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Preoperative Neutrophil-to-Lymphocyte Ratio as a New Prognostic Marker in Hepatocellular Carcinoma after Curative Resection[1]

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Abstract

BACKGROUND: Preoperative peripheral blood neutrophil-to-lymphocyte ratio (NLR) has been proposed to predict prognosis of hepatocellular carcinoma (HCC). However, the cutoff value of NLR in several studies is not consistent. This study aims to investigate the correlation of preoperative NLR with clinicopathologic features and the prognosis in patients who have undergone resection for HCC. *METHODS*: Clinical data of 256 patients with HCC who underwent radical hepatectomy were retrospectively analyzed. The patients were divided into the low-NLR group (NLR $\leq$ 2.31) and the high-NLR group (NLR > 2.31). A univariate analysis was performed to assess clinicopathologic characteristics that influenced disease-free survival (DFS) and overall survival (OS) in patients. The significant variables were further analyzed by a multivariate analysis using Cox regression. The Kaplan-Meier method was used to assess the DFS and OS rate. *RESULTS*: The value of NLR was associated with tumor size, clinical tumor-node-metastasis (TNM) stage, portal vein tumor thrombus (PVTT), distant metastasis, and aspartate aminotransferase (AST) in HCC. NLR > 2.31, size of tumor > 5 cm, number of multiple tumors, III-IV of TNM stage, PVTT, distant metastasis, and AST > 40 U/l were predictors of poorer DFS and OS. NLR > 2.31, size of tumor >5 cm, III-IV of TNM stage, and AST > 40 U/l were independent predictors of DFS and OS. *CONCLUSION*: Preoperative NLR > 2.31 was an adverse predictor of DFS and OS in HCC after hepatectomy. This study suggested that NLR might be a novel prognostic biomarker in HCC after curative resection.

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Introduction

An estimated 748,300 new liver cancer cases and 695,900 cancer deaths occurred worldwide in 2008. Half of these cases and deaths were estimated to occur in China [1]. There are significant geographical differences in the morbidity and mortality of hepatocellular carcinoma (HCC) all over the world. HCC is one of the common malignant tumors of digestive tract and is the major cancer burden in China [2]. The prognosis of HCC remains poor mainly because of high recurrence and metastasis rates even after surgical resection. Tumor recurrence rates are more than 70% of cases at 5 years [3,4]. Although surgical resection is a potentially curative treatment for HCC and despite improved diagnosis and advances in surgical and nonsurgical therapy, the clinical outcome of HCC remains poor [5]. Therefore, it is of great significance to carry out deep research in diagnosis and prognosis of HCC. Such researches might lead to a breakthrough in the field of HCC diagnosis, treatment, and prevention and furthermore, adoption of effective measures to improve surgical treatment for HCC.

Recently, there is increasing evidence that the presence of systemic inflammation correlates with poor cancer-specific survival. The prognostic value of various markers of systemic inflammatory, including cytokines such as intercellular adhesion molecule 1 and neutrophil-to-lymphocyte ratio (NLR) has been investigated in certain cancer populations [6-14]. Previous studies have demonstrated that an elevated NLR may correlate with a poor prognosis in patients who underwent curative resection of HCC. However, the cutoff value of NLR is not consistent; for instance, it is determined as 2.3 [15], 3.0 [16], and 5.0 [17,18] in different studies. So the cutoff value of NLR in patients who underwent curative resection of HCC should be optimized; otherwise, it is difficult to evaluate the clinical value of NLR and to compare different studies. Our study was designed to determine the optimal value of NLR and to evaluate the correlation of preoperative NLR with clinicopathologic features and prognosis in patients with HCC who underwent curative resection.

