Oncology and Translational Medicine
DOI 10.1007/s10330-015-0117-5
December 2015, Vol. 1, No. 6, P249–P255

ORIGINAL ARTICLE

The preoperative neutrophil-to-lymphocyte ratio predicts the outcomes of patients with hepatocellular carcinoma and cirrhosis after hepatectomy*

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Abstract

Objective The aim of the study was to investigate the prognostic value of the preoperative peripheral neutrophil-to-lymphocyte ratio (NLR) in patients with hepatocellular cancer (HCC) and cirrhosis after hepatectomy.

Methods This retrospective study included 321 patients with HCC who underwent resection. The NLR was calculated using the neutrophil and lymphocyte counts in routine preoperative blood tests. Receiver operating characteristic curve analysis was performed to select the most appropriate NLR cutoff value. The preoperative NLR, patient demographics, and clinical and pathological data, including disease-free survival (DFS) and overall survival (OS), were analyzed.

Results The NLR was correlated with alpha-fetoprotein levels (χ^2 = 5.876, P = 0.015), tumor size (χ^2 = 32.046, P < 0.001), portal vein tumor thrombus (PVTT; χ^2 = 4.930, P = 0.026), tumor encapsulation (χ^2 = 7.243, P = 0.007), and recurrence (χ^2 = 7.717, P = 0.005). Multivariate analyses illustrated that the number of tumors, PVTT, tumor size, and the NLR were independent factors for predicting DFS and OS. In patients with HCC and cirrhosis, but not among those without cirrhosis, a larger NLR predicted poorer postoperative DFS and OS (both P < 0.001).

Conclusion As a simple, effective independent predictor for patients with HCC, the preoperative NLR plays an important role in accurately predicting the postoperative outcomes of patients with HCC and cirrhosis, but not those of patients without cirrhosis.

Received: 1 September 2015
Revised: 16 September 2015
Accepted: 25 October 2015

Key words: hepatocellular cancer (HCC); neutrophil-to-lymphocyte ratio (NLR); pathology; prognosis

Hepatocellular cancer (HCC) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide, accounting for approximately 740 000 new cases and 600 000 deaths annually [1–3]. Moreover, approximately 70% of patients with HCC who are treated with a curative intent develop recurrence or metastasis within 5 years after resection. The long-term survival of patients undergoing potentially curative treatments remains poor [4–5]. It is therefore essential and urgent to identify risk factors in patients to personalize therapies and improve clinical outcomes.

It is increasingly recognized that a systemic inflammatory response is associated with tumor development through the inhibition of apoptosis, promotion of angiogenesis, and induction of DNA damage. The pathogenesis of HCC is based on inflammation, such as that associated with infection by hepatotropic viruses, or ethanol consumption. Moreover, 70%–90% of HCCs arise in patients with cirrhosis [6–7]. Recent studies support the role of inflammation-based prognostic scores as predictors of out-

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* Supported by grants from the National Natural Science Foundation of China (No. 81201918), the Science and Technology Project of Guangdong Province (No. 2012B031800099), the Doctorial Fellowship of Higher Education of China (No. 200805581172), and the Scientific Research Foundation for Returned Overseas Chinese Scholars and the State Education Ministry (No. 311, in 2015).

come in patients with HCC, including a combination of neutrophil and lymphocyte counts as the neutrophil-to-lymphocyte ratio (NLR) [8–10]. However, few studies have investigated the prognostic value of the NLR in predicting tumor recurrence and survival after curative resection for patients with HCC and cirrhosis. The present study revealed that a larger NLR predicted poorer postoperative disease-free survival (DFS) and overall survival (OS) in patients with HCC and cirrhosis.

Patients and methods

Study population

A total of 321 patients with histologically proven HCC who underwent hepatic resection were recruited in our hospital (The First Affiliated Hospital of Sun Yat-sen University, China) between 2006 and 2009. The study was approved by the First Affiliated Hospital of Sun Yat-sen University Review Board. A routine assessment, including a complete physical examination, assessments of hematologic and biochemistry profiles, chest radiography, abdominal ultrasonography, and computed tomography or magnetic resonance imaging, was performed within 7 days before surgery.

