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ORIGINAL SCIENTIFIC REPORT

Preoperative Neutrophil to Lymphocyte Ratio and Prognostic Nutritional Index Predict Overall Survival After Hepatectomy for Hepatocellular Carcinoma

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Abstract

Background and aim Several papers have shown that preoperative inflammation-based prognostic scores and/or immunonutritional status are associated with survival in patients with hepatocellular carcinoma (HCC). However, the validity of prognostic factors of these scores remains controversial. This study aimed to validate the power of prognostic scores based on the preoperative inflammatory and immunonutritional indices of patients who underwent hepatectomy for HCC with curative intent.

Methods Clinicopathological parameters and inflammation-based prognostic scores and immunonutritional status, including the Glasgow Prognostic Score, neutrophil to lymphocyte ratio (NLR), and prognostic nutritional index (PNI), were retrospectively analyzed to identify the predictors of overall and recurrence-free survival in 256 patients.

Results In multivariate analysis, NLR was an independent prognostic factor for overall, and recurrence-free survival (hazard ratio [HR] 2.59, 95 % confidence interval [CI] 1.56–4.31, $P < 0.001$, and HR 2.11, 95 % CI 1.44–3.11, $P < 0.001$, respectively). Additionally, PNI was an independent predictor of overall survival (HR 2.01, CI 1.21–3.36, $P = 0.007$).

Conclusions The present study shows that the NLR and PNI based on preoperative inflammatory and immunonutritional indices are predictors of overall survival in patients who undergo hepatectomy for HCC with curative intent.

Introduction

The pathogenesis of hepatocellular carcinoma (HCC) is based on inflammation. Chronically inflamed liver parenchyma represents a pre-neoplastic environment in which HCC can arise as a result of exposure to a plethora of pro-inflammatory stimuli, such as infection by hepatitis viruses, or ethanol consumption [1]. In contrast to other solid malignancies, the prognosis and treatment options for patients with HCC depend not only on tumor progression, but also on the extent of liver dysfunction [2]. As a consequence, staging systems, such as the tumor node metastasis (TNM) system which relies on purely pathological variables, retain limited prognostic value in HCC [3]. Several alternative systems have been proposed to predict prognosis. The two most widely used score systems are the Barcelona Clinic Liver Cancer (BCLC) [4] and Cancer of the Liver Italian Program (CLIP) scores [5]. However, there is no worldwide consensus on which is the best system for staging and predicting the prognosis of patients with HCC.

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On the contrary, there is increasing evidence that the presence of a systemic inflammatory response, as evidenced by elevated C-reactive protein (CRP) concentrations, is associated with poor survival in patients with various malignancies, including HCC [6, 7]. Several studies have shown that inflammation-based prognostic scores, including a combination of serum CRP and albumin as the Glasgow Prognostic Score (GPS), and a combination of neutrophils and lymphocyte counts as the neutrophil to lymphocyte ratio (NLR), are associated with survival in patients with HCC [8–13].

The preoperative immunonutritional status has been demonstrated to be associated with poor survival in patients with various malignancies [14–22]. The prognostic nutritional index (PNI), which is calculated based on serum albumin concentration and total lymphocyte count in the peripheral blood, was originally proposed to assess the perioperative immunonutritional status and surgical risk in patients undergoing gastrointestinal surgery [23].

There are few comprehensive studies of preoperative inflammation-based prognostic scores and/or immunonutritional status in HCC. This study aimed to validate the power of prognostic scores based on preoperative inflammation scores (the GPS and NLR) and immunonutritional status (PNI) of patients who underwent hepatectomy for HCC with curative intent. Moreover, their performance was compared with several clinicopathological factors, and established clinical prognostic systems, including TNM and BCLC scores, to ascertain whether systemic inflammation and/or immunonutritional status are accurate marker of prognosis.

Methods

Patients and methods

A total of 341 patients underwent hepatectomy as initial treatment with curative intent at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital for the period between September 2002 and November 2012. We retrospectively reviewed the database from this hospital until August 2013. Patients with a history of inflammatory disease or active concomitant infection, those who were lost to follow-up less than 6 months after surgery, and those whose entire set of preoperative laboratory data were not available, were excluded from the present study. A total of 256 patients with HCC were finally included and evaluated in the present study.

