Development a Nomogram for Predicting Intrahepatic Cholangiocarcinoma in Patients with Biliary Calculi after Surgery

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Research

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Abstract

Objective: To find out the risk factors of intrahepatic cholangiocarcinoma (ICC) in patients who underwent biliary surgery for biliary calculi, and to develop a nomogram to better predict the occurrence of ICC.

Methods: Data were collected and analyzed retrospectively from 322 patients who underwent biliary tract surgery for biliary calculi in the First Affiliated Hospital of Wenzhou Medical University from January 2000 to December 2017.Of these patients, 58 patients had biliary calculi complicated with ICC while the other 294 patients had simple biliary calculi. Both univariate and multivariate analyses were performed to find out the risk factors related to ICC, and a nomogram was further developed based on the results of multivariate analysis.

Results: The univariate analysis showed that there were significant differences in age composition (≤ 60 years old, > 60 years old), liver cirrhosis, stone history and previous hepatitis B infection (HBsAg- and HBcAb+) between the two groups. Logistic regression analysis indicated that liver cirrhosis (OR=2.011, 95%CI=1.023-3.952), stone history (OR=1.086, 95%CI=1.051-1.112) and age > 60 (OR=2.045, 95%CI=1.059-3.948) were the risk factors of ICC, while previous hepatitis B infection (HBsAg- and HBcAb+) (OR=0.461, 95%CI=0.215-0.989) was the protective factor. After drawing a nomogram, it was found that the area under the curve was 0.753 (95% CI=0.686-0.818), and the best cutoff value obtained by Youden index was 0.164. Moreover, the calibration curve indicated the best consistency between the predicted probability and the actual probability.

Conclusion: We developed a nomogram, which was novel and accurate, to predict the risk of ICC in patients received biliary surgery for biliary calculi. This nomogram is of certain significance for the early detection of ICC.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a primary malignant tumor of the liver, which mainly originates from the endothelial cells of the segment or proximal branch of the bile duct[1]. The incidence of ICC has been rising rapidly in various regions ,such as Europe, North America, Asia, Japan and Australia in the past few decades[2, 3], which is the second leading cause of primary liver cancer [4]. In the United States, the annual incidence of ICC has increased from 0.13 per 100000 cases to 0.58 per 100000 cases in just 25 years[5], and the incidence of ICC in Thailand is even more alarming, with 96 patients per 100000 people [6]. The pathogenic factors of ICC are complicated. Some studies have pointed out that the occurrence of ICC is related to cholelithiasis of biliary system[7, 8],Since the cholelithiasis of biliary system is more common in East Asia (such as South Korea and China)[9]. it may be one of the reasons casing higher incidence of ICC in the East. Both choledocholithiasis and hepatolithiasis are considered as the risk factors for ICC. Petrick[10] et al. found that the occurrence of choledocholithiasis promoted the occurrence of ICC, and its Odd Ratio(OR) value was 6.94 (95%CI = 5.64–8.54).Meanwhile, hepatolithiasis

was recognized as a risk factor for ICC. It was reported that 4–11% of hepatolithiasis developed into ICC [11–13]. Even if gallstones are treated actively and effectively, it may still lead to the occurrence of ICC [14]. However, because the early clinical symptoms of ICC are not obvious, it cannot be diagnosed until the late stage[15],usually causing patients losing the opportunity of operation. Therefore, how to prevent biliary calculi from developing into ICC is an issue of great concern to hepatobiliary surgeons, but as far as we know ,the factors that cause patients who have undergone biliary surgery for gallstones suffering from ICC are limited, so it is necessary to find out the leading risk factors in these patients with ICC

In order to further investigate the influence of biliary calculi on the occurrence and development of ICC, we retrospectively analyzed the patients who underwent biliary surgery for gallstones in the First Affiliated Hospital of Wenzhou Medical University, and summarized our experience of diagnosis and treatment. Furthermore, in order to find out the risk factors of such patients with ICC, we constructed a nomogram aiming to better predict the probability of ICC in such patients.

