Preoperative prognostic nutritional index predicts short- and long-term outcomes after liver resection in patients with hepatocellular carcinoma

YU SAITO, SATORU IMURA, YUJI MORINE, TETSUYA IKEMOTO, SHINICHIRO YAMADA and MITSUO SHIMADA

Department of Surgery, Tokushima University, Tokushima 770-8503, Japan

Abstract. The prognostic nutritional index (PNI) is one of the immune parameters calculated on the basis of the serum albumin and the total lymphocyte count. The aim of the present study was to investigate the prognostic significance of the PNI for short- and long-term outcomes after liver resection for patients with hepatocellular carcinoma (HCC). Data from 162 surgically treated patients with HCC (without any previous treatment) were retrospectively analyzed. The cutoff value of preoperative PNI was 45.0, which was calculated by a receiver operating characteristic curve for predicting the recurrence of HCC after liver resection. Patients were divided into low (n=86) and high (n=76) PNI groups. In short-term outcomes, patients in the low PNI group were more likely to experience postoperative complications compared with those in the high PNI group. The 5-year disease-free survival (DFS) rate in the low PNI group was significantly lower compared with that in the high PNI group (20.5% vs. 48.7%). In the multivariate analysis, a low PNI was an independent prognostic factor for DFS (HR, 1.65; 95% CI, 1.00-2.71). In conclusion, the preoperative PNI may be a prognostic factor for evaluating short- and long-term outcomes after liver resection in patients with HCC.

Correspondence to: Dr Yu Saito, Department of Surgery, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
E-mail: saito.yu.1001@tokushima-u.ac.jp

Introduction

Hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide, and the third most common cause of cancer-related death (1). For liver resection (Hx) in patients with HCC, the perioperative complications and mortality have improved in recent years from 30% to <5% in high-volume centers (2,3); however, it is crucial to manage patients with various comorbidities. Hx is still associated with a 40% morbidity rate, with post-hepatectomy liver failure (PHLF) being the most lethal complication (4). Furthermore, the recurrence rate after curative Hx for HCC is still higher compared with that for other digestive organ cancers, suggesting that it is also important to assess the risk factors for recurrence following curative Hx.

The prognostic nutritional index (PNI) was first established in 1980 in order to predict perioperative risk for gastrointestinal surgeries (5). However, the calculation method was highly complicated as it used a number of parameters such as serum albumin (Alb), triceps skinfold, transferrin and delayed hypersensitivity skin testing. A simpler modified PNI using serum Alb and total lymphocyte count (TLC) alone was reported 4 years later by Onodera *et al* (6), and the modified PNI has been widely used for perioperative risk assessment. In addition to perioperative risk prediction, the PNI has also been reported to be associated with long-term prognosis of various types of cancer after curative treatment, such as lung (7), ovarian (8), cervical (9), gastric (10) and colorectal (11) cancer.

In Hx for HCC, the preoperative PNI is associated with liver function markers such as the albumin-bilirubin grade and predicts short-term outcomes within the Milan criteria (12). A previous study has been reported that the preoperative PNI predicts long-term prognosis after Hx in only early Barcelona clinic liver cancer stage HCC (13). To the best of our knowledge, there have been no reports on the use of the preoperative PNI for predicting both short- and long-term outcomes in early and advanced stages of HCC.

The present study aimed to compare three types of immune parameters, namely the PNI, neutrophil-to-lymphocyte ratio (NLR) and aspartate aminotransferase (AST)-to-lymphocyte ratio (ALRI), as predictors of short- and long-term outcomes following Hx. Furthermore, the aim of the present study was to

determine the prognostic significance of the preoperative PNI for short- and long-term outcomes after Hx for patients with all stages of HCC.

Materials and methods

Patients. Among 229 patients who underwent Hx at Tokushima University Hospital (Tokushima, Japan) between January 2006 and December 2014, 162 patients were enrolled in the present study. The inclusion criteria were as follows: i) Primary Hx; ii) no other treatments before Hx; and iii) availability of the follow-up data. The study was approved by Tokushima University Hospital Ethics Committee, and the experiments were carried out in accordance with the approved guidelines (Tokushima Clinical Trial Management System Number, 3215). All patients involved in the study signed the informed consent form and agreed to participate.

Preoperative immune parameters. Blood samples were collected prior to Hx. The PNI was calculated as the sum of Alb level and 0.005x lymphocyte count. The NLR was calculated by dividing neutrophil count by lymphocyte count. The ALRI was calculated by dividing AST by lymphocyte count. The cutoff value of the PNI, NLR and ALRI was 45, 2.3 and 30.8, respectively, calculated by a receiver operating characteristic curve for predicting recurrence after Hx (Fig. S1).

