Surgery Today (2019) 49:661–669
https://doi.org/10.1007/s00595-019-01781-1

ORIGINAL ARTICLE

An elevated neutrophil-to-lymphocyte ratio predicts a poor postoperative survival in primary hepatocellular carcinoma patients with a normal preoperative serum level of alpha-fetoprotein

Takayuki Shiraki[1] · Mitsuru Ishizuka[1] · Keiichi Kubota[1] · Masato Kato[1] · Takatsugu Matsumoto[1] · Shozo Mori[1] · Takayuki Shimizu[1] · Taku Aoki[1]

Received: 28 September 2018 / Accepted: 27 January 2019 / Published online: 26 February 2019

Abstract

Purpose Although alpha-fetoprotein (AFP) is a useful prognostic marker in patients with hepatocellular carcinoma (HCC), a recent study has shown that the preoperative neutrophil-to-lymphocyte ratio (NLR) is also associated with the postoperative survival in such patients.

Objective To investigate the significance of the NLR in patients with primary HCC (p-HCC) showing a normal preoperative AFP.

Methods Among 478 p-HCC patients undergoing curative surgery, 112 who had a normal AFP (< 8 ng/ml) were enrolled. The patients were divided into two groups: group A, who did not have an elevated NLR (≤ 3.2); and group B, who had an elevated NLR (> 3.2). Uni- and multivariate analyses were performed to compare clinical features with the overall survival (OS).

Results A multivariate analysis of the clinical features showed that the NLR (> 3.2/≤ 3.2) (hazard ratio 2.366; 95% CI 1.069–5.235; $P = 0.034$) was closely associated with the OS, along with the age (> 65/≤ 65 years) ($P = 0.033$). Group B had a significantly lower survival ratio than group A in terms of not only the OS ($P = 0.013$), but also the cancer-specific survival ($P = 0.002$) and relapse-free survival ($P = 0.039$).

Conclusions An elevated NLR (> 3.2) is predictive of a poor survival in patients with primary HCC (p-HCC) showing normal AFP levels.

Keywords Alpha-fetoprotein · Hepatocellular carcinoma · Neutrophil-to-lymphocyte ratio · Postoperative survival

Abbreviations

AFP	Alpha-fetoprotein (α-fetoprotein)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CH	Chronic hepatitis
CRP	C-reactive protein
CSS	Cancer-specific survival
GPS	Glasgow Prognostic Score
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
ICG R15	Indocyanine green retention ratio at 15 min
NL	Normal liver
NLR	Neutrophil-to-lymphocyte ratio
LC	Liver cirrhosis
OS	Overall survival
PIVKA II	Protein induced by vitamin K absence or antagonists II
RFS	Relapse-free survival
ROC curve	Receiver operating characteristic curve
SIR	Systematic inflammatory response
Va	Hepatic arterial infiltration
Vp	Portal venous infiltration
Vv	Hepatic venous infiltration
WBC	White blood cell

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00595-019-01781-1) contains supplementary material, which is available to authorized users.

✉ Mitsuru Ishizuka
mm-ishizuka@umin.ac.jp

[1] Department of Gastroenterological Surgery, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan

Introduction

A number of scoring systems have been used to assess patients with hepatocellular carcinoma (HCC) [1–5]. Among them, tumor markers, such as alpha-fetoprotein (AFP) [6, 7] and protein induced by vitamin K absence or antagonists II (PIVKA II) [8, 9], are well-known to be useful for the prognostication of HCC patients undergoing surgery. AFP in particular is used worldwide as not only a prognostic factor, but also a surveillance marker.

However, it is not rare for the serum AFP level to be within normal limits even in patients with advanced HCC. This discrepancy between tumor growth and the level of a tumor marker is not surprising, as various individual tumors have their own specific characteristics, and while most will typically produce such markers, others may not do so as efficiently. Therefore, HCC patients who have a normal serum level of AFP may not receive any clinical benefit from the pre- or postoperative assessment of AFP levels for the prognostication and estimation of recurrence risk after surgery.

In the past decade, several studies have clearly shown that inflammation-based prognostic systems, such as the Glasgow Prognostic Score (GPS) [10, 11], neutrophil-to-lymphocyte ratio (NLR) [12, 13] and reactive thrombocytosis [14], are valuable for predicting the postoperative survival of patients with several types of cancer. Among these systems, the NLR seems particularly suitable for the prediction of the surgical outcome in patients with HCC. Because most HCC patients have liver dysfunction due to cirrhosis, the GPS, which is determined from the serum albumin and C-reactive protein (CRP) levels, and reactive thrombocytosis are unable to fully estimate the tumor-versus-host interaction in this situation. Furthermore, a recent study showed that the NLR in HCC patients is associated with the surgical outcome [15].