Materials And Methods

Patients:

Retrospective analysis of the data of patients who underwent biliary tract surgery for stones in the first affiliated Hospital of Wenzhou Medical University from January 2000 to December 2017. There are the inclusion criterias (1) intraoperative exploration of hepatolithiasis; (2) Patients who have undergone biliary surgery for choledocholithiasis or hepatolithiasis; (3) have complete clinical data. After excluding the cases of non-conformity, 352 patients were enrolled in the group, including 58 patients with cholelithiasis complicated with ICC and 294 patients with simple cholelithiasis. After excluding the inconsistent cases, 352 patients were enrolled in the group, including 58 patients with biliary calculi complicated with ICC and 294 patients with choledocholithiasis (Shown in Fig. 1). Among the 58 patients with ICC, 22 patients underwent R0 tumor resection and 36 patients received palliative treatment only. The basic clinical characteristics of the patients in the group are shown in Table 1. All patients in the group signed an informed consent form, which was reviewed and approved by the Institutional Review Committee of the first affiliated Hospital of Wenzhou Medical University. All research procedures were conducted in accordance with the 1964 Helsinki Declaration and its subsequent revisions or similar ethical standards.

Table 1

Basic clinical features	Patients(n = 352)	
Gender	Male: 127(36.1%)	Female: 225(63.9%)
Age(year)	61.5(28–85)	
Stone history(year)	10.6(0.25-42)	
Number of previous biliary operations	1(1–5)	
Hepatitis B infection(HBsAg+)	Yes: 20(5.7%)	No:332(94.3%)
Whether it is stone complicated with ICC	Yes: 58(16.5%)	No: 294(83.5%)
Previous hepatitis B infection (HBsAg- and HBcAb+)	Yes: 99(28.1%)	No:253(71.9%)
Liver cirrhosis	Yes: 40(11.4%)	No: 312(88.6%)
Fatty liver	Yes: 26(7.4%)	No: 326(92.6%)
Diabetes	Yes: 19(5.4%)	No: 306(94.6%)
Alcohol	Yes: 30(8.5%)	No: 322(91.5%)
Smoking	Yes: 49(13.9%)	No: 303(86.1%)

Methods:

General basic data of patients were collected, including sex, age, history of diabetes, history of smoking, history of drinking, number of previous biliary operations and stone history. Because this is an epidemiological risk study, tumor markers, such as CEA and CA199, were not included in this study. Among the indicators included in the study, HBsAg + was considered to be hepatitis B infection, while HBsAg- and HBcAb + were considered to be previous hepatitis B infection. According to the preoperative imaging examination and intraoperative findings, the patient was diagnosed as having fatty liver and liver cirrhosis by two experienced doctors. All patients were examined for blood routine, blood biochemistry and other laboratory indexes when they were admitted to hospital.

Statistical analysis:

Statistical analysis and graphic generation were carried out using IBM SPSS 20.0 (SPSS Inc, Armonk, NY) and R 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and rms statistical software package. The Kolmogorov–Smirnov test was used to determine whether the variables obey normal distribution. Mann-Whitney U test was used to compare variables with non-normal distribution, while t-test was used to compare variables with normal distribution. Univariate analysis was performed by $\chi 2$ test. Logistic regression model was used to analyze the factors affecting ICC in patients with previous biliary tract surgery for gallstones. Based on the results of multivariate analysis, a nomogram for predicting the occurrence of ICC was constructed. The performance of the nomogram was evaluated by

the calibration map, and the internal verification was carried out by using Bootsarap repeated sampling. The discriminant ability to evaluate the prediction accuracy of the nomogram was determined by the area under the ROC curve. For all analyses, $P < 0.05$ was considered to be statistically significant, and all tests were bilateral.

