

## Original Article

# Preoperative Nutritional Risk Index to predict postoperative survival time in primary liver cancer patients

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**Background and Objectives:** We designed this study to determine the predictive value of Nutritional Risk Index (NRI) for postoperative survival time of patients who had undergone hepatectomy for primary liver cancer.

**Methods and Study Design:** The 620 patients who underwent hepatectomy for primary liver cancer (PLC) in the Department of Hepatobiliary Surgery, Cancer Hospital of Henan Province, Zhengzhou, China from December 1, 2008 to December 1, 2012 were followed up. A nutritional risk index (NRI) was used to screen the patients with malnutrition (NRI  $\leq 100$ ). At the same time, the prognosis and survival of the patients were recorded. Kaplan-Meier curve with log-rank test was used to analyze the relationship between malnutrition and prognosis of the subjects. Also the postoperative survival time and its influencing factors were analyzed by Cox proportional hazards model. **Results:** The cumulative survival probability at 1, 3, and 5 years of the 620 subjects was 49%, 33% and 29% respectively. Kaplan-Meier analysis with log-rank test showed that non-malnourished (NRI values  $>100$ ) patients had longer postoperative survival time compared with malnourished patients. NRI values  $>100$  was significantly associated with longer postoperative survival time. Cox proportional hazards model showed that NRI was an independent predictor of postoperative survival time and that NRI varied inversely with the risk of death.

**Conclusion:** The patients with NRI values  $>100$  survived longer than those with NRI values  $\leq 100$ .

**Key Words:** Nutritional Risk Index, postoperative survival time, weight loss, primary liver cancer, hepatectomy

## INTRODUCTION

Malnutrition is a common finding and an important risk factor for increasing postoperative morbidity and mortality in patients with a variety of diseases, such as trauma, cancer, obstructive jaundice, and cirrhosis.<sup>1-5</sup> At the time of admission, approximately 20% to 50% of hospitalized patients are suffering from malnutrition.<sup>5-8</sup> How the problem of hospital-related malnutrition should be ameliorated has not been adequately addressed.<sup>5,9,10</sup>

PLC is the fifth most common cancer in the world, and the fourth most common cause of cancer mortality.<sup>11</sup> Chronic viral hepatitis plays a very substantial role in causing PLC, whereas nutritional status and specific nutritional factors may modify the disease risk. Although malnutrition is a well-recognized risk factor for patients undergoing surgery, its prevalence and severity is often underestimated.<sup>12</sup> Nutritional risk assessment is essential to guide surgeons before doing an operation. A previous study showed that the survival of patients after orthotopic liver transplantation (OLT) for primary liver malignancy is significantly lower than in patients with non-malignant diseases.<sup>13</sup> Therefore, a proper assessment of nutritional

status in PLC surgery patients is highly desired. There are two methods of assessing the nutritional status: the nutrition risk score (NRS) and the NRI.<sup>12</sup> NRI is based on albumin and weight loss,<sup>14-16</sup> which are not affected by subjective factors, and therefore is better than NRS for identifying patients at nutritional risk.<sup>3</sup> Using a specific NRI may increase long-term survival in PLC patients undergoing hepatic resection.

Therefore, the purpose of this study was to assess the association between preoperative NRI and their postoperative survival time in patients undergoing hepatectomy for PLC.

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## METHODS

### Subjects

The participants were the consecutive patients presenting in the Department of Hepatobiliary Surgery, Henan Cancer Hospital, Zhengzhou University, and Zhengzhou, China from December 1, 2008 to December 1, 2012. Of the 938 patients who presented, 151 were diagnosed as non-PLC, 99 did not undergo a hepatectomy, and 68 refused to participate in the study. A total of 620 patients remained eligible for the study. Incidence of the disease was based on the discharge diagnosis. All the study's participants met the following inclusion criteria: (1) aged 16 years old or older; (2) PLC patients with hepatectomy; (2) conscious, able to stand and answer questions. The exclusion criteria were: (1) presence of hepatic encephalopathy; (2) suffering from severe diseases that made it difficult for the investigators to evaluate their physical status; (3) presence of severe renal insufficiency; (4) presence of malnutrition that resulted from other disease; (5) being uncooperative. The study design was approved by the ethical committee of Zhengzhou University. Written informed consent was obtained from all patients.