We therefore investigated the significance of the NLR for primary HCC (p-HCC) patients with a normal serum level of AFP to determine whether or not it could be used as a substitute for AFP.

Methods

We retrospectively reviewed a database of 478 patients who had undergone potentially curative surgery for p-HCC performed by the same trained surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital between April 2000 and March 2012. Among these patients, 112 (23.4%; male:female = 102:10) who had a normal preoperative serum level of AFP (≤ 8 ng/ml) were enrolled in this study.

On the day of admission, all patients underwent routine laboratory tests, including those for tumor markers such as AFP (upper physiological value: 8 ng/ml) [6, 7] and PIVKA II (upper physiological value: 37 U/ml) [8, 9].

Pathological features, such as the background of the liver (NL: normal liver, CH: chronic hepatitis, LC: liver cirrhosis), vascular invasion (Vp: portal venous infiltration, Vv: hepatic venous infiltration, Va: hepatic arterial infiltration) and tumor histology (well differentiated, moderately differentiated, poorly differentiated and undetermined), were evaluated by the same pathologists. Staging was based on tumor dimension, lobar distribution and the presence or absence of vascular invasion, as outlined in "The General Rules for the Clinical and Pathological Study of Primary Liver Cancer" (5th Edition, February 2008, Liver Cancer Study Group of Japan). Child–Pugh classification was based on prothrombin time, albumin level and the presence and degree of ascites and encephalopathy. Because the indications for HCC surgery were based on the Makuuchi criteria [16, 17], no patients were evaluated as Child–Pugh C in this study.

Hepatitis B virus (HBV) infection was defined as positivity for HBV antigens, such as HBs Ag and HBe Ag, or positivity for HBV antibodies such as HBc Ab, HBe Ab and HBs Ab. Hepatitis C virus (HCV) infection was defined as positivity for HCV antibody.

Univariate analyses were performed to examine the relationship between the overall survival (OS) and clinical features, such as the age (> 65/≤ 65, years), sex (female/male), number of tumors (≥ 2/1), maximum tumor diameter (> 2.9/≤ 2.9, cm), white blood cell (WBC) count (> 4.2/≤ 4.2, $\times 10^3/mm^3$), platelet count (≤ 35/> 35, $\times 10^4/mm^3$), aspartate aminotransferase (AST) (> 42/≤ 42, IU/L), alanine aminotransferase (ALT) (> 27/≤ 27, IU/L), total bilirubin (> 0.9/≤ 0.9, mg/dl), albumin (≥ 3.5/< 3.5, g/dl), AFP (> 4.5/≤ 4.5, ng/ml), PIVKA II (> 125/≤ 125, U/ml), indocyanine green retention ratio at 15 min (ICG R 15) (> 16%/≤ 16%), viral infection (presence/absence), background of the liver (LC/NL, CH), pathology (other/well, moderately), liver resection (anatomical/non-anatomical) and NLR (> 3.2/≤ 3.2).

A multivariate analysis was then performed using clinical features with a P value of < 0.05 selected in the univariate analysis to assess those that were predictive of the OS. To investigate the influence of NLR on the relapse-free survival (RFS) for such patients, we also performed a multivariate analysis using the RFS (data presented in supplementary tables).

All of the above recommended cut-off values for continuous variables were decided using receiver operating characteristic (ROC) curve analyses. The recommended cut-off values were based on the most prominent point on the ROC curve for "sensitivity" and "1 − specificity", respectively,

and defined using the Youden index (maximum [sensitivity − (1 − specificity)]) [18]. For example, the recommended cut-off value for the NLR was based on the most prominent point on the ROC curve for sensitivity (0.205) and specificity (0.918). Because these 2 parameters were 3.2, the recommended cut-off value for the NLR was defined as 3.2. Based on this cut-off value, patients were divided into two groups: group A, who did not have an elevated NLR (≤ 3.2); and group B, who had an elevated NLR (> 3.2).

A Kaplan–Meier analysis and log-rank test were used to evaluate the OS, cancer-specific (CSS) and RFS survival curves for these two groups. To investigate the significance of the liver function for such patients, we also performed Kaplan–Meier analyses using the serum level of albumin (Fig. 4a, b) and Child–Pugh classification (Fig. 5a, b). To investigate the significance of the NLR for p-HCC patients with AFP > 8 ng/ml, we also performed Kaplan–Meier analyses using the same method (data presented in supplementary figures).