The eligibility criteria included International Union Against Cancer tumor-node-metastasis (TNM) stage I, II, IIIA, or IIIB disease (the seventh edition); Child-Pugh class A hepatic function; an age of 18–80 years; and signed written informed consent. The exclusion criteria included TNM stage IIIC, IVA, or IVB disease; an existing secondary malignancy or a history of secondary malignancy within the past 5 years; hematologic disorders; perioperative dysfunction of vital organs; and a previous percutaneous ablation, transcatheter arterial chemoembolization (TACE), chemotherapy, or radiotherapy within 1 month after surgery.

Blood samples were obtained before the initial treatment to measure neutrophil and lymphocyte counts. The NLR was calculated using the following formula: NLR = neutrophil count / lymphocyte count.

Treatment and follow-up

Hepatectomy was defined as radical when there was no evidence of distant metastases and tumor clearance was complete both macroscopically and histologically. All patients were regularly followed up according to institutional practice, including liver ultrasonography, chest radiography, and serum alpha-fetoprotein (AFP) measurements every 3 months and contrast-enhanced computed tomography every 6 months. Tumor recurrence was defined according to the clinical, radiological, and/or pathological diagnosis. After diagnosing recurrence, salvage treatments were selected, including re-operation, percutaneous ablation, and TACE.

Statistical analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the sensitivity and specificity of the NLR for predicting the 5-year OS rate. The Youden Index was estimated to select the optimal cutoff value of NLR [11]. The Student *t*-test was used for comparisons of continuous variables with a normal distribution. The chi-squared test was used for categorical variables. DFS was calculated from the date of surgery to that of recurrence, and OS was calculated from the date of surgery to that of HCC-associated death. The Kaplan-Meier method was used to estimate the survival rates for different groups, and the equivalences of the survival curves were tested using log-rank statistics. The Cox proportional hazards model was used for univariate and multivariate survival analyses. $P < 0.05$ was considered statistically significant.

Results

Patient and tumor characteristics

The study population included 285 male patients (88.8%) and 36 female patients (11.2%). The mean patient age was 51 years (range, 21–79 years). A total of 235 patients (73.2%) experienced recurrence, and 201 patients (62.6%) died during follow-up. Hepatitis B surface antigen (HBsAg) was positive in 281 patients (87.5%), and cirrhosis was noted in 253 (78.8%) patients. Increased AFP levels (≥ 200 μg/L) were observed in 182 patients (56.7%), and multiple tumor masses were detected in 95 patients (29.6%). The mean tumor size was 87.6 mm (range, 10–300 mm) in the greatest diameter, and 210 (65.4%) patients had tumors ≥ 50 mm in diameter. According to the Edmonson-Steiner stage of tumor differentiation, 248 (77.3%) and 73 patients (22.7%) were categorized into stages I–II and III–IV, respectively.

Cutoff determination of NLR

The results indicated that the optimal NLR cutoff value was 2, corresponding to the maximum joint sensitivity and specificity in the ROC curves analyses (Youden Index = 1.207). Then, patients were divided into NLR-high (NLR > 2; $n = 168$) and NLR-low groups (NLR ≤ 2; $n = 153$; Fig. 1).

Correlation between the NLR and 12 clinicopathologic characteristics in patients with HCC

The clinicopathologic characteristics of patients with different NLRs were analyzed. NLR > 2 was more frequently observed in patients with high AFP levels ($\chi^2 = 5.876$, $P = 0.015$), large tumors ($\chi^2 = 32.046$, $P < 0.001$), portal vein tumor thrombus (PVTT; $\chi^2 = 4.930$, $P = 0.026$), recurrence ($\chi^2 = 7.717$, $P = 0.005$), and incomplete encapsulation ($\chi^2 = 7.243$, $P = 0.007$; Table 1).