Results

Univariate analysis showed that there was no significant difference in sex, fatty liver, diabetes, smoking, drinking, frequency of previous biliary surgery and hepatitis B infection (HBsAg+) between the two groups, but significant differences were observed between the two groups ($P < 0.05$) in terms of age composition (≤ 60 years old, > 60 years old), liver cirrhosis, stone history and previous hepatitis B infection (HBsAg- and HBcAb+) ,which are shown in Table 2. The factors with statistical differences in the univariate analysis (age, liver cirrhosis, gallstone course and previous hepatitis B infection) were included in a logistic regression model for multivariate analysis. The results suggested that liver cirrhosis (OR = 2.011, 95%CI = 1.023–3.952), stone history (OR = 1.086.933, 95%CI = 1.051–1.112) and age > 60 (OR = 2.045, 95%CI = 1.059–3.948) were risk factors for ICC. Previous hepatitis B infection (HBsAg- and HBcAb+) (OR = 0.461, 95%CI = 0.215–0.989) was the protective factor ($P < 0.989$, Table 3). In order to better observe the distribution difference between the two groups, a box chart was drawn for the stone history (Shown in Fig. 2).

Table 2

Clinicopathological features	Cholelithiasis complicated with ICC(n = 58)	Simple cholelithiasis(n = 294)	$t/Z/X^2$	P
Gender			$X^2 = 0.332$	0.564
Male	19	108		
Female	39	186		
Age			$X^2 = 5.827$	0.016
≤60	15	126		
>60	43	168		
Hepatitis B infection(HBsAg+)			$X^2 = 1.242$	0.265
Yes	1	19		
No	57	275		
Previous hepatitis B infection (HBsAg- and HBcAb+)			$X^2 = 4.069$	0.044
Yes	10	89		
No	48	205		
Liver cirrhosis			$X^2 = 8.418$	0.004
Yes	13	27		
No	45	267		
Fatty liver			$X^2<0.0001$	>0.9999
Yes	4	22		
No	54	272		
Diabetes			$X^2<0.0001$	>0.9999
Yes	3	16		
No	55	278		
Alcohol			$X^2 = 1.12$	0.29
Yes	7	23		

Clinicopathological features	Cholelithiasis complicated with ICC(n = 58)	Simple cholelithiasis(n = 294)	$t/Z/X^2$	P
No	51	271		
Smoking			X^2<0.0001	0.976
Yes	8	41		
No	50	253		
Number of previous biliary operations	1(1⍰3)	1(1⍰5)	Z = 0.075	0.94
Stone history(year)	14.5(1–42)	8(0.25-42)	t = 4.497	<0.001

Table 3

Factor	β	S.E.	Wald	P	OR	95%CI
Age(≤60,>60)	0.699	0.345	4.108	0.043	2.011	1.023–3.952
Liver cirrhosis	0.829	0.402	4.250	0.039	2.290	1.042–5.034
Stone history	0.082	0.017	24.198	<0.001	1.086	1.051–1.112
Previous hepatitis B infection (HBsAg- and HBcAb+)	-0.773	0.389	3.951	0.047	0.461	0.215–0.989

On the basis of the final regression analysis, a nomogram (Shown in Fig. 3) was constructed, which included four key factors for predicting the occurrence of ICC. We calculated the total score using age, liver cirrhosis, stone history and previous hepatitis B infection, and the value of each factor was given a score on the dot axis. By adding up each individual score, we calculated the total score, through which we estimated the probability of the occurrence of ICC. At the same time, a calibration curve was drawn using the method of Bootsarap repeated sampling for 1000 times for internal verification. The results(Shown in Fig. 4) indicated that the predicted probability of ICC occurrence was in good agreement with the actual probability. Meanwhile, a χ^2 value of 2.871 was obtained from the hosmer-lemeshow test, which suggested that there was no statistical significance between the predicted value of the model and the actual observed value, and the prediction model had better calibration ability. The performance of the nomogram measured by the ROC curve (shown in Fig. 5) indicated an AUC of 0.753 (95% CI = 0.686–0.818), which was significantly higher than the area under the AUC curve of the other four indicators(age:0.585, liver cirrhosis:0.566, stone history:0.602, previous hepatitis B infection:0.565). The best cutoff value obtained by the Youden of the nomogram was 0.164 based on this threshold. The sensitivity of the nomogram was 70.1% and the specificity was 67.2%.

