Utility and Limitation of Preoperative Neutrophil Lymphocyte Ratio as a Prognostic Factor in Hepatocellular Carcinoma

Ei Uchinaka,* Masataka Amisaki,* Masaki Morimoto,* Naruo Tokuyasu,* Teruhisa Sakamoto,* Soichiro Honjo,* Hiroaki Saito* and Yoshiyuki Fujiwara*

**Division of Surgical Oncology, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504, Japan*

ABSTRACT

Background The neutrophil lymphocyte ratio (NLR) has been proposed to be a surrogate marker of inflammation and immunological status and to have prognostic value in various malignancies. This study was conducted to clarify the prognostic significance of preoperative NLR in hepatocellular carcinoma (HCC).

Methods We enrolled 135 patients with histologically-proven HCC who underwent initial curative hepatectomy. Based on the median NLR values, patients were divided into: NLR ≥ 2.0 (NLR-high, $n = 69$) and NLR < 2.0 (NLR-low, $n = 66$).

Results In univariate analysis, the 5-year overall survival (OS) rates were 59.8 % ± 6.7% and 75.6% ± 6.5% ($P = 0.028$) in the NLR-high and NLR-low groups, respectively. Furthermore, the 5-year disease specific survival rates were 68.6% ± 6.7%, and 81.2 ± 6.4% ($P = 0.048$) in the NLR-high and NLR-low groups, respectively.

Conclusion Our results showed that high NLR was an independent predictor for OS in hepatectomy-treated HCC, suggesting that NLR may be a novel prognostic biomarker for HCC. On the other hand, NLR also has a limitation to predict postoperative prognosis of HCC patients by itself.

Key words hepatocellular carcinoma; liver resection; neutrophil-lymphocyte ratio; prognostic factor

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third-leading cause of cancer-related deaths worldwide.[1] Hepatic resection is considered as a curative treatment for HCC.[2] However, the 5-year overall survival rate after curative resection for HCC patients has been reported to be 40%–50%,[3] which remains unsatisfactory. Therefore, to select patients with poor prognoses who should not be indicated for invasive hepatic resection, the development of pre-operative prognostic factors for HCC patients is urgently needed.

Several prognostic factors have been identified that predict long-term outcomes of HCC patients.[4-10] Increasing evidence has supported that the involvement of systemic inflammation and immunological status in HCC patients are closely associated with cancer progression.[11, 12] Recently, the neutrophil to lymphocyte ratio (NLR) was proposed to be a surrogate marker of inflammation and immunological status, as it was reported to render prognostic value in various malignancies,[13–16] including HCC, which is closely associated with hepatic inflammation.[17–20] Moreover, NLR is supposed to be associated with malignant potential and host-immunity, because a number of reports have indicated that neutrophils promote tumor angiogenesis and cancer metastasis, and that lymphocytes have antitumor activity with their cytotoxic function.[21, 22] Therefore, NLR could be a promising candidate for identifying HCC patients with poor prognosis who should avoid invasive liver resection. Thus far, few studies have demonstrated associations between preoperative NLR and the prognosis of HCC patients who underwent curative surgery. Thus, this study was conducted to clarify the prognostic significance of preoperative NLR in patients with HCC.

MATERIALS AND METHODS

Patients

This study enrolled 135 patients with histologically-proven HCC who underwent initial and curative hepatectomy at Tottori University Hospital between 2004 and 2013. This was a retrospective study, thus clinicopathological data was collected from medical records. Medical records were reviewed after approval by the Institutional Review Board (IRB) of our institution in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (IRB approval number: 17A135). Pathological findings were classified according to the 5th. edition of The General

Corresponding author: Masataka Amisaki, MD
amisakim@med.tottori-u.ac.jp
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Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PIVKA II, protein induced by vitamin-K absence II; RFS, recurrence-free survival

Rules for the Clinical and Pathological Study of Primary Liver Cancer.[23] After surgery, patients were routinely followed-up for disease recurrence with measurements of serum tumor markers such as alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA II), and diagnostic images including ultrasonography, computed tomography, or magnetic resonance imaging every 6 months. Information on the cause of death and type of recurrence were obtained from medical records.

Pre-operative NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count obtained from blood tests within a week before surgery. Overall survival (OS) was defined as the interval between the date of surgery and the date of death from any causes or the last date when the patient was confirmed to be alive. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the date of recurrence, the date of death from any cause, or the last date when the patient was last known to be alive.