Table 1 Correlation between clinicopathologic characteristics and the neutrophil-to-lymphocyte ratio (NLR) in our study groups [*n* (%)]

Variables	*n*	NLR		*P*
		NLR ≤ 2	NLR > 2	
Age (years)				
≥ 60	77	32 (41.6%)	45 (58.4%)	0.219
< 60	244	121 (49.6%)	123 (50.4%)	
Gender				
Male	285	135 (47.4%)	150 (52.6%)	0.766
Female	36	18 (50.0%)	18 (50.0%)	
HBsAg				
Positive	281	134 (47.7%)	147 (52.3%)	0.982
Negative	40	19 (47.5%)	21 (52.5%)	
Cirrhosis				
Yes	253	126 (49.8%)	127 (50.2%)	0.139
No	68	25 (36.8%)	43 (63.2%)	
AFP (μg/L)				
≥ 200	182	76 (41.8%)	106 (58.2%)	0.015
< 200	139	77 (55.4%)	62 (44.6%)	
Tumor size (cm)				
> 5	210	76 (36.2%)	134 (63.8%)	< 0.001
≤ 5	111	77 (69.4%)	34 (30.6%)	
Tumor number				
Single	226	112 (49.6%)	114 (50.4%)	0.295
Multiple	95	41 (43.2%)	54 (56.8%)	
Tumor differentiation				
I–II	248	119 (48.0%)	129 (52.0%)	0.832
III–IV	73	34 (46.6%)	39 (53.4%)	
PVTT				
Yes	58	20 (34.5%)	38 (65.5%)	0.026
No	263	133 (50.6%)	130 (49.4%)	
Tumor encapsulation				
Complete	211	112 (53.1%)	99 (46.9%)	0.007
Incomplete	110	41 (37.3%)	69 (62.7%)	
Recurrence				
Yes	235	101 (43.0%)	134 (57.0%)	0.005
No	86	52 (60.5%)	34 (39.5%)	
Complication				
No	273	130 (47.6%)	143 (52.4%)	0.970
Yes	48	23 (47.9%)	25 (52.1%)	

AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; PVTT, portal vein tumor thrombus

Independent prognostic factors of HCC

To further identify the risk factors linked to postoperative DFS and OS, the NLR and 11 clinicopathologic factors were evaluated via univariate analysis and a Cox regression model. The univariate analysis illustrated that the significant prognostic factors for DFS among patients with HCC were HBsAg, AFP, tumor size, tumor number, PVTT, tumor differentiation, and the NLR ($P < 0.05$). Similarly, the significant factors for OS among patients with HCC were gender, AFP, tumor size, tumor number, PVTT, tumor differentiation, and the NLR ($P < 0.05$). On multivariate analysis, we found that tumor size, tumor number, PVTT, and the NLR were significant independent predictors of DFS and OS ($P < 0.05$; Tables 2 and 3).

OS and DFS rates according to the NLR

First, 321 patients with HCC were divided into NLR-low ($n = 153$) and NLR-high groups ($n = 168$) using an NLR cutoff of 2. Using the Kaplan-Meier method to analyze patient survival, we found that the 1-, 3-, and 5-year DFS rates of the NLR-low group were markedly higher compared to those of the NLR-high group (53.6%, 39.2%, and 34.6%, respectively vs. 36.9%, 23.2%, and 20.6%, respectively, all $P < 0.001$; Fig. 2a). Additionally, the 1-, 3-, and 5-year OS rates of the NLR-low group were also significantly higher compared to those of the NLR-high group (79.7%, 58.8%, and 49.6%, respectively vs. 63.1%, 35.1%, and 29.7%, respectively, all $P < 0.001$; Fig. 2b). Therefore, our findings indicated that a larger NLR was correlated with low survival rates in patients with HCC.

Subgroup analysis of the NLR for OS and DFS rates according to the presence of cirrhosis

To further clarify the prognostic value of the preoperative NLR for patients with HCC with or without cirrhosis, we classified patients according to the presence of cirrhosis. Among patients without cirrhosis ($n = 68$), the DFS and OS rates after hepatic resection were not significantly different between the NLR-low and NLR-high groups ($P = 0.841$ and $P = 0.511$, respectively; Fig. 3a and 3b). Intriguingly, regarding patients with cirrhosis, the 1-, 3-, and 5-year DFS and OS rates of the NLR-low group were all remarkably better than those of the NLR-high group (all $P < 0.001$; Fig. 3c and 3d). The 1-, 3-, and 5-year DFS rates of the NLR-low group were 55.6%, 40.5%, and 36.4%, respectively, compared to 36.2%, 22.8%, and 19.3%, respectively, for the NLR-high group. Likewise, the 1-, 3-, and 5-year OS rates of the NLR-low group were 80.2%, 59.5%, and 50.7%, respectively, which were obviously superior to those of the NLR-high group (59.1%, 33.1%, and 28.3%, respectively; Fig. 3).

