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# Neutrophil to lymphocyte ratio changes predict small hepatocellular carcinoma survival

Wei Peng, MD, Chuan Li, MD, Tian-Fu Wen, MD,\* Lu-Nan Yan, MD, Bo Li, MD, Wen-Tao Wang, MD, Jia-Yin Yang, MD, and Ming-Qing Xu, MD

Department of Liver Surgery & Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu, China

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## ABSTRACT

**Background:** There is limited information available concerning the delta neutrophil to lymphocyte ratio ( $\Delta$ NLR) in hepatocellular carcinoma (HCC). The present study was designed to evaluate the predictive value of dynamic change of NLR in patients who undergo curative resection for small HCC.

**Methods:** A retrospective cohort study was performed to analyze 189 patients with small HCC who underwent curative resection between February 2007 and March 2012. Patient data were retrieved from our prospectively maintained database. Patients were divided into two groups: group A (NLR increased,  $n = 80$ ) and group B (NLR decreased,  $n = 109$ ). Demographic and clinical data, overall survival (OS), and recurrence-free survival (RFS) were statistically compared and a multivariate analysis was used to identify prognostic factors.

**Results:** The 1, 3, and 5-y OS in group A was 92.7, 70.0, and 53.0%, respectively, and 96.2, 87.5, and 75.9%, respectively, for group B ( $P = 0.003$ ); The corresponding 1, 3, and 5-y RFS was 58.7, 37.9, 21.8, and 81.2%, 58.5% and 53.8% for groups A and B, respectively ( $P < 0.001$ ). Multivariate analysis suggested that  $\Delta$ NLR was an independent prognostic factor for both OS ( $P = 0.004$ , Hazard Ratio (HR) = 2.637, 95% confidence interval (CI) 1.356–5.128) and RFS ( $P < 0.001$ , HR = 2.372, 95% CI 1.563–3.601).

**Conclusions:** Increased NLR, but not high preoperative NLR or postoperative NLR, helps to predict worse OS and RFS in patients with small HCC who underwent curative resection.

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## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, and the third leading cause of cancer-related death worldwide [1–3]. Curative resection is the standard method for HCC patients who meet Milan criteria [4,5]. Although advances in techniques and perioperative management have occurred, survival remains very poor in HCC patients [6]. Therefore, continuing efforts to explore the

prognostic factors that affect the survival after resection are necessary. Established prognostic factors include liver function reserve, tumor size, tumor multiplicity, satellite lesions, and vascular invasion, among others [7–10].

Recently, the effects of inflammation on carcinogenesis have been gaining attention and there is increasing evidence correlating the presence of systemic inflammatory response with relatively poor cancer-specific survival in certain malignancies [11–14]. Because Rudolf Virchow first postulated the

\* Corresponding author. Department of Liver Surgery & Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. Tel.: +86 18980601471; fax: +86 2885422871.

E-mail address: [ccwentianfu@sohu.com](mailto:ccwentianfu@sohu.com) (T.-F. Wen).

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relationship between inflammation and cancer, the role of inflammation in carcinogenesis has been universally accepted [15]. Systemic inflammatory response is thought to cause an upregulation of cytokines and inflammatory mediators, predisposing the tumor to proliferate and metastasize through the promotion of angiogenesis, damage to DNA, and inhibition of apoptosis [15–18]. The neutrophil to lymphocyte ratio (NLR) is a systemic inflammatory response marker, and has the advantage of being readily available from routine tests of blood cell counts. Furthermore, the prognostic value of NLR has been demonstrated in various cancers [19–22]. Elevated NLR has been shown to correlate with poor survival in patients with HCC who underwent curative resection [23], transcatheter arterial chemoembolization (TACE) [24], radiofrequency ablation (RFA) [25], and liver transplantation [26]. However, these studies focused on preoperative NLR or postoperative NLR in patients who received RFA [25,27].  $\Delta$ NLR which represents the change in preoperative to postoperative NLR, has been rarely studied in patients who received curative resection.

The present study was designed to evaluate the predictive value of  $\Delta$ NLR in patients with small HCC who underwent curative resection.

