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Original Article

Prognostic value of neutrophil-to-lymphocyte ratio in patients undergoing curative surgical resection for hepatocellular carcinoma

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Abstract

Aim: the purpose of this study is to determine the prognostic value of the preoperative Neutrophil-to-Lymphocyte ratio (NLR) in patients who underwent curative surgical treatment for hepatocellular carcinoma (HCC).

Materials and Methods: Patients who underwent curative resection for HCC between 2004 and 2015 were included in the study. Patients were divided into two groups based on the cut-off value: Group 1 (NLR low) and Group 2 (NLR elevated). Demographics and clinical characteristics, tumor characteristics, and mean survival of patients were compared between the groups.

Results: 41 patients were included in our study and Group 1 (NLR low) consisted of (n:11) patients; Group 2 (NLR elevated) consisted of (n:30) patients based on a cut-off value of 2.43. The number of males was higher in both groups (90.9% vs 90%, p:0.712). The Child-Plug class A was the most common one in both groups (81.8%vs76.7%, p:0.680). HBV infection was the most common etiological cause (81.8% vs 53.3%, p:0.344). Lesions were predominantly located in the right lobe (63.6% vs 66.7%, p:0.568). The total tumor diameter was similar (6.56 cm vs 8.69 cm, p:0.258). In the multivariate analysis for survival, tumor diameter greater than 5 cm (HR 1.412 95% - Cl0.345-5.780, p:0.018) and NLR higher than 2.43 (HR 0.100 95% -Cl 0.011-0.882, p:0.038) were independent risk factors. Overall survival time was found to be lower in Group 2 compared to Group 1 (171 vs 106 months p:0.033). Disease-free survival rates were similar in the groups (37 vs 43 months, p:0.485).

Conclusion: Although the elevated NLR level was found to be a risk factor for decreased overall survival in our study, this was not related to clinicopathological variables.

Keywords: Hepatocellular carcinoma; Neutrophil-to-lymphocyte ratio; surgical resection; prognosis.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide (1) The incidence rate of HCC is higher in developing countries, especially due to environmental factors, viral infections, nutritional habits, and inadequate medical care (2,3). Despite the improvement in surgical techniques, perioperative care, and patient selection, long-term outcomes of hepatic resection remain unsatisfactory. Five-year recurrence rates of up to 70% are seen in many series and the 5-year overall survival rate is less than 15% (4,5). Therefore, it is important to identify patients who might have a poor prognosis before performing major surgery, such as hepatic resection, as a method of treatment. Researching prognostic factors affecting survival after resection remains the center of attention.

Many systems including Barcelona-Clinic Liver Cancer (BCLC) staging system, Tumor-Node-Metastasis (TNM) classification system, The Cancer of the Liver Italian Program, The Child-Pugh classification system, and The Model for End-Stage Liver Disease (MELD) were used to identify or predict the prognosis of HCC patients (6). However, no global consensus has been reached on the best system to estimate HCC outcomes.

Although inflammation is a key feature of progressive liver disease and predisposition to HCC, the presence of systemic inflammation is associated with poor oncological outcomes and increased tumor progression in cancer patients by playing a dominant role in cancer cell spread, angiogenesis, and immunosuppression. (7). The systemic inflammatory response may be measured using simple biomarkers such as NLR elevation. In the literature, the prognostic value of NLR has been shown in different

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types of cancer in many studies (8-11). Inflammatory infiltrates in the tumor microenvironment highly affect the biological behavior of HCC. Previous studies on this subject have shown that the neutrophil-to-lymphocyte ratio (NLR) is a marker in tumor recurrence and survival in HCC patients (7,12). There are also studies in the literature reporting that the prognostic value of the neutrophil-to-lymphocyte ratio is superior to that of MELD stage or Child-Pugh classification system and that NLR correlates with BCLC and TNM staging criteria (13).

The purpose of this study is to determine the prognostic value of the preoperative neutrophil-to-lymphocyte ratio in patients who underwent curative surgical treatment for HCC and to present with the literature.

