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Analysis of Prognostic Factors and Establishment of Prediction Model after Radical Operation of Early Gallbladder Carcinoma in Han Population

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Abstract

Primary Gallbladder Carcinoma (GBC) is among one of the gastrointestinal malignancies with extremely dismal prognosis. This study was aimed to investigate the clinical effect and prognostic factors after radical operation of early primary GBC in Han population, and construct prediction model based on prognostic factors. Clinical data of 65 patients with early GBC who underwent radical surgery in our Department from August 24th, 2010 to August 24th, 2021 were collected for this retrospective study. Univariate analysis showed that age, Onodera Prognostic Nutrition Index (OPNI), Neutrophil Lymphocyte Ratio (NLR), CA199, differentiation degree, nerve invasion, T stage, lymphatic metastasis and adjuvant chemotherapy were the risk factors that could affect the prognosis of Han population after early GBC radical surgery (P<0.05). Multivariate analysis showed that age, OPNI, nerve invasion and lymphatic metastasis were independent risk factors for early GBC radical surgery in Han population (P<0.05), and a nomogram was established thereby. The composite survival probability score of each patient was obtained by using the nomogram. The Bootstrap method was used to repeat 1,000 samples for internal verification, and the consistency between OS and reality was high in 2, 3 and 5 years. The Consistency index (C-index) of this model was 0.860 (95% CI 0.822-0.897), and its prediction ability was higher than that of the eighth AJCC staging (C-index 0.820, 95% CI 0.7899-0.851). Therefore, age, OPNI, nerve invasion and lymphatic metastasis are independent risk factors for early GBC radical surgery in Han population. The nomogram model constructed based on the above independent risk factors has high accuracy, which can provide a reference for clinicians to evaluate the prognosis after early GBC radical surgery.

Keywords: Primary gallbladder carcinoma; Han population; OPNI; Nerve invasion; Nomogram

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Introduction

Primary Gallbladder Carcinoma (GBC) is the most common malignancy of the biliary tract. It is characterized by insidious onset and most patients have developed to advanced stage at diagnosis, so the prognosis is poor [1]. However, with the continuous improvement of medical level, more and more patients with gallbladder cancer were detected early. Accurate judgment of prognosis is an important condition for the development of postoperative follow-up treatment plan. Although AJCC staging can provide guidance for treatment, the risk factors included in AJCC staging are only tumor invasion scope, lymphatic metastasis and distant metastasis. However, the influence of clinicopathological features, patient nutrition and immune status on prognosis is often ignored; resulting in insufficient prediction accuracy, and visualization and personalized application cannot be realized.

"Onodera Prognostic Nutrition Index" was discovered by Japanese scholar Onodera et al. abbreviated as OPNI. It can objectively reflect the immune and nutritional status of patients by measuring their peripheral blood lymphocyte count, serum albumin and calculating them through a formula. A large number of studies have shown that the level of OPNI is significantly related

to the prognosis of many kinds of tumors, including gastric cancer, pancreatic cancer, liver cancer, etc. [2,3]. However, it is rarely reported in gallbladder cancer.

The invasion and metastasis routes of gallbladder carcinoma include invasion of adjacent tissues and organs, vasculature, nerve or abdominal cavity. At present, nerve invasion has been proved to be an independent prognostic risk factor for pancreatic cancer, bile duct cancer and other tumors [4-6], but there are few studies on the effect of nerve invasion on the prognosis of gallbladder cancer patients.

For gallbladder cancer, in addition to TNM staging, there are very limited tools that can be effectively used to predict the prognosis of patients. The nomogram is intuitive, accurate and visual, and is widely used in clinic [7]. It can help surgeons and oncologists understand the weight of risk factors contributing to disease prognosis. In addition, the nomogram allows clinicians to screen patients with poor prognosis for closer follow-up and adjuvant therapy.

