

Prognostic Nomogram for Patients with Primary Liver Cancer Combining Hematological Biomarkers and Clinical Characteristics

Chen Chuang¹, Wenxia Qiu², Farra Aidah Jumuddin^{3*}

^{1,3}Lincoln University College, Malaysia

²The Affiliated TCM Hospital of Guangzhou Medical University, China

*corresponding author

ABSTRACT:

Introduction: This research aims to establish and validate a prognostic nomogram for assessing overall survival (OS) of Primary Liver Cancer (PLC) patients. **Methods:** Between January 2016 and December 2020, we collected clinical data of 504 patients with primary liver cancer in The Affiliated Tumor Hospital of Guangxi Medical University to do retrospective analysis. These PLC patients were stochastically assigned into two groups: 352 patients in training cohort and 152 patients in validation cohort. In the training cohort, Cox proportional risk models identified independent risk factors for OS, and nomograms were developed to predict one-, three-, and five-year survival. Assessing the performance of nomogram through internal validation in the training cohort, and external validation in the validation cohort using the C-index, receiver operating characteristic (ROC) curves, and calibration curves. Independent samples t-tests were utilized for continuous variables and chi-square or Fisher exact tests were utilized for categorical variables. Univariate and multivariate analyses were performed using Cox proportional risk models. **Results:** This research identified Alanine Aminotransferase (ALT), Neutrophil to Lymphocyte Ratio (NLR), Alpha-Fetoprotein (AFP), Tumor number, Vascular invasion, and Albumin-Bilirubin (ALBI) grade as independent risk factors for predicting OS in PLC patients. The C index was 0.767 (95%CI 0.741-0.792) in the training cohort, and 0.721 (95%CI 0.673-0.768) in the validation cohort. **Conclusions** The nomogram established in this study was effective in predicting the OS in patients with primary liver cancer.

Keywords: Primary Liver Cancer, Prognostic, NLR, ALBI, Nomogram

INTRODUCTION

As the sixth most common cancer and the third leading cause of cancer deaths globally in 2020, PLC poses a heavy burden on society and the family [1]. Assessing the survival period of patients diagnosed with primary liver cancer is vital in clinical practice as it helps in developing optimal treatment plans and improving quality of life and reducing pain for these patients. Numerous researches have established a significant correlation between inflammation and various types of tumors [2]. Two indicators of systemic inflammation, namely NLR and PLR, have been found to be inversely associated with the prognosis of

malignant tumors [3-4]. The NLR, in particular, has gained attention as a potential biomarker for cancer prognosis due to its easy accessibility and the simplicity of calculating the ratio using routine blood cell counts [5]. Additionally, studies have demonstrated a link between the serum gamma-glutamyltransferase (GGT) level and the prognosis of colorectal and other gastrointestinal cancers [6-7]. ALBI has been recognized as an evidence-based and objective method for evaluating liver function in HCC. Different with the traditional Child-Pugh grading system, the ALBI grade eliminates subjective variables such as ascites and encephalopathy. The ALBI score is calculated using a simple equation: $-0.085 \times (\text{albumin [g/L]}) + 0.66 \times \log (\text{total bilirubin } [\mu\text{mol/L}])$. Several studies have demonstrated that the ALBI model is as effective as the Child-Turcotte-Pugh (CTP) scoring system in assessing liver function and predicting the prognosis of primary liver cancer patients[8].

MATERIALS AND METHODS

Study Population

From January 2016 to December 2020, patient cases (n=504) of Primary liver cancer(PLC) were retrospectively analyzed in the Affiliated Tumor Hospital of Guangxi Medical University, Nanning, Guangxi, China. The inclusion criteria follow. 1) The postoperative pathology of patients undergoing surgery or puncture surgery conformed to the PLC diagnosis. No pathological results were found in patients who were confirmed as PLC according to China's 2020 version of PLC diagnosis and treatment standards. 2) The patients were diagnosed for the first time in our hospital and did not receive any form of anti-tumor therapy before seeking treatment. 3) The results and imaging data of confirmed PLC were readily available. The patients who presented with cholangiocarcinoma, mixed liver cancer, or secondary primary tumors other than PLC, and patients who did not attend the follow-up appointments were excluded from the study.

Clinical Data Collection and Follow-Ups

Data collection included pre-treatment parameters within a week: leukocyte, neutrophil, lymphocyte, platelet counts, TBIL, ALB, ALT, AST, GGT, and AFP levels. Follow-up concluded on November 1, 2020. OS was defined from diagnosis to death or last follow-up.