Discussion

There is increasing evidence that the host inflammatory response is correlated with the occurrence and development of many cancers because of the induction of several pro-tumor factors. As a simple and effective marker of inflammation, the NLR has been recognized as an independent predictive factor for patients with cancers, such as esophageal cancer [11], gastric cancer [12–13], colorectal cancer [14], pancreatic adenocarcinoma [15], oral cancer [16], and HCC [8–10]. An elevated NLR is always associated with poor prognosis among patients with cancer, which may be explained by several factors. One explanation is that patients with a large NLR usually have an enhanced neu-

Table 2 Prognostic factors for disease-free survival (DFS) and overall survival (OS) on univariate analysis in our study groups

Variables	*n*	DFS			*P*	OS			*P*
		1-year	3-year	5-year		1-year	3-year	5-year	
Gender									
Male	285	43.5%	29.8%	25.8%	0.096	69.5%	44.6%	37.1%	0.026
Female	36	55.6%	38.9%	38.9%		83.3%	61.1%	55.6%	
Age (years)									
≥ 60	244	43.9%	32.4%	29.5%	0.565	70.1%	47.1%	39.7%	0.677
< 60	77	48.1%	26.0%	20.3%		74.0%	44.2%	37.6%	
HBsAg									
Positive	281	42.0%	29.5%	25.4%	0.049	69.4%	44.8%	38.0%	0.123
Negative	40	65.0%	40.0%	40.0%		82.5%	57.5%	47.5%	
AFP (μg/L)									
< 200	139	54.0%	36.7%	34.5%	0.002	77.7%	51.8%	45.3%	0.015
≥ 200	182	37.9%	26.4%	21.8%		65.9%	42.3%	34.5%	
Cirrhosis									
Yes	68	41.2%	27.9%	25.0%	0.541	76.5%	47.1%	38.2%	0.745
No	253	45.8%	31.6%	27.9%		69.6%	46.2%	39.5%	
PVTT									
Yes	263	52.5%	35.7%	31.8%	< 0.001	79.5%	52.9%	45.6%	< 0.001
No	58	10.3%	8.6%	6.9%		32.8%	17.2%	10.1%	
Tumor number									
Single	226	54.0%	38.5%	34.0%	< 0.001	77.0%	54.9%	48.6%	< 0.001
Multiple	95	23.2%	12.5%	11.0%		56.8%	26.3%	16.7%	
Tumor size (cm)									
> 5	210	31.9%	20.0%	18.5%	< 0.001	64.8%	34.3%	27.5%	< 0.001
≤ 5	111	69.4%	51.4%	43.9%		89.2%	69.4%	61.2%	
Complication									
No	273	44.7%	32.6%	28.4%	0.356	72.2%	46.9%	40.6%	0.345
Yes	48	45.8%	20.8%	20.8%		64.6%	43.8%	31.0%	
Tumor differentiation									
I–II	248	49.2%	34.3%	30.5%	0.001	73.4%	49.6%	43.5%	0.003
III–IV	73	30.1%	19.2%	16.4%		63.0%	35.6%	24.5%	
Resection margin (cm)									
< 2	184	42.1%	26.8%	23.4%	0.138	69.9%	41.5%	34.3%	0.041
≥ 2	137	48.2%	35.7%	32.0%		72.3%	52.6%	45.2%	
NLR									
≤ 2	153	53.6%	39.2%	34.6%	< 0.001	79.7%	58.8%	49.6%	< 0.001
> 2	168	36.9%	23.2%	20.6%		63.1%	35.1%	29.7%	

AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; PVTT, portal vein tumor thrombus; NLR, neutrophil-to-lymphocyte ratio

Table 3 Independent prognostic factors for disease-free survival (DFS) and overall survival (OS) using a multivariate Cox proportional hazards regression model in our study groups

Variables	DFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Tumor number	0.572	0.423–0.774	< 0.001	0.595	0.438–0.807	0.001
PVTT	2.255	1.606–3.165	< 0.001	2.408	1.710–3.391	< 0.001
Tumor size	1.836	1.299–2.596	0.001	1.856	1.314–2.623	< 0.001
NLR	1.429	1.068–1.912	0.016	1.451	1.086–1.840	0.012

