate.

We defined an objective response as a complete response and partial response. The factors affecting the objective response were analyzed using univariate and multivariate analyses with a logistic regression model and the following factors were used: age, sex, underlying liver disease, platelet count, initial dose of sorafenib, naïve, number of tumors, maximum tumor diameter, macroscopic vascular invasion, extrahepatic metastasis, α-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), and PNI. Variables with $p<0.05$ on a univariate analysis were subjected to a multivariate analysis.

The factors associated with the duration of sorafenib therapy and overall survival were analyzed using univariate and multivariate analyses by a Cox proportional hazard analysis. The following factors were used: age, sex, underlying liver disease, Child-Pugh, platelet count, initial dose of sorafenib, naive, previous hepatic resection, previous locoregional treatment, number of tumors, maximum tumor diameter, macroscopic vascular invasion, extrahepatic metastasis, AFP, DCP, and PNI. Variables with $p<0.05$ on a univariate analysis were subjected to a multivariate analysis.

The duration of sorafenib therapy and the survival curve were calculated by the Kaplan-Meier method and compared using a log-rank test. We defined the duration of sorafenib therapy as the interval between the start date of sorafenib treatment and the date of discontinuation. We also defined the survival time as the interval between the start date of sorafenib treatment and death or the last visit to the outpatient clinic, until 28 February 2017. Hazard ratio (HR) and 95% confidence interval (CI) were estimated by a logistic regression model and a Cox proportional hazard analysis. The results of univariate and multivariate analyses were presented as HR with the corresponding 95% CI and a p value. We dichotomized the continuous variables by a median of total patients. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences software version 24 (IBM SPSS 24, IBM, Armonk, USA).

Results

The area under the ROC curve, which was used to calculate the optimum cut-off value of the PNI for predicting the one-year survival, was 0.628. When the PNI was 46.77, the Youden index was maximized (Fig. 2). Therefore, the optimum cut-off value of the PNI was set at 46.8. We defined the 33 patients with a PNI≥46.8 as the PNI-high group and the 145 patients with a PNI<46.8 as the PNI-low group.

The patient characteristics are shown in Table 1. The median age was 72 (IQR: 63-75) years in the PNI-high group and 71 (IQR: 64-77) years in the PNI-low group. The underlying liver disease was hepatitis B virus (HBV)/hepatitis C virus (HCV)/alcohol/others in 3 patients (9.1%)/18 patients (54.5%)/5 patients (15.2%)/7 patients (21.2%) in the PNI-high group and in 15 patients (10.3%)/88 patients (60.7%)/11 patients (7.6%)/31 patients (21.4%) in the PNI-low group, respectively. The Child-Pugh Class was A and B in 32 (97.0%) and 1 patient (3.0%) in the PNI-high group and in 120 (82.8%) and 25 patients (17.2%) in the PNI-low group, respectively. The BCLC stage was early, intermediate and advanced in 3 (9.1%), 9 (27.3%) and 21 patients (63.6%) in the PNI-high group and in 16 (11.0%), 49 (33.8%) and 80 patients (55.2%) in the PNI-low group, respectively. There were 12 (36.4%) naïve cases in the PNI-high group and 40 (27.6%) in the PNI-low group. The lymphocyte count, platelet count, prothrombin time, serum albumin, AFP, DCP, and macroscopic vascular invasion were significantly different between the two groups.

The 1-year survival rates were 79.3% (95% CI: 64.6-93.6%) in the PNI-high group and 39.5% (95% CI: 31.3-47.7%) in the PNI-low group. The cumulative survival rate in the PNI-high group was significantly better than that in the PNI-low group (p=0.002) (Fig. 3). The median duration of sorafenib treatment was 287 (95% CI 67-506) days in the PNI-high group and 111 (95% CI 72-149) days in the PNI-low group. The duration of sorafenib treatment in the PNI-high group was longer than that in the PNI-low group (p=0.001) (Fig. 4).

In the PNI-high group, complete response (CR) was shown in 2 patients (6.7%), while 4 patients (13.3%) had a partial response (PR), 14 patients (46.7%) had stable disease (SD), and 10 patients (33.3%) had progressive disease, thus

Table 1. Patients' Characteristics.

