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The Preoperative Prognostic Nutritional Index in Hepatocellular Carcinoma After Curative Hepatectomy: A Retrospective Cohort Study and Meta-Analysis

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ABSTRACT

Objective: Conflicting results existed about the role of prognostic nutritional index (PNI) for hepatocellular carcinoma (HCC) patients who received curative hepatectomy. The aim of this study is to identify the predictive capacity of PNI for survival after hepatectomy. **Methods:** Preoperative PNI, neutrophil-to-lymphocyte ratio (NLR), tumor feature and clinical information of 187 patients with HCC from Sir Run Run Shaw hospital were evaluated. We also conducted a meta-analysis of seven cohort studies. **Results:** Our study showed that HCC patients with a low PNI of <45 had a poor recurrence-free survival (RFS) rate (hazard ratio [HR] 1.762, 95% confidence interval [CI] 1.066–2.911, $p = 0.027$, respectively). The 5-year OS and RFS rates of the high PNI (≥45) vs low PNI (<45) were 76.7% vs 50.1% ($p = 0.001$) and 47.0% vs 28.9% ($p = 0.001$), respectively. In HCC TNM I patients (n = 144), a low PNI remained an independent prognostic factor of OS and RFS (HR 2.305, 95% CI 1.008–5.268, $p = 0.048$; HR 2.122, 95% CI 1.149–3.920, $p = 0.016$). The 5-year OS and RFS rates of the high PNI vs low PNI were 81.3% vs 62.4% ($p = 0.041$) and 53.4% vs 45.6% ($p = 0.013$), respectively. In the pooled analysis, the data showed that a low PNI was significantly associated with poor OS and RFS (HR 2.27, 95% CI 1.03–4.07, $p < 0.001$ and HR 1.68, 95% CI 1.45–1.94, $p < 0.001$, respectively). **Conclusions:** The preoperative PNI was an independent prognostic factor for OS and RFS rates in HCC patients who received hepatectomy.

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KEYWORDS
Hepatocellular carcinoma; prognostic nutritional index; prognosis; meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 70–80% of all pathological variables [1]. Of note, compared with other countries, an estimated cases and deaths in liver cancer occurred in China are remarkably higher [2,3]. Within 5 years after curative resection, metastasis and recurrence of this malignancy are up to 70% [3]. Therefore, it is considerably imperative and essential to find an efficient system in HCC to predict prognosis and help to draw an individual treatment.

The therapeutic strategy for HCC largely depends on the tumor stage and the condition of liver function [4]. Plenty of variables such as body mass index (BMI) and glasgow prognostic score (GPS) be proposed to predict prognosis improves clinic treatments. However, some previous studies indicated that BMI and GPS could not be appropriate prognostic factors for HCC patients [5,6]. Noteworthily, indictors correlated with malnutrition and inflammation have been proven to be a reliable prognostic factors [7–12]. Nutritional status plays an important role on patients recovery from hepatectomy [13]. Otherwise, inflammatory status also has a decisive effect on many malignancies [14]. The prognostic nutritional index (PNI), which is obtained through serum albumin (ALB) and lymphocyte count in the peripheral blood, is firstly proposed to predict the prognosis in cancer patients [15]. Recent evidences also indicated that PNI is an effective predictive prognosis system for patients with HCC after curative hepatectomy [16]. However, there are no exclusively reports related to PNI for HCC patients. In addition, neutrophil-to-lymphocyte ratio (NLR), which is intimately correlated with inflammation, had been studied for prognostic role to predict outcomes in patients with HCC [9]. But there is no worldwide consensus on these prognostic makers.

To verify the prognostic role of PNI in patients with HCC after curative hepatectomy, we analyzed 187 patients in our institution and found PNI could be a promising system to predict the prognosis. Moreover, the results of meta-analysis were consisted with our results and demonstrated this system was worthy to promote in clinical practice.

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2. Methods

2.1. Study population

A cohort of 313 liver cancer patients who received hepatectomy as initial treatment between June 2012 and May 2017 at Sir Run Run Shaw hospital were collected. HBV-related HCC refers to HBV surface antigen (HBsAg)-positive, or detectable HBV DNA, or both HBV e antibody- and HBcAb-positive in HCC. Intrahepatic cholangiocarcinoma (ICC) patients were excluded for our study. Patients without complete laboratory data set or lost to follow-ups were also excluded. Finally, our study included a total of 187 HCC patients after curative hepatectomy.

According to the guidelines of American Association for the study of Liver Diseases, HCC was diagnosed. Before surgery with curative intents, the routine measurements were performed, including physical examination, hematologic profiles, biochemistry examination, and abdominal computed tomography (CT). The preoperative variables including preoperative α-fetoprotein (AFP), serum albumin, neutrophil granulocyte, and total lymphocyte count were also tested. This study protocol was approved by the Clinical Research Ethics Boards of the Sir Run Run Shaw Hospital and all patients in this study had obtained informed consents.