### Nutritional risk assessment by NRI

The basic variables and clinical variables were obtained by review of medical records at the time of the participants' first admission. The survival time was obtained by face-to-face consultations or telephone questionnaires. NRI, which was based on the serum albumin concentration and weight loss, was calculated within 1 week before the hepatectomy operation. The formula used for calculation was:

$$\text{NRI} = (1.519 \times \text{serum albumin, g/L}) + 41.7 \text{ (present weight/usual weight)}$$

NRI values <83.5 indicated high nutritional risk, NRI values between 83.5-97.5 indicated medium nutritional risk, NRI values between 97.5-100 indicated low nutritional risk; and NRI values >100 indicated no nutritional risk.<sup>14,15</sup>

### Follow-up

The primary endpoint was PLC mortality. For participants who continued to be seen at the Henan Cancer Hospital, Zhengzhou University, data were obtained at the time of the hospital visit. For the remaining participants, information was collected by means of a telephone questionnaire that was answered by either the participants or a close surviving relative. Participants were followed up at 3 months intervals in the first year after discharge from the hospital, 6 months intervals during the 1 to 3 years after discharge from the hospital, and 1 year intervals during the 3 to 5 years after discharge from the hospital.

### Statistical methods

Continuous variables were summarized as mean  $\pm$  standard deviation (mean $\pm$ SD) and categorical variables were summarized as frequencies and percentages. The sample size was indicated only where data was missing.

The statistical significance of differences was examined by using analysis of variance (ANOVA) (continuous variables including age, lymphocyte count, and maximal diameter of tumour), the chi-square test (categorical vari-

ables including sex, ascites, cirrhosis, and recurrence within 2 years), the trend of chi-square test (ordinal variables including tumour number, Barcelona Clinic Liver Cancer (BCLC), Child-Pugh grade and  $\alpha$ -fetoprotein (AFP)). The Kaplan-Meier analysis with log-rank test was used to analyze the PLC prognosis and survival time. The multivariable analysis was carried out by using Cox regression, and  $p < 0.05$  was considered to be the significant level.

## RESULTS

### Characteristics of participants

The baseline characteristics of the participants were following: 495 participants (79.8%) were men, 125 participants (20.2%) were women, the mean age was 53.8 $\pm$ 10.6 years (range: 28-80 y); 15 participants (2.4%) had high nutritional risks, 171 patients (27.5%) had medium nutritional risks, 62 subjects (10.0%) had low nutritional risks, and 372 participants (59.9%) had no nutritional risks (Table 1).

By 22 February, 2014, 559 participants had been followed up. 61 patients were lost to follow-up, so the follow-up rate was 90.2%. The mean and median survival times were 12 months and 23 months, respectively. The cumulative survival probabilities at 1, 3, and 5 years of the 620 participants were 49%, 33%, and 29%, respectively.

### Medical variables by NRI category

The chi-square test showed that NRI was associated with ascites and cirrhosis ( $p < 0.05$ ) but not sex ( $p = 0.092$ ) or recurrence within 2 years ( $p = 0.411$ ). ANOVA showed that lymphocyte count, and maximal diameter of tumour differed between NRI categories ( $p < 0.05$ ) regardless of age ( $p = 0.058$ , Table 2). The trend of chi-square test showed that Child-Pugh grade and BCLC differed between NRI categories, but tumour number and AFP did not (Table 2).

### Univariate analysis for PLC prognosis by Kaplan-Meier analysis with log-rank test

The Kaplan-Meier analysis with log-rank test was employed to analyze the prognosis of PLC and survival time, and this analysis showed that the cumulative survival probabilities at 1, 3, and 5 years of patients whose NRI values <83.5 were 43%, 26%, and 0%, respectively, NRI values 83.5 to  $\leq 97.5$  were 37%, 19%, and 17%, respectively, NRI values 97.5 to  $\leq 100$  were 34%, 22%, and 0, respectively; and NRI values > 100 were 58%, 42%, and 38%, respectively. The overall survival curves after surgery differed between NRI categories ( $p < 0.05$ , log-rank test). The Kaplan-Meier analysis with log-rank test also showed that, ascites, cirrhosis, lymphocyte count, recurrence within 2 years, tumour size, Child-Pugh grade, BCLC, AFP and tumour number showed differences regardless of categorizing by sex, age, cirrhosis, or types of virus (Table 2).