	PNI-high group (n=33)	PNI-low group (n=145)	p value
Age (y)	72 (63-75)	71 (64-77)	0.91
Males, n (%)	29 (87.9)	115 (79.3)	0.26
Underlying liver disease, n (%)			0.59
HBV	3 (9.1)	15 (10.3)	
HCV	18 (54.5)	88 (60.7)	
Alcohol	5 (15.2)	11 (7.6)	
Others	7 (21.2)	31 (21.4)	
Child-Pugh, n (%)			0.052
A	32 (97.0)	120 (82.8)	
B	1 (3.0)	25 (17.2)	
Lymphocyte (/mm^3)	1,529 (1,200-2,020)	988 (710-1,272)	<0.001
Platelet count (×10^4/mm^3)	16.5 (12.2-24.1)	11.8 (8.1-19.9)	0.011
ALT (IU/L)	34 (22-51)	36 (23-61)	0.43
Prothrombin time (%)	92 (83-101)	83 (75-93)	0.002
Albumin (g/dL)	4.2 (4.0-4.4)	3.3 (3.1-3.7)	<0.001
Total bilirubin (mg/dL)	0.7 (0.6-1.1)	0.8 (0.6-1.3)	0.31
PNI	49.1 (47.5-51.8)	39.3 (35.3-42.4)	
AFP (ng/mL)	44 (6.2-335)	149 (16.8-1,210)†	0.040
DCP (mAU/mL)	87.5 (26.5-1,000)	371 (51-6,340)	0.031
Naïve, n (%)	12 (36.4)	40 (27.6)	0.32
Previous treatment, n (%)			
Hepatic resection	9 (27.3)	23 (15.9)	0.12
Locoregional therapy	10 (30.3)	50 (34.5)	0.65
Transcatheter arterial chemoembolization	21 (63.6)	105 (72.4)	0.32
Number of the tumor, n (%)			0.16
1-3	15 (45.5)	48 (33.1)	
≥4	18 (54.5)	97 (67.4)	
Maximum tumor diameter (cm)	3.5 (2.3-6.1)	3.6 (2.2-7.1)	0.75
BCLC, n (%)			0.79
Early	3 (9.1)	16 (11.0)	
Intermediate	9 (27.3)	49 (33.8)	
Advanced	21 (63.6)	80 (55.2)	
Extrahepatic lesion, n (%)	16 (48.5)	59 (40.7)	0.41
Macroscopic vascular invasion, n (%)	5 (15.2)	28 (84.8)	0.049
Initial dose of sorafenib			0.65
>400 mg	8 (24.2)	30 (20.7)	
≤400 mg	25 (75.8)	115 (79.3)	

Continuous variables were represented by as the median (interquartile range). Categorical variables were represented as counts (percentages).

† There was two missing data in 4 patients.

PNI: prognostic nutritional index, HBV: hepatitis B virus, HCV: hepatitis C virus, ALT: alanine aminotransferase, AFP: α-fetoprotein, DCP: des-gamma-carboxy prothrombin, BCLC: Barcelona Clinic Liver Cancer

resulting in a response rate of 20.0% and disease control rate of 66.7%. In the PNI-low group, no patients had CR, and PR was shown in 9 patients (8.1%), SD in 53 patients (48.6%) and PD in 48 patients (43.2%), resulting in a response rate of 8.1 and disease control rate of 56.8%. The best radiological response was not significantly different between the two groups (Table 2). Three patients in PNI-high group and 34 patients in PNI-low group were excluded because of its lack of evaluation radiographic imaging. We could not identify any factors predicting the objective response in a multivariate analysis with a logistic regression model since no variables had p<0.05 on a univariate analysis (Table 3).

In the univariate analysis by a Cox proportional hazard analysis, sex, Child-Pugh, platelet count, naïve, previous hepatic resection, previous locoregional treatment, maximum tumor diameter, AFP and PNI were factors affecting the duration of sorafenib therapy among pretreatment factors. Child-Pugh class A (HR 0.57; 95% CI 0.37-0.89, p=0.013), previous locoregional treatment (HR 0.58; 95% CI 0.42-0.82, p=0.002), AFP≥100 ng/mL (HR 1.52; 95%CI 1.11-2.09, p=0.009) and the PNI-high group (HR 0.58; 95% CI 0.39-0.87, p=0.008) were independent factors affecting the duration of sorafenib therapy in a multivariate analysis by a