BMI was calculated as the ratio of weight (kg) and height (m) squared. The calculation formula of PNI as follow: serum albumin (g/L) + $0.005 \times$ lymphocyte count (per mm^3), and preoperative NLR was calculated as the ratio of neutrophil granulocyte (per mm^3) and lymphocyte count (per mm^3).

2.2. Treatment and follow-up

Before carrying out curative hepatectomy, HCC patients were fully assessed. According to Child-Pugh grade, there were 181 patients for grade A. The rest six HCC patients of grade B were changed to grade A after conservative treatment. The data in our study were collected before nutritional interventional approaches. The definition of curative hepatectomy is R0 hepatectomy [17]. The ways of follow-up in this study were outpatient examination and telephone interview. The routine evaluated measurements, including abdominal enhanced CT and serum AFP, were performed to monitor the incidence of recurrence. At the first year after curative hepatectomy, the time of follow-up was every three months, and then six months thereafter. Routinely, patients with recurrence would receive transcatheter arterial chemoembolization (TACE) or other salvage treatments. The final time of follow-up for patients was in February 2018 and the median was 23 months (range from 1 to 60).

2.3. Meta-analysis

A literature search was independently performed by two authors (XXF and ZQS). We searched the Medline, EMBASE, Ovid, Google Scholar, and Cochrane databases for studies published before February 2019. Terms used for the final search in all databases were "preoperative prognostic nutritional index," "PNI."

Titles and abstracts were used for preliminary screening, and the full texts were then analyzed. The references of the identified publications were also examined. The quality of non-randomized trials was critically assessed according to the Newcastle–Ottawa Scale (NOS).

Inclusion criteria were as follows: study type (all case-control studies); participants (HCC patients who received hepatectomy); comparison (compared between the low PNI group and high PNI group); outcomes (OS and RFS). The following exclusion criteria were applied: studies without a control group (case series, case reports); reviews; articles that could not provide comparative outcomes.

Data were extracted by two authors (XXF and ZQS) independently according to the same standards. The initial search yielded 235 records from the database. Nine additional records were identified by retrieving the reference lists. A total of 131 records obtained after removal of duplicates. After screening of title and abstract, 108 records were excluded. Then, 16 articles were excluded with various reasons. Finally, seven studies were included in qualitative synthesis (Supplementary material Figure S1). Extracted data included the first author, publication year, patients' number, sex, country, journal, age, follow-up, PNI cutoff values, hazard ratio (HR) and their 95% confidence interval (CI) for overall rate (OS), and recurrence-free survival rate (RFS).

2.4. Statistical analysis

Continuous variables were presented as median and range in Table 1 and mean in Table 2. Univariate and multivariate analyses were performed using the Cox's proportional hazards model. OS and RFS were analyzed using the Kaplan-

Table 1. Characteristics of included HCC patients.

Characteristics	
Age(years)[a]	57 (29–85)
Gender (male/female)	165/22
Complaint (with/without)	66/121
Alcohol consumed (>50g/d) (%)	72/115
HBV-related HCC (%)	149/38
HBsAg-positive (%)	149/38
Cirrhosis (with/without)	121/66
Albumin (g/L)[a]	40.00 (27.20–62.90)
Total bilirubin (μmol/L)[a]	15.80 (4.20–40.00)
Neutrophil count (μL)	3000.00 (800.00–7600.00)
Lymphocyte count (μL)	1400.00 (300.00–3700.00)
AFP (μg/L)[a]	53.66 (0.90–104502.00)
CEA (μg/L)[a]	2.56 (0.60–124.71)
Child-Pugh grade (A/B/C)	181/6/0
Maximum tumor diameter (mm)[a]	46.00 (10.00–225.00)
Tumor number (multiple)	19/168
Tumor thrombosis (with/without)	19/168
Micro-venous vein invasion (with/without)	33/154
Microsatellite lesions (with/without)	7/180
Encapsulation (incomplete/not)	41/146
TNM (I/II/III)	144/34/9
BCLC (A/B/C)	135/12/40
Postoperative TACE	61/126
Postoperative TACE in HCC recurrence	48/126
BMI (kg/m^2)[a]	23.39 (16.18–36.93)
NLR[a]	2.25 (0.72–14.20)
PNI[a]	47.00 (29.20–69.90)

[a]values are expressed as the median (range).

Table 2. Correlation between the characteristics and prognostic nutritional index (PNI).