This study intends to analyze the demographic characteristics, laboratory and imaging results, clinicopathological features and other related factors of early GBC patients in the Han population, and build a prediction model in the form of a graph. The aim is to accurately predict the outcome of the disease and make reasonable and effective treatment to improve the prognosis of gallbladder cancer patients.

Materials and Methods

Study queues and groups

The subjects of this study were Han patients who were diagnosed with GBC and underwent radical gallbladder cancer surgery in our hospital. The medical record information was retrieved in the medical record management system of the medical record room of our hospital, and the search term of the discharge diagnosis was "gallbladder malignant tumor and gallbladder cancer" from August 24th, 2010 to August 24th, 2021. Case data included age, sex, gallstone, gallbladder polyp, hypertension, diabetes, alcohol consumption, smoking history, albumin, CEA, CA199, OPNI, NLR, degree of differentiation, nerve invasion, vascular invasion, T stage, lymphatic metastasis, and postoperative adjuvant chemotherapy.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Han population; (2) The pathological results after radical surgery confirmed the diagnosis of GBC; (3) Patients with stage T1 and stage T2 of the eighth edition of AJCC; The exclusion criteria were as follows: (1) non-Han population; (2) inexact clinical diagnosis; (3) Patients with tumor lesions of other organs; (4) Patients with incomplete clinical data or lost to follow-up.

Follow-up

Follow-up was carried out by telephone and outpatient, and the follow-up contents included postoperative survival, whether the patients received systematic chemotherapy, treatment plan and course of treatment. Follow-up lasted until August 24th, 2022, and the endpoint event was death. Overall survival time was defined as from the date of surgery to the date of last follow-up or death (measured in months).

Statistical analysis

SPSS 26.0 was used for statistical analysis, Kaplan-Meier method was used to calculate the survival rate, and Log-rank test was used to compare the difference in survival rate between groups. Multivariate analysis used COX regression analysis to screen the independent risk factors that affected the prognosis and $P<0.05$ was considered to have significant statistical significance. Survival package and rms package of R language (The R Project for Statistical Computing, Vienna, Austria) were used to draw the nomogram. The accuracy of nomogram was mainly evaluated by Concordance index (C-index) and calibration curve. The internal verification was completed through Bootstrap method with 1,000 repeated samples. Compared with the prediction ability of the 8th AJCC stage, this study was implemented using the rcorrp.cens function of R language.

Results

Demographic characteristics and risk factors

Among the 65 patients included, 23 were male, accounting for 35.4%; 42 cases were female, accounting for 64.6%. The age of the patients ranged from 23 years old to 84 years old, with an average age of 61.4 years old. Forty-four cases (67.7%) were complicated with gallstones. Thirteen cases (20%) complicated with gallbladder polyp; 26 patients with hypertension, accounting for 40%; 10 patients with diabetes mellitus, accounting for 15.4%; 8 cases were drinkers, accounting for 12.3%; Smokers accounted for 9 cases (13.8%) (Table 1).

Laboratory test results

The results of fasting blood routine, biochemical and tumor markers of 65 patients were included in the first admission. Among them, albumin, OPNI and NLR were introduced to evaluate the nutritional, immune and inflammatory status. The serum albumin value was lower than the normal level (40 g/L) in 38 patients, accounting for 58.5%; OPNI=albumin value (g/L) +5 × Total number of lymphocytes (10^9/L). According to the standards formulated by Onodera et al. [8], the whole group of cases were divided into poor nutrition group (OPNI<45), 29 cases (44.6%), and better nutrition group (OPNI ≥ 45), 36cases (55.4%). Twenty-one cases (32.3%) had NLR ≥ 2.5 and 44 cases (67.7%) had NLR<2.5. The positive rates of CEA and CA199 were 7/65 (10.8%) and 25/65 (38.5%) (Table 2).

