

Retrospective Study

Blood neutrophil-lymphocyte ratio predicts survival after hepatectomy for hepatocellular carcinoma: A propensity score-based analysis

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Abstract

AIM: To investigate whether an elevated preoperative neutrophil-to-lymphocyte ratio (NLR) can predict poor survival in patients with hepatocellular carcinoma (HCC).

METHODS: We retrospectively reviewed 526 patients with HCC who underwent surgery between 2004 and

2011.

RESULTS: Preoperative NLR ≥ 2.81 was an independent predictor of poor disease-free survival (DFS, $P < 0.001$) and overall survival (OS, $P = 0.044$). Compared with patients who showed a preoperative NLR < 2.81 and postoperative increase, patients who showed preoperative NLR ≥ 2.81 and postoperative decrease had worse survival (DFS, $P < 0.001$; OS, $P < 0.001$). Among patients with preoperative NLR ≥ 2.81 , survival was significantly higher among those showing a postoperative decrease in NLR than among those showing an increase (DFS, $P < 0.001$; OS, $P < 0.001$). When elevated, alpha-fetoprotein (AFP) provided no prognostic information, and so preoperative NLR ≥ 2.81 may be a good complementary indicator of poor OS whenever AFP levels are low or high.

CONCLUSION: Preoperative NLR ≥ 2.81 may be an indicator of poor DFS and OS in patients with HCC undergoing surgery. Preoperative NLR ≥ 2.81 may be a good complementary indicator of poor OS when elevated AFP levels provide no prognostic information.

Key words: Blood neutrophil-to-lymphocyte ratio; Hepatocellular carcinoma; Liver resection; Prognosis; Postoperative change in neutrophil-to-lymphocyte ratio

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Core tip: We retrospectively analyzed a relatively large cohort of patients and used propensity score matching to balance out biases related to patient selection. Our results suggest that preoperative neutrophil-to-lymphocyte ratio (NLR) is a significant predictor of poor overall and disease-free survival. We further suggest that postoperative decrease in NLR is associated with poor survival, although only in patients with high preoperative NLR. Finally, we show that preoperative NLR ≥ 2.81 may be a good complementary indicator of poor overall survival when elevated alpha-fetoprotein levels provide no prognostic information.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a devastating malignancy that is the third most frequent cause of cancer-associated mortality worldwide. Hepatectomy and transplantation are considered curative treatments

for HCC, but long-term survival is far from satisfactory due to the high frequency of tumor recurrence^[1,2].

The prognosis of HCC patients who undergo resection varies, as it is dependent on such factors as tumor size, tumor number, vascular invasion, and tumor capsule, but these factors can only be assessed after surgery and so cannot be used for preoperative patient selection. One potential preoperative prognostic indicator is the neutrophil-to-lymphocyte ratio (NLR). This indicator of systemic inflammation is easy and inexpensive to determine^[3-7], and elevated pretreatment NLR has been associated with poor outcome in numerous malignancies, including colon cancer^[4], gastric cancer^[8], HCC^[3], and breast cancer^[6].

Although studies have suggested that an elevated pretreatment NLR may correlate with a poor outcome in patients with HCC^[9-11], other studies failed to detect such a correlation^[12-14]. To gain a clearer picture of the influence of preoperative NLR on survival and recurrence after surgery for HCC, we carried out a retrospective study on propensity score-matched patients.

NLR often changes after hepatic resection in HCC patients, perhaps reflecting the shifting balance between inflammatory activity and immune activity. This raises the question of whether a postoperative change in NLR also serves as a predictor of prognosis after surgery. A study of 189 patients with early stage HCC suggested that a postoperative increase in NLR was associated with poorer overall survival and disease-free survival^[13], but this has yet to be confirmed in larger samples.

The present study retrospectively analyzed a relatively large sample of Chinese patients with HCC in order to assess the usefulness of both preoperative NLR and postoperative change in NLR as prognostic indicators.

MATERIALS AND METHODS

This research was approved by the Ethics Committee of the Tumor Hospital of Guangxi Medical University. Written informed consent was obtained from participating patients.