Statistical analysis

For statistical analyses, GraphPad Prism (GraphPad Software Inc., La Jolla, CA) and SPSS version 25 (IBM, Armonk, NY) were used. OS and RFS rates were calculated according to the Kaplan–Meier method and compared using the log-rank test. Critical factors identified as unity variability by $P < 0.05$ were further investigated by the multivariate Cox proportional hazards model to determine independent and significant factors for survival. The hazard ratio (HR) and 95% confidence interval (CI) were calculated for all estimates. The cutoff value for NLR in this study was the median value to divide the cohort into two groups without any bias from statistical intervention. $P < 0.05$ was considered significant. All continuous values are presented as mean ± standard deviation. Statistical analyses were conducted using the chi-squared test for categorical variables and Welch's two-sample t test for continuous variables, with the exception of categorical variables containing factors < 5, which were analyzed using Fisher's exact test.

RESULTS

The median follow-up period of 135 HCC patients was 54.7 ± 33.6 months. Based on the median NLR value, patients were divided as follows: NLR ≥ 2.0 (NLR-high, $n = 69$), NLR < 2.0 (NLR-low, $n = 66$). Table 1 shows the correlation of clinicopathological factors between the NLR-high and the NLR-low groups. Pearson's chi-square test between the two groups showed that only vascular invasion ($P = 0.021$) was significantly more common in the NLR-low group (Table 1). There were no significant differences between the two groups in other clinicopathological factors.

In the univariate analysis using the Kaplan-Meier method, the 5-year OS rates were 59.8% ± 6.7%, and 75.6% ± 6.5% ($P = 0.028$) in the NLR-high and NLR-low groups, respectively (Fig. 1A). Furthermore, the 5-year disease specific survival rates were 68.6% ± 6.7%, and 81.2% ± 6.4% ($P = 0.048$) in the NLR-high and NLR-low groups, respectively (Fig. 1B). Multivariate analysis was performed to determine whether preoperative NLR was an independent predictor of OS and confirmed that the NLR-high group (HR: 2.221, 95%

Table 1. Correlations of clinicopathological factors between the NLR-high and NLR-low groups

		NLR < 2.0 $n = 66$	NLR ≥ 2.0 $n = 69$	
				P value
Age (y)	< 65/65 ≤	16/50	17/52	0.957
Gender	Male/Female	58/8	55/14	0.199
HBsAg	Positive/Negative	23/43	26/43	0.732
HCV	Positive/Negative	23/43	21/48	0.584
DM	Yes/No	23/43	23/46	0.853
AFP (ng/mL)	< 10/10 ≤	29/37	38/26	0.13
Operation duration (min)	< 360/360 ≤	27/39	27/41	0.746
Extent of resection	Miner/Major	51/15	48/21	0.233
Number	Single/Multiple	50/16	57/12	0.326
Tumor size (cm)	< 5.0/5.0 ≤	48/18	47/22	0.558
Histotype	Well, Moderately/Poor	61/5	64/5	0.535
vp	(–)/(+)	26/40	37/32	0.021
Stage	I/II-	38/28	31/38	0.142
Liver cirrhosis	Yes/No	24/42	21/47	0.625

AFP, alpha-fetoprotein; DM, diabetes mellitus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NLR, neutrophil to lymphocyte ratio; vp, portal vein invasion; y, years.

Table 2. Univariate and multivariate analyses of prognostic factors of overall survival for HCC patients

		Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age (y)	< 65/65 ≤	1.324	0.679–2.582	0.411			
Gender	Male/Female	0.723	0.350–1.494	0.381			
HBsAg	Positive/Negative	0.689	0.490–1.602	0.689			
HCV	Positive/Negative	1.659	0.953–2.890	0.074			
DM	Yes/No	0.764	0.417–1.401	0.384			
NLR	< 2/2 ≤	1.872	1.061–3.301	0.03	2.221	1.113–4.431	0.024
AFP (ng/mL)	< 10/10 ≤	2.09	1.134–3.851	0.018	2.481	1.226–5.020	0.011
Operation duration (time)	< 360/360 ≤	1.367	0.746–2.503	0.312			
Extent of resection	Miner/Major	1.023	0.553–1.895	0.941			
Number	Single/Multiple	1.84	1.004–3.371	0.048	4.785	1.974–11.60	0.001
Tumor size (cm)	< 5.0/5.0 ≤	1.986	1.134–3.477	0.016	1.951	1.012–3.760	0.046
Histotype	Well, Moderately/Poor	7.294	2.954–18.01	< 0.001	3.36	1.060–10.64	0.039
vp	(–)/(+)	2.238	1.268–3.949	0.005	3.321	1.122–9.832	0.030
Stage	I/II-	2.019	1.114–3.659	0.021	0.369	0.106–1.291	0.119
Liver cirrhosis	Yes/No	1.402	0.754–2.607	0.286			

AFP, alpha-fetoprotein; CI, confidence interval; DM, diabetes mellitus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; vp, portal vein invasion; y, years.