HR, hazard ratio; CI, confidence interval; PVTT, portal vein tumor thrombus; NLR, neutrophil-to-lymphocyte ratio

trophil response, which could promote the production of pro-angiogenic factors, including vascular endothelial growth factor [17], interleukin-8 [18], and matrix metalloproteinase [19]. These pro-angiogenic factors may promote tumor growth, resulting in a poor prognosis. Another explanation is that the host's immune response to tumors depends on lymphocytes, whereas patients with a large NLR have relative lymphocytopenia, which results in the

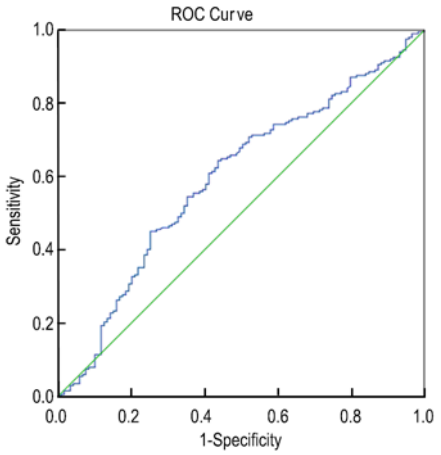

Fig. 1 Receiver operating characteristic (ROC) curve for determination of the cutoff value for the neutrophil-to-lymphocyte ratio (NLR) among patients with hepatocellular carcinoma after hepatic resection

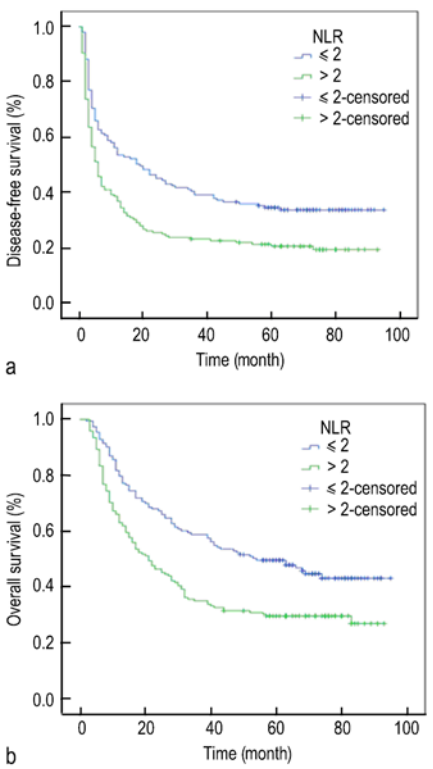

Fig. 2 Relationship of the neutrophil-to-lymphocyte ratio (NLR) with disease-free survival (DFS) / overall survival (OS) among patients with hepatocellular carcinoma after hepatectomy. (a) DFS was longer among patients with NLR ≤ 2 than among those NLR > 2 (P < 0.001, log-rank test). (b) OS was longer among patients with NLR ≤ 2 than among those with NLR > 2 (P < 0.001, log-rank test)