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL) and R software (version 3.1.4; <http://www.Rproject.org>). Hematological biomarker cutoffs were determined using X-tile 3.6.1 software (Yale University, New Haven, CT, USA). Independent samples t-tests were utilized for continuous variables and chi-square or Fisher exact tests were utilized for categorical variables. These PLC patients were stochastically assigned into two groups:352 patients(70%) in training cohort and 152 patients(30%) in validation cohort. In the training queue, Cox regression obtained risk factors through univariate analysis ($P<0.05$), and further

identified risk factors through multivariate analysis ($P < 0.05$). A forward stepwise selection process determined progressive risk factors. Subsequently, nomogram was created for 1-year, 3-year, and 5-year survival rates based on independent risk factors (using the rms package in R). Nomogram dependability was evaluated using C-index and calibration curves in both cohorts. All statistical tests were two-sided, with P values < 0.05 considered significant.

Ethical Statement

The study was approved by the Ethics Committee of the Tumor Hospital of Guangxi Medical University, but informed consent was not required because the study was a retrospective study of anonymized patient data and did not involve the use of human tissue.

RESULTS

Basic Characteristics

The study included 504 patients, split into 352 in the training formation and 152 in the validation formation Table 1 illustrates their baseline characteristics. Notably, in the training group, 16.07% were over 60 years, 87.3% were male, and 74.4% had passed away by the last follow-up. There is a similar trend in the validation queue.

Table 1 Baseline Clinical Characteristics

Variable	Total (n=504)	Training Cohort (n = 352) No. (%)	Validation cohort (n = 152) No. (%)	P
Gender				0.704
Female	64 (12.7)	46 (13.07)	18 (11.84)	
Male	440 (87.3)	306 (86.93)	134 (88.16)	
Age				0.089
≥60	81 (16.07)	63 (17.90)	18 (11.84)	
<60	423 (83.93)	289 (82.10)	134 (88.16)	
HBV				0.642
Yes	439 (87.1)	305 (86.65)	134 (88.16)	
No	65 (12.9)	47 (13.35)	18 (11.84)	
HCV				0.545
Yes	17 (3.37)	13 (3.69)	4 (2.63)	
No	487 (96.63)	339 (96.31)	148 (97.37)	
TBIL				0.854
>21	97 (19.25)	67 (19.03)	30 (19.74)	
≤21	407 (80.75)	285 (80.97)	122 (80.26)	
ALB				0.426
≥35	414 (82.14)	286 (81.25)	128 (84.21)	
<35	90 (17.86)	66 (18.75)	24 (15.79)	
ALT				0.934
>40	270 (53.57)	189 (53.69)	81 (53.29)	
≤40	234 (46.43)	163 (46.31)	71 (46.71)	

Table 1 Baseline Clinical Characteristics

Variable	Total (n=504)	Training Cohort (n = 352) No. (%)	Validation cohort (n = 152) No. (%)	P
AST				0.670
≥40	322 (63.89)	227 (64.49)	95 (62.50)	
≤40	182 (36.11)	125 (35.51)	57 (37.50)	
WBC				0.074
>9.16	71 (14.09)	56 (15.91)	15 (9.87)	
≤9.16	433 (85.91)	296 (84.09)	137 (90.13)	
Neutrophil count				0.175
>7.7	35 (6.94)	28 (7.95)	7 (4.61)	
≤7.7	469 (93.06)	324 (92.05)	145 (95.39)	
Lymphocyte count				0.557
>4	3 (0.6)	3 (0.85)	0 (0.00)	
≤4	501 (99.4)	349 (99.15)	152 (100.00)	
Platelets				0.127
>300	60 (11.9)	47 (13.35)	13 (8.55)	
≤300	444 (88.1)	305 (86.65)	139 (91.45)	
AFP				0.002
≥400	213 (42.26)	133 (37.78)	80 (52.63)	
<400	291 (57.74)	219 (62.22)	72 (47.37)	
Child-Pugh classification				0.074
A	424 (84.13)	291 (82.67)	133 (87.50)	
B	79 (15.67)	61 (17.33)	18 (11.84)	
C	1 (0.2)	0 (0.00)	1 (0.66)	
Tumor number				0.081
1	316 (62.7)	212 (60.23)	104 (68.42)	
≥2	188 (37.3)	140 (39.77)	48 (31.58)	
Tumor maximum diameter				0.677
≤5	371 (73.61)	261 (74.15)	110 (72.37)	
>5	133 (26.39)	91 (25.85)	42 (27.63)	
Vascular invasion				0.522
Yes	251 (49.8)	172 (48.86)	79 (51.97)	
No	253 (50.2)	180 (51.14)	73 (48.03)	
Extra-hepatic metastasis				0.040
Yes	51 (10.12)	42 (11.93)	9 (5.92)	
No	453 (89.88)	310 (88.07)	143 (94.08)	
Cirrhosis				0.417
Yes	352 (69.84)	242 (68.75)	110 (72.37)	
No	152 (30.16)	110 (31.25)	42 (27.63)	