Clinicopathological characteristics and postoperative adjuvant chemotherapy

Among the 65 patients included, 17 were poorly differentiated, accounting for 26.2%; 48 cases (73.8%) were moderately to highly differentiated; 13 cases (20%) had nerve invasion in tumor tissue; 52 cases (80%) had no nerve invasion; 8 cases (12.3%) had vascular invasion; 57 cases (87.7%) had no vascular invasion. With respect to

Table 1: Baseline data of demographic characteristics and risk factors.

Characteristics	n (%)	Characteristics	n (%)
Sex		Age	
Female	42 (64.6%)	≥ 60	41 (63.1%)
Male	23 (35.4%)	<60	24 (36.9%)
Cholecystolithiasis		Gallbladder polyps	
Yes	44 (67.7%)	No	52 (80%)
No	21 (32.3%)	Yes	13 (20%)
Hypertension		Diabetes Mellitus	
No	39 (60%)	No	55 (84.6%)
Yes	26 (40%)	Yes	10 (15.4%)
Alcohol Intake		Smoking	
No	57 (87.7%)	No	56 (86.2%)
Yes	8 (12.3%)	Yes	9 (13.8%)

Table 2: Baseline data sheet of laboratory results.

Characteristics	n (%)	Characteristics	n (%)
ALB		OPNI	
≥ 40	27 (41.5%)	≥ 45	36 (55.4%)
<40	38 (58.5%)	<45	29 (44.6%)
NLR		CEA	
<2.5	44 (67.7%)	≤ 5	58 (89.2%)
≥ 2.5	21 (32.3%)	>5	7 (10.8%)
CA-199			
>37	25 (38.5%)		
≤ 37	40 (61.5%)		

Table 3: Clinicopathological characteristics and baseline data of postoperative adjuvant chemotherapy.

Characteristics	n (%)	Characteristics	n (%)
Degree of differentiation		Nerve invasion	
Medium-high differentiation	48 (73.8%)	No	52 (80%)
Low differentiation	17 (26.2%)	Yes	13 (20%)
Vascular invasion		Stage-T	
No	58 (89.2%)	T2	42 (64.6%)
Yes	7 (10.8%)	T1	23 (35.4%)
Lymphatic metastasis		Adjuvant therapy	
No	51 (78.5%)	No	57 (87.7%)
Yes	14 (21.5%)	Yes	8 (12.3%)

the T stage, there were 23 cases in T1 stage, accounting for 35.4%, and 42 cases in T2 stage, accounting for 64.6%; The tumor tissue was divided into non-lymphatic metastasis group (51/65), accounting for 78.5%, and lymphatic metastasis group (14/65), accounting for 21.5%; Postoperative adjuvant chemotherapy is regular chemotherapy involving gemcitabine hydrochloride, fluorouracil, tegafur, gimeracil and oteracil potassium capsules, platinum for more than 3 cycles. In this study, postoperative adjuvant chemotherapy was performed in 8 cases (12.3%); 57 cases (87.7%) did not undergo adjuvant chemotherapy (Table 3).

Follow-up

According to the postoperative follow-up results, the overall 2-year, 3-year and 5-year survival rates were 74.7%, 69.2% and 59.3%. The median survival time was 40 months. The overall survival curve is shown in Figure 1.

Univariate analysis of prognosis

The results of univariate analysis showed that age ≥ 60 years, OPNI<45, NLR ≥ 2.5, CA-199 >37 μmol/L, low differentiation, nerve invasion, T2 stage, lymphatic metastasis and adjuvant chemotherapy were the risk factors affecting the prognosis of early primary GBC after radical surgery (P<0.05) (Table 4).

Multivariate analysis of prognosis

The factors with P<0.05 in the univariate analysis were brought into the multivariate analysis. The results of the multivariate analysis showed that age ≥ 60 years old, OPNI<45, nerve invasion and lymphatic metastasis were independent risk factors (P<0.05) affecting the prognosis of primary GBC in the early Han population after radical surgery (Table 5).

Table 4: Univariate regression analysis of prognosis after early GBC radical surgery in Han population.