	PNI					
	All patients			TNM I		
Variables	≥45 (n = 122)	<45 (n = 65)	*p*	≥45 (n = 102)	<45 (n = 42)	*p*
Age (≥57 years) (%)	56 (46)	40 (62)	0.042*	49 (48)	31 (74)	0.005*
Male sex (%)	111 (91)	53 (82)	0.061	93 (91)	33 (79)	0.038*
Complaint (%)	29 (24)	37 (57)	0.001**	23 (23)	22 (52)	0.001**
Alcohol consumed(>50g/d) (%)	49 (40)	23 (35)	0.522	41 (40)	12 (29)	0.189
HBV-related HCC (%)	98 (80)	51 (78)	0.763	81 (79)	30 (71)	0.300
HBsAg-positive (%)	98 (80)	51 (78)	0.763	81 (79)	30 (71)	0.300
Cirrhosis (%)	75 (61)	46 (71)	0.205	66 (65)	32 (76)	0.179
Albumin (g/L)[a]	42.50	35.29	0.001**	42.46	35.34	0.001**
Total bilirubin (μmol/L)[a]	16.89	16.93	0.978	17.11	16.19	0.486
Neutrophil count (μL)	3476.23	2900.00	0.004**	3409.80	2521.43	0.001**
Lymphocyte count (μL)	1601.64	1083.08	0.001**	1624.51	1123.81	0.001**
AFP (μg/L)[a]	4165.08	6811.46	0.308	1134.05	3613.98	0.220
CEA (μg/L)[a]	3.77	4.11	0.825	4.01	4.75	0.720
Child-Pugh grade A (%)	122 (100)	59 (91)	0.003**	102 (100)	39 (93)	0.006**
Maximum tumor diameter (mm)[a]	51.56	57.51	0.006**	43.61	45.89	0.569
Multiple tumor number (%)	11 (9)	8 (12)	0.478	5 (5)	1 (2)	0.491
Tumor thrombosis (%)	8 (7)	11 (17)	0.025*	0 (0)	0 (0)	NA
Micro-venous vein invasion (%)	19 (16)	14 (22)	0.308	12 (12)	3 (7)	0.409
Microsatellite lesions (%)	4 (2)	3 (5)	0.957	0 (0)	0 (0)	NA
Incomplete encapsulation (%)	24 (20)	17 (26)	0.308	17 (17)	8 (19)	0.732
TNM I (%)	102 (84)	42 (65)	0.013*	–	–	–
BCLC stage A (%)	95 (78)	40 (62)	0.042*	94 (92)	39 (93)	0.729
Postoperative TACE (%)	38 (31)	23 (35)	0.556	32 (31)	12 (29)	0.740
BMI[a]	24.07	22.74	0.008**	23.97	22.51	0.015*

HBV hepatitis B virus, HBsAg hepatitis B surface antigen, AFP alpha-fetoprotein, CEA carcinoembryonic antigen, TNM Tumor Node Metastasis, BCLC Barcelona Clinic Liver Cancer, TACE transcatheter arterial chemoembolization, NLR neutrophil to lymphocyte ratio, PNI prognostic nutritional index, NA not available.
[a]Values are expressed as the mean,.
*$p < 0.05$.
**$p < 0.01$.

Meier method and compared using Log-rank test. The cutoff values of prognostic factors were defined as the upper or lower limit of the reference ranges except age and maximum tumor diameter which set as the median values. The median of BMI (23.39 kg/m^2) was set as the cutoff value to balance the patients in our study. The cutoff value of PNI and NLR was respectively defined as 45 and 2.8 according to the literature [7,9,16,18–20]. SPSS 21.0 (SPSS, Chicago, IL, USA) was used to perform statistical analysis.

A meta-analysis was performed according to the PRISMA Statement [21]. Continuous variables were analyzed using the inverse variance method. We pooled the HR and 95% CI. The I^2 and p statistics were used to test heterogeneity. $I^2 < 50\%$ and $p > 0.05$ was considered indicative of no or low heterogeneity, in which situation a fixed-effects model was used; otherwise, a random-effects model was used. Review Manager version 5.3 was used to perform meta-analysis. A p value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of patients and tumor feature

The patients' characteristics were summarized in Table 1. The median age of all patients was 57 (range from 29 to 85). During follow-up period, 54 patients relapsed and 41 died of HCC. A total of 149 patients were HBV-related HCC. Among the laboratory data, the median of serum albumin and AFP were 40.00 g/L and 53.66 μg/L, respectively. As for the pathological features, the median value of maximum tumor diameter was 46.0 millimeter (mm) (range from 10.0 to 225.0 mm). According to the TNM staging system from 8th Edition of the AJCC [22], 144 of all HCC patients were categorized as stage I. The median value of NLR and PNI was 2.62 (range from 0.72 to 14.20) and 47.09 (range from 29.2 to 69.9), respectively.

We classified the patients into high PNI group ((≥45) and low PNI group (<45) (Table 2). In all patients, the patients with low PNI accounted for 34%. Four patients appeared serious complications (major bleeding) which lead to death. Three of the patients are presented in low PNI group. The low PNI group were more likely to have complaints ($p < 0.001$), maximum tumor diameter ($p = 0.006$), lower BMI ($p = 0.008$), and tumor thrombosis ($p = 0.025$). Moreover, we conducted the comparison of clinicopathological factors between PNI-high and PNI-low patients in TNM I patients. The high PNI group has 102 patients and low PNI group has 42 patients. The low PNI group in TNM I were likely to have lower albumin ($p = 0.001$), neutrophil count ($p = 0.001$), lymphocyte count ($p = 0.001$), and lower BMI ($p = 0.015$).

