

Preoperative prognostic nutritional index predicts both short and long-term outcomes after liver resection for hepatocellular carcinoma.

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Abstract

Background The aim of this study was to investigate the prognostic significance of the prognostic nutritional index (PNI) for both short and long term outcomes after liver resection for hepatocellular carcinoma (HCC). **Methods** 162 (without any previous treatment) of 229 surgically treated HCC patients were retrospectively analyzed. The cut off value of the preoperative PNI was 45.0. Patients were divided into two groups, PNI low (n=76) and high (n=86) group. **Results** Among some immune parameters such as PNI, neutrophil to lymphocyte ratio (NLR) and aspartate aminotransferase (AST) to lymphocyte ratio (ALRI), PNI had most reliable parameters in terms with prediction of both short and long term outcomes. Preoperative PNI tended to correlate with low skeletal muscle mass (SMM). In short term outcomes, PNI low group were more likely to have postoperative complications. The disease-free survival rate in PNI low group was significantly worse than that in the PNI high group (20.5 vs. 48.7 %, 5 year SR, p=0.03). On multivariate analysis, Low PNI was an independent prognostic factor for disease free survival (HR 1.65, p= 0.04). **Conclusions** The preoperative PNI was the most significant prognostic factor for evaluating both short and long-term outcomes after liver resection for HCC.

Background

In liver resection (Hx) for hepatocellular carcinoma (HCC), the perioperative complications and mortality has been improved recent years, however, it has been critical to manage patients with various comorbidity. Furthermore, the recurrent rate after curative Hx for HCC is still higher than other digestive organ cancers and it has been also important to assess risk factors for recurrence after curative Hx.

PNI (Prognostic nutritional index) was firstly reported in 1980 by Buzby et al. ¹⁾ in order to predict perioperative risk. However, calculation method was too complicated using many parameters such as serum albumin (Alb), triceps skinfold (TSF), transferrin (TFN) and delayed hypersensitivity skin testing (DHS). 4 years later, Japanese Onodera et al. ²⁾ reported simpler modified PNI using serum Alb and total lymphocytes count (TLC) alone, and that Onodera's PNI has been widely used for perioperative risk assessment. In addition to perioperative risk prediction, PNI was also reported that it correlated with long-term prognosis of various cancers after curative treatment such as lung ³⁾, ovarian ⁴⁾, cervical ⁵⁾, gastric ⁶⁾ and colorectal ⁷⁾ cancers and so on.

In Hx for HCC, preoperative PNI was already reported to correlate with liver function such as albumin-bilirubin (ALBI) grade, and to predict short-term outcomes after Hx for HCC within the Milan criteria ⁸⁾. Chan et al. ⁹⁾ reported that preoperative PNI predicted long-term prognosis after Hx in only early BCLC stage HCC. There were no reports of preoperative PNI for predicting both short and long term outcomes in whole HCC stage.

In the present study, among various immune parameters such as PNI, neutrophil to lymphocyte ratio (NLR) and aspartate aminotransferase (AST) to lymphocyte ratio (ALRI), the most reliable parameter was

examined. The aim of this study was to investigate the prognostic significance of the preoperative PNI for both short and long term outcomes after Hx for whole stage HCC patients.

Methods

Patients

Among 229 patients who underwent Hx from January 2006 to December 2014, 162 patients were enrolled in this study. Inclusion criteria of this study were 1) Primary Hx, 2) No any other treatments before Hx, 3) Availability of follow up data. The study was approved by Tokushima University Hospital ethics committee and with the approval of corresponding regulatory agencies, and all the experiments were carried out in accordance with the approved guidelines (Tokushima Clinical Trial Management System Number; 3215). Meanwhile, all the patients involved in the study signed the informed consent form and agreed to participate.

Preoperative immune parameters

Blood samples were taken prior to Hx. The PNI was the sum of serum albumin and $0.005 \times$ lymphocyte count. The NLR was calculated by dividing neutrophil count by lymphocyte count. ALRI was calculated by dividing AST by lymphocyte count. The cutoff value of PNI, NLR and ALRI was 45, 2.3 and 30.8 calculated by receiver-operating characteristic (ROC) curve for predicting recurrence after Hx.

Assessment of fat mass (FM) and skeletal muscle mass (SMM)

Preoperative fat mass (FN) or skeletal muscle mass (SMM) was investigated from CT modality using Synapse Vincent[®]. Visceral FM (cm²), subcutaneous FM (cm²) and SMM / height (cm² / m²) were automatically calculated.