Table 1 Baseline Clinical Characteristics

Variable	Total (n=504)	Training Cohort (n = 352) No. (%)	Validation cohort (n = 152) No. (%)	P
Ascites				0.214
Yes	82 (16.27)	62 (17.61)	20 (13.16)	
No	422 (83.73)	290 (82.39)	132 (86.84)	
NLR				0.543
>2.43	269 (53.37)	191 (54.26)	78 (51.32)	
≤2.43	235 (46.63)	161 (45.74)	74 (48.68)	
PLR				0.890
≥114.57	243 (48.21)	169 (48.01)	74 (48.68)	
<114.57	261 (51.79)	183 (51.99)	78 (51.32)	
GGT				0.825
>71	308 (61.11)	214 (60.80)	94 (61.84)	
≤71	196 (38.89)	138 (39.20)	58 (38.16)	
ALBI				0.549
≤-2.61	239 (47.42)	170 (48.30)	69 (45.39)	
>-2.61	265 (52.58)	182 (51.70)	83 (54.61)	

Analysis of the Training Cohort

Clinical characteristics and hematological parameters of 352 patients in the training cohort were comprehensively analyzed for the 352 patients in the training queue (refer to Table 2). In univariate analysis, a significant association was observed between TBIL, ALB, ALT, AST, WBC, Neut, AFP, Child Pugh, Tumor Count, Vascular Invasion, Metastasis, Ascites, NLR, PLR, GGT, ALBI, and prognosis of primary liver cancer. Subsequent multivariate analyses pointed to ALT, AFP, tumor count, vascular invasion, NLR and ALBI as key prognostic indicators.

Table 2 Univariate and Multivariate Cox Hazards Analysis of Overall Survival in the Training Cohort

Variables	P	HR (95%CI)	P ^a	HR ^a (95%CI)
Gender	0.419	0.86 (0.59 - 1.24)		
Age	0.346	0.86 (0.63 - 1.18)		
HBV	0.519	0.88 (0.60 - 1.30)		
HCV	0.138	0.57 (0.27 - 1.20)		
TBIL	<.001	1.75 (1.31 - 2.34)	0.936	1.01 (0.74 - 1.39)
ALB	<.001	3.22 (2.40 - 4.33)	0.121	1.34 (0.92 - 1.96)
ALT	0.002	1.47 (1.15 - 1.89)	0.036	1.37 (1.02 - 1.85)
AST	<.001	2.26 (1.71 - 2.97)	0.616	1.10 (0.76 - 1.58)
WBC	<.001	1.82 (1.33 - 2.51)	0.273	1.30 (0.82 - 2.06)
Neut	<.001	2.07 (1.36 - 3.15)	0.127	0.62 (0.34 - 1.14)

Variables	P	HR (95%CI)	P ^a	HR ^a (95%CI)
Lym	0.882	0.90 (0.22 - 3.62)		
PLT	0.063	1.39 (0.98 - 1.98)		
AFP	0.001	0.66 (0.51 - 0.85)	0.017	0.72 (0.55 - 0.94)
Child Pugh	<.001	2.10 (1.55 - 2.84)	0.779	1.06 (0.72 - 1.54)
Tumor number	<.001	1.71 (1.34 - 2.19)	0.012	1.42 (1.08 - 1.87)
Tumor diameter	<.001	0.48 (0.35 - 0.65)	0.799	0.95 (0.66 - 1.37)
Vascular invasion	<.001	2.51 (1.95 - 3.23)	<.001	1.67 (1.24 - 2.25)
Metastasis	<.001	2.00 (1.40 - 2.87)	0.708	0.93 (0.62 - 1.38)
Cirrhosis	0.852	1.03 (0.79 - 1.33)		
Ascites	<.001	2.16 (1.59 - 2.91)	0.109	1.34 (0.94 - 1.90)
NLR	<.001	2.17 (1.69 - 2.80)	0.049	1.37 (1.01 - 1.88)
PLR	<.001	1.69 (1.32 - 2.15)	0.591	1.09 (0.80 - 1.49)
GGT	<.001	2.45 (1.88 - 3.20)	0.186	1.25 (0.90 - 1.75)
ALBI	<.001	3.67 (2.83 - 4.75)	<.001	2.63 (1.94 - 3.57)