Characteristics	n (%)	MST (month)	χ^2	P value
Sex			0.049	0.825
Female	42 (64.6%)	40		
Male	23 (35.4%)	46		
Age			6.246	0.012
≥ 60	41 (63.1%)	33		
<60	24 (36.9%)	54.5		
Cholecystolithiasis			0.037	0.847
No	21 (32.3%)	33		
Yes	44 (67.7%)	45.5		
Gallbladder polyps			1.073	0.3
No	52 (80%)	38.5		
Yes	13 (20%)	53		
Hypertension			0.92	0.338
No	39 (60%)	48		
Yes	26 (40%)	29.5		
Diabetes mellitus			0.162	0.688
No	55 (84.6%)	40		
Yes	10 (15.4%)	45.5		
Drinking			1.23	0.267
No	57 (87.7%)	37		
Yes	8 (12.3%)	52.5		
Smoking			0.006	0.94
No	56 (86.2%)	40		
Yes	9 (13.8%)	46		
ALB			1.808	0.179
≥ 40	27 (41.5%)	33		
<40	38 (58.5%)	47		
OPNI			11.892	0.001
≥ 45	36 (55.4%)	51		
<45	29 (44.6%)	34		
NLR			8.897	0.003
<2.5	44 (67.7%)	51		
≥ 2.5	21 (32.3%)	19		
CEA			0.721	0.396
≤ 5	58 (89.2%)	45.5		
>5	7 (10.8%)	19		
CA-199			9.225	0.002
>37	25 (38.5%)	24		
≤ 37	40 (61.5%)	56.5		
Degree of differentiation			9.969	0.002
Medium-high differentiation	48 (73.8%)	54.5		
Low differentiation	17 (26.2%)	19		
Nerve invasion			15.974	<0.001
No	52 (80.0%)	51		
Yes	13 (20.0%)	11		
Vascular invasion			3.57	0.059

No	58 (89.2%)	47		
Yes	7 (10.8%)	21		
Stage-T			14.194	<0.001
T2	42 (64.6%)	24		
T1	23 (35.4%)	86		
Lymphatic metastasis			60.005	<0.001
No	51 (78.5%)	53		
Yes	14 (21.5%)	8.5		
Adjuvant chemotherapy			4.004	0.045
No	57 (87.7%)	46		
Yes	8 (12.3%)	32.5		

Construction and evaluation of prediction model

Based on the above independent factors, a nomograph model was constructed to predict the prognosis of the Han population after early GBC radical surgery (Figure 2). The C-Index of the nomogram is 0.860 (0.822-0.897), which has high prediction accuracy. In addition, the plotting of calibration curves for 2, 3 and 5 years also show that the nomogram has good predictive value (Figures 3A-3C). Compared with the 8th AJCC edition of staging, the prediction ability of this nomogram is better than that of AJCC stage (C-index 0.860 *vs.* 0.820).

Discussion

The early stage of GBC has no specific clinical symptoms and manifestations, and its invasion is strong, and the prognosis is poor [1]. Most patients are in the late stage when they go to hospital. There are many risk factors affecting the prognosis of GBC, but few have been identified. Therefore, identifying relevant risk factors and establishing an effective risk assessment model for GBC can further optimize the management of high-risk population with poor prognosis.

In previous studies, there are differences in the effects of gender and age on the prognosis of GBC patients. Most domestic studies believe that gender and age are not prognostic risk factors, but some literatures report that age and gender are important prognostic factors for GBC patients, and suggest that male and elderly patients have a poor prognosis. Our study showed that gender was not a risk factor for prognosis (P=0.825), which was consistent with the conclusion of most studies. However, we found that age was an independent risk factor for the postoperative prognosis of GBC in the Han population (P=0.012), and the prognosis of elderly patients (≥ 60 years old) was worse, which might be attributed to the influence of age-induced decline in systemic resistance and organ function. Other studies have shown that gallstones and chronic cholecystitis are important risk factors for GBC [9,10], but our study shows that gallstones and gallbladder polyps are unrelated to the prognosis of patients with early GBC, which may be related to the widespread implementation of laparoscopic cholecystectomy in primary hospitals, which reduces secondary GBC caused by gallstones and gallbladder polyps. However, for patients over 60 years old with a history of gallbladder stones or polyps, we should still be on high alert for the possibility of GBC.