Patients

All patients who underwent hepatic resection for primary HCC as initial treatment at the Affiliated Tumor Hospital of Guangxi Medical University between May 2004 and September 2011 were considered for inclusion in the study. Patients were diagnosed with primary HCC when two types of imaging technique showed features typical of HCC, or when one imaging technique gave positive findings and the alpha fetoprotein (AFP) level was > 400 ng/mL. Diagnosis of HCC was confirmed by histopathological examination.

Patients were excluded from the study if they underwent transarterial chemoembolization (TACE),

radiofrequency ablation (RFA), percutaneous ethanol injection, or other anti-tumor therapies before hepatic resection. Patients were also excluded if they suffered from preoperative fever.

Baseline clinical characteristics and laboratory results were recovered from the hospital database.

Definition of NLR

NLR was calculated by dividing the neutrophil count by the lymphocyte count. Preoperative NLR was determined within 7 d of surgery, and postoperative NLR was determined at the first follow-up visit in the outpatient department a month after surgery. Postoperative change in NLR was calculated by dividing postoperative NLR by preoperative NLR. The resulting numerical changes were transformed into a binary outcome of postoperative increase in NLR (when the ratio was ≥ 1) or postoperative decrease in NLR (when the ratio was < 1). For certain analyses, patients were divided into groups with low or high preoperative NLR using a cutoff value of 2.81, as reported in the literature^[9,11].

Follow-up visits and outcomes

All patients were followed up 1 mo after liver resection, every subsequent 3 mo during the first postoperative year, and every 6 mo thereafter until 60 mo after surgery or until death. At each follow-up visit, routine blood tests, serum AFP assay, ultrasound and computed tomography (CT), or magnetic resonance imaging (MRI) were performed.

Outcomes were overall survival (OS) and disease-free survival (DFS). DFS was defined as the interval from hepatectomy to imaging-based discovery of tumor relapse. OS was defined as 60 mo for those who survived more than 60 mo and DFS was defined as 60 mo if tumor relapse did not occur within 60 mo.

Propensity score analysis

Since patients were assigned to groups based on a preoperative NLR cut-off rather than randomization, propensity score analysis was used to balance out patient differences related to patient selection for hepatic resection. Propensity scores for all patients were estimated using a logistic regression model, which included all covariates that might have affected patient assignment to a high or low preoperative NLR group, as well as patient survival (Table 1). One-to-one nearest-neighbor matching was performed between high and low preoperative NLR using a 0.1 caliper width^[14]. The resulting score-matched pairs were used in subsequent analyses as indicated.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM, United States). Intergroup differences in categorical data were assessed for significance using χ^2 test, while intergroup differences in continuous

data were assessed using the Mann-Whitney *U* test or *t* test. OS and DFS were analyzed using the Kaplan-Meier approach, and differences were assessed for significance using the log-rank test. Independent prognostic factors were identified using the Cox proportional hazards model. $P < 0.05$ served as the threshold of significance.

RESULTS

Study population

Between May 2004 and September 2011, 858 patients underwent hepatectomy for HCC at the Affiliated Tumor Hospital of Guangxi Medical University. Of these, 332 (38.7%) were excluded from our study because they (1) received initial HCC treatment at other centers ($n = 288$, 33.5%); (2) had already undergone RFA, TACE, percutaneous ethanol injection, or another pre-resection procedure ($n = 24$, 2.8%); or (3) suffered from preoperative fever ($n = 20$, 2.3%).

Ultimately, 526 patients (61.5%) were enrolled in the study, of whom 452 (85.9%) received curative hepatectomy. The remaining 74 patients (14.1%) received hepatectomy that was considered palliative because they had macroscopic vessel invasion^[15].