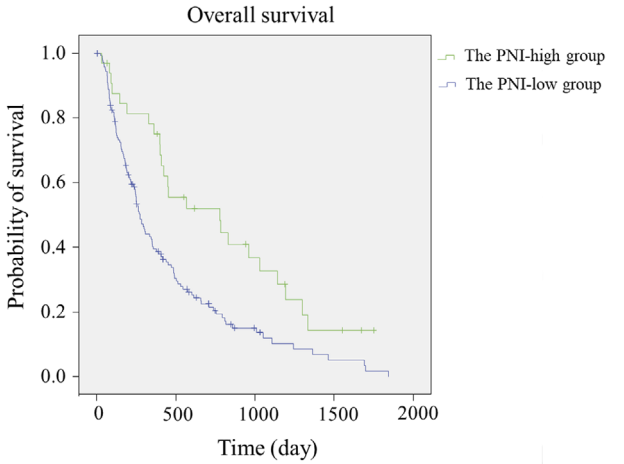

Figure 3. **Overall survival. The Kaplan-Meier analyses estimated that the 1-year survival rates of HCC patients treated with sorafenib were 79.3% (95% CI: 64.6-93.6%) in the PNI-high group and 39.5% (95% CI: 31.3-47.7%) in the PNI-low group. The cumulative survival rate in the PNI-high group was significantly better than in the PNI-low group (p=0.002). PNI: prognostic nutritional index, HCC: hepatocellular carcinoma, CI: confidence interval**

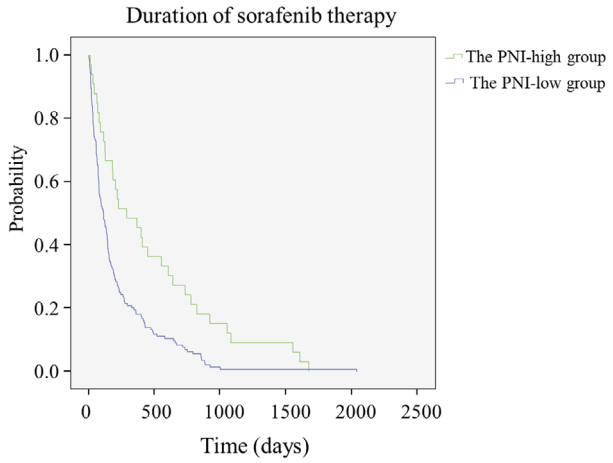

Figure 4. **Duration of sorafenib treatment. The graph illustrated that the median duration of sorafenib treatment was 287 (95% CI 67-506) days in the PNI-high group and 111 (95% CI 72-149) days in the PNI-low group. The patients in the PNI-high group received sorafenib treatment longer than those in the PNI-low group (p=0.001). PNI: prognostic nutritional index, CI: confidence interval**

Cox proportional hazard analysis (Table 4).

In the analysis of factors predictive of the overall survival, Child-Pugh, naïve, previous hepatic resection, maximum tumor diameter, macroscopic vascular invasion, AFP, DCP, and PNI were identified on a univariate analysis by a Cox proportional hazard analysis. Child-Pugh class A (HR 0.57; 95% CI 0.34-0.96, p=0.033), previous hepatic resection (HR 0.60; 95% CI 0.37-0.99, p=0.050), maximum tumor diameter ≥3.5 cm (HR 1.66; 95% CI 1.15-2.40, p=0.007), AFP ≥ 100 ng/mL (HR 1.78; 95%CI 1.24-2.55, p=0.002) and the PNI-high group (HR 0.62; 95% CI 0.39-0.99, p=0.046) were independent factors associated with the overall survival in a multivariate analysis by a Cox proportional hazard analysis (Table 5).

Among the drug-related adverse events, HFSR was the most frequent adverse event in both groups. While the rate of grade 3/4 severity HFSR was not significantly different between the two groups, the rate of all-grade HFSR was significantly higher in the PNI-high group than in the PNI-low group. Other commonly experienced adverse events were fatigue and diarrhea. The rate of adverse events of all grades other than HFSR was not significantly different between the two groups (Table 6).

Discussion

The major finding of our study was that the PNI was the significant factor associated with the duration of sorafenib therapy and the overall survival among pretreatment factors although there were no significant differences in the sorafenib efficacy and rate of serious adverse events between the two groups. Because several factors were significantly different between the two groups, we used the multivariate analysis to avoid any confounding factors, thus demonstrating that a high PNI was a significant factor associated with the duration of sorafenib therapy and the overall survival.