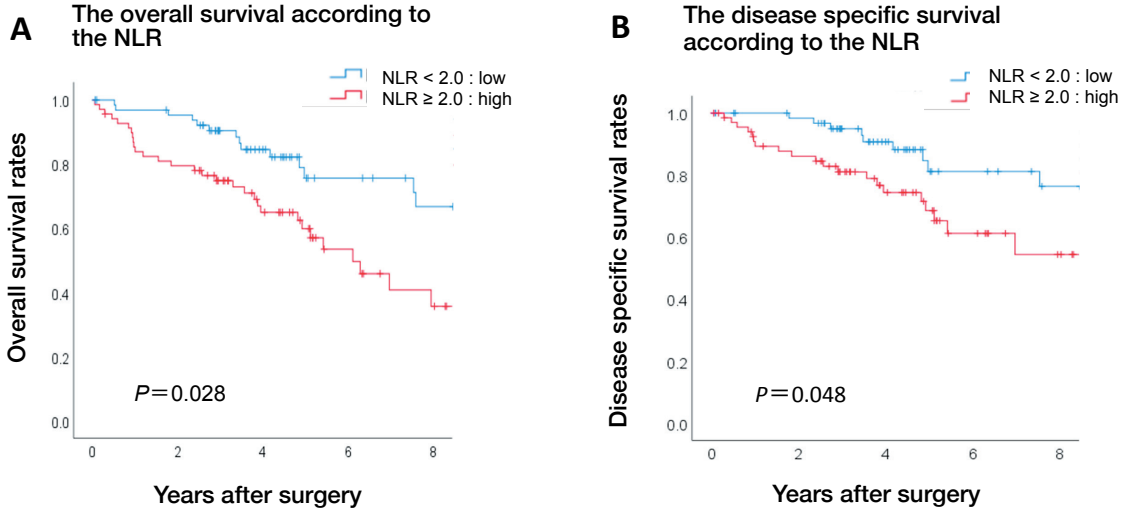

Fig. 1. Survival curves of this cohort according to preoperative NLR. (**A**) Overall survival; the 5-year survival rates were 59.8% ± 6.7% and 75.6% ± 6.5% in the NLR-high and NLR-low groups, respectively. (**B**) The disease-specific survival and the 5-year survival rates were 68.6% ± 6.7% and 81.2% ± 6.4% in the NLR-high and NLR-low groups, respectively. NLR, neutrophil to lymphocyte ratio.

CI: 1.113–4.431, *P* = 0.024), the high AFP value (HR: 2.481, 95% CI: 1.226–5.020, *P* = 0.011), multiple tumors (HR: 4.785, 95% CI: 1.974–11.60, *P* = 0.001), large tumors (HR: 1.951, 95% CI: 1.012–3.760, *P* = 0.046), poor differentiation (HR: 3.360, 95% CI: 1.060–10.64, *P* = 0.039), and vascular invasion (HR: 3.321, 95% CI: 1.122–9.832, *P* = 0.030) were independent prognostic factors (Table 2). On the contrary, there was no significant association between NLR value and RFS (Fig. 2). We suspect that this discrepancy is from the difference between survival periods after disease recurrence. To confirm this, we analyzed survival durations after recurrence among patients whose disease had recurred during follow-up (*n* = 78). The 5-year survival rates after recurrence were significantly lower in the NLR-high group than in the NLR-low group among relapsed patients (22.8 ± 8.7 % and 59.4 ± 9.3 %, respectively, *P* = 0.004; Fig. 3A). We also confirmed that the OS of patients who had

no recurrence during follow-up showed no difference between the NLR-high and NLR-low groups ($P = 0.657$, Fig. 3B).

DISCUSSION

NLR has been reported to be useful as a prognostic predictor for patients with colorectal cancer,[13] gastric cancer,[14] and lung cancer.[15] In this study, we evaluated the relationships between preoperative NLR, clinicopathological features and long-term outcomes in HCC patients that had undergone curative resection. Our results clearly showed that preoperative high NLR was a surrogate marker of advanced HCC and an independent prognostic factor for survival after complete resection. These results were consistent with those of previous reports.[17, 24, 25] However, we also revealed that NLR predicts limited clinical outcomes but does not predict HCC recurrence after curative resection.