Statistical analyses

Data are presented as the mean ± standard deviation (SD). Differences between groups were analyzed using the Chi-squared test and Mann–Whitney *U* test. Hazard ratios with 95% confidence intervals (95% CIs) were calculated using a Cox proportional hazard model. A Kaplan–Meier analysis and log rank test were used to evaluate the OS, CSS and RFS curves for groups A and B. Deaths prior to March 31, 2012, were included in this analysis. Statistical analyses were performed using the IBM SPSS statistics version 23.0 software package for Windows (IBM Co., New York, NY, USA) at a significance level of $P < 0.05$.

Results

Table 1 shows the relationships between the clinicolaboratory background features and the NLR in 112 p-HCC patients with a normal preoperative serum level of AFP. There were 102 males and 10 females, and groups A and B comprised 98 and 14 patients, respectively. There were no significant differences between the two groups in the clinicolaboratory background features, except for the background of the liver ($P = 0.001$) and the outcome ($P = 0.007$).

During the observation period, 39 patients died, and 53 experienced recurrence. Twenty-seven of the 39 patients died of HCC. Therefore, univariate analyses were performed to evaluate the relationship between clinical features, including the NLR, and the OS. The results of univariate analyses using 17 clinical features showed that the age (> 65/≤ 65 years) (hazard ratio 2.415; 95% CI 1.140–5.116; $P = 0.021$) and NLR (> 3.2/≤ 3.2) (hazard ratio 2.630; 95% CI 1.191–5.806; $P = 0.017$) were associated with the OS (Table 2). The results of univariate analyses using 17 clinical features showed that the AST (> 42/≤42 IU/L) (hazard ratio 1.394; 95% CI 1.039–1.873; $P = 0.025$), PIVKA-II (> 125/≤ 125 U/ml) (hazard ratio 1.449; 95% CI 1.103–1.902; $P = 0.006$), Pathology (other/well, moderately) (hazard ratio 2.511; 95% CI 1.214–5.196; $P = 0.004$) and NLR (> 3.2/≤ 3.2) (hazard ratio 1.487; 95% CI 1.011–2.188; $P = 0.039$) were associated with RFS (Supplementary Table 2).

The results of multivariate analyses showed that both the age (> 65/≤ 65 years) (hazard ratio 2.271; 95% CI 1.068–4.827; $P = 0.033$) and NLR (> 3.2/≤ 3.2) (hazard ratio 2.366; 95% CI 1.069–5.235; $P = 0.034$) were associated with the OS (Table 3). Furthermore, both the pathology (other/well, moderately) (hazard ratio 6.624; 95% CI 1.453–30.20; $P = 0.015$) and NLR (> 3.2/≤ 3.2) (hazard ratio 2.419; 95% CI 1.102–5.309; $P = 0.028$) were associated with the RFS (Supplementary Table 3).

The median and maximum follow-up periods for survivors were 984 and 4089 days, respectively. The mean postoperative survival period was 1204 ± 946 days (mean ± SD).

Although there was no significant difference in the postoperative survival period between groups A and B (Table 1), the Kaplan–Meier analysis and log-rank test showed that there were significant inter-group differences in the OS ($P = 0.013$, Fig. 1), CSS ($P = 0.002$, Fig. 2) and RFS ($P = 0.039$, Fig. 3). In addition, although the results of Kaplan–Meier analyses and log rank tests revealed that there were no significant inter-group differences for several factors (albumin ≥ 3.5 g/dl vs. albumin < 3.5 g/dl and Child–Pugh A vs. Child–Pugh B) in the OS ($P = 0.602$, Fig. 4a, $P = 0.286$, Fig. 5a) or RFS ($P = 0.214$, Fig. 4b, $P = 0.630$, Fig. 5b), p-HCC patients with an AFP level > 8 ng/ml did show significant inter-group differences (NLR ≤ 3.2 vs. NLR > 3.2) in the OS ($P = 0.002$, Supplementary Fig. 1), CSS ($P = 0.008$, Supplementary Fig. 2) and RFS ($P = 0.011$, Supplementary Fig. 3).