3.2. Univariate and multivariate analyses of clinicopathologic factors in relation to OS and RFS

The results of the Cox's proportional hazards model for OS were presented in Table 3. In univariate analysis, nine factors including PNI and NLR were considered significant. In multivariate analysis, PNI was calculated based on albumin and lymphocyte count, so these variables were excluded. Positive tumor thrombosis ($p = 0.003$) remained as

Table 3. Univariate and multivariate analysis of prognostic factors of overall survival and recurrence-free survival in HCC patients.

	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*
Age (≥57 years)	0.700 (0.378–1.298)	0.258			0.985 (0.618–1.570)	0.949		
Gender (male)	0.976 (0.347–2.745)	0.964			1.512 (0.608–3.760)	0.373		
Complaints (with)	1.991 (1.079–3.674)	0.028*	1.507 (0.739–3.075)	0.260	1.551 (0.968–2.484)	0.068		
Alcohol consumed (>50g/d)	1.210 (0.652–2.243)	0.546			1.143 (0.713–1.832)	0.580		
HBsAg-positive (positive)	1.959 (0.769–4.994)	0.159			1.027 (0.572–1.845)	0.928		
Cirrhosis (positive)	1.472 (0.738–2.939)	0.273			0.945 (0.581–1.538)	0.821		
Albumin (<40g/L)	1.915 (1.014–3.618)	0.045*	NA[a]		1.771 (1.100–2.854)	0.019*	NA[a]	
Neutrophil count (>3000μL)	1.219 (0.659–2.255)	0.528			1.049 (0.657–1.673)	0.842		
Lymphocyte count (>1400μL)	0.691 (0.365–1.306)	0.255			0.880 (0.548–1.414)	0.598		
AFP (≥400μg/L)	1.513 (0.790–2.900)	0.212			1.189 (0.706–2.001)	0.515		
Maximum tumor diameter (≥46mm)	2.751 (1.404–5.393)	0.003**	1.714 (0.796–3.694)	0.169	2.413 (1.468–3.968)	0.001**	1.775 (1.022–3.084)	0.042*
Tumor number (multiple)	2.801 (1.386–6.098)	0.009**	1.511 (0.593–3.846)	0.387	2.641 (1.408–4.954)	0.002**	1.458 (0.691–3.076)	0.322
Tumor thrombosis (positive)	5.555 (2.824–10.925)	0.001**	7.230 (2.003–26.100)	0.003**	5.369 (3.026–9.527)	0.001**	3.870 (1.64072–9.132)	0.002**
Micro-venous vein invasion (positive)	1.725 (0.844–3.525)	0.135			1.189 (0.661–2.139)	0.564		
Microsatellite lesions (positive)	3.965 (1.549–10.146)	0.004**	1.447 (0.463–4.525)	0.525	3.259 (1.404–7.563)	0.006**	1.408 (0.515–3.845)	0.505
Encapsulation (incomplete)	1.618 (0.825–3.172)	0.162			1.846 (1.114–3.060)	0.017*	1.332 (0.776–2.288)	0.299
TNM (I)	3.866 (2.077–7.195)	0.001**	1.513 (0.473–4.839)	0.485	3.482 (2.153–5.630)	0.001**	1.304 (0.566–3.004)	0.534
Postoperative TACE (multiple)	0.791 (0.414–1.510)	0.477			0.997 (0.606–1.641)	0.991		
BCLC stage C	2.007 (1.039–3.877)	0.038*	0.279 (0.077–1.015)	0.053	2.204 (1.339–3.629)	0.002**	0.675 (0.301–1.516)	0.341
BMI (<23.39 kg/m^2)	1.273 (0.688–2.353)	0.442			1.162 (0.728–1.852)	0.529		
NLR (>2.8)	2.105 (1.129–3.927)	0.019*	1.540 (0.770–3.081)	0.222	1.635 (1.003–2.666)	0.049*	1.335 (0.801–2.227)	0.268
PNI (<45)	2.644 (1.428–4.894)	0.002**	1.855 (0.927–3.711)	0.081	2.118 (1.326–3.382)	0.002**	1.762 (1.066–2.911)	0.027*

HBsAg hepatitis B surface antigen, AFP alpha-fetoprotein, TNM Tumor Node Metastasis, TACE transcatheter arterial chemoembolization, NLR neutrophil to lymphocyte ratio, PNI prognostic nutritional index.
[a]PNI was calculated with albumin and lymphocyte count.
*$p < 0.05$.
**$p < 0.01$.

Table 4. Univariate analysis of prognostic factors of overall survival and recurrence-free survival in HCC patients with TNM I.