Patients with a diagnosis of HCC made according to radiological or histological criteria as recommended by the American Association for the Study of Liver Diseases guidelines were included [24]. Clinical variables, including demographic data, complete blood count, albumin levels, CRP levels, alpha-fetoprotein (AFP) levels, des-γ-carboxyprothrombin (DCP) levels, aspartate and alanine aminotransferase (AST, ALT) levels, staging of the tumor (including the number of focal hepatic lesions and maximum diameter detected during contrast enhancement phase), and Child-Turcotte-Pugh class, were examined [25]. The cut-off points of laboratory data were defined as normal upper limit in our institution. In the present study, BCLC score but CLIP score was adopted as established clinical prognostic system because the factor of tumor morphology in CLIP score was difficult to evaluate objectively. TNM system was assessed using the seventh edition of the Union Internationale Contra le Cancer classification (UICC) [26]. The cut-off values of NLR were defined as 2.81 in accordance with published literature [12]. The cut-off values of PNI were determined for postoperative prognosis, using time-dependent receiver operating characteristic (ROC) curve because there was no paper that has shown the impact of PNI on prognosis after curative surgery for HCC. A PNI of 48.5 was the best cut-off point for operative prognosis. The GPS, NLR, and PNI were constructed as described in Table 1.

Statistical analysis

Continuous variables were presented as median and range, and compared using the Mann–Whitney U test. Categoric variables were compared using the χ^2 test or Fisher's exact test, where appropriate. Cumulative recurrence-free and overall survival curves were analyzed using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards model was used for univariate and multivariate analyses. All factors that found to be significant predictors for recurrence-free and overall survival ($P < 0.05$) in univariate analysis were entered into a

Table 1 Inflammation-based prognostic scores and immunonutritional status

Scoring systems	Score
The GPS	
CRP (≤10 mg/L) and albumin (≥35 g/L)	0
CRP (≤10 mg/L) and albumin (<35 g/L)	1
CRP (>10 mg/L) and albumin (≥35 g/L)	1
CRP (>10 mg/L) and albumin (<35 g/L)	2
Neutrophil lymphocyte ratio	
Neutrophil count : lymphocyte count < 2.81:1	Low
Neutrophil count : lymphocyte count ≥ 2.81:1	High
Prognostic nutritional index	
Albumin (g/L) + 0.005 × total lymphocyte (/μL) < 48.5	Low
Albumin (g/L) + 0.005 × total lymphocyte (/μL) ≥ 48.5	High

GPS Glasgow Prognostic Score, *CRP* C-reactive protein

multivariate analysis. All statistical analyses were performed using SPSS 21.0 (SPSS, Inc., Chicago, IL). *P* values of less than 0.05 in the two-tailed test were considered significant.

Results

Patient characteristics

The patient characteristics are shown in Table 2. The present study included 205 men (80.1 %) and 51 women (19.9 %), with a median age of 69.5 years (range 30–86 years). The patients with underlying cirrhosis were relatively small proportion (29 %).

Univariate and multivariate analyses of prognostic factors for overall and recurrence-free survival

The median follow-up duration was 36.3 months (range 6.9–115 months). One hundred seventy (66.4 %) patients were alive at the follow-up period, and 86 (33.6 %) patients had died. The 1-, 3-, and 5-year overall survival rates were 94.5, 79.0, and 61.6 %, respectively (Fig. 1a). One hundred and fifty-nine (60.5 %) patients had recurrence. The 1-, 3-, and 5-year recurrence-free survival rates were 72.3, 36.9, and 25.6 %, respectively (Fig. 1b).

The results of the Cox regression hazards model for predictors of overall survival are shown in Table 3. In univariate analyses, serum albumin level lower than 40 g/L ($P = 0.009$), lymphocyte count less than 1500/μL ($P < 0.001$), elevated AFP ($P < 0.001$) and DCP levels ($P = 0.016$), a larger tumor than 5 cm ($P = 0.033$), and the presence of microsatellite lesions ($P = 0.007$) were significant predictors of overall survival. In addition, inflammation-based prognostic scores such as GPS 1 + 2 ($P = 0.021$) and a high NLR ($P < 0.001$), and immunonutritional status such as a low PNI ($P < 0.001$) were significant predictors of overall survival. The factors of albumin and lymphocyte count were excluded in multivariate analysis because these factors were major constituents of PNI and duplicable for PNI. In multivariate analysis, a high NLR (hazard ratio [HR] 2.41, 95 % confidence interval [CI] 1.44–4.01, $P = 0.001$), elevated AFP level (HR 2.21, 95 % CI 1.38–3.53, $P = 0.001$), a low PNI (HR 1.96, 95 % CI 1.21–3.18, $P = 0.006$), and elevated DCP level (HR 2.01, 95 % CI 1.12–3.62, $P = 0.020$) remained as significant independent predictors of overall survival.