Discussion

In this study, the results of a multivariate analysis clearly showed that an elevated NLR (> 3.2) was associated with a poor OS in p-HCC patients undergoing potentially curative surgery. In addition, a Kaplan–Meier analysis and log rank test showed that p-HCC patients with an elevated NLR had a lower survival ratio than those without an elevated NLR in terms of not only the OS, but also the CSS. Similarly, such patients had earlier HCC recurrences than those without an elevated NLR. Although this study was conducted using a retrospective cohort, there were also no significant differences between the two groups in the clinical background

Table 1 Relationships between clinical background features and the NLR in patients with primary HCC and a normal preoperative serum level of AFP

Variable	Group A NLR (≤3.2) ($n=98$)	Group B NLR (>3.2) ($n=14$)	P value
Gender			
Male	90	12	
Female	8	2	0.452[a]
Number of tumors			
1	76	11	
≥2	22	3	0.932[a]
Liver resection			
Non-anatomical resection	26	5	
Anatomical resection	72	9	0.472[a]
Viral infection			
HBV alone	24	2	
HCV alone	21	2	
Both HBV and HCV	30	2	
None	23	8	0.071[a]
Pathology			
Well or moderately	96	14	
Others	2	0	0.590[a]
Vascular invasion			
Vp −	67	10	
Vp +	30	4	0.916[a]
Undetermined	1	0	
Vv −	93	13	
Vv +	4	1	0.817[a]
Undetermined	1	0	
Va −	97	14	
Va +	0	0	Undetermined[a]
Undetermined	1	0	
Background of liver			
Normal liver	2	3	
Chronic hepatitis	46	9	
Liver cirrhosis	44	2	**0.002**[a]
Undetermined	6	0	
Serum albumin level			
<3.5 g/dl	38	8	
≥3.5 g/dl	60	6	0.248[a]
Outcome			
Alive	67	6	
Cancer-related death	19	4	
Liver-related death	2	3	
Other cause of death	10	1	**0.007**[a]
Stage			
I	13	3	
II	45	4	
III	32	6	
IV	8	1	0.614[a]
Age (years)	67 ± 8	67 ± 10	0.888[b]
Maximum tumor diameter (cm)	4.6 ± 4.3	5.6 ± 3.9	0.393[b]
WBC count ($\times 10^3/mm^3$)	5.0 ± 1.4	5.4 ± 1.9	0.303[b]
Platelet count ($\times 10^4/mm^3$)	17 ± 7	19 ± 9	0.426[b]
AST (IU/L)	34 ± 13	36 ± 18	0.972[b]

Table 1 (continued)

Variable	Group A NLR (≤3.2) (*n*=98)	Group B NLR (>3.2) (*n*=14)	*P* value
ALT (IU/L)	34±20	41±48	0.376[b]
Total bilirubin (mg/dl)	0.6±0.2	0.6±0.3	0.922[b]
AFP (ng/ml)	5.3±1.6	5.2±1.5	0.903[b]
PIVKA II (U/ml)	5140±22,624	1525±3726	0.822[b]
ICG R15 (%)	14±9	14±12	0.781[b]
Postoperative survival period (day)	1246±969	903±716	0.246[b]

Bold—$P < 0.05$

HBV hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, moderately: moderately differentiated adenocarcinoma, *NLR* neutrophil-to-lymphocyte ratio, *Va* hepatic arterial infiltration, *Vp* portal venous infiltration, *Vv* hepatic venous infiltration, well: well differentiated adenocarcinoma, *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICG R15* indocyanine green retention ratio at 15 min, *PIVKA II* protein induced by vitamin K absence or antagonists II, *WBC* white blood cell, *SD* standard deviation

[a]Chi-squared test

[b]Mann–Whitney *U* test (mean±SD)

Table 2 Univariate analyses in relation to the overall survival

Variable	*P* value	Hazard ratio	95% CI
Age (>65/≤65) (years)	**0.021**	2.415	1.140–5.116
Sex (female/male)	0.855	1.092	0.426–2.800
Number of tumors (≥2/1)	0.197	1.566	0.792–3.098
Maximum tumor diameter (>2.9/≤2.9) (cm)	0.050	1.963	0.999–3.854
WBC count (>4.2/≤4.2) ($\times 10^3$/mm^3)	0.146	0.623	0.329–1.179
Platelet count (>35/≤35) ($\times 10^4$/mm^3)	0.134	2.223	0.781–6.326
AST (>42/≤42) (IU/L)	0.892	1.050	0.517–2.133
ALT (>27/≤27) (IU/L)	0.287	0.711	0.379–1.334
Total bilirubin (>0.9/≤0.9) (mg/dl)	0.645	1.322	0.403–4.342
Albumin (≥3.5/<3.5) (g/dl)	0.602	1.184	0.627–2.234
AFP (>4.5/≤4.5) (ng/ml)	0.352	1.576	0.605–4.106
PIVKA-II (>125/≤125) (U/ml)	0.084	1.749	0.927–3.299
ICG R15 (>16/≤16) (%)	0.571	1.214	0.621–2.374
Viral infection (presence/absence)	0.380	0.746	0.387–1.436
Background of liver (LC/NL, CH)	0.684	1.527	0.199–11.73
Pathology (others/well, moderately)	0.126	4.963	0.639–38.54
Liver resection (anatomical/non-anatomical)	0.714	0.882	0.451–1.724
NLR (>3.2/≤3.2)	**0.017**	2.630	1.191–5.806