Clinicopathological characteristics

Of the 526 patients, 125 (23.8%) had NLR levels higher than the cut-off value and were included in the high NLR group, while the remaining 401 (76.2%) were included in the low NLR group. The two groups were balanced in terms of gender, age, Edmondson grade, surgical margin, Child-Pugh class, and tumor number, as well as levels of albumin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (all $P > 0.05$; Table 1). However, the two groups were unbalanced in terms of the presence of hepatitis B surface antigen (HbsAg), liver cirrhosis, tumor capsule, and vascular invasion; levels of AFP, platelets, and total bilirubin; Barcelona Clinic Liver Cancer (BCLC) stage; and tumor size (all $P < 0.05$; Table 1). Propensity score matching was used to generate 111 pairs of patients from the two groups, who showed no significant differences (Table 1).

Survival among all patients and propensity-matched pairs

Among all patients in the study, DFS was 55.4% at 1 year, 37.3% at 3 years, and 19.6% at 5 years. The corresponding OS rates were 78.2%, 57.9%, and 35.6%, respectively. Among propensity-matched pairs of patients, DFS was significantly higher in the low-NLR group than in the high-NLR group at 1, 3, and 5 years (Figure 1A). Similar results were obtained for OS (Figure 1B).

Risk factors for prognosis after hepatectomy

Among all patients in the study, univariate analysis

Table 1 Clinicopathological variables in Chinese patients with hepatocellular carcinoma treated by hepatic resection

Variable	Before propensity matching			After propensity matching		
	NLR < 2.81	NLR ≥ 2.81	P value	NLR < 2.81	NLR ≥ 2.81	P value
	n = 401	n = 125		n = 111	n = 111	
Gender, M/F	358/43	107/18	0.262	94/17	97/14	0.561
Age (yr)	46.8 ± 10.9	47.9 ± 11.5	0.309	46.1 ± 11.6	47.2 ± 11.2	0.487
HbsAg						
Negative	50	25	0.041	18	19	0.857
Positive	351	100		93	92	
Liver cirrhosis						
Yes	338	94	0.023	85	86	0.873
No	63	31		26	25	
AFP (ng/mL)						
< 400	268	70	0.032	67	67	1.000
≥ 400	133	55		44	44	
Edmonson grade						
I - II	238	84	0.166	71	71	1.000
III-IV	163	41		40	40	
Surgical margin (cm)						
< 1	195	51	0.126	48	50	0.787
≥ 1	206	74		63	61	
BCLC stage						
0 or A	180	69	0.044	53	57	0.591
B or C	221	56		58	54	
Child-Pugh class						
A	385	117	0.260	105	105	1.000
B	16	8		6	6	
Tumor number						
Single	293	86	0.363	75	79	0.560
Multiple	108	39		36	32	
Tumor size (cm)	6 (4-8)	8 (5.5-12)	< 0.001	7.5 (6-11)	8 (5-12)	0.769
Tumor capsule						
Complete	181	40	0.010	33	39	0.390
Incomplete	220	85		78	72	
Vascular invasion						
Absent	354	98	0.008	91	91	1.000
Present	47	27		20	20	
Albumin (g/L)	40.1 ± 4.4	39.8 ± 4.1	0.399	40.3 ± 5.1	39.9 ± 4.2	0.583
Platelet count (10 ⁹ /L)	180.6 ± 76.6	202.1 ± 84.7	0.008	206.5 ± 82.6	200.91 ± 85.73	0.624
AST (U/L)	41 (36-60)	49 (37-67.5)	0.371	47 (31-70)	49 (37-70)	0.138
ALT (U/L)	40 (29-58)	42 (27.5-54)	0.393	37 (26-59)	42 (33-55)	0.400
Total bilirubin (μmol/L)	12 (9-16.8)	14 (9.9-19.5)	0.010	12.3 (9.2-17.4)	14 (9.9-19.4)	0.051

Data are mean ± SD or median (25th-75th interquartile range) unless otherwise indicated. AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBsAg: Hepatitis B surface antigen; NLR: Blood neutrophil-to-lymphocyte ratio.