Discussion

The mechanism of ICC caused by biliary calculi is not clear at present. Some studies have found that both inflammatory infection caused by gallstones and mechanical stimulation of the gallstones have long-term effect on the bile duct wall and lead to stepwise progression of pathology, such as changes in the mucosal epithelium of the bile duct, dysplasia, intraepithelial neoplasia and eventually cancer[16]. Therefore, predicting the occurrence of ICC is of great significance to the treatment of ICC. In this study, we retrospectively analyzed the patients who underwent biliary surgery for stones. The results showed that the age > 60 years old, liver cirrhosis and the stone history were the factors affecting them to develop ICC, while the previous hepatitis B infection (HBsAg- and HBcAb+) was the protective factor. Based on this, a nomogram was constructed, which can be used to predict the probability of ICC in these patients with more intuitive methods.

Liver cirrhosis commonly results from chronic damage of liver parenchyma. Its formation is due to the replacement of normal liver tissue with fibrous scar tissue and regenerated nodules. Liver cirrhosis leads to clinical complications such as progressive liver insufficiency, portal hypertension and even death[17]. Some studies have shown that liver cirrhosis is closely related to the occurrence of ICC[18, 19]. Palmer et al. performed a meta-analysis in 2012[18] and discovered that the odds ratio of ICC in patients with liver cirrhosis was 22.9 (95%CI:18.2–28.8). A case-control study from China reported similar results [20]. The possible underlying mechanism that liver cirrhosis promotes the occurrence and development of ICC may be due to tissue microenvironmental changes in the cirrhotic liver, such as chronic inflammation, increased cell renewal and progressive fibrosis, which are similar to the microenvironment observed in many other high-risk conditions such as primary sclerosing cholangitis[21]. In the present study, liver cirrhosis is also a risk factor for the occurrence and development of ICC in patients undergoing biliary surgery for gallstones, which confirms the appeal point of view. In addition, it was also found that the age (> 60 years old) and the long history of gallstones were also risk factors for the development of ICC. Liu et al. also confirmed that [22] symptom caused by cholelithiasis (such as long-term recurrent epigastric discomfort) lasting for more than 10 years is a powerful risk factor for ICC. Kim et al.[23] reported that the incidence of ICC increased in patients older than 40 years old, and the incidence of ICC was the highest in patients aged 60–79 years old. We believe that the three risk factors, which are the age of the patient (> 60 years old), liver cirrhosis and the gallstone history, complement to each other. Repeated attacks of gallstones can lead to long-term mechanical stimulation, resulting in cholestasis and chronic inflammation, which may cause hepatocyte necrosis and liver cirrhosis. Moreover, the age of a patient might be related to the length of gallstone history as well as the length of chronic inflammation. Long-term chronic inflammation increases the risk of liver cirrhosis, and this persistent inflammation results in DNA damage, activated tissue repair and proliferation, and promotes carcinogenicity by creating a local environment rich in cytokines and other growth factors [24]. These may lead to an increase in the risk of ICC in patients. Therefore, elderly patients who have received biliary surgery might have higher possibility of ICC when they are found with long-term unexplained epigastric discomfort.

In addition, previous hepatitis B infection (HBsAg- and HBcAb+) was considered to be a protective factor for ICC in our study. Some literatures[25] have shown that current or past HBV-activated immune response infection can enhance the anti-ICC activity against the body. When ICC occurs, the immune memory activated by previous HBV infection produces strong and effective anti-tumor immunity, thus improving the prognosis of HBV-related ICC. From this, we can also boldly infer that the anti-ICC activity enhanced by HBV-activated immune response can also reduce the risk of ICC in these patients. Of course, this needs to be confirmed by further large sample research.

Some studies [19, 26, 27] believe that hepatitis B infection (HBsAg+) can promote the occurrence of ICC. However, in our study, there is no significant relationship between hepatitis B infection (HBsAg+) and the occurrence of ICC, and a previous study of China [22] expressed the same point of view as ours. It is reported that both diabetes and alcohol drinking are related to the development of ICC [18, 28], but no obvious relationship between them was found in this study. The possible reason is that the patients selected in this study are those who have received biliary surgery in the past, different from those in other researches. In addition, appeal studies are mostly performed in the Western countries, and the specific situation in China may be different.