Bold—$P < 0.05$

HBV hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, moderately: moderately differentiated adenocarcinoma, *NLR* neutrophil-to-lymphocyte ratio, *Va* hepatic arterial infiltration, *Vp* portal venous infiltration, *Vv* hepatic venous infiltration, well: well differentiated adenocarcinoma. *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICG R15* indocyanine green retention ratio at 15 min, *PIVKA II* protein induced by vitamin K absence or antagonists II, *WBC* white blood cell, *CI* confidence interval

features, except for the background of the liver (NL, CH and LC). Therefore, the clinical background features of the two groups, including the age, were almost the same, so it was not surprising that the inter-group differences in the postoperative survival and HCC recurrence were merely attributable to the difference in the NLR.

According to a recent retrospective study that investigated the prognostic value of the preoperative NLR in 958 patients undergoing hepatectomy for HCC, the NLR was an independent prognostic factor in terms of both the OS and RFS [15]. The authors showed that the best cut-off value for the NLR was 2.81 and that the accumulation of tumor-associated

Table 3 Multivariate analyses in relation to the overall survival

Variable	*P* value	Hazard ratio	95% CI
Age (> 65/≤ 65) (years)	**0.033**	2.271	1.068–4.827
NLR (> 3.2/≤ 3.2)	**0.034**	2.366	1.069–5.235

Bold—$P < 0.05$

NLR neutrophil-to-lymphocyte ratio, *CI* confidence interval

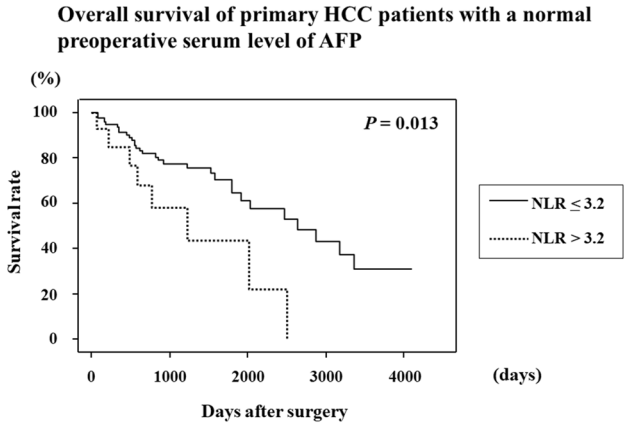

Fig. 1 The relationship between the NLR [groups A (NLR ≤ 3.2) and B (NLR > 3.2) from top to bottom] and the overall survival in patients undergoing surgery for primary HCC

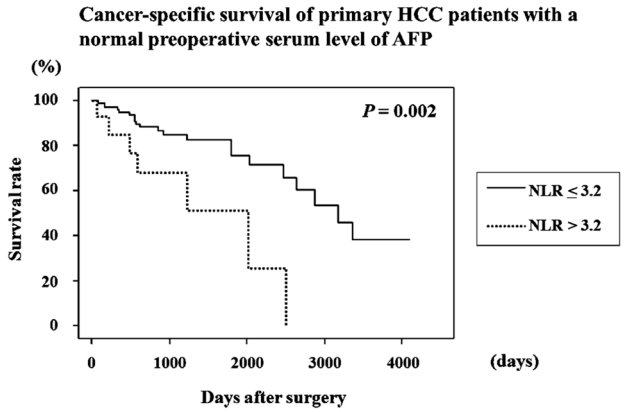

Fig. 2 The relationship between the NLR [groups A (NLR ≤ 3.2) and B (NLR > 3.2) from top to bottom] and the cancer-specific survival in patients undergoing surgery for primary HCC

macrophages was associated with a high NLR, as the intratumoral CD163-positive cell counts were significantly higher in the group with an NLR of ≥ 2.81 than in the group with an NLR of < 2.81 [15]. Thus, it was revealed that HCC patients with a high NLR had poorer postoperative survival than those with a low NLR, and the interaction between the