	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*	Hazard ratio (95% confidence interval)	*p*
Age (≥57 years)	0.979 (0.429–2.234)	0.960			1.216 (0.660–2.244)	0.530		
Gender (male)	0.649 (0.192–2.196)	0.487			1.008 (0.358–2.835)	0.998		
Complaints (with)	2.231 (0.984–5.059)	0.055			1.633 (0.885–3.011)	0.117		
Alcohol consumed (>50g/d)	0.696 (0.286–1.693)	0.424			0.870 (0.464–1.631)	0.664		
HBsAg-positive (positive)	2.102 (0.624–7.076)	0.230			0.826 (0.416–1.640)	0.584		
Cirrhosis (positive)	2.362 (0.803–6.947)	0.119			0.967 (0.511–1.831)	0.918		
Albumin (<40g/L)	1.621 (0.710–3.699)	0.252			1.850 (1.007–3.397)	0.047	NA[a]	
Neutrophil count (>3000μL)	0.827 (0.362–1.889)	0.652			0.873 (0.476–1.600)	0.660		
Lymphocyte count (>1400μL)	0.550 (0.232–1.300)	0.173			1.085 (0.595–1.975)	0.790		
AFP (≥400μg/L)	0.753 (0.255–2.229)	0.609			0.719 (0.318–1.625)	0.428		
Maximum tumor diameter (≥46mm)	2.096 (0.919–4.782)	0.079			2.036 (1.115–3.719)	0.021*	2.052 (1.111–3.789)	0.022*
Tumor number (multiple)	1.177 (0.158–8.757)	0.873			2.010 (0.616–6.556)	0.247		
Micro-venous vein invasion (positive)	1.365 (0.404–4.615)	0.617			0.579 (0.178–1.880)	0.363		
Encapsulation (incomplete)	2.056 (0.845–5.003)	0.162			1.698 (0.853–3.380)	0.132		
Postoperative TACE (multiple)	0.838 (0.344–2.041)	0.697			1.240 (0.624–2.462)	0.539		
BCLC stage C	0.043 (0.001–33.450)	0.355			0.260 (0.036–1.894)	0.184		
BMI (<23.39 kg/m^2)	2.009 (0.851–4.742)	0.111			1.402 (0.767–2.562)	0.272		
NLR (>2.8)	1.400 (0.551–3.556)	0.480			1.128 (0.555–2.291)	0.739		
PNI (<45)	2.305 (1.008–5.268)	0.048*			2.122 (1.149–3.920)	0.016*	1.978 (1.082–3.616)	0.027*

HBsAg hepatitis B surface antigen, AFP alpha-fetoprotein, TNM Tumor Node Metastasis, TACE transcatheter arterial chemoembolization, NLR neutrophil to lymphocyte ratio, PNI prognostic nutritional index.
[a]PNI was calculated with albumin and lymphocyte count.
*$p < 0.05$.

significant independent predictors for overall survival. However, a low PNI of <45 ($p = 0.081$) and high NLR of >2.8 ($p = 0.222$) lost its capacity to predict overall survival.

Likewise, the results of the Cox's proportional hazards model for RFS were also presented in Table 3. In univariate analysis, nine factors including PNI and NLR were considered significant. In multivariate analysis, a low PNI of <45 ($p = 0.027$), positive tumor thrombosis ($p = 0.002$), and tumor diameter of ≥46mm ($p = 0.042$) remained as significantly independent predictors of RFS, but not a high NLR of >2.8 ($p = 0.268$).

3.3. Univariate and multivariate analyses of clinicopathologic factors in relation to OS and RFS for patients with TNM I

To further identify the risk factors including PNI and NLR to postoperative OS in HCC patients after curative hepatectomy with TNM I, 15 factors were evaluated using the Cox's proportional hazards model (Table 4). In univariate analysis, the only significant factor for OS in HCC patients with TNM I was PNI of <45 ($p = 0.048$).

Similarly, univariate and multivariate analysis of 15 factors including PNI were performed to further determine the risk factors of RFS in HCC patients with TNM I. Univariate analysis showed that the significant factors for RFS were albumin of <40 g/L ($p = 0.047$), maximum tumor diameter of ≥46 mm ($p = 0.021$), and PNI of <45 ($p = 0.016$). Multivariate analysis showed the parallel data, a maximum tumor diameter of ≥46mm ($p = 0.022$) and PNI of <45 ($p = 0.027$) were two independent predictors of RFS in HCC patients with TNM I. We further analyzed the patients with TNM stage II and III and found only tumor thrombosis was significant in OS and RFS (Supplementary material Table S1).