The results of the Cox regression hazards model for predictors of recurrence-free survival are shown in Table 4. In univariate analysis, serum albumin level lower than

Table 2 Clinicopathological characteristics of the patients

Characteristics	
Age (years)[a]	69.5 (30–86)
Sex (male/female)	205 (80.1)/51 (19.9)
Etiology of liver disease (viral/non-viral)	161/95
HBsAg-positive (%)	44 (17.2)
Anti-HCV Ab-positive (%)	115 (44.9)
Dual infection (%)	2 (0.8)
Cirrhosis (absent/present)	183/73
AST (IU/L)[a]	40 (16–143)
ALT (IU/L)[a]	38 (7–281)
Albumin (g/L)[a]	41 (23–50)
Total serum bilirubin (mg/dL)[a]	0.6 (0.2–2.3)
CRP (mg/L)[a]	1.1 (0–69.9)
WBC (/μL)[a]	4,980 (2,400–11,320)
Neutrophil count (/μL)[a]	2,940 (750–8,830)
Lymphocyte count (/μL)[a]	1,460 (560–3,880)
Platelet count ($\times 10^4$/μL)[a]	15.1 (4.8–42.9)
PT (%)[a]	88 (53–130)
AFP (ng/mL)[a]	15.1 (1.4–343,422)
DCP (mAU/mL)[a]	188 (0–272,000)
Child-Pugh grade	
A	250 (97.7)
B	6 (2.3)
Maximum tumor diameter (mm)[a]	35 (9–180)
Tumor number	
Solitary	198 (77.3)
Multiple	58 (22.7)
Microscopic portal vein invasion (present)	41 (16.0)
Mircosatellite lesions (present)	32 (12.5)
BCLC score	
A	147 (57.4)
B + C	109 (42.6)
Tumor stage	
I + II	226 (88.3)
III + IV	30 (11.7)
GPS (0/1/2)	
0	226 (88.3)
1	26 (10.2)
2	4 (1.5)
High NLR	49
Low PNI	122

Values in parentheses are percentages unless indicated otherwise; value is [a]median (range)

HBsAg hepatitis B surface antigen, *HCV* hepatitis C virus, *Ab* antibody, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CRP* C-reactive protein, *WBC* white cell count, *PT* prothrombin time, *AFP* alfa-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *BCLC* the Barcelona Clinic Liver Cancer, *GPS* Glasgow Prognostic Score, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