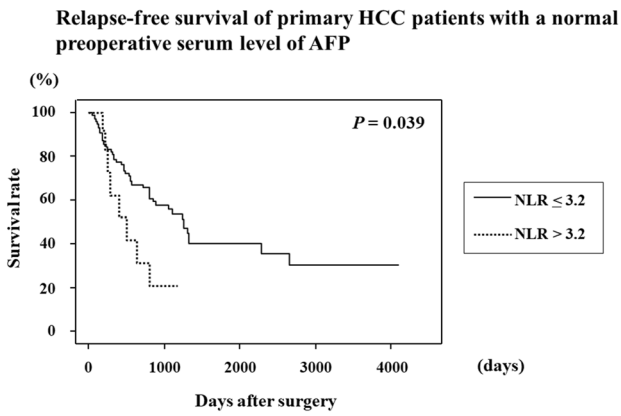

Fig. 3 The relationship between the NLR [groups A (NLR ≤ 3.2) and B (NLR > 3.2) from top to bottom] and the relapse-free survival in patients undergoing surgery for primary HCC

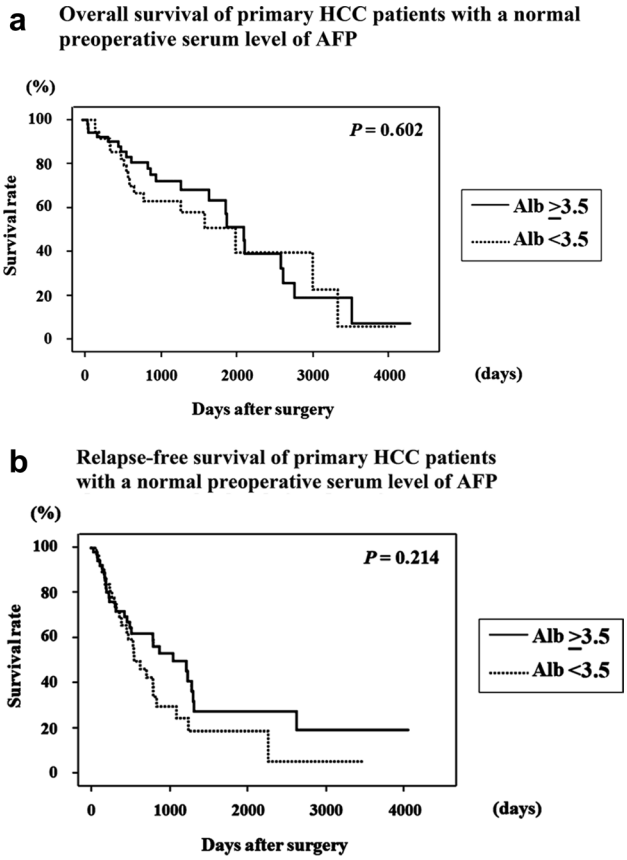

Fig. 4 **a** The relationship between the serum albumin level (albumin ≥ 3.5 and albumin < 3.5 g/dl from top to bottom) and the overall survival in patients undergoing surgery for primary HCC. **b** The relationship between the serum albumin level (albumin ≥ 3.5 and albumin < 3.5 g/dl from top to bottom) and the relapse-free survival in patients undergoing surgery for primary HCC

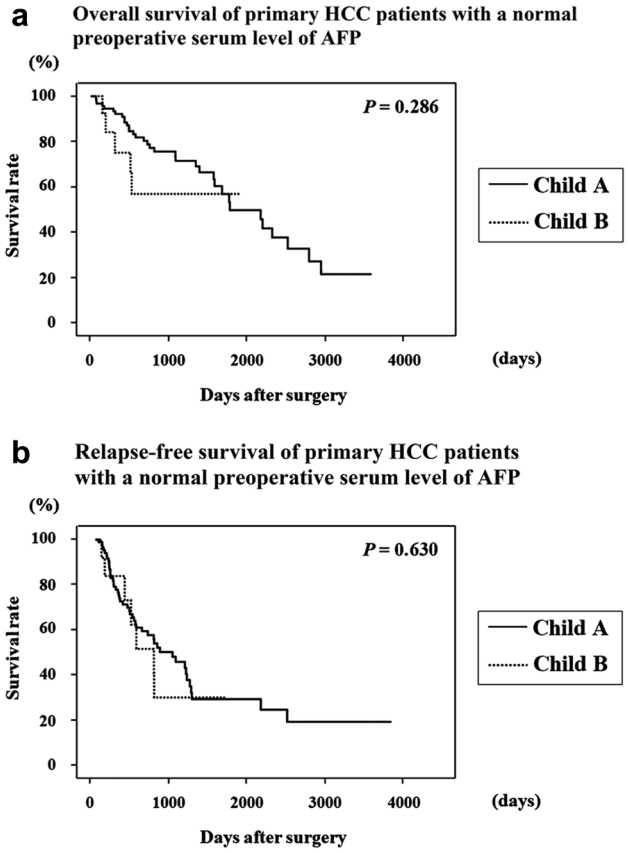

Fig. 5 **a** The relationship between the Child–Pugh classification (Child A and Child B from top to bottom) and the overall survival in patients undergoing surgery for primary HCC. **b** The relationship between the Child–Pugh classification (Child A and Child B from top to bottom) and the relapse-free survival in patients undergoing surgery for primary HCC

tumor and the host immune system may be one cause of local and systemic inflammatory responses [15].