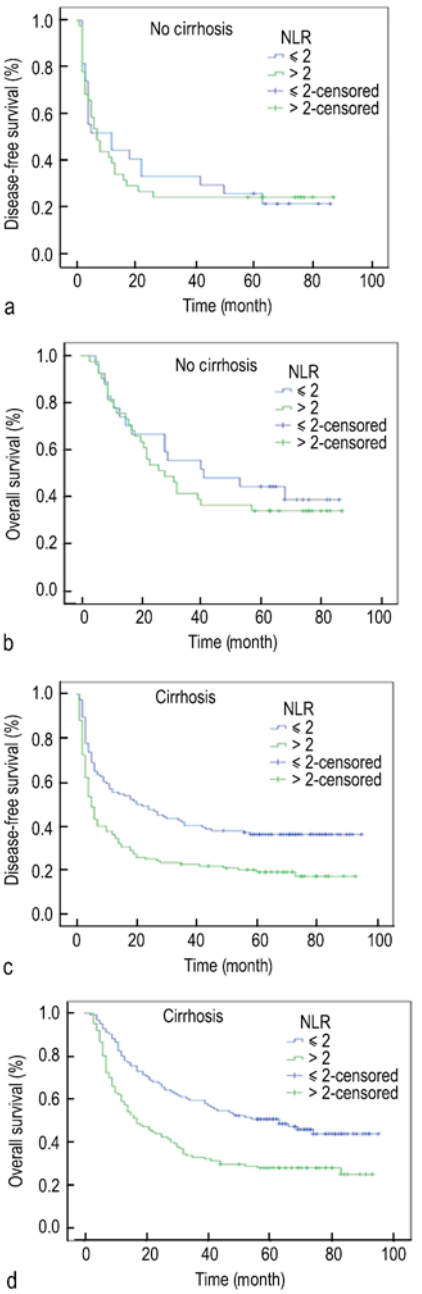

Fig. 3 Relationship of the neutrophil-to-lymphocyte ratio (NLR) with disease-free survival (DFS) / overall survival (OS) among patients with hepatocellular carcinoma with or without cirrhosis. (a and b) In patients without cirrhosis, the DFS and OS rates after hepatic resection were not significantly different between the NLR ≤ 2 and NLR > 2 groups (P = 0.841 and P = 0.511, respectively, log-rank test). (c and d) Among patients with cirrhosis, DFS and OS were significantly shorter among patients with NLR > 2 than among those with NLR ≤ 2 (both P < 0.001, log-rank test)

attenuation of lymphocyte-mediated antitumor immune responses in these patients.

HCC is the sixth most common malignancy, and an estimated one-half million new cases are diagnosed each year worldwide. A three-step process of hepatitis – liver fibrosis/cirrhosis – HCC is considered the most important

mechanism of hepatocarcinogenesis. The annual incidence of liver cancer in patients with cirrhosis is 1%–6% [20]. Furthermore, liver cirrhosis plays pivotal roles in the development, metastasis, and recurrence of HCC. As a result, HCC is the leading cause of mortality among patients with cirrhosis [21]. Thus, it will be extremely valuable to identify a factor that predicts the prognosis of patients with HCC and cirrhosis.

In the present study, we performed ROC curve analysis and determined that the optimal NLR cutoff value was 2 because the Youden Index was maximal. We identified close correlations between NLR and several factors, including AFP, tumor size, PVTT, incomplete encapsulation, and recurrence. Using univariate analysis, we discovered many significant prognostic factors for DFS and OS among patients with HCC, including AFP, tumor size, tumor number, PVTT, tumor differentiation, and the NLR. However, after Cox regression multivariate analysis, we determined that the independently related factors for both DFS and OS included AFP, tumor size, tumor number, PVTT, tumor differentiation, and the NLR. Our results illustrated that the NLR independently predicted the survival rates of patients with HCC who underwent hepatic resection, and a larger NLR was positively correlated with poor outcomes among patients with HCC, which is consistent with the results of several studies involving patients with HCC who underwent surgical resection [22], transplantation [23], TACE [24], and radiofrequency ablation (RFA) [8].

Further, we assessed the roles of the NLR in predicting the outcomes of patients with HCC with or without cirrhosis after hepatectomy. Concerning patients without cirrhosis, we confirmed that the NLR could not predict their prognosis after resection. However, a small NLR was correlated with good prognoses among patients with HCC and cirrhosis. The 1-, 3-, and 5-year DFS and OS rates of the NLR-low group were all obviously superior to those of the NLR-high group. These results support the hypothesis that the preoperative NLR plays an important role in accurately predicting the postoperative outcomes of patients with HCC and cirrhosis, but not those of patients without cirrhosis.

In conclusion, the NLR is an important, accurate, and independent predictive factor for survival among patients with HCC who underwent hepatic resection. Intriguingly, a large NLR was positively correlated with poor outcomes among patients with HCC and cirrhosis, but not among those without cirrhosis. Although the underlying mechanisms are largely unclear, the NLR is worthy of further investigation and utilization for accurately predicting the outcomes of patients with HCC.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-015-0117-5
Cite this article as: Hua YP, Ji F, Fu SJ, *et al*. The preoperative neutrophil-to-lymphocyte ratio predicts the outcomes of patients with hepatocellular carcinoma and cirrhosis after hepatectomy. Oncol Transl Med, 2015, 1: 249–255.