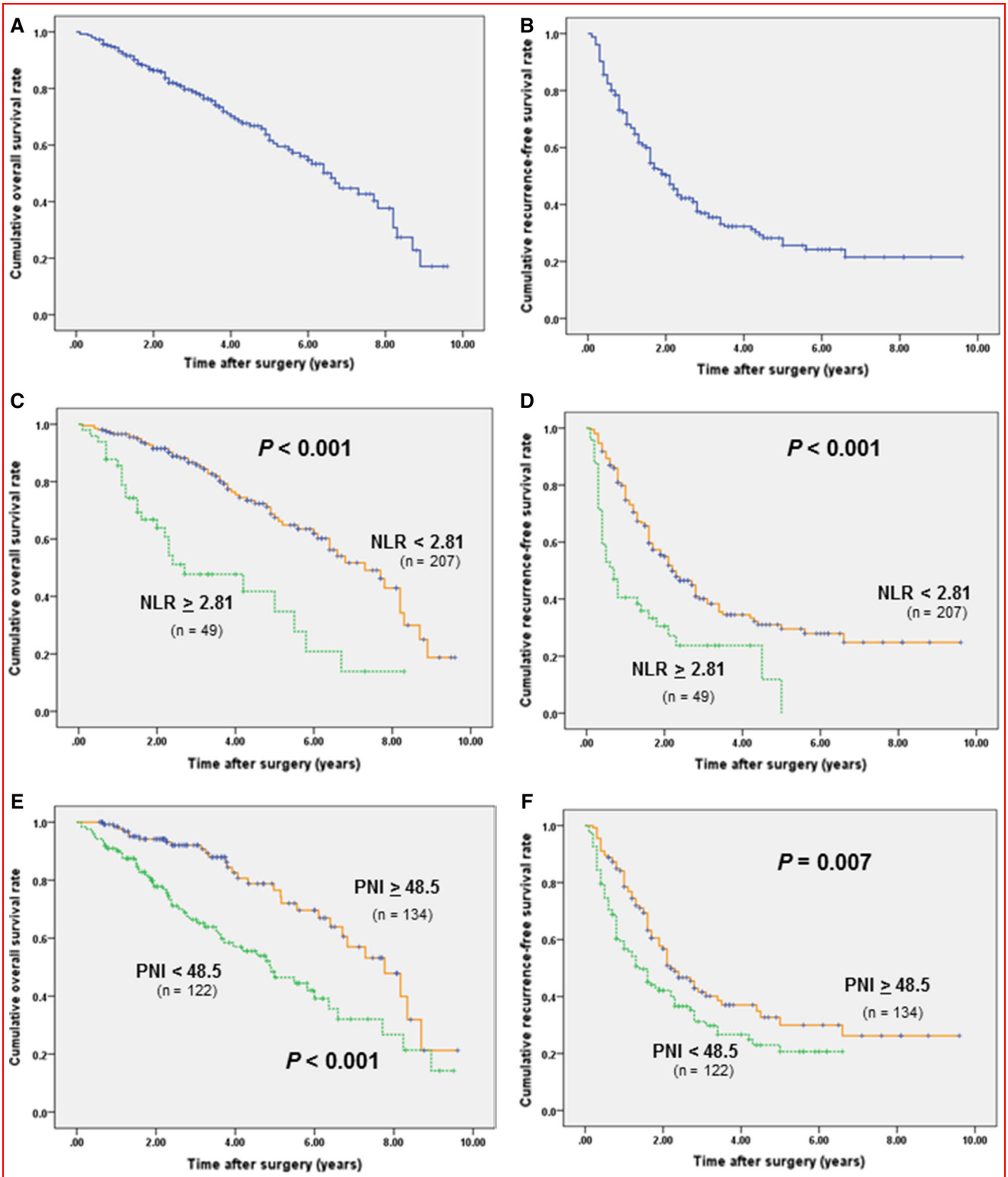

Fig. 1 Survival curves according to the Kaplan–Meier method in the patients who underwent hepatectomy as the initial treatment. **a** Overall survival curve for all study patients. **b** Recurrence-free survival curve for all study patients. **c** Overall survival curve with a comparison of the survival rates in the low- and high-NLR groups. **d** Recurrence-free survival curve with a comparison of the survival rates in the low- and high-NLR groups. **e** Overall survival curve with a comparison of the survival rates in the low- and high-PNI groups. **f** Recurrence-free survival curve with a comparison of the survival rates in the low- and high-PNI groups

Table 3 Prognostic factors for overall survival in patients with HCC by univariate and multivariate analyses

Variables	Univariable		Multivariable	
	Hazard ratio (95 % confidence interval)	*P*	Hazard ratio (95 % confidence interval)	*P*
Age (≥70 years)	0.90 (0.59–1.37)	0.622		
Sex (male)	0.65 (0.39–1.08)	0.093		
Etiology of liver disease (viral)	0.85 (0.55–1.32)	0.460		
Cirrhosis (present)	1.43 (0.91–2.24)	0.124		
Albumin (<40 g/L)	1.76 (1.15–2.69)	0.009	Not applicable[a]	
CRP (≤0.3/>0.3 mg/dL)	1.61 (0.99–2.63)	0.057		
Lymphocyte count (<1,500/μL)	2.36 (1.50–3.69)	< 0.001	Not applicable[a]	
AFP (≥20 ng/mL)	2.37 (1.51–3.73)	< 0.001	2.21 (1.38–3.53)	0.001
DCP (≥40 mAL/mL)	1.95 (1.13–3.36)	0.016	2.01 (1.12–3.62)	0.020
Tumor size (≥5 cm)	1.60 (1.04–2.47)	0.033	0.96 (0.57–1.60)	0.866
Tumor number (multiple)	1.22 (0.76–1.97)	0.427		
Microscopic portal vein invasion (present)	1.23 (0.74–2.06)	0.427		
Microsatellite lesions (present)	1.99 (1.21–3.30)	0.007	1.64 (0.93–2.87)	0.086
BCLC score (A/B + C)	1.41 (0.92–2.16)	0.111		
Tumor stage (I + II/III + IV)	1.80 (0.99–3.26)	0.053		
GPS (0/1 + 2)	1.97 (1.11–3.50)	0.021	1.71 (0.92–3.16)	0.089
High NLR	3.37 (2.11–5.39)	<0.001	2.41 (1.44–4.01)	0.001
Low PNI	2.41 (1.54–3.76)	<0.001	1.96 (1.21–3.18)	0.006

CRP C-reactive protein, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *BCLC* the Barcelona Clinic Liver Cancer, *GPS* Glasgow Prognostic Score, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

[a] Albumin and lymphocyte count are major constituents of the PNI

40 g/L ($P = 0.024$), lymphocyte count less than 1,500/μL ($P = 0.001$), elevated AFP ($P < 0.001$) and DCP levels ($P = 0.022$), a larger tumor than 5 cm ($P = 0.006$), the presence of microscopic portal vein invasion ($P = 0.013$) and microsatellite lesions ($P < 0.001$), BCLC score B + C ($P = 0.007$), UICC stage III + IV ($P = 0.011$), a high NLR ($P < 0.001$) as inflammation scores, and a low PNI ($P = 0.007$) as immunonutritional status were significant predictors of recurrence-free survival in HCC. The factors of albumin level, lymphocyte count, tumor size, and microscopic portal vein invasion were excluded in multivariate analysis because these factors were major constituents of PNI and BCLC score. The presence of microsatellite lesions (HR 1.99, 95 % CI 1.29–3.05, $P = 0.002$), a high NLR (HR 1.96, 95 % CI 1.32–2.93, $P = 0.001$), elevated AFP level (HR 1.75, CI 1.26–2.43, $P = 0.001$), and BCLC score B + C (HR 1.41, CI 1.02–1.94, $P = 0.036$) remained as significant independent predictors of recurrence-free survival in HCC.