Regarding the cut-off value for the NLR, a previous study showed that 238 of 958 patients (24.8%) had an NLR of > 2.81 [15], and in the present study, 14 of 112 patients (12.5%) had an NLR of > 3.2. The magnitude of the NLR in HCC patients in these two studies appeared to be roughly the same. Similarly, the ROC curve-based NLR cut-off values reported for several other malignancies have been as follows: colorectal cancer 2.5 [19], gastric cancer 2.52 [20], esophageal cancer 3.0 [21] and hepato-pancreato-biliary malignancies 5.0 [22]. All of these NLR cut-off values have been shown to be useful because patients with a high NLR beyond the cut-off level had a poorer postoperative outcome than those with a value below the cut-off. Therefore, the NLR cut-off values for HCC patients in the two studies were as significant as those for other types of malignancies.

A multivariate analysis also showed that old age (> 65 years) was correlated with a poor OS in p-HCC patients undergoing potentially curative surgery, as was the case for an elevated NLR (> 3.2). However, several other studies have demonstrated the impact of age on the postoperative survival of HCC patients undergoing surgery [23, 24]. Therefore, although old age was selected by our multivariate analysis as a clinical feature related to the postoperative survival of p-HCC patients, it is not a new observation.

As our series included only 16 p-HCC patients with stage I HCC (14.3%), which is regarded as early-stage disease, most of the patients had advanced disease. Therefore, the preoperative normal serum level of AFP in our subjects may have been attributable to the characteristics of the tumor itself, i.e., a form that did not secrete large amounts of the protein, rather than to the fact that the tumors were at an early stage and could not produce much of the protein due to an insufficient tumor volume. In fact, a similar relationship between such patients and the preoperative serum level of PIVKA II has been reported previously, with a univariate analysis showing that PIVKA II could not be used as a substitute for AFP as a tumor marker [9]. However, even if HCC does not fully secrete AFP into the bloodstream, the host immune system might correctly recognize such advanced tumors, and a full complement of inflammatory interleukins may be secreted into the bloodstream as a result of tumor-versus-host interaction.

In particular, among inflammatory cytokines, interleukin-6 [25, 26], which is well-known to have multiple functions, can evoke several physical reactions, such as the production of CRP and albumin in the liver, an increased platelet count, and AEs on neutrophil and lymphocyte proliferation in the bone marrow. Numerous studies focusing on this phenomenon resulting from tumor-versus-host interaction in patients with neoplasms have shown that there is a close relationship between cancer and the systemic inflammatory response, which reflects hypercytokinemia.

Over the last decade, inflammation-based prognostic systems, such as the GPS [11], NLR [12] and reactive thrombocytosis, have been established as simple and valuable tools for cancer prognostication. However, because most HCC patients have liver dysfunction due to viral infection, it is difficult to predict the postoperative outcome using inflammation-based prognostic systems based on protein factors such as CRP and albumin as well as the platelet count. In fact, in a previous study, we had to adapt the modified GPS (mGPS) to a hepatic version (hGPS) to predict the postoperative survival of HCC patients [27]. In comparison with inflammation-based prognostic systems based on protein components that are produced in the liver, other systems based on cellular components are more suitable for prognostication of patients with HCC. Unfortunately, reactive thrombocytosis cannot be applied to the prognostication of HCC patients because most such patients have a decreased platelet count due to splenomegaly resulting from portal hypertension. However, because the NLR is unaffected by

this condition, it would be suitable for the prognostication of HCC. In fact, a recent study showed that the NLR can predict the postoperative outcome of HCC patients undergoing surgery [15].

HCC patients who have not only a normal preoperative AFP level, but also an elevated preoperative NLR should undergo postoperative surveillance using computed tomography [28] within a shorter interval than those who do not have an elevated preoperative NLR to detect recurrence after surgery. Because such patients are regarded as a high-risk group for early recurrence and high mortality, close follow-up should be performed to improve their postoperative survival [29–31].

Accordingly, there is now significant evidence to indicate that pre- or postoperative NLR measurement can be used as a substitute for AFP to predict the postoperative survival of p-HCC patients with a normal preoperative serum level of AFP.