Follow-up after Hx

Monthly follow-up was conducted by assessment of tumor markers (AFP, DCP, and AFP-L3) and ultrasonography. Dynamic computed tomography (CT) scan and Gd-EOB-DTPA-enhanced magnetic resonance imaging (MRI) were conducted at 3 and 6 months post operation. We defined recurrence as the appearance of new lesions with radiological features typical of HCC, as confirmed by at least two imaging methods.

Statistical analysis

All statistical analysis was performed using SPSS Version 21.0 statistical software (SPSS, Chicago, IL). A *p*-value of less than 0.05 was considered statistically significant. Relationships between PNI and the clinicopathological variables were analyzed using the chi-square test and Mann-Whitney U test. Survival curves were calculated using the Kaplan-Meier method and compared with the log-rank test. All factors significant by univariate analysis were included in the Cox's proportional hazards model of multivariate

analysis to identify independent factors influencing survival. The factors included for analyses were patient age (under 70 / over 70 y.o.), gender (male / female), HBsAg (absent / present), HCVAb (absent / present), AFP (under 200 / over 200 ng/ml), DCP (under 400/over 400 mAU/ml/), tumor number (single / multiple), tumor size (under 3 / over 3cm), tumor differentiation (well, moderate / poor), portal invasion (absent / present), staging (I,II / III,IV) and PNI (high / low).

Results

Comparison of immune parameters among PNI, NLR and ALRI

Table 1 showed the comparison in both short and long-term outcomes among PNI, NLR and ALRI. The PNI alone predicted short-term outcomes, and both the PNI and NLR were reliable parameters for predicting the long-term outcomes. In terms with prediction of both short and long-term outcomes, PNI was most reliable parameters among three parameters.

Correlation between preoperative PNI and the clinicopathological variables

Correlations between preoperative PNI values and clinicopathological variables are shown in Table 2. Low PNI significantly correlated with high age, or impaired liver function such as higher AST, higher ICGR15 and lower platelet levels. In tumor factors, low PNI tended to correlate with the only presence of microscopic vp alone. Furthermore, low PNI significantly correlated with lower SMM, which was called Sarcopenia.

Preoperative PNI and short-term outcomes

There were no significant differences in operative procedures between PNI low and high groups. Blood loss was significant much more in Low PNI group. Low PNI group tended to have more frequent severe postoperative complications, and had significant longer hospital stays after Hx (Table 3).

Preoperative PNI and long-term outcomes

In overall survival (OS), Low PNI group tended to have worse prognosis (Figure 1A). In disease free survival (DFS), Low PNI group had significant worse prognosis than high PNI group (Figure 1B). In univariate analysis for DFS, high AFP, high DCP, multiple tumors, the presence of microvascular invasion, more advanced stage and low PNI were selected for poor prognostic factors. In multivariate analysis revealed that high AFP, multiple tumors and low PNI were independent prognostic factors for DFS (Table 4). Regarding recurrent patterns, there was no significant difference between PNI low and high group (Figure 2).

Discussion

In the present study, some immune parameters including PNI, NLR and ALR were compared in terms with both short and long term outcome, and PNI was the most reliable parameters. In addition to the prediction

of outcomes after HX, PNI significantly correlated with low SMM, Sarcopenia. This is the first reports of preoperative PNI for predicting both short and long term outcomes in whole HCC stage.

First of all, there were several reports about NLR for prognostic factors in HCC after curative treatment. He et al.¹⁰⁾ reported the usefulness of NLR and platelets to lymphocytes ratio (PLR) after transarterial chemoembolization. Taussig et al. also reported¹¹⁾ that NLR predicted disease progression following intra-arterial therapy of HCC. In the present study, NLR was good biomarkers for predicting long-term outcomes after Hx. The molecular mechanism of an elevated NLR involved many factors and it remains poorly understood. However, a close relationship between the accumulation of tumor-associated macrophages in HCC and high NLR values has been observed in patients with HCC who underwent hepatic resection and living-donor liver transplantation¹²⁾. A high NLR was also associated with a high infiltration of tumor-associated macrophages and high inflammatory cytokine production in the tumor, such as interleukin-6, interleukin-8 and interleukin-17, which promote systemic neutrophilia^{13), 14)}.