3.4. OS and RFS according to PNI in HCC patients after curative hepatectomy

In Overall survival, the 5-year OS of high PNI group (≥45) was 76.7% and low PNI group (<45) was 50.1% ($p = 0.001$, Figure 1(a)). The 5-year RFS of the high PNI group was 47.0% and low PNI group was 28.9% ($p = 0.001$,

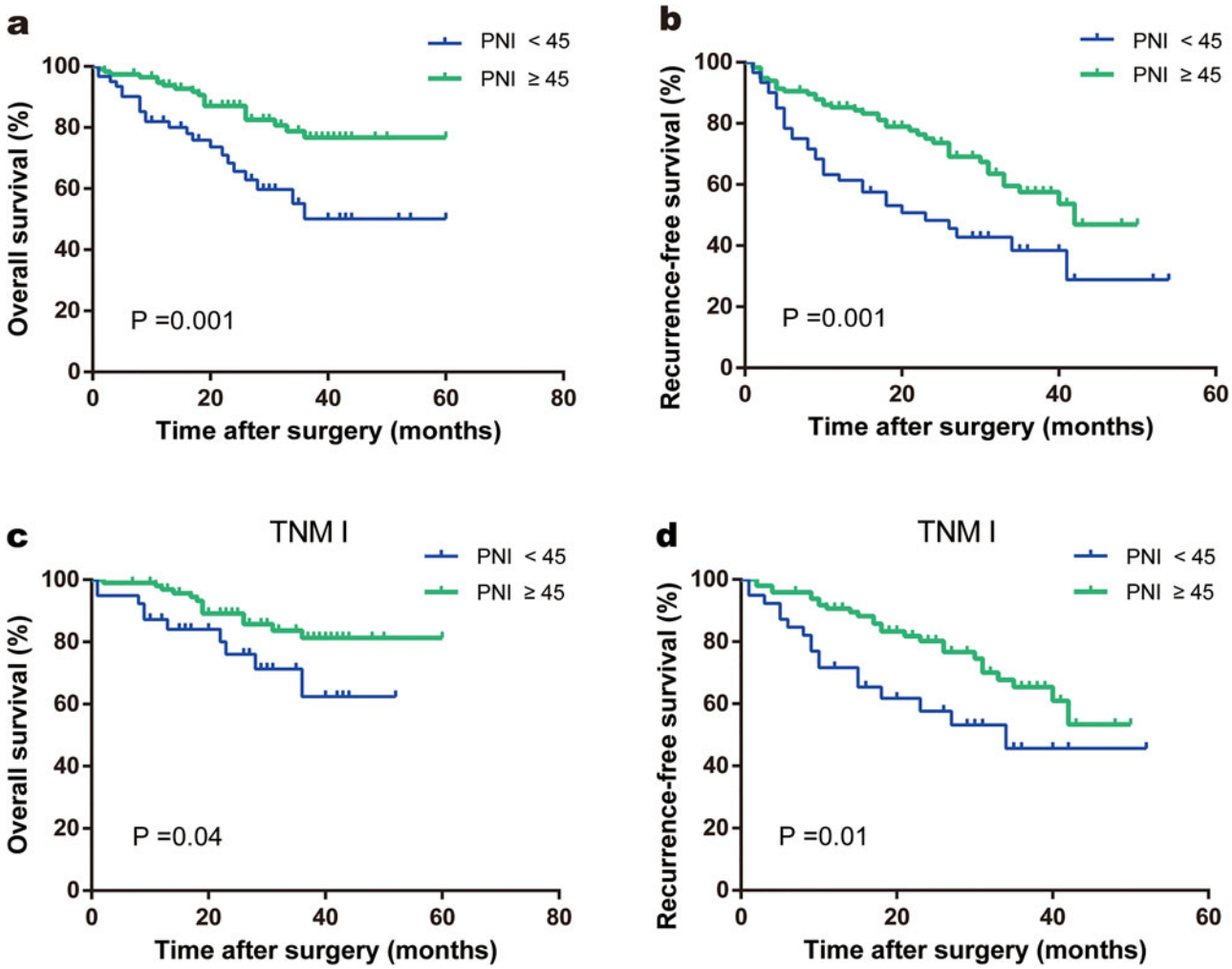

Figure 1. Kaplan-Meier analysis of overall (OS) and recurrence-free survival (RFS) for HCC patients after hepatectomy. (a) Overall survival curve in HCC patients after hepatectomy. (b) Recurrence-free survival curve in HCC patients after hepatectomy. Kaplan-Meier analysis of overall (OS) and recurrence-free survival (RFS) for HCC patients with TNM I after hepatectomy. (c) Overall survival curve in HCC patients with TNM I after hepatectomy. (d) Recurrence-free survival curve in HCC patients with TNM I after hepatectomy.