Overall and recurrence-free survival curve according to NLR and PNI

The overall and recurrence-free survival rates in the low-NLR (<2.81) group were significantly better than those in the high-NLR group (both $P < 0.001$). The 1-, 3-, and 5-year overall, and recurrence-free survival rates were 96.6, 85.9, and 67.4 %, and 79.9, 40.1, and 29.6 % in the low-NLR (<2.81) group, and 85.6, 47.7, and 34.8 %, and 40.5, 23.8, and 0 % in the high-NLR (≥2.81) group, respectively (Fig. 1c, d).

On the other hand, the overall and recurrence-free survival rates in the high-PNI (≥48.5) group were significantly better than those in the low PNI (<48.5) group ($P < 0.001$, and $P = 0.007$, respectively). The 1-, 3-, and 5-year overall, and recurrence-free survival rates were 98.4, 92.1, and 76.5 %, and 84.1, 41.6, and 30.0 % in the high-PNI (≥48.5) group, and 91.0, 66.4, and 46.5 %, and 59.4, 31.2, and 20.7 % in the low PNI (<48.5) group, respectively (Fig. 1e, f).

Overall and recurrence-free survival curve of patients with both low-NLR and high-PNI values

The overall and recurrence-free survival rates in the patients with both low-NLR (<2.81) and high-PNI (≥48.5) values were significantly better than those observed in the other patients ($P < 0.001$ and $P = 0.001$, respectively). The 1-, 3-, and 5-year overall and recurrence-free survival rates were 98.3, 93.1, and 76.9 % and 88.1, 42.5, and

Table 4 Prognostic factors for recurrence-free survival in patients with HCC by univariate and multivariate analyses

Variables	Univariable		Multivariable	
	Hazard ratio (95 % confidence interval)	*P*	Hazard ratio (95 % confidence interval)	*P*
Age (≥70 years)	1.02 (0.74–1.40)	0.897		
Sex (male)	1.03 (0.68–1.55)	0.888		
Etiology of liver disease (viral)	1.10 (0.79–1.56)	0.565		
Cirrhosis (present)	1.36 (0.97–1.90)	0.071		
Albumin (<40 g/L)	1.45 (1.05–1.99)	0.024	Not applicable[a]	
CRP (>0.3 mg/dL)	1.27 (0.88–1.84)	0.202		
Lymphocyte count (<1,500/μL)	1.71 (1.24–2.35)	0.001	Not applicable[a]	
AFP (≥20 ng/mL)	2.07 (1.51–2.85)	< 0.001	1.75 (1.26–2.43)	0.001
DCP (≥40 mAL/mL)	1.55 (1.07–2.25)	0.022	1.32 (0.90–1.93)	0.154
Tumor size (≥5 cm)	1.56 (1.13–2.15)	0.006	Not applicable[b]	
Tumor number (multiple)	1.34 (0.93–1.94)	0.111		
Microscopic portal vein invasion (present)	1.62 (1.11–2.37)	0.013	Not applicable[b]	
Microsatellite lesions (present)	2.38 (1.58–3.58)	<0.001	1.99 (1.29–3.05)	0.002
BCLC score (A/B + C)	1.54 (1.12–2.10)	0.007	1.41 (1.02–1.94)	0.036
Tumor stage (I + II/III + IV)	1.80 (1.15–2.84)	0.011	1.26 (0.78–2.04)	0.355
GPS (0/1 + 2)	0.92 (0.56–1.52)	0.745		
High NLR	2.25 (1.55–3.27)	<0.001	1.96 (1.32–2.93)	0.001
Low PNI	1.54 (1.12–2.11)	0.007	1.31 (0.94–1.81)	0.108

CRP C-reactive protein, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *BCLC* the Barcelona Clinic Liver Cancer, *GPS* Glasgow Prognostic Score, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

[a] Albumin and lymphocyte count are major constituent of the PNI

[b] Tumor size and microscopic portal vein invasion are major constituents of BCLC score

32.3 % in the patients with both low-NLR (<2.81) and high-PNI (≥48.5) values and 91.9, 67.6, and 47.9 % and 58.4, 31.5, and 19.5 % in the other patients, respectively (Fig. 2a, b).