MATERIALS and METHODS

Patients who underwent curative surgery for hepatocellular carcinoma between January 2004 and January 2015 were included in the study. Patient files and hospital information system records were reviewed and patients were analyzed retrospectively. Patients undergoing palliative surgery, patients with metastatic disease, patients under the age of eighteen, patients with chronic inflammatory disease (such as tuberculosis, sarcoidosis), patients with the hematological disease, patients using steroids, patients with missing medical records, patients whose pathological diagnosis was not hepatocellular carcinoma, and patients receiving non-resection therapy were excluded from the study.

The cutoff value was determined using the ROC curves and the patients were divided into two groups based on the cutoff value: Group 1 (NLR low) and Group 2 (NLR elevated). In these groups, the demographic characteristics and body mass indexes (BMI) (Cachectic <18.5, Normal 18.5-25, Obese> 25) of patients were evaluated. The proven presence of ascites, history of encephalopathy, Child-Pugh classes, etiological cause identified for HCC etiology, laboratory parameters, alpha-fetoprotein (AFP) level, MELD score, tumor localization, number of tumors, total tumor diameter, multicentricity, type of surgical operation performed, postoperative complication, presence of perioperative mortality, whether recurrence occurred during follow-up, current clinical conditions, overall and disease-free survival times, and the 1-year, 3-year, 5-year overall and disease-free survival rates were compared between two groups.

Blood samples were collected from patients before surgery as part of a routine preoperative study during hospitalization. The total blood count was measured by an automated hematology analyzer (Roche Hitachi *Cobas*® 8000 Roche Diagnostics, Indianapolis, IN, USA) But, NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

All surgical resections were performed to achieve microscopically negative surgical margins. During the laparotomy, after a comprehensive examination to exclude metastatic disease, the clamp-crush technique was used for the parenchymal resection. Vessels and bile ducts were ligated by clip or suture techniques. Remnant liver volume was determined as 40% for the determination of the extent of the resection. If there was a suspicion of surgical margin involvement, the frozen examination was performed.

After the surgery, patients were routinely monitored for the disease recurrence by the measurement of serum tumor markers and methods such as Ultrasonography (USG), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) were used every six months to identify recurrence of the disease. Overall survival was defined as the time between diagnosis and death. Disease-free survival was defined as the time from hepatectomy to the identification of tumor recurrence on imaging.

Statistical evaluation

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as means and standard deviations (median and minimum-maximum, where necessary). Pearson's Chi-square test statistic was used to compare categorical variables. Shapiro-Wilk test was used to find out whether the parameters in the study showed normal distribution. The distributions were controlled and independent student t-test was used for parameters with normal distribution, and Mann Whitney U test for parameters with non-normal distribution for the comparison of continuous measurements between groups. In the study, ROC analysis and the ROC curve were performed to determine a cutoff value for NLR. The cut-off value was determined by calculating the overall survival under the ROC curve. Multinomial logistic regression analysis was conducted to determine the independent variables affecting the dependent variable. The statistical significance level was considered to be 0.05 for all tests.

RESULTS

ROC analysis and the ROC curve were performed to determine a cutoff value for NLR. Forty-one patients were included in our study. Groups were formed based on the cutoff value of 2.43 in the ROC curve and Group 1 (NLR low) consisted of 11 patients, Group 2 (NLR elevated) consisted of 30 patients.

The mean age of the patients was similar in the groups p:0.383. The number of males was higher in both groups (90.9% vs 90%, p: 0.712) and there was no significant difference regarding BMI (p: 0.572) and the presence of ascites (p: 0.087). The Child-Plug class A was the most common one in both groups (81.8% vs 76.7%, p: 0.680). HBV infection was the leading etiological cause in both groups (81.8% vs 53.3%, p: 0.344). The demographic and clinical characteristics are shown in Table 1.