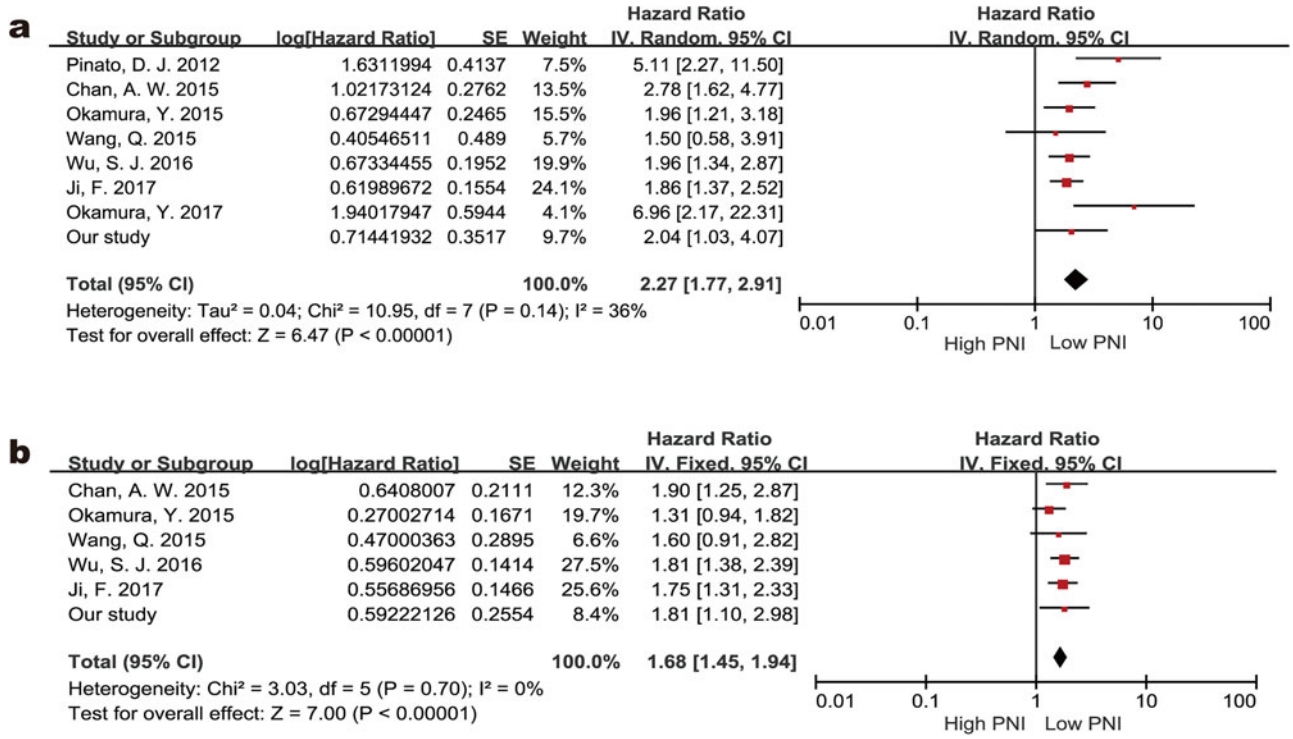

Figure 2. Forest plot of comparison between prognostic nutritional index (PNI) and survival of HCC patients after hepatectomy using. (a) overall survival in HCC patients after hepatectomy. (b) Recurrence-free survival in HCC patients after hepatectomy.

Figure 1(b)). The results suggested that the high PNI (≥45) was positively related to OS and RFS.

3.5. OS and RFS according to PNI in HCC patients after curative hepatectomy with TNM I

As for TNM I patients, the 5-year OS of high PNI group was 81.3% and low PNI group was 62.4% ($p = 0.041$, Figure 1(c)). The 5-year RFS of high PNI group was 53.4% and low PNI group was 45.6% ($p = 0.013$). The results showed that the high PNI (≥45) was positive correlation with OS and RFS (Figure 1(d)).

3.6. Meta-analysis of the correlation between PNI and OS/RFS

Seven published studies and our study were included in this meta-analysis (Supplementary material Figure S1). The characteristics of the seven published studies were listed in Supplementary material Table S2. All the included studies were considered as relative high quality (Supplementary material Table S2). A total of 2073 HCC patients after curative hepatectomy were included in our meta-analysis. The cutoff values of PNI were 45 to 52. The results of our meta-analysis showed that a high PNI group was significantly related to improved OS and RFS (HR 2.27, 95% CI 1.77–2.91, $p < 0.001$ and HR 1.68, 95% CI 1.45–1.94, $p < 0.001$, respectively, Figure 2(a,b)). After pooled analysis, a significant heterogeneity was observed in OS ($I^2 = 36\%$; Figure 2(a)) and then a random-effects model was used. The analysis of RFS was no significant heterogeneity ($I^2 = 0\%$; Figure 2(b)). The funnel plots indicated little publication bias was existed (Supplementary material Figure S2(a,b)).

4. Discussion

The PNI was first proposed to be a potential prognostic maker in HCC patients who received hepatectomy by Pinato et al. [16]. After that, several studies have explored the application of PNI in HCC patients [9,23]. However, Huang et al. [24] and Yamamura et al. [5] cast a doubt on the idea that preoperative PNI is an independent prognostic factor. Zhang et al. [25] supported that postoperative PNI is a potential prognostic factor of OS and RFS in HCC patients. On the contrary, Peng et al. [26] found that preoperative PNI wasn't an independent prognostic factor for both OS and RFS. Controversy exists about the prognostic role of PNI for HCC patients. Hence, we collected and analyzed the data of HCC patients in our institution and conducted a meta-analysis to draw a more definite conclusion.