Assessment of fat mass (FM) and skeletal muscle mass (SMM). Preoperative FM and SMM was determined from CT using Synapse Vincent® (Version 4, Fujifilm Corporation). Visceral FM (cm^2), subcutaneous FM (cm^2) and SMM/height (cm^2/m^2) were automatically calculated.

Short-term outcomes after Hx. The short-term outcomes were defined as follows: i) Operative factors (surgical procedures, surgery time, blood loss and the presence or absence of transfusion); and ii) postoperative factors (the presence or absence of complications and hospital stay duration) according to our previous studies (14,15). The '50-50 criteria' introduced by Balzan *et al* (16) was used as to determine postoperative liver failure. Postoperative complications of grade III or IV in the Clavien-Dindo classification (14,15) were recorded in the present study.

Follow-up after Hx. The mean follow-up period was 2.48 years (0.02-7.96 years). Monthly follow-up was conducted by ultrasonography and assessment of the tumor markers α-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) and AFP-L3. Dynamic CT scan and gadoliniumethoxybenzyl-diethylene-triaminepentaacetic acid-enhanced MRI were conducted at 3 and 6 months post-surgery. Recurrence was defined as the appearance of new lesions with radiological features typical of HCC confirmed by at least two imaging methods. Overall survival (OS) was defined as the time between Hx and death from any cause, and disease-free survival (DFS) was defined as the time between Hx and recurrence.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation. Statistical analysis was performed using SPSS Version 21.0 statistical software (IBM Corp.).

Associations between the PNI and patient clinicopathological characteristics were analyzed using the χ^2 and Mann-Whitney U tests. Survival curves were drawn using the Kaplan-Meier method and compared with the log-rank test. Univariate analysis of differences between two groups was also determined by log-rank tests. Multivariate analysis was performed based on the Cox proportional hazards regression model. The factors included for analyses were patient age (>70 years vs. 70 years), sex (male vs. female), hepatitis B antigen (absent vs. present), hepatitis C virus antibody (absent vs. present), AFP (>200 ng/ml vs. ≥200 ng/ml), DCP (<400 mAU/ml vs. ≥400 mAU/ml), tumor number (single vs. multiple), tumor size (<3 cm vs. ≥3 cm), tumor differentiation (well- and moderately vs. poorly differentiated), portal invasion (absent vs. present), stage (I and II vs. III and IV) and PNI (high vs. low). P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of immune parameters among the PNI, NLR and ALRI. Table I presents the comparison in of short-term (postoperative factors; frequency of postoperative complications and hospital stays) and long-term (OS and DFS) outcomes among patients divided into groups based on the PNI, NLR or ALRI. Postoperative factors alone are presented as short-term outcomes for simplicity. The PNI alone was associated with short-term outcome, and both the PNI and NLR were reliable parameters for predicting the long-term outcomes (Table I).

Associations between the preoperative PNI and clinicopathological characteristics. Associations between the preoperative PNI values and clinicopathological characteristics are presented in Table II. A low PNI was significantly associated with an older age, female sex and impaired liver function, such as high AST and indocyanine green retention test values. Among the tumor factors, a low PNI only exhibited a tendency towards the presence of microscopic portal vein invasion. In addition, a low PNI was significantly associated with a low SMM (sarcopenia).

Preoperative PNI and short-term outcomes. No significant differences were observed in the operative procedures between the low and high PNI groups. Blood loss was significantly higher in the low PNI group compared with that in the high PNI group. The low PNI group had significantly longer hospital stays after Hx compared with those in the high PNI group (Table III).

Preoperative PNI and long-term outcomes. Patients in the low PNI group exhibited a tendency towards a lower OS rate (Fig. 1A). In addition, patients in the low PNI group had a significantly poorer DFS compared with that in the high PNI group (Fig. 1B). In the univariate analysis of DFS, high AFP, high DCP, multiple tumors, the presence of microvascular invasion, advanced stage and low PNI were identified as indicators of a poor prognosis. The results of the multivariate analysis revealed that high AFP, multiple tumors and a low PNI were independent prognostic factors for DFS (Table IV). Regarding the recurrence patterns, no significant differences were observed between the low and high PNI groups (Fig. 2).

Table I. Comparison of immune parameters in short- and long-term outcomes.