The components of NLR are lymphocyte and neutrophil counts. Neutrophils, a component of NLR, are related to inflammation caused from tumors.[26] Indeed, inflammatory responses are closely related to stages of tumor development, including initiation, progression, malignant conversion, invasion, and metastasis.[11] Moreover, the circulating neutrophils induced from inflammation are known to produce chemokines, and cytokines, such as tumor necrosis factor, interleukin-1, interleukin-6, and vascular endothelial growth factor, which promote tumor proliferation, angiogenesis, invasion, and metastasis.[20, 27, 28] Conversely, lymphocytes, the other component of NLR, are related to host-immunity and suppress cancer progression by producing cytotoxic cell death ligands and cytokines that inhibit tumor cell proliferation and metastasis.[25, 29, 30] Therefore, a high NLR, which is calculated from results of both decreased lymphocyte count and an increased neutrophil count, may reflect highly malignant HCC and poor host-immunity against HCC.

This study revealed that NLR reflects patient immunity in addition to tumor malignancy. First, we

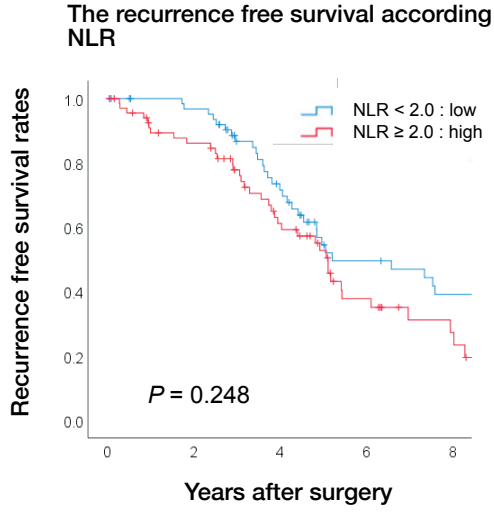

Fig. 2. Recurrence-free survival according to NLR; the 5-year recurrence-free survival rates were 52.8% ± 6.8% and 54.5% ± 7.0% in the NLR-high and NLR-low groups, respectively. NLR, neutrophil to lymphocyte ratio.

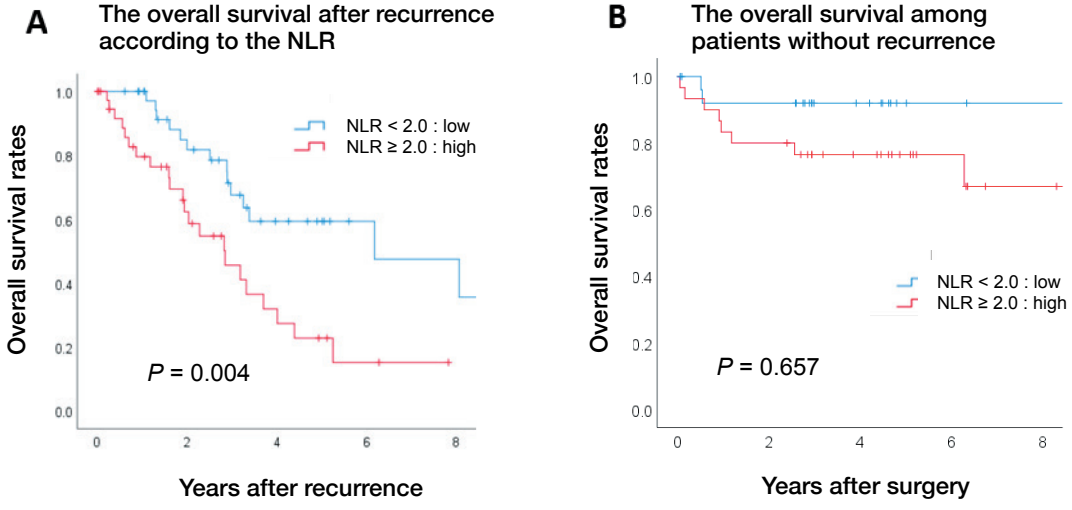

Fig. 3. Survival curves of relapsed and non-relapsed patients. (**A**) Survival rates after recurrence ($n = 78$) according to NLR values; the 5-year survival rates after recurrence were 59.4% ± 9.3% and 22.8% ± 8.7% in the NLR-high, and NLR-low groups, respectively. (**B**) Survival rates of patients without recurrence ($n = 56$) according to NLR value. No significant difference was seen among patients who had not recurred during the follow-up period. NLR, neutrophil to lymphocyte ratio.