Since the study was a single-center retrospective analysis, it may have its own shortcomings, which needs to be confirmed by further multicenter and large-sample research, and the lack of external verification of the nomogram may affect its large-scale application to some extent. Nevertheless, based on the results of the appeal study, we have established a novel and a practical nomogram to predict the risk of ICC in patients underwent previous biliary surgery for gallstones with good sensitivity and specificity. The nomogram has good prediction ability (AUC = 0.753). To the best of our knowledge, this is the first nomogram to predict the risk of ICC in patients with previous biliary tract surgery for gallstones, which is of certain significance in predicting the incidence of ICC in such patients.

Conclusion

This nomogram is helpful to evaluate the risk of ICC in patients with previous biliary tract surgery because of biliary calculi.

Abbreviations

Intrahepatic Cholangiocarcinoma	ICC

Declarations

Ethics approval and consent to participate:

This retrospective study was reviewed and approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Wenzhou Medical University（2020074）.

Consent for publication :

A waiver of written informed consent was granted by the IRB due to the retrospective nature of this study in which de-identified data were used and analyzed.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Author Contributions

Hong Li: Conception and design of the study, revision of the article, administrative support.

Junyu Chen Analysis and interpretation of data, collection and assembly of data, drafting of the article, These authors contributed equally

Lijun Wu , Xiandong Zhu Wangxin Zhou : Collection of data.