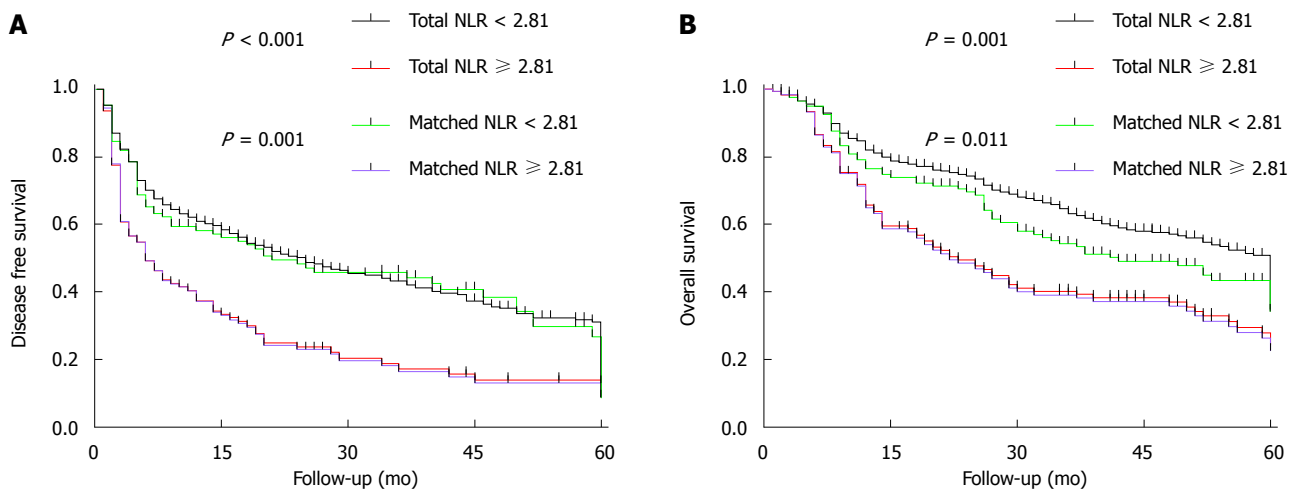


Figure 1 Post-hepatectomy disease-free survival (A) and overall survival (B) of hepatocellular carcinoma patients with high or low neutrophil-to-lymphocyte ratio. Separate curves are shown for the entire cohort ($n = 526$) and the propensity-matched cohort ($n = 222$). NLR: Neutrophil-to-lymphocyte ratio.

Preoperative NLR	Postoperative change in NLR	<i>n</i>	Disease-free survival, mo	<i>P</i> value		
< 2.81	Decrease	227	32.3 ± 1.8	<div><div><div><div><div></div><div><i>P</i> = 0.562</div></div><div><div><div><div></div><div><i>P</i> < 0.001</div></div><div><div><div><div></div><div><i>P</i> < 0.001</div></div><div><div><div><div></div><div><i>P</i> < 0.001</div></div></div></div></div></div></div></div></div></div></div>	<i>P</i> = 0.001	<div><div><div><div></div><div><i>P</i> < 0.001</div></div></div></div>
< 2.81	Increase	124	33.7 ± 2.3			
≥ 2.81	Decrease	92	20.9 ± 2.4			
≥ 2.81	Increase	13	2.9 ± 0.5			
< 2.81	Decrease	227	44.6 ± 1.3	<div><div><div><div><div></div><div><i>P</i> = 0.173</div></div><div><div><div><div></div><div><i>P</i> < 0.001</div></div><div><div><div><div></div><div><i>P</i> < 0.001</div></div></div></div></div></div></div></div></div>	<i>P</i> = 0.013	<div><div><div><div></div><div><i>P</i> < 0.001</div></div></div></div>
< 2.81	Increase	124	47.7 ± 1.6			
≥ 2.81	Decrease	92	37.1 ± 2.3			
≥ 2.81	Increase	13	10.6 ± 2.6			

Figure 2 Comparison of survival of Chinese patients with hepatocellular carcinoma, stratified by preoperative neutrophil-to-lymphocyte ratio and postoperative change in neutrophil-to-lymphocyte ratio. NLR: Neutrophil-to-lymphocyte ratio.