Materials and Methods

The Source of Specimens and Clinical Data

Two hundred fifty-six cases of patients with HCC underwent hepatic resection at the Affiliated Hospital of Guilin Medical University (Guilin, People's Republic of China) from September 1999 to June 2007, and these patients were recruited for this study. These subjects were confirmed by clinical, serological, ultrasonography (US), computerized tomography, magnetic resonance imaging, and pathologic examination, and HCC diagnoses in this study followed the Primary Liver Cancer Clinical Diagnosis and Staging Criteria (Ministry of Health, Beijing, China). Clinicopathologic characteristics of these patients including NLR, age, gender, hepatitis B surface antigen (HBsAg), α-fetoprotein (AFP), the size and the number of tumors, combined liver cirrhosis, clinical tumor node metastasis (TNM) stage, portal vein tumor thrombus (PVTT), distant metastasis, and aspartate aminotransferase (AST) were collected and detailed in Table 1. All subjects gave written informed consent, and the local ethics committee approved this study. This study was conducted as a retrospective analysis of a prospectively collected computerized database in a single hospital. Among them, 256 patients who met the inclusion criteria were enrolled in this study. Patients were obviated if they 1) were patients with cholangiocarcinoma or were not primary patients with HCC, 2) died in perioperative period, 3) could not provide detailed and needed clinical data, 4) had clinical evidence of infection, immune-system disease, or hematology disease or used hematology-influenced drugs within 1 month, 5) lost contact during the follow-up time, or 6) were HIV positive.

Our research group investigated patients with HCC with long-term follow-up after surgery including using serum AFP test and US examination every 2 months and chest radiography every 6 months during the first two postoperative years and at 3- to 6-month intervals thereafter. Computerized tomography or magnetic resonance imaging scans were performed if recurrence was suspected due to an abnormal AFP test or US examination. The mean postoperative follow-up time was 38.0 months (median, 21.0 months; range, 2.0-161.0 months). Disease-free survival (DFS) was measured from the date of surgery to the date of recurrence, metastasis, death, or last follow-up. Overall survival (OS) was measured from the date of surgery to the date of death or last follow-up.

Selection of Cutoff Score

To avoid predetermined cut point, receiver operating characteristic (ROC) curve analysis was applied to define the cutoff score for preoperative NLR. The score was selected as the cutoff value that was closest to the point with both maximum sensitivity and specificity. Other clinicopathologic parameters used were dichotomized: age (≤55 *vs* >55 years), gender (female *vs* male), HBsAg (negative *vs* positive), AFP level (≤20 *vs* >20 ng/ml), tumor size (≤5 *vs* >5 cm), cirrhosis (yes *vs* no), tumor number (single *vs* multiple), TNM stage (I-II *vs* III-IV), distant metastasis (yes *vs* no), PVTT (yes *vs* no), recurrence (yes *vs* no), and AST (yes *vs* no). Subsequently, the clinicopathologic and prognostic significance of the NLR level in HCC was investigated.

Table 1. Patients with HCC (256 Cases) Categorized by NLR and Their Clinical Pathologic Characteristics.

Clinical Character	Variable	No. of Patients	NLR		χ^2	*P* Value
			≤2.31 n (%)	>2.31 n (%)		
Age (yr)	≤ 55	176	81 (46.0)	95 (54.0)	0.349	.555
	> 55	80	40 (50.0)	40 (50.0)		
Gender	Female	30	15 (50.0)	15 (50.0)	0.102	.750
	Male	226	106 (46.9)	120 (53.1)		
HBsAg	Negative	41	18 (43.9)	23 (56.1)	0.222	.638
	Positive	215	103 (47.9)	112 (52.1)		
AFP (ng/ml)	≤ 20	62	31 (50.0)	31 (50.0)	0.245	.620
	> 20	194	90 (46.4)	104 (53.6)		
Tumor size (cm)	≤ 5	47	36 (76.6)	11 (23.4)	19.869	< .001
	> 5	208	85 (40.7)	124 (59.3)		
Cirrhosis	No	27	14 (51.9)	13 (48.1)	0.255	.614
	Yes	229	107 (46.7)	122 (53.3)		
Tumor no.	Single	163	79 (48.5)	84 (51.5)	0.259	.610
	Multiple	93	42 (45.2)	53 (54.8)		
TNM stage	I-II	109	73 (67.0)	36 (33.0)	29.576	< .001
	III-IV	147	48 (32.7)	99 (67.3)		
PVTT	No	184	98 (53.3)	86 (46.7)	9.434	.002
	Yes	72	23 (31.9)	49 (68.1)		
Distant metastasis	No	218	111 (50.9)	107 (49.1)	7.858	.005
	Yes	38	10 (26.3)	28 (73.7)		
Recurrence	No	164	71 (43.3)	93 (56.7)	2.890	.089
	Yes	92	50 (54.3)	42 (45.7)		
AST (U/l)	≤ 40	117	64 (54.7)	53 (45.3)	4.779	.029
	> 40	139	57 (41.0)	82 (59.0)		

NLR, neutrophil-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; TNM, tumor-node-metastasis; PVTT, portal vein tumor thrombus; AST, aspartate aminotransferase.