Discussion

The present study, which analyzed the validity of inflammation-based prognostic scores and the immunonutritional status for predicting the prognosis after hepatectomy for HCC, showed several novel findings.

First, the present findings demonstrated that NLR and PNI were independent predictors of overall survival after hepatectomy with curative intent. The NLR and PNI were more useful predictors than the UICC stage and the BCLC score, which were not found to be independent predictors of overall survival in this study, despite the fact that these parameters have been established to be clinical prognostic factors.

Second, the NLR as well as BCLC, in addition to factors (AFP and microsatellite lesions) that have been previously reported to be predictors of recurrence-free survival, were also identified to be independent predictors in the present study, and the hazard ratio for recurrence-free survival associated with NLR was significantly higher than that for BCLC. In contrast, the PNI was not found to be a predictor of recurrence-free survival, although significant differences were observed in the univariate analysis.

While the present study is the first to compare several inflammation-based prognostic scores and the immunonutritional status after hepatectomy for HCC with curative intent, several previous studies have compared these scores in patients with unresectable lesions [11, 12, 14]. Previous studies have also shown the validity of inflammation-based prognostic scores, such as the NLR [9] and GPS [10], after curative surgery for HCC. The present findings showed that the NLR and PNI values are superior to the GPS as independent predictors of overall survival.

Although the prognostic significance of inflammation-based prognostic scores and the immunonutritional status has been previously reported in various types of cancer, including HCC [9–21], it remains unclear whether these scores predict which patients are at high risk of recurrence after surgery for HCC. To the best of our knowledge, only one report has evaluated inflammation-based prognostic scores and/or the immunonutritional status in terms of recurrence-free survival after hepatectomy for HCC [13]. For

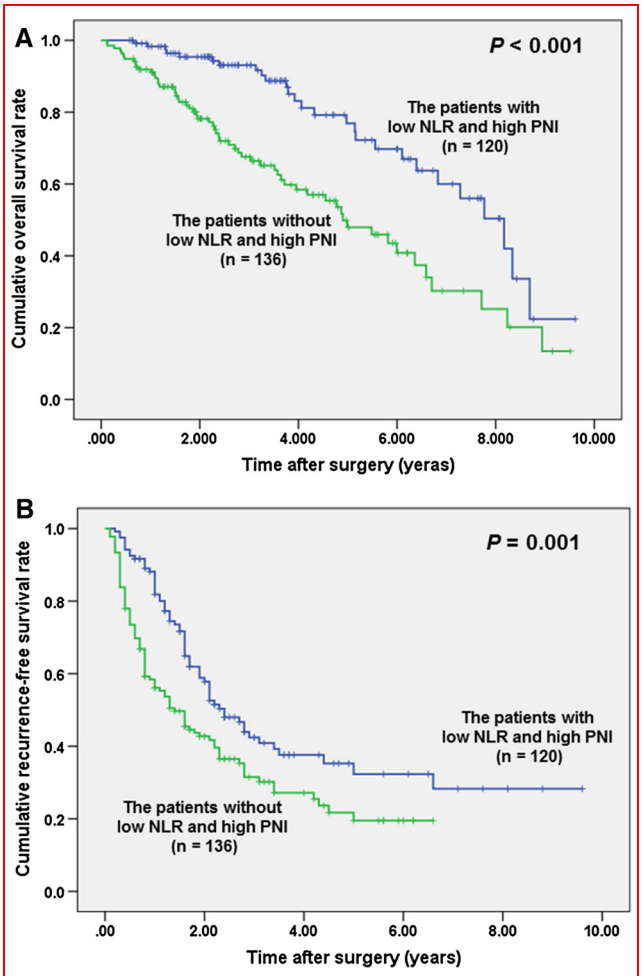

Fig. 2 Survival curves according to the Kaplan–Meier method in the patients classified based on the NLR and PNI status. **a** Overall survival curve with a comparison of the survival rates in the patients with both low-NLR and high-PNI values and the other patients. **b** Recurrence-free survival curve with a comparison of the survival rates in the patients with both low-NLR and high-PNI values and the other patients

example, Mano et al. [13] showed a high preoperative NLR to be an independent predictor of both overall and recurrence-free survival. The present results also showed that a high preoperative NLR is an independent predictor of overall and recurrence-free survival, similar to the findings of a previous study [11], and is the second report to evaluated inflammation-based prognostic scores and/or the immunonutritional status in terms of recurrence-free survival for HCC.