Nomogram Construction

Based on the multivariate Cox regression analysis, we established a nomogram to forecast the one, three, and five-year OS rates (see Figure 1). The C-index for the training cohort was 0.767 (95%CI: 0.741-0.792), and the calibration curves for the one, three, and five-year OS predictions closely aligned with the standard line (depicted in Figure 2A, B, and C).

Nomogram Validation

Internal validation within the validation cohort revealed a C-index of 0.721 (95%CI: 0.673-0.768). The calibration curves for the one, three, and five-year OS predictions here also showed a strong correlation with the standard line (illustrated in Figure 2D, E, and F).

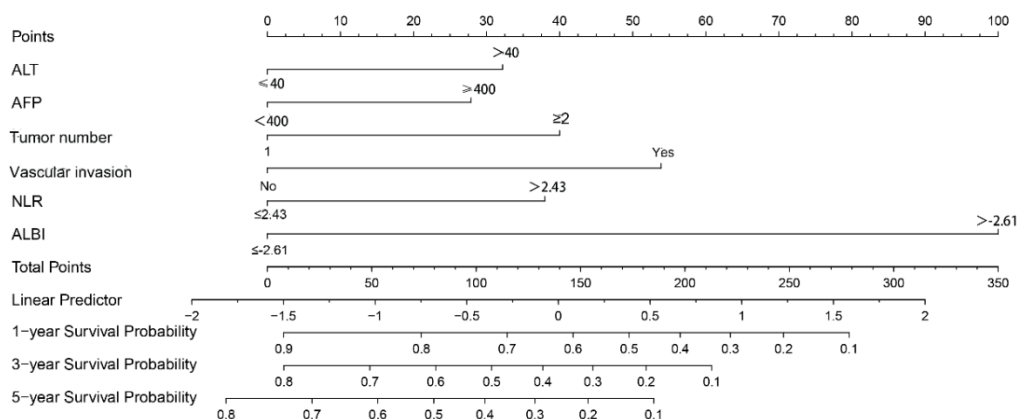


Figure 1 Nomograms for predicting overall survival.

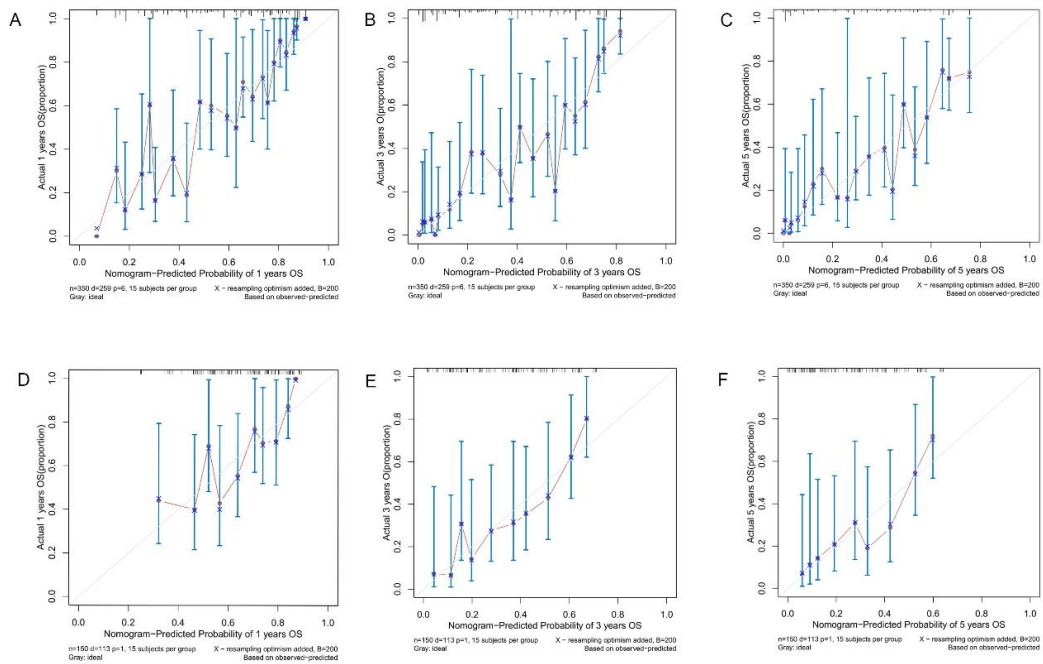


Figure 2 The calibration curves for predicting the one-year and three- and five-year overall survival in the training (A, B, C) and validation (D, E, F) cohorts.