Table 1. Demographic and Clinical Characteristics				
		Group 1 NLR Low (n: 11)	Group 2 NLR Elevated (n: 30)	p*
Age Mean+ Std (min-max)		60.36±12.95 (29-72)	64.23±12.25 (22-83)	0.383
Sex	Male	10 (90.9)	27 (90.0)	0.712
	Female	1 (9.1)	3 (10.0)	
BMI	Cachectic	0 (0.0)	1 (3.3)	0.572
	Normal	6 (54.5)	20 (66.7)	
	Obese	5 (45.5)	9 (30.0)	
Ascites	Present	1 (9.1)	11 (36.7)	0.087
	None	10 (90.9)	19 (63.3)	
Encephalopathy	Present	0 (0.0)	2 (6.7)	0.530
	None	11 (100.0)	28 (93.3)	
Child class	A	9 (81.8)	23 (76.7)	0.680
	B	2 (18.2)	5 (16.7)	
	C	0 (0.0)	2 (6.7)	
Etiological cause	HBV	9 (81.8)	16 (53.3)	0.344
	HCV	0 (0.0)	3 (10.0)	
	Alcohol	0 (0.0)	2 (6.7)	
	Cryptogenic	2 (18.2)	9 (30.0)	

BMI-Body Mass Index; HBV- Hepatitis B virus; HCV-Hepatitis C virus

Table 2. Laboratory Characteristics			
	Group 1 NLR Low (n: 11)	Group 2 NLR Elevated (n: 30)	p*
Neutrophil count mm³/L Mean+ Std (min-max)	3.68±1.31 (2.25-6.50)	6.53±3.86 (2.93-18.80)	**0.023***
Lymphocyte count mm³/L Mean+ Std (min-max)	2.34±1.58 (1.12-7.0)	1.38±0.68 (0.3-3.60)	**0.009***
Na mEq/L Mean+ Std (min-max)	135.0±3.49 (129-140)	136.0±3.60 (126-142)	0.432
Creatinine mg/dl Mean+ Std (min-max)	0.89±0.22 (0.51-1.20)	1.01±0.21 (0.73-1.63)	0.130
INR Mean+ Std (min-max)	1.21±0.25 (0.98-1.71)	1.16±0.11 (0.99-1.43)	0.376
Total Bilirubin mg/dL Mean+ Std (min-max)	1.23±0.44 (0.67-2.10)	1.64±2.44 (0.36-14.3)	0.582
Albumin gr/dl Mean+ Std (min-max)	3.46±0.70 (2.50-4.61)	3.45±0.69 (2.1-4.60)	0.967
AFP ng/mL Mean+ Std (min-max)	4049.89±8195.83 (6.03-26830)	4191.24±10397.62 (1.6-47523)	0.968
CHILD score Mean+ Std (min-max)	5.91±1.44 (4-9)	6.33±1.44 (4-11)	0.410
MELD score Mean+ Std (min-max)	10.91±5.08 (6-21)	11.53±4.36 (6-24)	0.700

INR- International Normalized Ratio, AFP-Alpha Fetoprotein

Neutrophil count (mm³/L) was higher in Group 2 (3.68 vs 6.53, p: 0.023), lymphocyte count (mm³/L) was higher in Group1 (2.34 vs 1.38, p: 0.009). AFP levels were similar in groups (4049 vs. 4191, p: 0.968). MELD scores were similar in groups (10.91 vs 11.53, p: 0.700). The laboratory characteristics of the groups are shown in Table 2.

Lesions were predominantly located in the right lobe (63.6% vs 66.7%, p: 0.568). Total tumor diameters were similar in the groups (6.56 cm vs 8.69 cm, p: 0.258). Postoperative complications occurred in one patient of Group 1 and four patients of Group 2. Perioperative mortality rates were similar in the groups (9.1% vs. 6.7%, p: 0.619). Tumor and operative characteristics of the groups are shown in Table 3.

Although the rate of recurrence was higher in Group 2, there was no statistical difference between the groups (27.3% vs 50%, p: 0.173). When we evaluated the current clinical situation, the number of patients who died was higher in Group 2 (9.1% vs. 50%, p: 0.018). The oncological outcomes of the groups are shown in Table 4.