The NLR and PNI, which include no tumor factors, are regarded as predictors of survival for various types of cancer [8–20]. With respect to the NLR values, several papers have shown a negative impact of a high preoperative NLR on the outcome of surgery for gastrointestinal cancers, such as gastric [14–16] and colorectal cancer [17–19]. Only two previous papers have demonstrated that a high preoperative NLR is a predictor of overall survival after curative resection for HCC [8, 12]. Gomez et al. [8] adopted a cut-off value for the NLR of five, while Mano et al. [12] suggested the best cut-off value for the NLR to be 2.81 based on a time-dependent ROC curve. Although we attempted to determine the best cut-off value for NLR using a ROC curve, the area under the curve (AUC) was only 0.58. The AUC must be at least more than 0.7 in order to discriminate significance; hence, the cut-off value calculated from the ROC analysis in the present study cannot be used [27], and we thus applied the cut-off value for NLR reported in previous papers. Adopting the cut-off value obtained in the former paper, the current analysis showed 12 patients (4.6 %) in the high preoperative NLR group. The prognostic score is not practical for use in a limited number of patients (<10 %). Therefore, we applied the cut-off value of 2.81 in accordance with the findings of the latter paper, although the best cut-off value for NLR remains controversial. A high preoperative NLR is also a predictor of the prognosis after liver transplantation for HCC [28, 29]. It is very interesting that the recurrence-free survival rates were significantly lower in the liver transplant recipients with high-NLR values who had not undergone splenectomy than in those who had in a recent liver transplantation series [29]. This observation suggests that the recurrence-free survival rates may improve if patients with high preoperative NLR values undergo hepatectomy for HCC with splenectomy.

Furthermore, with respect to the PNI values, the PNI as a parameter was first reported by Onodera in Japan, as the name implies, as a measurement of the nutritional status incorporating the albumin level and lymphocyte count [23]. The PNI was originally proposed to be a preoperative risk factor and determinant of the surgical indication for colorectal cancer, although it is now widely used as a barometer of the immunonutritional status and a prognostic factor. Several papers also have shown a negative impact of a low preoperative PNI on the outcomes after surgery for gastrointestinal cancers, such as gastric [20], colorectal [21], and pancreatic [22] cancer. However, the number of papers assessing the efficacy of PNI as a predictor after surgery for gastrointestinal cancers is lower than that for NLR. The impact of the PNI on recurrence-free survival has been mentioned in only one gastric cancer series [20]. Although several studies have demonstrated the PNI to be a poor prognostic factor in cancer patients, including those with unresectable HCC [10, 11, 13], there are no previous papers regarding the impact of the PNI on the outcomes after curative hepatectomy for HCC. Hence, the present study is the first study on this issue. The cut-off value for PNI was proposed to be 45 by Onodera [23], although the PNI was originally employed as a determinant of the surgical indication, not at prognostic factor. We therefore

calculated the cut-off value to be 48.5 using a time-dependent ROC curve in the present study. Using this cut-off value, nearly half of the patients were included in the low preoperative PNI group. Therefore, we consider this cut-off value to be useful for predicting the prognosis after hepatectomy for HCC with curative intent.

It is interesting that the PNI predicts only overall survival, not recurrence-free survival, whereas the NLR is an independent predictor of both overall and recurrence-free survival. We have no clear explanation for this difference at the present time. Further research on this issue may show the PNI to be a significant predictor of both overall and recurrence-free survival, and significant difference in the PNI values was identified in the current univariate analysis.

The NLR and PNI include the lymphocyte count in their calculation. A previous study showed that HCC with marked inflammatory cell infiltration has a better prognosis due to the antitumor effect induced by the cellular immunity of CD8+ and CD4+ lymphocytes [30]. Several studies in patients with colorectal carcinoma and corresponding metastases have found patients with weaker lymphocytic infiltration at the tumor margin to have a worse prognosis [31]. These results suggest that lymphocytes play a role in anticancer effects. Moreover, hypoalbuminemia and lymphopenia have been reported in patients with liver cirrhosis [32], suggesting that PNI values in patients with a worse liver function are lower than those in patients with a better liver function. With respect to the PNI values, the survival rates in patients with low PNI values may improve with nutritional therapy, such as the administration of branched-chain amino acid-enriched nutrient support [33].

There are several limitations associated with the present study. First, the study design was retrospective, and routine measurements of the preoperative CRP levels and differential leukocyte counts were not performed. Second, 78 patients, representing 23 % of the overall population, were excluded. Hence, it is essential to evaluate the results of the present study prospectively, as obtaining routine measurements of the preoperative CRP levels and differential leukocyte counts may provide a simple and inexpensive means of identifying patients with a poorer prognosis.

In conclusion, the NLR and PNI are easily measurable inflammatory and immunonutritional biomarkers. The present findings showed that the NLR and PNI values, which are determined based on the preoperative inflammatory and immunonutritional status, are predictors of overall survival in patients undergoing hepatectomy for HCC with curative intent.

Conflict of interest None declared.