Table 2 Multivariate analysis to identify factors predicting poor overall survival and disease-free survival in Chinese patients with hepatocellular carcinoma after hepatectomy

Factor	HR	95%CI	P value
Disease-free survival			
AFP > 400 ng/mL	1.493	1.062-2.100	< 0.001
Multiple tumors	1.766	1.385-2.252	< 0.001
Tumor size ≥ 5 cm	1.313	1.018-1.693	0.036
Vascular invasion	2.656	1.962-3.594	< 0.001
NLR ≥ 2.81	1.610	1.250-2.075	< 0.001
Overall survival outcome			
Multiple tumors	1.649	1.257-2.16	< 0.001
Tumor size ≥ 5 cm	1.912	1.407-2.59	< 0.001
Incomplete tumor capsule	1.480	1.139-1.92	0.003
Vascular invasion	2.239	1.496-3.350	< 0.001
NLR ≥ 2.81	1.333	1.007-1.76	0.044

Calculated over all patients in the study ($n = 526$). AFP: Alpha-fetoprotein.

identified several factors significantly associated with poor DFS: AFP ≥ 400 ng/mL, Edmondson grade III-IV, surgical margin < 1 cm, multiple tumors, tumor size ≥ 5 cm, incomplete tumor capsule, vascular invasion, preoperative NLR ≥ 2.81, AST ≥ 80 U/L, and BCLC stage B or C. With the exception of AFP level, all of the aforementioned factors were also found to be significantly associated with poor OS.

Multivariate analysis (Table 2) identified the following independent predictors of poor DFS: AFP ≥ 400 ng/mL, multiple tumors, tumor size ≥ 5 cm, vascular invasion, and preoperative NLR ≥ 2.81. Excluding AFP level, all of these factors were also found to be independent predictors of poor OS.

Postoperative change in NLR as possible prognostic factor

In the complete cohort of 526 patients, postoperative NLR data were available for 456 (86.7%). These fell into the following four subgroups (Figure 2): 227 patients (49.8%) who had a preoperative NLR < 2.81

and showed a postoperative decrease in NLR; 124 (27.2%) who had a preoperative NLR < 2.81 and showed a postoperative increase in NLR; 92 (20.2%) with preoperative NLR ≥ 2.81 and a postoperative decrease in NLR; and 13 (2.9%) with NLR ≥ 2.81 and a postoperative increase in NLR.

Compared with the patients who show preoperative NLR < 2.81 and postoperative increase, the patients who show preoperative NLR ≥ 2.81 and postoperative decrease have worse survival (DFS, $P < 0.001$; OS, $P < 0.001$; Figure 2). Among patients with preoperative NLR ≥ 2.81, survival was significantly higher for those showing a postoperative decrease in NLR than for those showing a postoperative increase (DFS, $P < 0.001$; OS, $P < 0.001$; Figure 2).

Prognostic value of preoperative NLR based on AFP levels

Since univariate analysis identified preoperative AFP ≥ 400 ng/mL as a predictor of poor DFS but not OS, we wanted to examine whether the prognostic value of preoperative NLR varied with AFP level. Analysis of patient subgroups with AFP levels of 200, 400 ng/mL showed that, when elevated, AFP levels provide no prognostic information and that preoperative NLR ≥ 2.81 may be a complementary indicator of poor OS whenever alpha-fetoprotein (AFP) levels are low or high (Figure 3).