On the other hand, NLR was not correlated with short-term outcomes in the present study. PNI was only predictors for postoperative complications and hospital stays. PNI value, a combination of the albumin and total lymphocyte count, was parameters to evaluate the immunological and nutritional aspects of patients undergoing surgery. Ke et al.¹⁵⁾ reported that PNI was constructed as a reflection of a patient's nutritional status and it made sense that the PNI might be related to postoperative complications. The PNI included the lymphocyte count in its calculation. It has been found that the level of serum Alb and the count of lymphocyte had a tight relationship with the induction of the inflammatory response¹⁶⁾. Therefore, it not only reflected the status of nutrition but also systemic inflammation.

For patients with a low PNI, it was essential to improve their outcomes through perioperative nutritional interventions, for example, the administration of branched-chain amino acid-enriched nutrient support^{17), 18)}. In the present study, PNI significantly correlated with Sarcopenia, so further nutritional intervention might be necessary for patients with a low PNI.

Conclusions:

Low PNI correlated with Sarcopenia reflecting low nutritional and inflammatory response. Furthermore, preoperative PNI, rather than NLR and ALRI was the most significant and reliable prognostic factor for evaluating both short and long-term outcomes after Hx for HCC. Some nutritional interventions might be necessary for the patients with a low PNI.

Abbreviations

Prognostic nutritional index; PNI

Liver resection; Hx

Hepatocellular carcinoma; HCC

Neutrophil to lymphocyte ratio; NLR

Aspartate aminotransferase to lymphocyte ratio; ALRI

indocyanine green retention test; ICG R15

Area under curve; AUC

Receiver operating characteristic; ROC

Declarations

Ethics approval and consent to participate

The study was approved by Tokushima University Hospital ethics committee and with the approval of corresponding regulatory agencies, and all the experiments were carried out in accordance with the approved guidelines (Tokushima Clinical Trial Management System Number; 3215). Meanwhile, all the patients involved in the study signed the informed consent form and agreed to participate.

Consent for publication

Not applicable

Availability of data and materials

The current datasets are either deposited in publicly available repositories (where available and appropriate).

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

Yu Saito (YS) MD, PhD, FACS: Participated in the research design, performance of the research, data analysis and writing manuscripts.

Satoru Imura (SI) MD, PhD, FACS: Participated in the research design and data analysis.

Yuji Morine (YM) MD, PhD, FACS: Participated in the research design.

Tetsuya Ikemoto (TI) MD, PhD, FACS: Participated in the research design.

Shinichiro Yamada (SY) MD, PhD, FACS: Participated in data analysis.

Mitsuo Shimada (MS) MD, PhD, FACS: Participated in the critical comments and administrative support.

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Tables

Table 1 Comparison of immune parameters in short and long-term outcomes

	Cut off		Incidence of complications	<i>p</i> value	Hospital Stays (days)	<i>p</i> value
PNI	45.0	Low	8.2 %	0.12	31 ± 34	<u><0.01</u>
		High	2.7 %		17 ± 9	
NLR	2.3	Low	5.7 %	0.98	21 ± 16	0.13
		High	5.6 %		27 ± 33	
ALRI	30.8	Low	6.5 %	0.87	23 ± 34	0.67
		High	5.8 %		25 ± 18	

	Cut off		OS 3y SR	p value	DFS 3y SR	p value
PNI	45.0	Low	68.4 %	0.06	38.2 %	<u>0.03</u>
		High	79.1 %			
NLR	2.3	Low	83.9 %	<u>0.01</u>	49.5 %	<u>0.04</u>
		High	65.7 %			
ALRI	30.8	Low	77.8 %	0.25	51.6 %	0.25
		High	71.5 %			

Table 2: Correlation between preoperative PNI and the clinicopathological variables