Parameter	Incidence of complications		Hospital stay		3-year OS		3-year DFS	
	%	P-value	Days	P-value	%	P-value	%	P-value
PNI		0.12		<0.01[a]		0.06		0.03[a]
<45.0	8.2		31±34		68.4		38.2	
≥45.0	2.7		17±9		79.1		53.7	
NLR		0.98		0.13		0.01[a]		0.04[a]
<2.3	5.7		21±16		83.9		49.5	
≥2.3	5.6		27±33		65.7		40.5	
ALRI		0.87		0.67		0.25		0.25
<30.8	6.5		23±34		77.8		51.6	
≥30.8	5.8		25±18		71.5		41.5	

[a]$P<0.05$. PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; ALRI, aspartate aminotransferase-to-lymphocyte ratio.
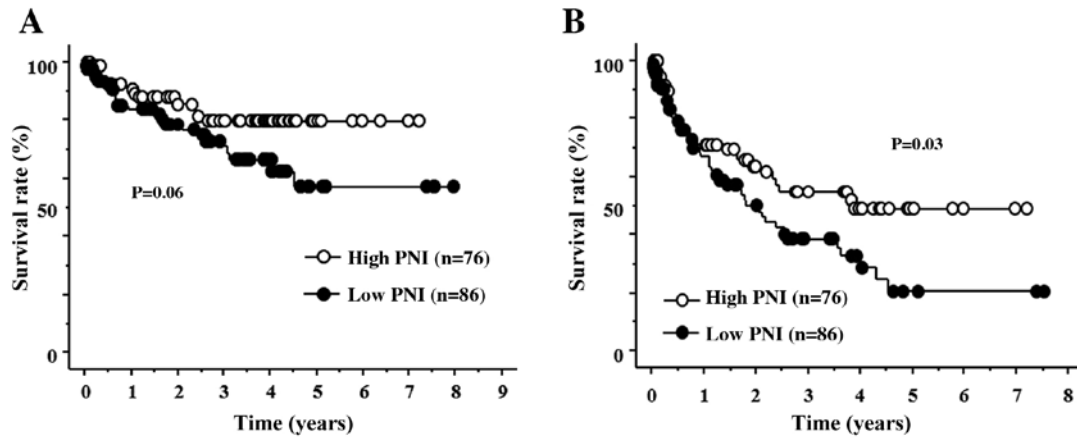

Figure 1. Long-term survival of patients with hepatocellular carcinoma. (A) Overall survival. Patients in the low PNI group tended to exhibit a poorer prognosis compared with those in the high PNI group. (B) Disease-free survival. Patients in the low PNI group exhibited a significantly poorer prognosis compared with those in the high PNI group (5-year survival, 20.5 vs. 48.7%). PNI, prognostic nutritional index.
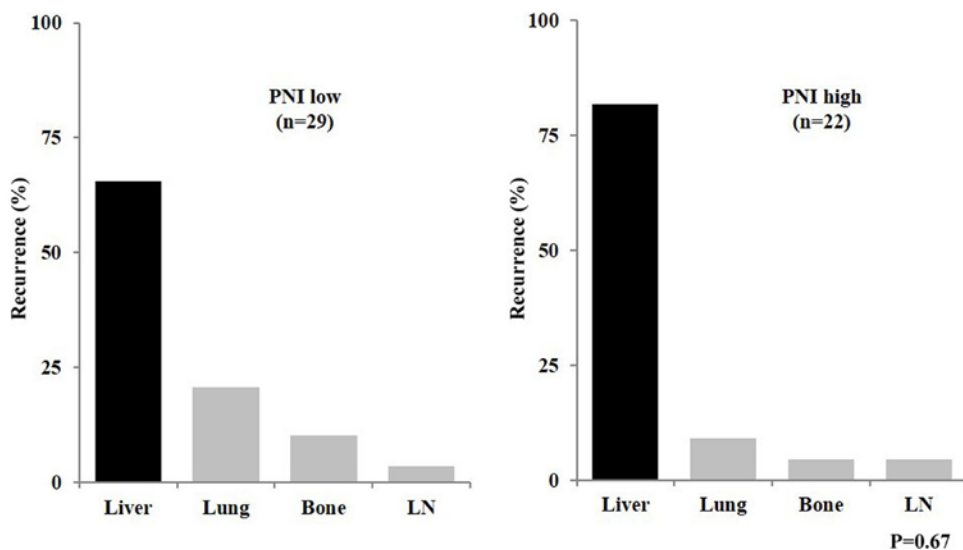

Figure 2. Recurrence patterns. No significant differences were observed in recurrence patterns between patients in the low and high PNI groups. PNI, prognostic nutritional index; LN, lymph node.

Table II. Associations between the preoperative PNI and patient clinicopathological characteristics.