Some researchers have reported predictive markers for the survival in patients receiving sorafenib treatment. Llovet et al. (20) reported that baseline vascular endothelial growth factor-A (VEGF-A), hepatocyte growth factor (HGF) and Angiopoietin-2 levels were plasma biomarkers predicting the overall survival of HCC patients treated with sorafenib. The α-fetoprotein response (21, 22), changes in the dynamic contrast-enhanced MRI findings (23) and drug-related adverse events, such as hypertension (24) and toxic skin reaction (25, 26), have also been suggested as potential early surrogate markers. However, these plasma biomarkers are not available in daily clinical practice and cannot be used for making treatment decisions in advance. In contrast, we emphasized that the PNI, the value of which can be easily calculated based on the serum albumin and total lymphocyte count at baseline, can be measured in daily clinical practice and it is a reliable marker for predicting the overall survival, based on our results.

Several investigators (27-29) recently showed that the neutrophil-to-lymphocyte ratio (NLR) was associated with the overall survival of HCC patients administered sorafenib. Because the NLR is shown to be easily affected by many comorbidities, such as acute coronary syndrome, diabetes mellitus, essential hypertension, renal failure and thyroid disease (30), caution must be practiced when using the NLR to predict the overall survival of HCC patients, especially in Japanese HCC patients, who tend to be older than those in other countries (31).

The preoperative PNI was initially intended to evaluate

Table 2. A Summary of the Treatment Effect.

	PNI-high group (n=33)	PNI-low group (n=145)	p value
Overall survival (days)			
Median (95% CI)	778 (240-1,315)	275 (230-319)	0.002
1-year survival rate (95% CI)	79.3 (64.6-93.6)	39.5 (31.3-47.7)	
Duration of sorfenib therapy (days)			
Median (95% CI)	287 (67-506)	111 (72-149)	0.001
Best radiological response, n (%)‡			0.061
CR	2 (6.7)	0 (0.0)	
PR	4 (13.3)	9 (8.1)	
SD	14 (46.7)	54 (48.6)	
PD	10 (33.3)	48 (43.2)	
Response rate (%)	20.0	8.1	0.090
Disease control rate (%)	66.7	56.8	0.41

‡ Evaluated by the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Three patients in PNI-high group and 34 patients in PNI-low group were excluded because of its lack of evaluation radiographic imaging.

Categorical variables were represented as counts (percentages).

PNI: prognostic nutritional index, CI: confidence interval, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 3. Pretreatment Factors Affecting the Objective Response.

Variable		Hazard ratio (95% CI)	p value
Univariate analysis			
Age	≥71 years	1.30 (0.44-3.81)	0.63
	≤70 years	1	
Sex	Male	0.64 (0.14-3.00)	0.58
	Female	1	
Underlying liver disease	HCV	0.54 (0.18-1.57)	0.25
	HBV, alcohol, other	1	
Platelet count	$\geq 14\times10^4/mm^3$	0.82 (0.28-2.40)	0.72
	$<14\times10^4/mm^3$	1	
Initial dose of sorafenib	>400 mg	0.46 (0.14-1.46)	0.19
	≤400 mg	1	
Naïve	Naïve	0.78 (0.21-2.96)	0.72
	Recurrence	1	
Number of tumors	1, 2, 3	1.08 (0.36-3.22)	0.89
	≥4	1	
Maximum tumor diameter	≥3.5 cm	1.20 (0.41-3.51)	0.74
	<3.5 cm	1	
Macroscopic vascular invasion	Present	1.08 (0.32-3.62)	0.90
	Absent	1	
Extrahepatic metastasis	Present	0.70 (0.24-2.04)	0.51
	Absent	1	
AFP	≥100 ng/mL	1.16 (0.40-3.41)	0.78
	<100 ng/mL	1	
DCP	≥300 mAU/mL	2.25 (0.66-7.71)	0.20
	<300 mAU/mL	1	
PNI	The PNI-high group	0.36 (0.12-1.11)	0.075
	The PNI-low group	1	

CI: confidence interval, HCV: hepatitis C virus, HBV: hepatitis B virus, AFP: α-fetoprotein, DCP: des-gamma-carboxy prothrombin, PNI: prognostic nutritional index

the nutritional and immunological status of patients with gastrointestinal malignant tumors (13). Regarding HCC, some investigators (17, 18) have reported that the PNI influences the survival of HCC patients at an early stage while undergoing surgical treatment. Pinato et al. (32) also reported that the PNI was an independent factor associated

Table 4. Pretreatment Factors Affecting the Duration of Sorfenib Therapy.