Table 3. Tumor and Operative Characteristics

		Group 1 NLR Low (n: 11)	Group 2 NLR Elevated (n: 30)	p*
Lesion location	Right	7 (63.6)	20 (66.7)	0.568
	Left	4 (36.4)	10 (33.3)	
The number of tumors Mean+ Std (min-max)		1.36±0.67 (1-3)	1.57±1.00 (1-4)	0.540
Total tumor diameter Mean+ Std (min-max)		6.56±4.59 (2-14)	8.69±5.48 (2-23)	0.258
Multicentric	Present	2 (18.2)	9 (30.0)	0.371
	None	9 (81.8)	21 (70.0)	
Operation performed	Right lobectomy	4 (36.4)	15 (50.0)	0.399
	Segmentectomy	4 (36.4)	5 (16.7)	
	Left lobectomy	3 (27.3)	10 (33.3)	
Postoperative Complication	Present	1 (9.1)	4 (13.3)	0.592
	None	10 (90.9)	26 (86.7)	
Perioperative Mortality	Present	1 (9.1)	2 (6.7)	0.619
	None	10 (90.9)	28 (93.3)	

SD- Standard Deviation

Table 4. Oncological outcomes

		Group 1 NLR Low (n: 11)	Group 2 NLR Elevated (n: 30)	p*
Recurrence	Present	3 (27.3)	15 (50.0)	0.173
	None	8 (72.7)	15 (50.0)	
Current Clinical Status	Ex	1 (9.1)	15 (50.0)	**0.018***
	Alive	10 (90.9)	15 (50.0)	

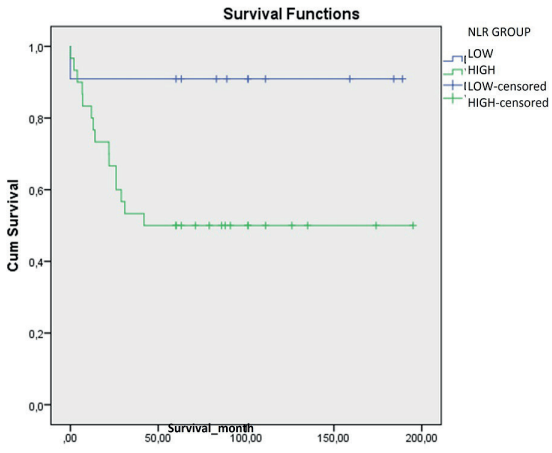

Figure 1. Total survival according to NLR groups

In univariate and multivariate analysis for survival, tumor diameter greater than 5 cm (HR 1.412 95% - CI 0.345-5.780, p: 0.018), Child-Plug Class B-C (HR 0.112 95% - CI 0.019-0.644, p: 0.014), the presence of ascites (HR 0.190 95% - CI 0.045-0.812, p:0.025), NLR rate higher than 2.43 (HR 0.100 95% - CI 0.011-0.882, p:0.038) were found to be factors related to survival. Analysis results are shown in Table 5.

Overall survival time was lower in Group 2 compared to Group 1 (171.85 vs 106.065, p: 0.033). 1-year, 3-year, and 5-year overall survival percentages are shown in Table 6 and Figure 1. Disease-free survival rates were similar in the groups (37.62 vs 43.72 months, p: 0.48). 1-year, 3-year, and 5-year disease-free survival rates are shown in Table 7 and Figure 2.

Table 5. Univariate and multivariable analysis of factors associated with overall survival in Hepatocellular Carcinoma