We retrospectively analyzed 187 HCC patients after curative hepatectomy and generally investigated the prognostic factors potentially affecting survival, such as albumin, AFP, NLR, PNI, and some features about tumor characteristics. The study showed that PNI was an independent prognostic factor to predict postoperative OS and RFS. Our results were consisted with several previous studies [9,11,16,23,27,28]. To further investigate the application value of PNI in HCC surgery, we conducted a meta-analysis and try to draw a more comprehensive conclusion. To the best of our knowledge, a meta-analysis including eight studies for surgical resection, has conclude that the preoperative PNI is a prognostic maker in HCC, but the study didn't

mainly emphasize HCC patients after curative surgery and was heterogeneous in nature for the surgical resection ($I^2 = 89.8\%$ and $p < 0.001$) [18]. In our meta-analysis including eight studies, we exclusively analyzed HCC patients who received curative hepatectomy, and there is no heterogeneous ($I^2 < 50\%$). Results showed that PNI was a very sensitive prognostic factor for prediction of HCC patients. Low PNI was significantly related to poor survival for HCC patients after curative hepatectomy.

As for a potential prognostic factor, the PNI which reflects nutritional and immunological status is supposed to be correlated with cancer survival [11]. On the one hand, nutrition plays an important role on patients' recovery and helps to improve their life qualities. Low serum albumin level contributes to the reaction of inflammatory and the disturbance of nutrition delivery [29]. Lower BMI was detected in the low PNI group. It suggested that low PNI in HCC patients reflected poor nutritional status. For another, immune system should be paid attention to carcinogenesis and cancer progression [30]. Krall et al. [31] reported that tumor-specific T cell response could restrict growth of breast cancer through mice model. It is supposed to be correlated with recurrence of tumor. Low preoperative PNI indicates a relatively poor immunonutrition status, oxidative stress, malnutrition and immune dysfunction, which is related with cancer progression, high tumor load, and complications [32]. Therefore, it could be a promising maker to predict prognosis. Moreover, based on the conclusion, we speculated the HCC patients could benefit from the preoperative treatment, such as enteral nutrition supporting and preoperative non-steroid anti-inflammatory drug, to help HCC patients reach a satisfied PNI value. A randomized controlled trial is expected. Besides, this system can also be added into a prognosis scoring system, such as cancer of the liver Italian program (CLIP) to predict prognosis more effectively.

Based on the conclusion showed by Okamura et al. [8] that the preoperative PNI is a favorable prognostic factor for TNM stage I HCC, the HCC patients within TNM stage I in our institution were also analyzed. Our study demonstrated that the PNI showed an improved capacity to predict the postoperative survival for HCC patients with TNM I. However, we failed to find the PNI was significant in OS and RFS in stage II and III patients. Therefore, our study was preferential to the idea that the impact of PNI is much greater in HCC patients with TNM I after hepatectomy. However, it remains to be doubt because of the small sample size for TNM II and III ($n = 43$). Further researches need to be conducted about this topic.

In addition, the maker of NLR closely related to inflammation-based prognostic algorithm [9] is demonstrated to be significant for OS and RFS only in our univariate analysis of HCC patients with all TNM stages, whereas it's showed that NLR is related to poor prognosis in HCC patients in previous studies [10,33,34]. Based on our results and the recent researches, we suppose that the NLR only reflects the inflammation status, whereas PNI refers to both inflammation and nutrition status. HCC is indeed correlated with inflammatory factor, such as interleukin-6 (IL-6), which plays an important part in progression of liver fibrosis and HCC. It was reported that activation of IL-6/STAT3 pathway in HCC tissues is related to poor post-surgical outcome [35]. However, the nutrition is also indispensable for prognostic factor [36]. Malnutrition is important for HCC patients with concomitant cirrhosis and is a common problem among them, which manifested as impaired immune function, decreased serum protein levels [37]. Okabayashi et al. [38] showed that oral supplementation with some nutrition could improve postoperative quality of life in patients after hepatectomy. Therefore, the results showed that NLR was not an appropriate prognostic factors for HCC patients after curative hepatectomy. Herein, NLR remains to be controversial and these results need to be verified by more studies.

There were some limitations for our study. First, the race of our study was relative single, and the number of patients was limited. Second, our study sets the cutoff value of NLR and PNI to be 2.8 and 45, but the optimal cutoff values of NLR and PNI remain to be settle. Third, our study did not take into consideration the postoperative complication.

5. Conclusions

Our study showed that the preoperative PNI, as an easily measurable barometer related to immunonutrition, is an independent prognostic factor to predict OS and RFS rates in HCC patients who underwent hepatectomy, especially for TNM I. Moreover, the result from meta-analysis confirmed that low PNI was significantly related to a poor prognosis.

Disclosure statement

All the authors declare no conflict of interest.

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