Factor	Preoperative PNI		P-value
	<45 (n=86)	≥45 (n=76)	
Age, years, mean ± SD	70±10	60±10	<0.01[a]
Sex			0.03
Male	57	62	
Female	29	14	
Hepatitis B antigen			0.66
Absent	67	57	
Present	19	19	
Hepatitis C virus antibody			0.34
Absent	48	48	
Present	38	28	
Aspartate aminotransferase, IU/I, mean ± SD	60±36	42±24	<0.01[a]
Prothrombin, %, mean ± SD	100±17	103±22	0.31
Total bilirubin, mg/dl, mean ± SD	0.9±0.4	0.8±0.3	0.19
Indocyanine green retention test, %, mean ± SD	16±10	11±8	<0.01[a]
Platelet count, x10^4, mean ± SD	21±32	20±14	0.79
Tumor size, cm, mean ± SD	4.9±4.5	4.1±2.7	0.18
Tumor number			0.46
Single	60	57	
Multiple	26	19	
Portal vein invasion			0.06
Absent	62	65	
Present	24	11	
Intrahepatic metastasis			0.65
Absent	79	70	
Present	7	6	
Tumor differentiation			0.47
Well- or moderately differentiated	17	19	
Poorly differentiated	69	57	
Stage			0.73
I and II	57	53	
III and IV	29	23	
AFP, ng/ml, mean ± SD	4,385±22,223	1,350±5,256	0.25
DCP, mAU/ml, mean ± SD	9,359±32,458	3,172±13,090	0.22
BMI, mean ± SD	22±3	23±3	0.43
Visceral FM, cm^2, mean ± SD	76±47	87±47	0.11
Subcutaneous FM, cm^2, mean ± SD	108±77	108±64	0.97
SMM/height, cm^2/m^2, mean ± SD	51±13	56±15	0.03[a]

[a]$P<0.05$. PNI, prognostic nutritional index; FM, fat mass; SMM, skeletal muscle mass; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin.

Discussion

In the present study, a number of immune parameters including the PNI, NLR and ALRI were compared in terms of short- and long-term outcomes after Hx in patients with HCC. In addition to the prediction of outcomes following Hx, the PNI was significantly associated with a low SMM. Previous

studies have reported similar benefits of the PNI, especially in the prediction of long-term outcomes after Hx. For example, the preoperative (13,17) and postoperative (18) PNIs have been reported to be prognostic factors for OS, especially in early-stage HCC. Furthermore, a meta-analysis has also demonstrated that preoperative PNI is a prognostic marker for long-term survival after not only Hx, but also TACE or

Table III. Associations between the preoperative PNI and short-term outcomes.

A, Operative factors

	Preoperative PNI		
Factor	<45 (n=86)	≥45 (n=76)	P-value
Procedure			0.65
Hr0	29	17	
S	4	25	
1	22	18	
2	10	15	
3	1	1	
Surgery time, min, mean ± SD	328±93	318±85	0.48
Blood loss, m, mean ± SD	394±433	253±224	<0.01[a]
Transfusion			0.48
Absent	75	63	
Present	11	12	

B, Postoperative factors

	Preoperative PNI		
Factor	<45 (n=86)	≥45 (n=76)	P-value
Complications of CD grade III or IV			0.12
Absent	79	74	
Present	7	2	
Liver failure	3	0	0.10
Intra-abdominal abscess	3	1	0.37
Resistant ascites	1	1	0.92
Hospital stay, days, mean ± SD	31±34	17±9	<0.01[a]

[a]P<0.05. PNI, prognostic nutritional index; CD, Clavien-Dindo classification; Hr 0, partial resection; Hr S, subsegmentectomy; Hr 1, segmentectomy; Hr 2, lobectomy; Hr 3, trisectionectomy.

Table IV. Univariate and multivariate analysis of disease-free survival.

	Univariate		Multivariate	
Factor	P-value	Hazard ratio	95% CI	P-value
AFP ≥200 ng/ml	<0.01[a]	1.77	1.00-3.13	0.04[a]
DCP ≥400 mAU/ml	0.04[a]	1.04	0.59-1.84	0.89
Multiple tumors	<0.01[a]	2.09	1.25-3.51	<0.01[a]
Portal vein invasion present	<0.01[a]	1.39	0.79-2.44	0.25
PNI <45	0.03[a]	1.65	1.00-2.71	0.04[a]

[a]P<0.05. PNI, prognostic nutritional index; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin.

non-surgical treatment (19). By contrast, a limited number of studies on the prediction of short-term outcomes after Hx are currently available. One previous report focused on the prognostic ability of the PNI for postoperative complications after Hx within the Milan criteria (12). Therefore, the novelty of the present study compared with the previous ones was that the prognostic ability of the PNI was analyzed in both short- and long-term outcomes after Hx, that the analysis included

all stages of HCC, and that the PNI was compared with other immune parameters including the NLR and ALRI.