The Kaplan-Meier analysis with log-rank test showed that survival differed between the 4 NRI categories (Figure 1) ( $p < 0.05$ , Figure 1). There was no difference in survival between the three malnourished risk categories ( $p = 0.856$ , Figure 2). However survival did differ between

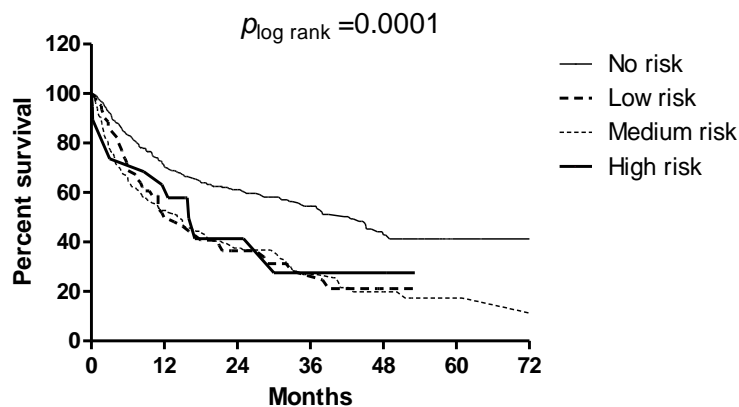
**Table 1.** Characteristics of the participants by NRI category

Variable	Total (n=620)	NRI category				p
		<83.5 (n=15)	83.5 to ≤97.5 (n=171)	97.5 to ≤100 (n=62)	>100 (n=372)	
Sex						0.092 <sup>†</sup>
Men	495	14 (2.8%)	128 (25.9%)	54 (10.9%)	299 (60.4%)	
Women	125	1 (0.8%)	43 (34.4%)	8 (6.4%)	73 (58.4%)	
Mean age (yr)	53.8±10.6	54.2±15.9	55.7±10.6	53.8±10.2	52.9±10.3	0.058 <sup>‡</sup>
Lymphocyte count (10 <sup>9</sup> /L)	1.4±0.6	1.3±0.5	1.3±0.6	1.3±0.6	1.5±0.6	0.001 <sup>‡</sup>
Maximal diameter of tumour (cm)	8.4±5.2	7.8±3.3	9.6±5.7	7.9±3.6	8.0±5.2	0.013 <sup>‡</sup>
Ascites						<0.001 <sup>†</sup>
Yes	68	2 (0.3%)	34 (5.6%)	8 (1.6%)	24 (3.9%)	
No	543	13 (2.1%)	136 (22.3%)	53 (8.7%)	341 (55.8%)	
Cirrhosis						0.001 <sup>†</sup>
Yes	541	13 (2.1%)	158 (25.5%)	59 (9.5%)	311 (50.2%)	
No	72	1 (0.2%)	11 (1.8%)	3 (0.5%)	57 (9.2%)	
Recurrence within 2 years						0.411 <sup>†</sup>
Yes	232	3 (0.5%)	60 (9.7%)	23 (3.7%)	146 (23.5%)	
No	388	12 (1.9%)	111 (17.9%)	39 (6.3%)	226 (36.5%)	
Tumour number						0.537 <sup>§</sup>
1	453	11 (2.4%)	126 (27.8%)	37 (8.2%)	279 (61.6%)	
1 to ≤3	90	3 (3.3%)	23 (25.6%)	14 (15.6%)	50 (55.6%)	
>3	77	1 (1.3%)	22 (28.6%)	11 (14.3%)	43 (55.8%)	
BCLC						<0.001 <sup>§</sup>
A	335	4 (1.2%)	68 (20.3%)	35 (10.4%)	228 (68.1%)	
B	88	1 (1.1%)	19 (21.6%)	13 (14.8%)	55 (62.5%)	
C	197	10 (5.1%)	84 (42.6%)	14 (7.1%)	89 (45.2%)	
Child-Pugh grade						<0.001 <sup>§</sup>
A	554	6 (1.1%)	133 (24.0%)	59 (10.6%)	356 (64.3%)	
B	66	9 (13.6%)	38 (57.7%)	3 (4.5%)	16 (24.2%)	
AFP (ug/L)						0.064 <sup>§</sup>
≤20	199	6 (3.0%)	42 (21.1%)	15 (7.6%)	136 (68.3%)	
20-400	146	4 (2.7%)	41 (28.1%)	22 (15.1%)	79 (54.1%)	
≥400	275	5 (1.8%)	88 (32.0%)	25 (9.1%)	157 (57.1%)	

<sup>†</sup>Frequency data (sex, ascites, cirrhosis, and recurrence within 2 years) were compared by using chi-square test.

<sup>‡</sup>Continuous data (mean age, lymphocyte count, and maximal diameter of tumour) were compared by ANOVA.

<sup>§</sup>The ordinal variables (tumour number, BCLC, Child-Pugh grade and AFP) were compared by using trend chi-square test.