Funding We received no funding/grant support for this study.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

References

1. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
2. No authors listed. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology. 1998;28:751–5.
3. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer. 1985;56:918–28.
4. Huang YH, Chen CH, Chang TT, Wang SY, Lee HS, Lin PW, et al. Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. J Gastroenterol Hepatol. 2005;20:765–71.
5. Cho CS, Gonen M, Shia J, Kattan MW, Klimstra DS, Jarnagin WR, et al. A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. J Am Coll Surg. 2008;206:281–91.
6. Beale G, Chattopadhyay D, Gray J, Stewart S, Hudson M, Day C, et al. AFP, PIVKAII, GP3, SCCA-1 and follisatin as surveillance biomarkers for hepatocellular cancer in non-alcoholic and alcoholic fatty liver disease. BMC Cancer. 2008;8:200.
7. Kim HS, Park JW, Jang JS, Kim HJ, Shin WG, Kim KH, et al. Prognostic values of alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II in hepatitis B virus-related hepatocellular carcinoma: a prospective study. J Clin Gastroenterol. 2009;43:482–8.
8. Suehiro T, Sugimachi K, Matsumata T, Itasaka H, Taketomi A, Maeda T, et al. Protein induced by vitamin K absence or antagonist II as a prognostic marker in hepatocellular carcinoma. Comparison with alpha-fetoprotein. Cancer. 1994;73:2464–71.
9. Zhu R, Yang J, Xu L, Dai W, Wang F, Shen M, et al. Diagnostic performance of des-gamma-carboxy prothrombin for hepatocellular carcinoma: a meta-analysis. Gastroenterol Res Pract 2014;2014:529314.
10. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based Prognostic Score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer. 2004;90:1704–6.
11. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013;39:534–40.
12. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88:218–30.
13. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91:181–4.
14. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Preoperative thrombocytosis is associated with survival after surgery for colorectal cancer. J Surg Oncol. 2012;106:887–91.
15. Mano Y, Shirabe K, Yamashita Y, Harimoto N, Tsujita E, Takeshi K, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: a retrospective analysis. Ann Surg. 2013;258:301–5.
16. Makuuchi M, Takayama T, Kubota K, Kimura W, Midorikawa Y, Miyagawa S, et al. Hepatic resection for hepatocellular carcinoma—Japanese experience. Hepatogastroenterology. 1998;45(Suppl 3):1267–74.
17. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res. 2009;39:107–16.
18. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32–5.
19. Shibutani M, Maeda K, Nagahara H, Noda E, Ohtani H, Nishiguchi Y, et al. A high preoperative neutrophil-to-lymphocyte ratio is associated with poor survival in patients with colorectal cancer. Anticancer Res. 2013;33:3291–4.
20. Gunaldi M, Goksu S, Erdem D, Guduz S, Okuturlar Y, Tiken E, et al. Prognostic impact of platelet/lymphocyte and neutrophil/lymphocyte ratios in patients with gastric cancer: a multicenter study. Int J Clin Exp Med. 2015;8:5937–42.
21. Duan H, Zhang X, Wang H, Cai MY, Ma GW, Yang H, et al. Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma. World J Gastroenterol. 2015;21:5591–7.
22. Spolverato G, Maqsood H, Kim Y, Margonis G, Luo T, Ejaz A, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after resection for hepato-pancretatico-biliary malignancies. J Surg Oncol. 2015;111:868–74.
23. Faber W, Stockmann M, Schirmer C, Mollerarnd A, Denecke T, Bahra M, et al. Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. Eur J Surg Oncol. 2014;40:208–13.
24. Faber W, Sharafi S, Stockmann M, Dennecke T, Bahra M, Klein F, et al. Patient age and extent of liver resection influence outcome of liver resection for hepatocellular carcinoma in non-cirrhotic liver. Hepatogastroenterology. 2014;61:1925–30.
25. Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? Cancer Treat Rev. 2013;39:89–96.

26. Ohsugi Y. Recent advances in immunopathophysiology of interleukin-6: an innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biol Pharm Bull. 2007;30:2001–6.
27. Ishizuka M, Kubota K, Kita J, Shimoda M, Kato M, Sawada T. Usefulness of a modified inflammation-based prognostic system for predicting postoperative mortality of patients undergoing surgery for primary hepatocellular carcinoma. J Surg Oncol. 2011;103:801–6.
28. Murakami T, Oi H, Hori M, Kim T, Takahashi S, Tomoda K, et al. Helical CT during arterial portography and hepatic arteriography for detecting hypervascular hepatocellular carcinoma. Am J Roentgenol. 1997;169:131–5.
29. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery. 2007;141:330–9.
30. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg. 2003;238:703–10.
31. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg. 2000;232:10–24.