Measurements		Univariate	Multivariate	
		p	HR (95% - CI)	p
Age	<65	0.192	1.000	0.196
	>65		0.420 (0.112-1.565)	
Sex	Male	0.123	1.000	0.181
	Female		0.181 (0.017-1.915)	
INR	<1.4	0.832	1.000	0.834
	>1.4		1.304 (0.108-15.685)	
Total Bilirubin	<1	0.570	1.000	0.571
	>1		0.682 (0.181-2.567)	
Albumin (g/dl)	<3.5	0.309	1.000	0.311
	>3.5		1.929 (0.541-6.875)	
AFP (ng/mL)	<400	0.185	1.000	0.190
	>400		0.406 (0.105-1.564)	
The number of tumors	One	0.631	1.000	0.632
	Two and more		1.412 (0.345-5.780)	
Tumor diameter	<5	**0.010***	1.000	**0.018***
	≥5		0.132 (0.025-0.705)	
MELD score	<10	0.202	1.000	0.206
	>10		0.438 (0.121-1.576)	
Presence of recurrence	None	0.055	1.000	0.060
	Present		0.282 (0.076-1.052)	
Etiological cause	HBV	0.620	1.000	0.723
	Others		0.723 (0.201-2.605)	
Presence of ascites	None	**0.020***	1.000	**0.025***
	Present		0.190 (0.045-0.812)	
Presence of encephalopathy	None	0.747	1.000	0.746
	Present		0.625 (0.036-10.761)	
CHILD	A	**0.007***	1.000	**0.014***
	B.C		0.112 (0.019-0.644)	
Lesion location	Right	0.323	1.000	0.327
	Left		2.000 (0.500-7.997)	
NLR 2.43	<2.43	**0.010***	1.000	**0.038***
	>2.43		0.100 (0.011-0.882)	

INR- International Normalized Ratio; AFP-Alpha Fetoprotein; NLR- Neutrophil/Lymphocyte Ratio

Table 6. Total survival duration according to NLR groups

			95% Confidence Interval for mean		1-year survival	3-year survival	5-year survival	p
NLR	Estimated mean	Std. Error	Lower limit	Upper limit	%	%	%	
Low	171.85	16.38	139.74	203.97	100.0	100.0	90.9	**0.033**
Elevated	106.06	16.31	74.09	138.03	80.0	53.3	50.2	

Table 7. Disease-free survival duration according to NLR groups

			95% Confidence Interval for mean		1-year survival	3-year survival	5-year survival	p
NLR	Estimated mean	Std. Error	Lower limit	Upper limit	%	%	%	
Low	37.62	13.50	11.15	64.09	66.7	33.3	0.0	0.485
Elevated	43.72	9.13	25.81	61.62	59.9	20.0	6.6	

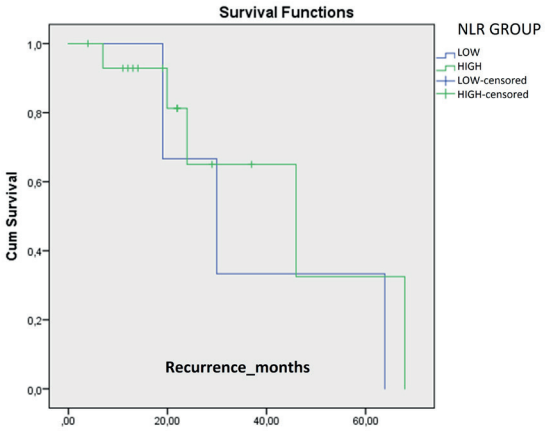

Figure 2. Disease-free survival according to NLR groups

DISCUSSION

Cancer is characterized by complex tissues closely associated with the chronic inflammatory response contributing to its progression and high postoperative recurrence risk (14).

Carcinogenesis due to chronic inflammation is a widely accepted concept in many malignancies, including HCC, with which chronic hepatitis is strongly associated. Hepatitis B or C infection causes the migration of immune system cells to the liver and can, then, lead to proliferation-related cirrhosis, malignant transformation, neo-angiogenesis, tumor progression, and metastasis. Systemic inflammation not only contributes to the pathogenic microenvironment but also causes impaired nutritional status in patients with HCC, which further increases disease-related morbidity and mortality (15).

The association between elevated NLR and poor outcomes in HCC is complex and remains unclear; however, several hypotheses have been proposed with both neutrophilia and lymphocytopenia potentially contributing to HCC recurrence.

Neutrophils are the primary source of circulating vascular endothelial growth factor, (VEGF), which plays a crucial role in angiogenesis. Neutrophils contribute to metastasis by promoting the motility of tumor cells and adhesion of metastatic tumor cells within hepatic sinusoids. Lymphocytes are responsible for host immunity and suppression of cancer progression by producing cytotoxic cell death ligands and cytokines that inhibit tumor cell proliferation and metastasis. Lymphocytopenia can indicate the suppression of innate cellular immunity, which may attenuate lymphocyte-mediated antitumor immunity. Therefore, patients with elevated NLR may have mild lymphocytopenia and neutrophilic leukocytosis, which creates a microenvironment that supports metastasis and suppresses cellular immunity (13-19). As expected, neutrophilia was accompanied by lymphocytopenia in the group with elevated NLR in our series.