**Figure 1.** Survival curves for 4 NRI categories. The categories were: no nutritional risk (NRI >100, n=372), low nutritional risk (NRI 97.5 to ≤100, n=62) medium nutritional risk (NRI 83.5 to ≤97.5, n=171) and high nutritional risk (NRI <83.5, n=15).

malnourished and non-malnourished participants (Figure 3).

#### The multivariable analysis with Cox regression

Multivariable analysis with Cox proportional-hazards model showed that NRI, lymphocyte count, tumor number, and tumor size were all independent predictors of survival (Table 3). In particular, participants without preoperative malnutrition (NRI values >100) survived longer

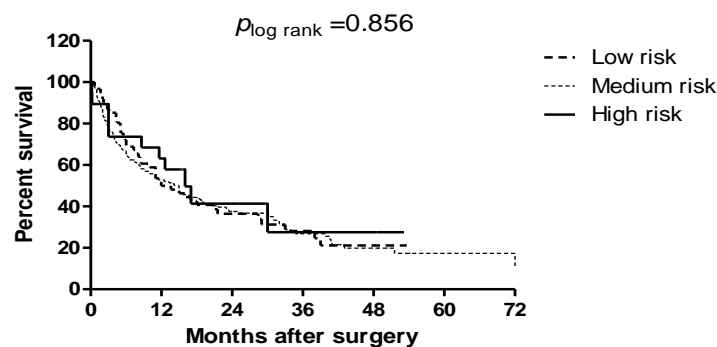
than those with preoperative malnutrition (NRI values ≤100).

#### DISCUSSION

Assessing the risk of death or morbidity related to malnutrition at an early stage during the hospital stay has a crucial impact on surgical practice.<sup>3</sup> Cross et al found that malnutrition can increase the risk of surgical site infection and that preoperative nutrition assessment may reduce the

**Table 2.** Univariate analysis for PLC prognosis

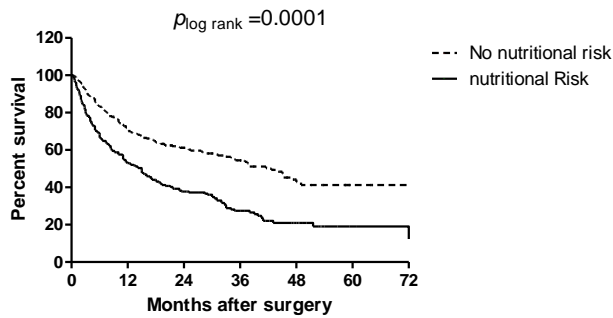
Variable	Total (n=620)	Cumulative survival probability (%)			Median survival time (month)	<i>p</i> (log-rank)
		1-yr	3-yr	5-yr		
Sex						0.069
Male	495	49	33	28	23.0	
Female	125	50	33	33	23.5	
Age						0.551
<60	447	50	36	35	24.3	
≥60	173	48	25	18	22.1	
Lymphocyte count (10 <sup>9</sup> /L)						<0.001
<0.8	150	33	18	0	10.9	
≥0.8	470	54	36	32	28.9	
Tumour size (cm)						<0.001
≤5	200	68	47	43	45.1	
>5	420	40	26	22	15.0	
Ascites						0.012
Yes	68	35	23	0	14.4	
No	543	51	34	30	26.0	
Cirrhosis						0.579
Yes	541	50	33	29	24.1	
No	72	43	31	31	15.3	
Recurrence within 2 years						0.003
Yes	232	51	31	21	24.9	
No	388	48	34	34	21.1	
Tumour number						<0.001
1	453	54	38	35	30.5	
1 to ≤3	90	41	19	19	18.3	
>3	77	30	19	0	9.2	
BCLC						<0.001
A	335	58	39	37	35.4	
B	88	32	13	0	10.7	
C	197	41	30	28	15.9	
Child-Pugh grade						0.001
A	554	51	34	30	25.1	
B	66	32	18	0	12.6	
AFP (ug/L)						<0.001
≤20	199	61	41	38	37.0	
20-400	146	52	34	29	29.2	
≥400	275	38	27	23	14.0	
NRI category						<0.001
<83.5	15	43	26	0	19.0	
83.5 to ≤97.5	171	37	19	17	13.5	
97.5 to ≤100	62	34	22	0	11.3	
>100	372	58	42	38	38.4	
Total	620	49	33	29	23.1	

**Figure 2.** Survival curves for 3 malnourished categories. The categories were: low nutritional risk (NRI 97.5 to ≤100, n=62) medium nutritional risk (NRI 83.5 to ≤97.5, n=171) and high nutritional risk (NRI <83.5, n=15).

risk of postoperative complications, including infection.<sup>17</sup> Rhoads et al demonstrated that protein deficiency lowers defenses against certain infections and, in addition, the incidence of infection during postoperative complications is associated with serum protein levels.<sup>18</sup> The present study indicates that NRI can be used to identify the pa-

tients who are at risk of nutritionally related postoperative complications and death.<sup>19</sup> NRI may be an important risk predictor for patients with hepatectomy for PLC.