Table 3. Past literature of preoperative NLR in HCC patients who underwent curative resection

Author	Year	Location	*N*	Cutoff value	OS (5-year): low/high (%, *P* value)	RFS (5-year): low/high (%, *P* value)
Fu YP, et al[33]	2013	China	282	2	50/28.6 (< 0.001)	32.2/20.3 (< 0.001)
Mano Y, et al[35]	2013	Japan	958	2.81	72.9/51.5 (< 0.0001)	NA
Weijia L, et al[25]	2014	China	256	2.31	76/38 (< 0.001)	70/30 (< 0.001)
Okamura Y, et al[36]	2016	Japan	375	2.8	76.4/45 (< 0.001)	NA
Ji F, et al[37]	2016	China	321	2	49.6/29.7 (< 0.001)	34.6/20.6 (< 0.001)
Galun D, et al[38]	2018	Serbia	109	1.28	45/26 (0.015)	NA
Uchinaka E, et al	2018	Japan	135	2	75.6/59.8 (0.028)	54.5/52.8 (0.248)

HCC, hepatocellular carcinoma; NA, not available; OS, overall survival; RFS, recurrence-free survival.

confirmed that NLR reflects tumor malignancy, because NLR was well associated with tumor size and portal vein invasion. Second, to confirm that NLR reflects host-immunity, we used multivariate analysis and concluded that high NLR is a prognostic factor independent from tumor malignancy, such as high AFP value, multiple tumors, and poor differentiation, which are reported to be risk factors after liver resection from previous studies.[5, 31] Taken together, these results suggested that NLR is informative for predicting patients' oncological outcomes before surgery.

However, patients with higher NLR correlated with lower OS in this study, but there was no statistically significant difference for RFS between the NLR-high and NLR-low groups. Consistently, several previous studies have shown no or weak associations between NLR and RFS.[32] Since OS is affected by treatments for recurrent HCC and RFS is not, these results imply that high-NLR indicate patients with a low tolerance for treatments after recurrence. At the same time, because treatments for recurrent HCC depend on patients' and tumor status and vary wide range, the predictive value of the NLR for patients at surgical stage may be limited. Indeed, we confirmed that patients in the NLR-high group had shorter survival after tumor relapse than those in the NLR-low group. On the contrary, the OS of patients without recurrence showed no significant difference between the NLR-high and NLR-low groups, suggesting that NLR purely predicted oncological outcomes. Thus, it is purely limited to use as a prognostic prediction after first resection. In other words, patients with high NLR have an equal potential to survive as those with low NLR when HCC is curatively resected and not recurrent.

We reviewed past literature evaluating preoperative NLR for cases after HCC resection in Pubmed (Table 3). There were two values that might affect the predictive value of the NLR: One was the cutoff value of NLR. In this study, we almost equally divided this cohort into two groups without determining an optimal cutoff value for NLR because there is no universal consensus regarding the cut-off level of NLR for predicting the prognosis of HCC patients.[33, 34] The range of these values were wide from 1.28[25] to 2.81.[35] Thus, this made conclusions slight differ and the optimal NLR values for predicting patients' prognoses should be determined for routine clinical usage by a large-scale study. The other notable value was the survival period of patients. The 5-year RFS in this study was tended to be better than those of past studies. A possible reason of better prognosis in this study was that a certain number of early HCC patients were included in our cohort, resulting in canceling out predictive effect of NLR on HCC recurrence. There are also several limitation to be mentioned. This survey was a retrospective study from a single institution with a relatively small sample size.

In conclusion, our results showed that high NLR was an independent predictor of OS, suggesting that NLR may be a novel prognostic biomarker for HCC. Because patients with high NLR are supposed to be less tolerant of treatments for recurrent HCC than those with low NLR, patients with preoperative high NLR should be carefully monitored for invasive hepatectomy because they are less tolerant of treatments after recurrence. On the other hand, because NLR is supposed to be associated with treatment of recurrence after resection as well as malignancy of HCC, the predictive value of NLR depends on not only surgical procedure, but also the other unguessed factors derived from multidisciplinary therapy. From this aspect, NLR also has a limitation to predict postoperative prognosis of HCC patients by itself.

The authors declare no conflict of interest.

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