DISCUSSION

The present retrospective study with a relatively large cohort of Chinese HCC patients suggests that elevated preoperative NLR is associated with poor OS and DFS, and that a postoperative increase in NLR is associated with poor survival. This result may not only assist surgeons in predicting HCC patient survival before and after surgery, but also act to remind the surgeon to perform timely adjuvant treatment to improve the

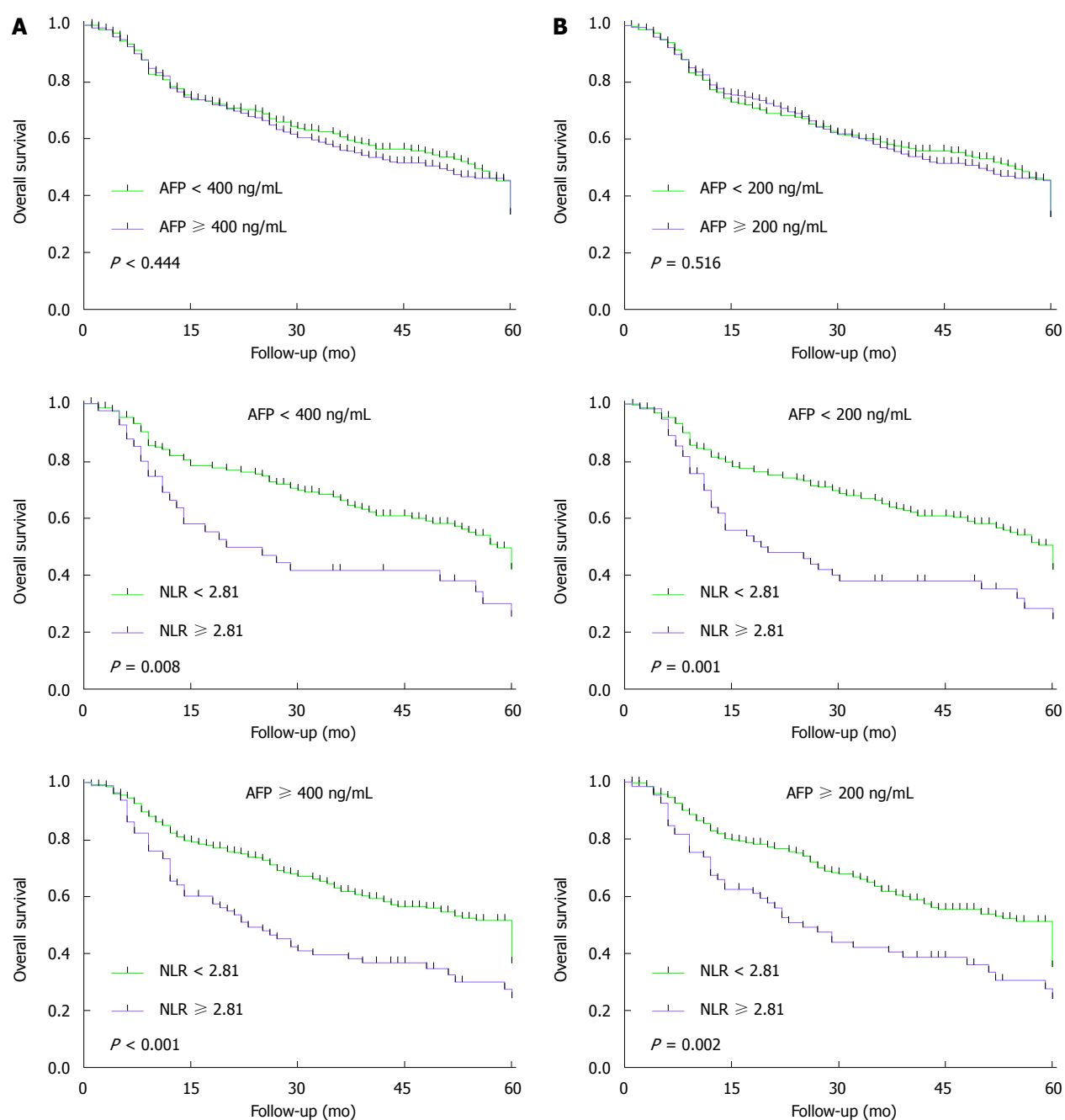


Figure 3 Comparison of overall survival of hepatocellular carcinoma patients stratified based on preoperative alpha-fetoprotein level and on high or low preoperative neutrophil-to-lymphocyte ratio. Patients were grouped using alpha-fetoprotein cut-off values of 400 ng/mL (A), 200 ng/mL (B). Results are shown only for the entire cohort ($n = 526$). NLR: Neutrophil-to-lymphocyte ratio.

prognosis of patients with preoperative NLR ≥ 2.81 .