Previous studies have reported the use of the NLR as a prognostic factor in HCC after curative treatment. The usefulness of the NLR and platelet-to-lymphocyte ratio after transarterial chemoembolization has been demonstrated (20). Another study has reported that the NLR predicted disease progression following intra-arterial therapy of HCC (21). In the present study, the NLR was a predictor of long-term outcomes after Hx. The molecular mechanism of the increase in the NLR involves a number of factors and remains poorly understood. However, an association between the accumulation of tumor-associated macrophages in HCC and high NLR values has been observed in patients with HCC who underwent Hx and living donor liver transplantation (22). A high NLR is also associated with high levels of infiltration of tumor-associated macrophages and inflammatory cytokine production in the tumor, such as interleukin-6, interleukin-8 and interleukin-17, which promote systemic neutrophilia (23,24).

In the present study, a low PNI was significantly associated with a longer hospital stays and a poor DFS. In addition, patients with a low PNI exhibited a poor OS. By contrast, the NLR was a good prognostic factor predicting long-term outcomes including both OS and DFS. There were no significant associations between the NLR and short-term outcomes. This suggests that the preoperative PNI may be a prognostic factor for evaluating both short- and long-term outcomes. However, there were insufficient data in the present study to conclude that the preoperative PNI was the most significant prognostic factor for evaluating both short- and long-term outcomes among the PNI, NLR and ALRI.

The PNI value, which is a combination of Alb and the total lymphocyte count, may be used to evaluate the immunological and nutritional aspects of patients undergoing surgery. A previous study has reported that the PNI was established as an indirect measure of a patient's nutritional status, suggesting that the PNI may be associated with postoperative complications (12). The level of Alb and the lymphocyte count have been reported to be closely associated with the induction of the inflammatory response (25). Therefore, the PNI may not only reflect the nutritional status, but also systemic inflammation. In the patient cohort included in the present study, Alb level was also a good prognostic factor for both OS and DFS (data not shown). However, no statistically significant differences were observed between Alb levels and the short-term outcomes (data not shown). The PNI appeared to be a better prognostic factor compared with Alb level alone.

Recently, the lymphocyte-to-C-reactive protein ratio (LCR) was reported as a useful marker for predicting surgical and oncological outcomes (26). The present study also investigated the association between the preoperative LCR and prognosis in the study cohort; a low LCR exhibited a tendency towards an association with OS (P=0.08), but not with DFS. There was no significant association between the LCR and short-term outcomes (data not shown).

A low PNI was not associated with tumor characteristics such as differentiation, stage or tumor markers in the present study. A low PNI was associated with female sex, older age, a poor liver function and low skeletal muscle levels. The same tendency was observed in previous studies (13,17). We therefore speculate that the PNI may reflect the immune-nutritional condition rather than tumor malignancy. Tumor-infiltrating lymphocytes (TILs) are a specific histological feature of human cancers, reflecting an individual's immunological tumor response (27). Previous studies have reported that TILs may be associated with peripheral blood cells, such as the TLC and absolute neutrophil count (28,29). In esophageal cancer, the PNI and TIL score have been reported to be associated with clinical outcomes (30). Considering the relationship between the PNI and TILs, nutritional status and systemic immune competence may affect patient prognosis through local immune response.

For patients with a low PNI, it is essential to improve their outcomes through perioperative nutritional interventions, e.g. the administration of branched-chain amino acid-enriched nutrient support (31,32). In the present study, the PNI was significantly associated with sarcopenia; thus, further nutritional intervention may be necessary for patients with a low PNI.

In conclusion, the results of the present study demonstrated that a low PNI and sarcopenia reflected a poor nutritional status in patients with HCC. Furthermore, the preoperative PNI was a reliable prognostic factor for evaluating both short- and long-term outcomes after Hx for patients with HCC. Therefore, nutritional intervention may be beneficial for patients with HCC with a low preoperative PNI.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YS participated in the study design, performed the research and data analysis, and wrote the manuscript. SI participated in the study design and data analysis. YM, TI and MS participated in the study design. SY and MS participated in data analysis. MS also critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by Tokushima University Hospital Ethics Committee (Tokushima, Japan), and all experiments

were carried out in accordance with the approved guidelines (Tokushima Clinical Trial Management System Number; 3215). All patients involved in the study signed the informed consent form and agreed to participate.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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