Variable		Hazard ratio (95% CI)	p value
Univariate analysis			
Age	≥71 years	1.21 (0.90-1.64)	0.21
	≤70 years	1	
Sex	Male	0.66 (0.45-0.97)	0.036
	Female	1	
Underlying liver disease	HCV	1.14 (0.84-1.54)	0.40
	HBV, alcohol, other	1	
Child-Pugh	A	0.49 (0.32-0.74)	0.001
	B	1	
Platelet count	$\geq 14\times10^4/mm^3$	0.72 (0.53-0.97)	0.033
	$<14\times10^4/mm^3$	1	
Initial dose of sorafenib	>400 mg	1.02 (0.71-1.47)	0.91
	≤400 mg	1	
Naïve	Naïve	0.62 (0.44-0.85)	0.004
	Recurrence	1	
Previous hepatic resection	Present	0.62 (0.42-0.91)	0.015
	Absent	1	
Previous locoregional treatment	Present	0.58 (0.42-0.80)	0.001
	Absent	1	
Number of tumors	1, 2, 3	1.27 (0.93-1.74)	0.133
	≥4	1	
Maximum tumor diameter	≥3.5 cm	1.39 (1.03-1.89)	0.034
	<3.5 cm	1	
Macroscopic vascular invasion	Present	1.28 (0.92-1.78)	0.14
	Absent	1	
Extrahepatic metastasis	Present	0.82 (0.60-1.11)	0.20
	Absent	1	
AFP	≥100 ng/mL	1.49 (1.10-2.03)	0.01
	<100 ng/mL	1	
DCP	≥300 mAU/mL	1.32 (0.97-1.80)	0.078
	<300 mAU/mL	1	
PNI	The PNI-high group	0.51 (0.34-0.75)	0.001
	The PNI-low group	1	
Multivariate analysis			
Child-Pugh	A	0.57 (0.37-0.89)	0.013
	B	1	
Previous locoregional treatment	Present	0.58 (0.42-0.82)	0.002
	Absent	1	
AFP	≥100 ng/mL	1.52 (1.11-2.09)	0.009
	<100 ng/mL	1	
PNI	The PNI-high group	0.58 (0.39-0.87)	0.008
	The PNI-low group	1	

CI: confidence interval, HCV: hepatitis C virus, HBV: hepatitis B virus, AFP: α-fetoprotein, DCP: des-gamma-carboxy prothrombin, PNI: prognostic nutritional index

with the survival of HCC patients treated with locoregional treatment, systemic treatment and best supportive care. However, the role of the PNI in patients with advanced HCC treated with sorafenib remains uncertain. Our study corroborates these previous findings and extends them by showing that the PNI is a good marker for assessing the overall survival of patients with advanced HCC treated with sorafenib.

Precisely why the PNI influences the overall survival of HCC patients treated with sorafenib remains unclear. Several mechanisms have been proposed. Albumin is affected not only by the liver function due to underlying liver disease but also by cancer-related inflammation (33). Albumin is a well-known prognostic factor for HCC patients and has been included in some staging systems, such as the Japan Integrated Staging score (JIS score) and the Cancer of the Liver Italian Program (CLIP) score (34, 35). Lymphocytes play a crucial role in the host immune response, helping inhibit the formation and progression of tumors (36). In the tumor microenvironment, the presence of dense or conspicuous lymphocyte infiltration has been reported to be associated with a

Table 5. Pretreatment Factors Affecting the Overall Survival.

Variable		Hazard ratio (95% CI)	p value
Univariate analysis			
Age	≥71 years	1.04 (0.75-1.45)	0.82
	≤70 years	1	
Sex	Male	1.01 (0.66-1.53)	0.98
	Female	1	
Underlying liver disease	HCV	11.23 (0.88-1.72)	0.23
	HBV, alcohol, other	1	
Child-Pugh	A	0.57 (0.34-0.84)	0.007
	B	1	
Platelet count	$\geq 14\times10^4/mm^3$	0.72 (0.52-1.01)	0.058
	$<14\times10^4/mm^3$	1	
Initial dose of sorafenib	>400 mg	1.03 (0.69-1.52)	0.89
	≤400 mg	1	
Naïve	Naïve	0.59 (0.41-0.85)	0.004
	Recurrence	1	
Previous hepatic resection	Present	0.55 (0.35-0.87)	0.010
	Absent	1	
Previous locoregional treatment	Present	1.40 (0.98-1.99)	0.067
	Absent	1	
Number of tumors	1, 2, 3	1.34 (0.94-1.90)	0.11
	≥4	1	
Maximum tumor diameter	≥3.5 cm	1.68 (1.19-2.36)	0.003
	<3.5 cm	1	
Macroscopic vascular invasion	Present	1.57 (1.02-2.42)	0.042
	Absent	1	
Extrahepatic metastasis	Present	1.11 (0.79-1.55)	0.55
	Absent	1	
AFP	≥100 ng/mL	1.89 (1.34-2.65)	<0.001
	<100 ng/mL	1	
DCP	≥300 mAU/mL	1.56 (1.11-2.20)	0.010
	<300 mAU/mL	1	
PNI	The PNI-high group	0.50 (0.32-0.79)	0.003
	The PNI-low group	1	
Multivariate analysis			
Child-Pugh	A	0.57 (0.34-0.96)	0.033
	B	1	
Previous hepatic resection	Present	0.60 (0.37-0.99)	0.050
	Absent	1	
Maximum tumor diameter	≥3.5 cm	1.66 (1.15-2.40)	0.007
	<3.5 cm	1	
AFP	≥100 ng/mL	1.78 (1.24-2.55)	0.002
	<100 ng/mL	1	
PNI	The PNI-high group	0.62 (0.39-0.99)	0.046
	The PNI-low group	1	