In this study, the ANOVA analysis showed that albumin, maximal diameter of tumour and lymphocyte count were all useful in identifying malnutrition in patients un-



**Figure 3.** Survival curves for participants with no nutritional risk (NRI >100, n=372) and nutritional risk (NRI ≤100, n=248).

**Table 3.** The multivariable analysis with cox regression

Prognostic factor	RR	95% CI		p
		Lower	Upper	
Tumour size	1.05	1.03	1.07	<0.001
Tumour number	1.27	1.16	1.40	<0.001
Lymphocyte count	0.703	0.567	0.872	0.001
NRI category	0.976	0.965	0.987	<0.001

dergoing hepatectomy for PLC. In contrast, age did not reach statistical significance (Table 2), which was consistent with the study of Clugston et al.<sup>20</sup> Also the trend of chi-square test showed that there were significant differences across NRI category for tumour number, BCLC, AFP and Child-Pugh grade (Table 2).

We also found an association between low albumin and increased mortality in hospital patients that was consistent with previous findings.<sup>13,21,22</sup> In our study, the Kaplan-Meier analysis with log-rank test revealed that the lower the NRI, the greater the probability of death.

Previous studies reported that NRI values <83.5 was associated with mortality in patients with obstructive jaundice.<sup>20,23,24</sup> The present study found that patients without malnutrition (NRI values >100) had significantly longer postoperative survival time compared with those with malnutrition (NRI values ≤100), but did not find the significant difference among the survival time of the patients in the lower three NRI categories (NRI <83.5, 83.5 to ≤97.5, and 97.5 to ≤100). Therefore, we recommend that surgeons should not only be concerned about nutritional risk for poor outcome in PLC patients with NRI values <83.5, but also be concerned about patients with NRI values between 83.5 and 100.

A limitation of this study was that we only gave all these subjects preoperative nutrition assessments, but we did not consider appropriate nutritional support to optimize nutritional parameters, including normalization of albumin and safe weight loss. In subsequent research, the survival of malnourished patients (NRI values ≤100) given appropriate nutritional supports should be studied.

### Conclusion

NRI is a useful tool to assess nutritional status and may be a significant predictor for postoperative survival time in patients undergoing hepatectomy for PLC. Patients without preoperative malnutrition (NRI values >100) sur-

vive longer than those with preoperative malnutrition (NRI values ≤100).

### AUTHOR DISCLOSURES

All authors have no conflicts of interest to declare. This work is supported by National Natural Science of China (81372679), the National S&T Major Project “the 11th Five-Year” issue for the prevention and control of AIDS and viral hepatitis and other major infectious diseases (2008ZX10002-012).

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## Original Article

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## 术前营养风险指数对原发性肝癌患者术后生存时间的预测

**背景与目的：**探讨术前营养风险指数（Nutritional Risk Index NRI）对原发性肝癌肝切除术患者术后生存时间的预测。**方法与研究设计：**收集河南省肿瘤医院肝胆外科2008年12月1日到2012年12月1日期间的620例原发性肝癌经手术治疗的患者，并对其进行随访。运用NRI筛选营养不良患者（NRI≤100），并记录病人的预后和生存状况。运用Kaplan-Meier和log-rank检验分析患者营养不良和预后的关系。同时采用Cox比例风险模型分析术后生存时间的影响因素。**结果：**620名患者第1、3和5年累积生存概率分别为49%、33%和29%。Kaplan-Meier和log-rank检验分析表明：与营养不良患者相比，非营养不良（NRI>100）患者术后存活时间更长。NRI>100与较长的术后生存时间显著相关。Cox比例风险模型显示：NRI是患者术后生存时间的独立预测因素，随着NRI的降低，患者的死亡风险升高。**结论：**NRI>100的患者术后生存时间长于NRI≤100的患者。

**关键词：**营养风险指数、术后生存时间、体重减少、原发性肝癌、肝切除术