Since most cancer patients are complicated with malnutrition, a clinical study found that low preconditioning serum albumin level is associated with poor prognosis [11]. Lymphocytes play a key role in cell-mediated immune monitoring and anti-tumor immunity [12]. Therefore, the indicators reflecting the nutritional and immune status of patients are particularly important in predicting the prognosis of patients. For GBC patients, there is still a lack of specific criteria to quantify nutritional and immune status to predict specific interventions for subsequent treatment. OPNI can objectively reflect the immune and nutritional status of patients by measuring their peripheral blood lymphocyte count and serum albumin and calculating them through a formula. Current studies have shown that OPNI is closely related to the prognosis of various malignant

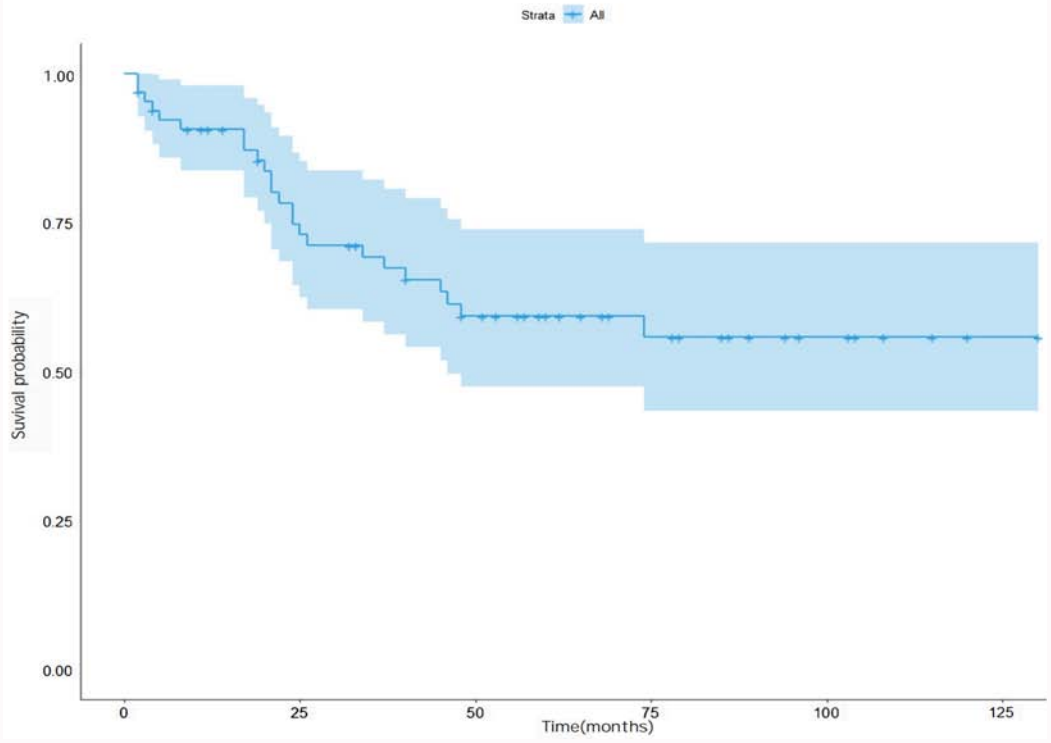

Figure 1: Overall survival curve of Han population after early GBC radical surgery.