CI: confidence interval, HCV: hepatitis C virus, HBV: hepatitis B virus, AFP: α-fetoprotein, DCP: des-gamma-carboxy prothrombin, PNI: prognostic nutritional index

better outcome in patients with various common solid tumors (33). Previous reports on HCC have found that an increased number of tumor-infiltrating effector T lymphocytes is associated with better prognostic results after surgical resection (37), and reduced lymphocyte infiltration is a negative predictive factor affecting tumor recurrence after liver transplantation (38). Another mechanism that had been suggested is that a longer duration of sorafenib treatment inhibits tumor progression, thereby leading to a better overall survival.

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (39), the rate of response to chemotherapy and its duration are poorer in cancer patients with malnutrition than in those with a good nutritional status. With respect to duration, it is consistent with the present findings that the PNI is the predictive factor of the duration of sorafenib therapy. However, we failed to detect a relationship between the PNI and the patients' re-

Table 6. Drug-related Adverse Events.

	PNI-high group (n=33)		PNI-low group (n=145)		p value	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Fatigue	8 (24.2)	0 (0)	36 (24.8)	2 (1.4)	0.94	1.00
Hand-foot skin reaction	22 (66.7)	4 (12.1)	53 (36.6)	11 (7.6)	0.002	0.40
Diarrhea	14 (42.4)	1 (3.0)	39 (26.9)	6 (4.1)	0.078	0.77
Nausea	2 (6.1)	0 (0)	22 (15.2)	1 (0.7)	0.26	1.00
Vomitting	1 (3.0)	0 (0)	5 (3.4)	0 (0)	1.00	NA
Rash/desquamation	7 (21.2)	1 (3.0)	24 (16.6)	1 (0.7)	0.53	0.34
Hypertension	3 (9.1)	1 (3.0)	16 (11.0)	3 (2.1)	0.74	0.56
Upper GI hemorrhage	0 (0)	0 (0)	2 (1.4)	1 (0.7)	1.00	1.00

The data are expressed as the counts (percentage).

PNI: prognostic nutritional index, NA: not available, GI: gastrointestinal

sponse to sorafenib therapy. A larger number of cases may be needed to detect significant differences, as the response of sorafenib therapy for HCC is low (10, 11).

The drug-related adverse events found in our study were similar to those reported in the GIDEON study (31), with HFSR being the most frequently reported event. In our study, the rate of all-grade HFSR was significantly higher in the PNI-high group than in the PNI-low group. This may be due to the longer duration of sorafenib treatment in the PNI-high group than in the PNI-low group. Patients with HFSR may also have a better prognosis than those without HFSR, based on the findings of a previous report (25).

Several limitations associated with the present study warrant mention. First, this is a retrospective study. Second, we did not routinely measure the lymphocyte count at pretreatment, and we excluded those cases lacking data on the lymphocyte count. Third, the optimum cut-off value of the PNI needs to be validated. A large-scale prospective validation study is needed to confirm the optimum cut-off value of the PNI.

In conclusion, this study demonstrated that the PNI was a simple and useful marker for predicting the duration of sorafenib therapy and the overall survival of patients with advanced HCC treated with sorafenib. Assessing the nutritional status using the PNI may provide clinicians better prognostic information for determining the efficacy of sorafenib treatment.

The authors state that they have no Conflict of Interest (COI).

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