Decision Curve Analysis

Clinical utility of the nomogram, as confirmed in the validation cohort, indicated its efficacy in predicting PLC survival across varied threshold probabilities (Figure 3).

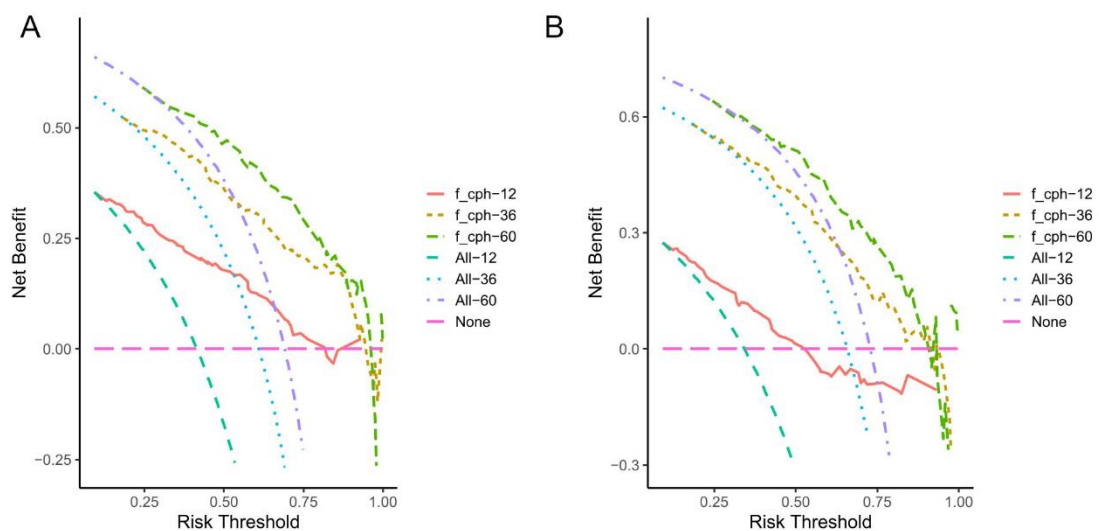


Figure 3 Decision curve analysis for overall survival in the training (A) and validation (B) cohorts.

DISCUSSION

This study successfully developed and validated a nomogram combining hematologic-al biomarkers and clinical characteristics for predicting OS in PLC patients. Key findings include ALT, AFP, tumor count, vascular invasion, NLR, and ALBI as significant independent predictors.

Inflammation, particularly chronic, can facilitate tumor progression, with infection and inflammation contributing to around 25% of cancer etiologies [9-10]. NLR's significance in cancer prognosis is well-documented, with higher NLR indicative of an elevated inflammatory response and diminished lymphocyte-mediated tumor resistance, potentially exacerbating tumor progression and metastasis, thereby affecting prognosis adversely [11-14]. NLR's utility extends to cancer stratification and monitoring response to oncological therapies, including biological and immune checkpoint inhibitors [15]. The epidemiological relevance of NLR in various solid tumors has been underscored [16]. Accurate liver function assessment in PLC patients is critical for personalized treatment. The ALBI grade, a straightforward calculation, provides an objective alternative to the more subjective CTP score. Studies have underscored ALBI's superiority in predicting long-term survival and recurrence post-surgery compared to the CTP score, particularly in the context of treatments like RFA and MWA [17-21].

However, the study faces limitations due to its single-center, small sample nature. Future studies should involve larger, prospective cohorts with external validations to enhance the nomogram's applicability.

In summary, ALT, AFP, tumor count, vascular invasion, NLR, and ALBI emerged as reliable prognostic markers in PLC. The ALBI grade, combined with these factors, offers promising predictive accuracy for PLC prognosis, guiding personalized clinical treatments and follow-ups.

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