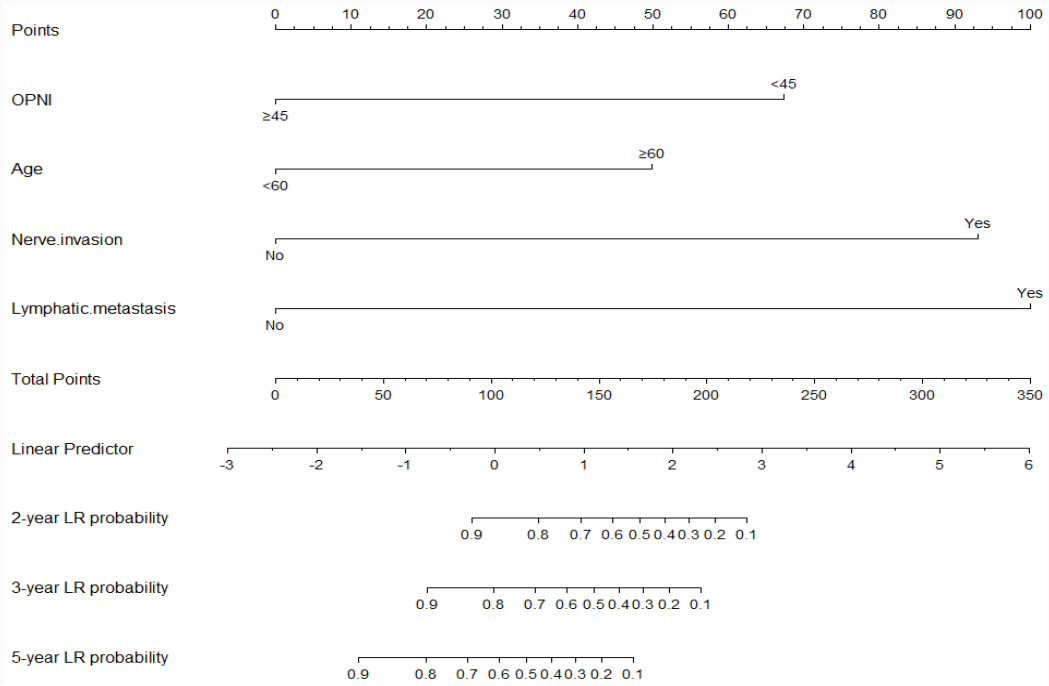

Figure 2: A nomogram to predict the survival rate after early GBC radical surgery in the Han population. The nomogram is based on the score of four risk factors, and the total score finally corresponds to the OS of 2, 3 and 5 years. As the score increases, the OS gradually decreases.

Table 5: COX multivariate regression analysis of the prognosis after GBC radical operation in Han population.

Characteristics	Multivariate analysis	
	Hazard ratio (95% CI)	P value
Age		
≥ 60	3.949 (1.035-15.066)	0.044
OPNI		
<45	5.530 (1.553-19.683)	0.008
NLR		
≥ 2.5	0.851(0.241-3.001)	0.802
CA-199		
>37	1.637 (0.541-4.950)	0.383
Degree of differentiation		
Low differentiation	1.320 (0.313- 5.569)	0.705
Nerve invasion		
Yes	7.640 (1.564-37.330)	0.012
Vascular invasion		
Yes	0.913(0.227-3.679)	0.898
Stage-T		
T2	3.985 (0.842 - 18.864)	0.081
Lymphatic metastasis		
Yes	8.811 (2.180-35.618)	0.002
Adjuvant chemotherapy		
No	1.789(0.393-8.137)	0.452

tumors such as esophageal cancer, gastric cancer, liver cancer and pancreatic cancer [13]. However, its correlation with the prognosis of gallbladder cancer is rarely reported. In this study, we included OPNI for analysis and found that it was an independent risk factor affecting the prognosis after radical surgery for early GBC (P=0.008). Clinically, the calculation of OPNI is simple, convenient, low cost and easy to implement. Therefore, OPNI is expected to become a standard tool for clinical quantitative evaluation of the nutritional and immune status of patients with GBC. For patients with low OPNI, nutritional and immunotherapy interventions can be carried out in advance, so as to improve the prognosis of patients to the greatest extent.