References

1. Berasain C, Castillo J, Perugorria MJ et al (2009) Inflammation and liver cancer: new molecular mechanisms. Ann N Y Acad Sci 1155:206–221
2. Huitzil-Melendez FD, Capanu M, O'Reilly EM et al (2010) Advanced hepatocellular carcinoma: which staging system best predict prognosis? J Clin Oncol 28:2889–2895
3. Zhou L, Rui JA, Wang SB et al (2010) LCSGJ-T classification, 6th or 5th edition TNM staging did not independently predict the long-term prognosis of HBV-related hepatocellular carcinoma after radical hepatectomy. J Surg Res 159:538–544
4. Llovet JM, Bru C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19:329–338
5. The Cancer of the Liver Italian Program (CLIP) Investigators (1998) A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 352:751–755
6. Hashimoto K, Ikeda Y, Korenaga D et al (2005) The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer 103:1856–1864
7. Nagaoka S, Yoshida T, Akiyoshi J et al (2007) Serum C-reactive protein levels predict survival in hepatocellular carcinoma. Liver Int 27:1091–1097
8. Gomez D, Farid S, Malik HZ et al (2008) Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg 32:1757–1762. doi:10.1007/s00268-008-9552-6
9. Ishizuka M, Kubota K, Kita J et al (2012) Impact of an inflammation-based prognostic system on patients undergoing surgery for hepatocellular carcinoma: a retrospective study of 398 Japanese patients. Am J Surg 203:101–106
10. Pinato DJ, Stebbing J, Ishizuka M et al (2012) A novel and validated prognostic index in hepatocellular carcinoma: The inflammation based index (IBI). J Hepatol 57:1013–1020
11. Kinoshita A, Onoda H, Imai N et al (2012) Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Br J Cancer 107:988–993
12. Mano Y, Shirabe K, Yamashita Y et al (2013) Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma. A retrospective analysis. Ann Surg 258:301–305
13. Pinato DJ, North BV, Sharma R (2012) A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer 106:1439–1445
14. Mohri Y, Tanaka K, Ohi M et al (2010) Prognostic significance of host- and tumor-related factors in patients with gastric cancer. World J Surg 34:285–290. doi:10.1007/s00268-009-0302-1
15. Jung MR, Park YK, Jeong O et al (2011) Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 104:504–510
16. Shimada H, Takiguchi N, Kainuma O et al (2010) High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 13:170–176
17. Malietzis G, Giacometti M, Askari A et al (2013) A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Ann Surg. [Epub ahead of print]
18. Jankova L, Dent OF, Chan C et al (2013) Preoperative neutrophil/lymphocyte ratio predicts overall survival but does not predict recurrence or cancer-specific survival after curative resection of node-positive colorectal cancer. BMC Cancer 13:442. doi:10.1186/1471-2407-13-442

19. Absenger G, Szkandera J, Stotz M et al (2013) Preoperative neutrophil-to-lymphocyte ratio predicts clinical outcome in patients with stage II and III colon cancer. Anticancer Res 33:4591–4594
20. Migita K, Takayama T, Saeki K et al (2013) The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol 20:2649–2654
21. Mohri Y, Inoue Y, Tanaka K et al (2013) Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World J Surg 37:2688–2692. doi:10.1007/s00268-013-2156-9
22. Kanda M, Fujii T, Kodera Y et al (2011) Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 98:268–274
23. Onodera T, Goseki N, Kosaki G (1984) Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nippon Geka Gakkai Zasshi 85:1001–1005 [in Japanese]
24. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
25. Pugh RNH, Murray-Lyon IM, Dawson JL et al (1973) Transection of the esophagus for bleeding oesophageal varices. Br J Surg 60:646–649
26. Sobin LH, Gospodarowicz MK, Wittekind CH (eds) (2009) TNM classification of malignant tumours, 7th edn. Wiley-Liss, New York
27. Halazun KJ, Hardy MA, Rana AA et al (2009) Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. Ann Surg 250:141–151
28. Motomura T, Shirabe K, Mano Y et al (2013) Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 58:58–64
29. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (roc) curve. Radiology 143:29–36
30. Wada Y, Nakashima O, Kutami R et al (1998) Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. Hepatology 27:407–414
31. Okano K, Maeba T, Moroguchi A et al (2003) Lymphocytic infiltration surrounding liver metastases from colorectal cancer. J Surg Oncol 82:28–33
32. O'Keefe SJ, El-Zayadi AR, Carraher TE et al (1980) Malnutrition and immuno-incompetence in patients with liver disease. Lancet 20:615–617
33. Okabayashi T, Nishimori I, Sugimoto T et al (2008) Effects of branched-chain amino acids-enriched nutrient support for patients undergoing liver resection for hepatocellular carcinoma. J Gastroenterol Hepatol 23:1869–1873