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## 2. Methods

### 2.1. Patients

Patients included in our study were recruited from the Department of Liver Surgery & Liver Transplantation Center of West China Hospital, Sichuan University, Chengdu, China between February 2007 and March 2012. The study was approved by the Ethics Committee of West China Hospital, Sichuan University.

Between February 2007 and March 2012, 283 newly diagnosed small HCC patients received curative resection as initial treatment in the Department of Liver Surgery & Liver Transplantation Center of West China Hospital, Sichuan University. Patients were diagnosed with small HCC when two types of imaging examination revealed the typical features of HCC or positive findings on one imaging examination together with an alpha fetoprotein (AFP) level of  $>400$  ng/mL. The diagnosis of HCC was confirmed by a postoperative pathologic report. Oncological data, including size and number of lesions, vascular invasion, and AFP level; auxiliary examinations, including reports of ultrasound, computed tomography, or magnetic resonance imaging; results of blood cell counts and differentiation; liver function tests; hepatitis B virus (HBV) markers; and recurrence and survival data were retrieved from our prospectively maintained database.

In the present study, our inclusion criteria were as follows: (1) primary small HCC (solitary tumor  $<5$  cm in diameter or  $\leq 3$  nodules that were  $\leq 3$  cm in diameter); (2) receiving curative liver resection; and (3) appropriate liver reserve function (Child–Pugh grade A) and renal function (serum creatinine,  $124$  mmol/L).

Exclusion criteria included the following: (1) extrahepatic malignancies or massive intrahepatic metastasis; (2) previous resection, TACE, RFA or liver transplantation; (3) recurrent HCC; (4) loss to follow up within 3 mo after curative resection; (5) poor liver reserve function with a Child–Pugh grade B or C; (6) clinical

symptoms or signs of sepsis at the time of blood sampling for NLR, or white blood cell counts  $>10 \times 10^9/L$ ; (7) rupture of HCC; and (8) poor data integrity.

Based on our inclusion and exclusion criteria, a total of 94 patients were excluded from this study. Details about patient selection are shown in Figure 1.

### 2.2. Definition of NLR

All preoperative white blood cell counts and differential counts were taken 2 days before operation. The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. Postoperative NLR was obtained at the first follow-up visit at the outpatient department 1 mo after operation.  $\Delta$ NLR was calculated by postoperative NLR minus preoperative NLR. If the NLR value was  $\leq 0$ ,  $\Delta$ NLR was defined as decreased; if not, it was defined as increased. Overall survival (OS) and recurrence-free survival (RFS) were used to demonstrate the prognostic value of NLR.

### 2.3. Follow-up visit

All the 189 patients were regularly followed up at the first, third, and sixth months in the first half year after surgery, every 3 mo during the following 3 y, and every 6 mo in the subsequent years.

Physical examination, blood cell and differential counts, AFP level, liver function test, HBV markers, and HBV-DNA, if the patient was diagnosed with an HBV infection, and radiology examination based on specific situations were included in the follow-up examinations. Tumor recurrence was diagnosed by the criteria mentioned previously. Once identified, the patient was advised to receive additional treatment, for example, liver resection, RFA, TACE, or Sorafenib. The last follow-up date was the end of March 2013.

### 2.4. Statistical analysis

We used SPSS software version 21.0 (SPSS Company, Chicago, IL) to perform statistical analysis.  $\Delta$ NLR was determined by postoperative NLR minus preoperative NLR, and was used to categorize patients into group A (NLR increased) or group B (NLR decreased). Categorical data were compared by the chi-square test or Fisher exact test. Continuous variables were compared by the independent sample t-test. The OS and RFS were analyzed by the Kaplan–Meier method, and the differences were analyzed by a log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate the prognostic factors. Calculated *P* values were two-sided, and a *P* value  $<0.05$  was considered statistically significant.

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## 3. Results

### 3.1. Baseline characteristics

In the present research, we studied 189 patients who received curative resection during February 2007 and March 2012 in our center that matched our criteria. Among them, there were 164 males (86.8%) and 25 females (13.2%), with the mean age of  $50.2 \pm 11.5$  (range from 22–78) y. The median follow-up time

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