It is well known that clinicopathologic features such as lymphatic metastasis and tumor differentiation have important effects on the prognosis of cancer patients [14,15]. In this study, lymphatic metastasis was found to be one of the independent prognostic factors, with the most significant effect on prognosis, which was consistent with the literature [16]. However, T stage was not an independent risk factor, which may be related to the fact that all the patients in our study were at stage T1 and T2. The degree of differentiation reflects the biological model of the tumor. The poorly differentiated tumor usually has the characteristics of rapid growth, early metastasis and insensitivity to chemotherapy. A total of 48 cases with medium-high differentiation and 17 cases with low differentiation were reported in this study. Univariate analysis also showed a correlation with the prognosis of GBC, but it could not be confirmed as an independent risk factor in multivariate analysis. This may be due to the fact that patients with low differentiation usually have reached stage T3 and T4 when found and are not enrolled in the group.

Malignant tumors occur and develop through various transmission routes. As a representative of local invasion, nerve invasion is recognized as an independent prognostic factor for pancreatic cancer and cholangiocarcinoma [5,6]. For gallbladder cancer, some studies showed that nerve infiltration was an independent prognostic factor after radical gallbladder cancer surgery [12,17]. Feo et al. [18] compared the prognosis of gallbladder cancer patients with and without nerve invasion and found no statistical significance (P=0.16). In this study, we found that nerve invasion was an independent risk