When elevated preoperative NLR was compared with low NLR in their metanalysis of HCC patients who underwent hepatectomy, Wang, Y., et al. have shown that elevated NLR has a close relationship with shorter postoperative overall survival and the pooled (HR) ratio was 1.52 (95% CI 1.37-1.69; p <0.00001). These rates revealed a clear relationship between elevated preoperative NLR and recurrence-free survival and the pooled HR was 1.64 (95% CI 1.44-1.87; p <0.00001). The pooled HR value of elevated preoperative NLR in terms of Disease-free survival (DFS) was 1.50 (95% CI 1.35-1.67; P <0.00001) and this rate showed that patients with elevated preoperative NLR had shorter DFS after liver resection. When they evaluate the relationship between NLR and clinicopathological characteristics, elevated preoperative NLR was associated with the presence of tumor vascular invasion (OR 2.08; 95% CI 1.60-2.70; p <0.00001), the presence of HBV (OR 0.68; 95% CI 0.51-0.90; p = 0.008), and large tumor size (maximum diameter of the lesions > 5 cm) (OR: 4.07; 95% CI 2.60–6.37; p <0.00001). However, it was not associated with multiple tumors (intrahepatic) (OR 1.18; 95% CI 0.93-1.50; p = 0.17) and advanced clinical stage (OR 1.04; 95% CI 0.49-2.20; P = 0.92) (20).

In another meta-analysis in the literature, Zheng, J et al. found that the pooled results revealed that an elevated pretreatment NLR predicted poor OS (HR: 1.54, 95% CI: 1.34 to 1.76, p <0.001) and poor RFS (HR: 1.45, 95% CI: 1.16 to 1.82, p = 0.001) in their study where they included patients who received different treatments for HCC. Their study included subgroups of curative resection, liver transplantation, transarterial chemoembolization (TACE), Radiofrequency Ablation (RFA), and chemotherapy. All results were statistically significant in subgroups. Zheng, J et al argued that an elevated NLR is associated with poor prognostic outcomes in HCC patients and can be used as a reliable biomarker for making clinical decisions regarding HCC treatment (21).

Hung, H. C. et al. found a cutoff value of 2.5 for NLR in their series of 672 patients who underwent curative resection. In their study, they showed that the 1-, 3-, and 5-year overall survival rates were 95.2%, 85.9%, and 75.8%, respectively, in the low NLR group and 90.3%, 71.0%, and 61.8%, respectively, in the elevated NLR group (p: 0.001). Like overall survival rates, disease-free survival rates were also found to be significantly better in the low NLR group than in the elevated NLR group. While the 1-, 3-, and 5-year disease-free survival rates were 64.1%, 45.2%, and 35.5%, respectively, in the elevated NLR group, they were 77.4%, 55.2%, and 44.8%, respectively, in the low NLR group (p: 0.016). Hung, H. C. et al. demonstrated that NLR may be used in survival estimates (22).

In our study, the elevated NLR rate was associated with decreased overall survival but not with disease-free survival. In multivariate analysis, an elevated NLR ratio was found to be a prognostic factor for survival. Tumor diameter, Child-Plug Class, and the presence of ascites were other prognostic factors.

The most important limitation of our study was its retrospective nature and small patient population. Resection number decreases as the options of thermal ablation and liver transplantation come to the fore in HCC treatment and considering this situation, our number of patients was acceptable for a single center.

CONCLUSION

Elevated NLR was found to be associated with decreased overall survival in our study. Although it was not found to be associated with clinicopathological parameters in HCC cases who underwent curative resection, NLR may be used as a prognostic factor. Elevated NLR is closely related to the more aggressive HCC phenotype which contributes to lower OS.

Conflict of interest: The authors declare that they have no competing interest.

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