Factors	Preoperative PNI		p-value
	< 45 (n=86)	≥45 (n=76)	
Age: Mean	70 ± 10	60 ± 10	<u><0.01</u>
Gender:			
Male / Female	57 / 29	62 / 14	<u>0.03</u>
HBs Ag:			
absent / present	67 / 19	57 / 19	0.66
HCV Ab:			
absent / present	48 / 38	48 / 28	0.34
AST (IU / l) (13-30) : Mean	60 ± 36	42 ± 24	<u><0.01</u>
PT (%) (> 70) : Mean	100 ± 17	103 ± 22	<u>0.31</u>
T-bil (mg / dl) (0.4-1.5) : Mean	0.9 ± 0.4	0.8 ± 0.3	0.19
ICG R15 (%) (< 10): Mean	16 ± 10	11 ± 8	<u><0.01</u>
Platelet (15-35) :			
< / ≥ 10×10 ⁴	21 / 65	4 / 72	<u><0.01</u>
Tumor size: Mean	4.9 ± 4.5	4.1 ± 2.7	0.18
Tumor number:			
single / multiple	60 / 26	57 / 19	0.46
vp:			
absent / present	61 / 24	65 / 11	0.06
im:			
absent / present	79 / 7	70 / 6	0.65
Tumor differentiation:			
well, moderate / poor	17 / 69	19 / 57	0.47
Staging:			
I, II / III, IV	57 / 29	53 / 23	0.73
AFP (< 10) :			
< / ≥ 200 ng/ml	69 / 17	59 / 17	0.69
DCP (< 40) :			
< / ≥ 400 mAU/ml	52 / 34	49 / 27	0.60
BMI: Mean	22 ± 3	23 ± 3	0.43
Visceral FM (cm ²): Mean	76 ± 47	87 ± 47	0.11
Subcutaneous FM (cm ²): Mean	108 ± 77	108 ± 64	0.97
SMM / height (cm ² / m ²): Mean	51 ± 13	56 ± 15	<u>0.03</u>

Table 3: Preoperative PNI and short-term outcomes

Factors	Preoperative PNI		p-value
	< 45 (n=86)	≥45 (n=76)	
Operative factors			
Operative procedures:			
Hr0 / S / 1 / 2 / 3	29 / 4 / 22 / 10 / 1	17 / 25 / 18 / 15 / 1	0.65
Operative time (min): Mean	328 ± 93	318 ± 85	0.48
Blood loss (ml): Mean	394 ± 433	253 ± 224	<u><0.01</u>
Transfusion			
absent / present	75 / 11	63 / 12	0.48
Post-operative factors			
Complications			
absent / present	79 / 7	74 / 2	0.12
Liver failure	3	0	
Intra-abdominal abscess	3	1	
Resistant ascites	1	1	
Hospital stays (days): Mean	31 ± 34	17 ± 9	<u><0.01</u>

Table 4: Univariate and Multivariate analysis of DFS

	Univariate	Multivariate		
	p-value	Hazard ratio	95% C.I.	p-value
≥200 ng/ml	<u><0.01</u>	1.77	1.00 - 3.13	<u>0.04</u>
≥400 mAU/ml	0.04	1.04	0.59 - 1.84	<u>0.89</u>
or number: multiple	<u><0.01</u>	2.09	1.25 - 3.51	<u><0.01</u>
resent	<u><0.01</u>	1.39	0.79 - 2.44	<u>0.25</u>
<45	0.03	1.65	1.00 - 2.71	<u>0.04</u>

Figures

Overall survival (OS)

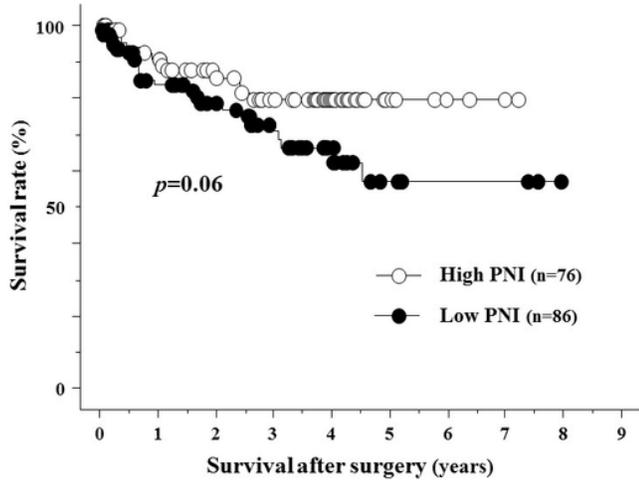


Fig. 1A

Disease free survival (DFS)