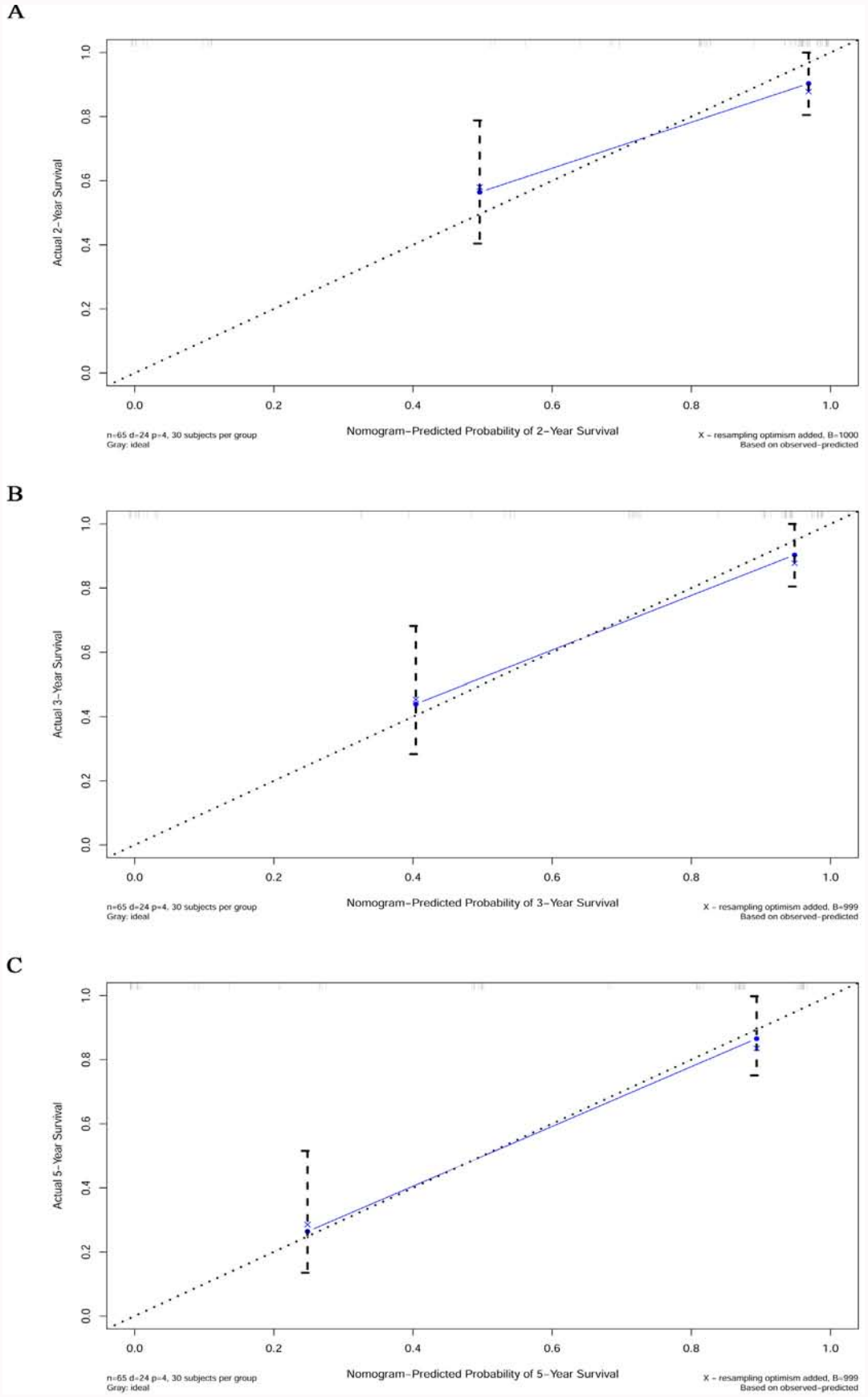

Figure 3: (A) Nomograph Calibration curve for 2 years; (B) Nomogram Calibration curve for 3 years; (C) Nomogram Calibration curve for 5 years. The calibration curve was used to judge the consistency between the predicted value and the actual value. The higher the fitting degree of the two, the better the prediction ability of the nomogram.

factor after radical surgery on early GBC, suggesting that clinicians should attach importance to the guiding role of nerve invasion in the prognosis assessment of gallbladder cancer.

The efficacy of chemotherapy for GBC is still controversial, and there is no universally accepted program. Gold et al. [19] found that there was no significant difference between postoperative adjuvant chemotherapy for gallbladder cancer patients who underwent R0 resection and patients who did not receive postoperative chemotherapy, but John et al. [20] believed that postoperative adjuvant chemotherapy could improve the postoperative survival rate of gallbladder cancer patients, which was worth popularizing. At present, the number of patients receiving adjuvant chemotherapy in our study is small (8 cases), and the chemotherapy regiments are also different. Univariate analysis showed that there was no statistical difference in prognosis (P=0.053). A multi-center, long-term, large-sample, prospective, controlled clinical study is needed to verify the efficacy of postoperative adjuvant chemotherapy for patients after radical resection.

The nomogram can be used to predict the probability of survival time of individual patients and has good clinical practicability [7]. By associating various prognostic factors, the risk of malignant tumors can be assessed, quantified, and a nomogram can be constructed, which is widely used in the prognosis assessment of cancer patients. Based on the above prognostic independent risk factors, this study established a nomogram for predicting the survival rate after early radical GBC in the Han population, and the 2, 3 and 5-year OS was in good agreement with the reality. Compared with the 8thedition of AJCC staging, this nomogram shows a higher C-index (0.860 *vs.*0.820), which may be related to the fact that the traditional AJCC staging only looked at tumor invasion, lymphatic metastasis, and distant metastasis without considering other risk factors such as age, immune index, nutritional index, and nerve invasion. The nomogram constructed in this study not only helps surgeons and oncologists understand the weight of contribution of each risk factor to the prognosis of gallbladder cancer, but also enables clinicians to screen patients with poor prognosis for more comprehensive treatment.

Although we provided a column chart model with high accuracy, this study still has the following shortcomings: (1) As a single-center retrospective study with a small sample size, this study cannot represent the overall situation of gallbladder cancer patients, and there might exist biases; (2) Because the survival time of some cases has not reached a certain number of years, there are more truncated data, which might have certain impact on the survival analysis results.

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