In our cohort, elevated serum AFP levels were not significant predictors of poor OS after resection: OS did not vary significantly with preoperative AFP levels of 200, 400 ng/mL. AFP remains controversial as a predictor of HCC patient survival after resection; while some studies have associated elevated serum AFP levels with poor prognosis^[11,16-18], others have failed to find such an association^[10,13,15,19]. Our results suggest that, when elevated AFP levels provide no prognostic information, preoperative NLR ≥ 2.81 may be a complementary indicator of poor OS whenever AFP

levels are low or high.

Why elevated NLR and postoperative NLR increase should predict poor survival remains unclear, but some studies have proposed explanations. One such explanation is that many patients with elevated NLR have lymphocytopenia, which may contribute to a weak lymphocyte-mediated immune response to tumors^[20]. This lymphocyte-mediated response normally aids in the elimination of abnormal cells and in the production of cytokines that inhibit tumor proliferation, invasion, and metastasis^[21]. Another possible explanation is that elevated NLR reflects a stronger neutrophil response

and higher numbers of peripheral neutrophils, leading to higher secretion of pro-angiogenic factors such as interleukin-8^[22], vascular endothelial growth factor (VEGF)^[23,24], and matrix metalloproteinase (MMP)^[25,26], which may contribute to tumor growth and therefore to poor prognosis. Studies have indicated that a postoperative NLR increase may reflect that the body has not recovered from tumor control after surgery^[27], potentially leading to worse survival.

The findings of the present study should be interpreted with caution in light of several limitations. First, this study is retrospective and based on patients at a single institution. Indeed, more than 85% of our cohort was chronically infected with hepatitis B virus, which is not the case in other parts of the world. Secondly, the cut-off value of NLR was obtained from published papers^[9,11]. Thirdly, owing to the distribution of HCC patients, the number of patients who showed preoperative NLR ≥ 2.81 and postoperative increase was more than 10 times less than others, which may have led to variance in the results.

In conclusion, our results suggest that both preoperative NLR and postoperative change in NLR are predictors of OS and DFS in HCC patients undergoing hepatic surgery. Elevated NLR may be a complementary, or even an alternative, biomarker of survival when elevated AFP levels prove uninformative.

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COMMENTS

Background

An elevated preoperative neutrophil-to-lymphocyte ratio (NLR) may predict poor survival in patients with hepatocellular carcinoma (HCC), but this requires confirmation.

Research frontiers

The prognosis of HCC patients who undergo resection depends on factors such as tumor size and number, vascular invasion, and tumor capsule, but these factors can only be assessed after surgery and so cannot be used for preoperative patient selection. One potential preoperative prognostic indicator is the neutrophil-to-lymphocyte ratio. This indicator of systemic inflammation is easy and inexpensive to determine.

Innovations and breakthroughs

The authors retrospectively analyzed a relatively large cohort of patients and used propensity score matching to balance out biases related to patient selection in order to investigate the impact of preoperative NLR and postoperative NLR on survival. This study will provide more evidence for NLR after curative resection of HCC in the future.

Applications

Preoperative NLR ≥ 2.81 may be an indicator of poor DFS and OS in patients with HCC undergoing surgery. Preoperative NLR ≥ 2.81 may be a good complementary indicator of poor OS when elevated AFP levels provide no prognostic information.

Terminology

NLR was calculated by dividing the neutrophil count by the lymphocyte count. Postoperative change in NLR was calculated by dividing postoperative NLR by preoperative NLR. The resulting numerical changes were transformed into a binary outcome of postoperative increase in NLR (when the ratio was ≥ 1) or postoperative decrease in NLR (when the ratio was < 1).

Peer-review

This is an interesting manuscript that shows the benefit of using an easily available tool for prognosis after resection for HCC.

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