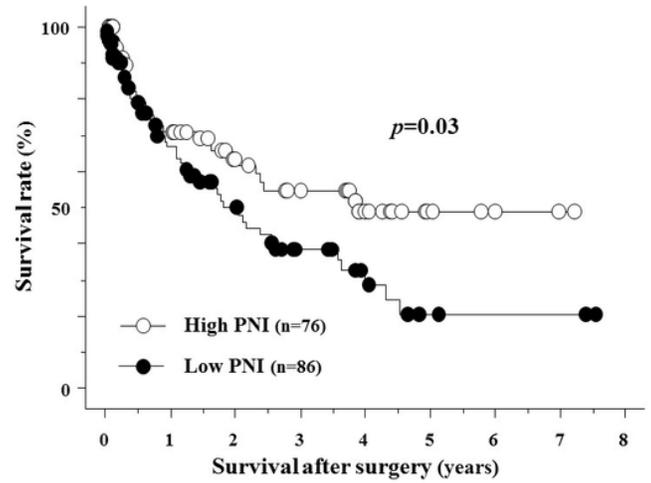


Fig. 1B

Figure 1

Long-term survival A. Overall survival Low PNI group tended to have worse prognosis ($p=0.06$). B. Disease free survival Low PNI group had significant worse prognosis than high PNI group (20.5 vs.

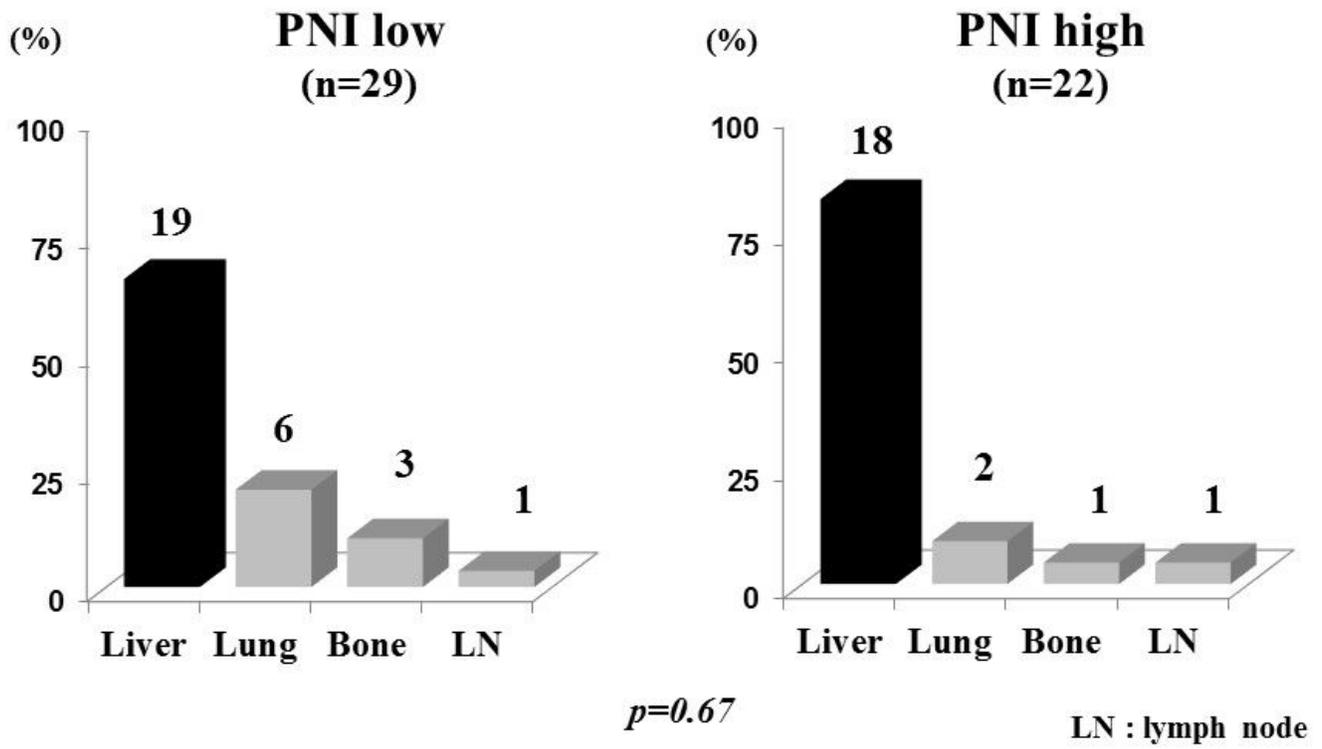


Fig. 2

Figure 2

Recurrence patterns There was no significant difference in recurrent patterns.