Yinhe Tang, Haibiao Wang : Collection of data, critical revision of the article

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Figures

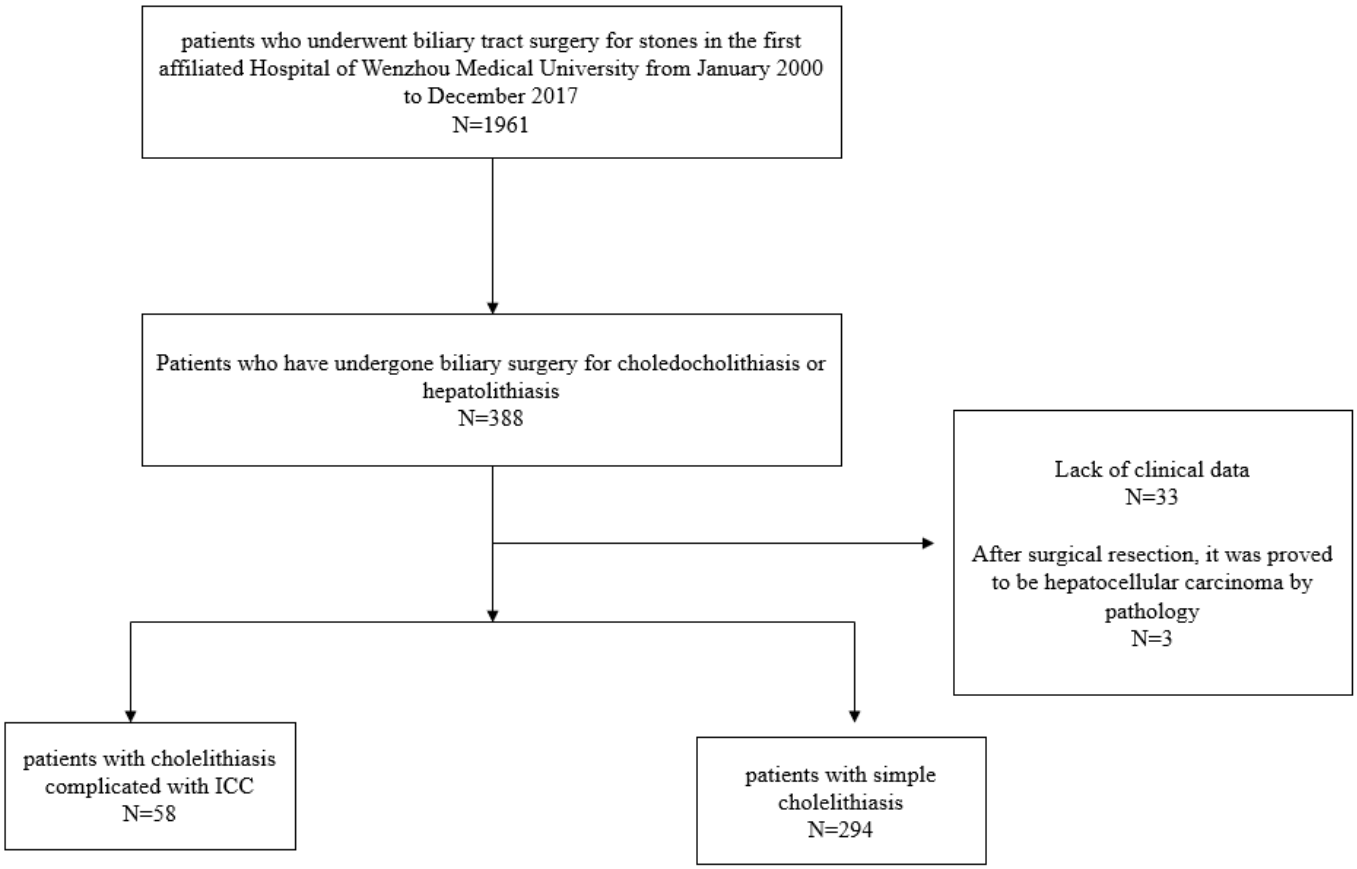

Figure 1

Flow diagram of the study design

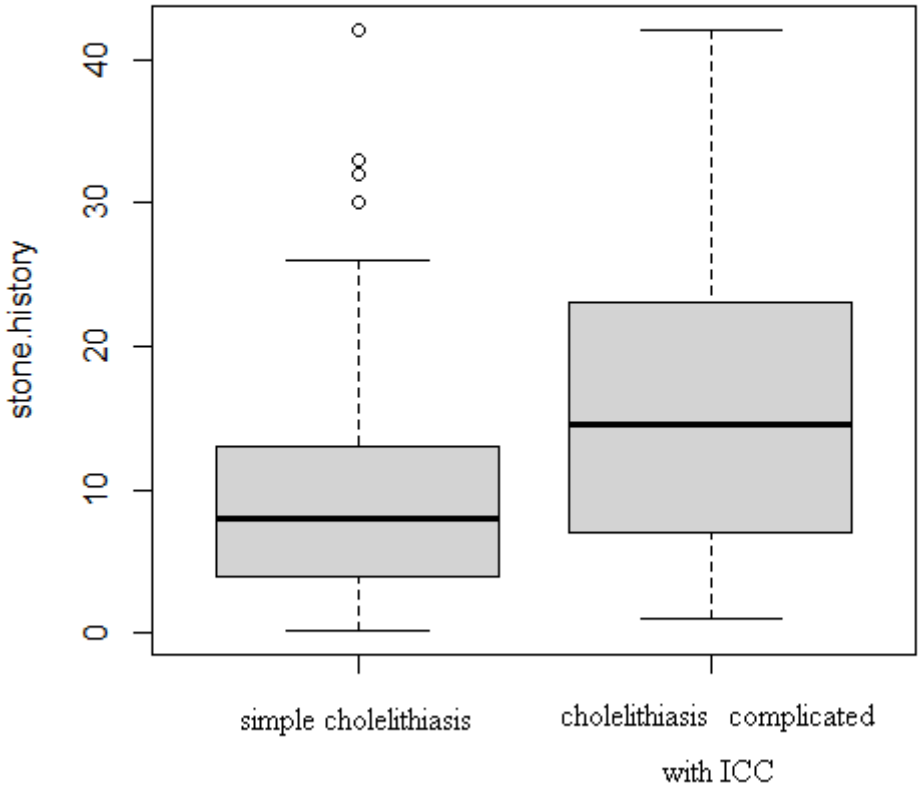

Figure 2

The box chart of the stone history. The lines in each box represented the median of the group. The upper and lower limits of each box represented the 25th and 75th percentiles, respectively. The circle outside the box represented the outliers.

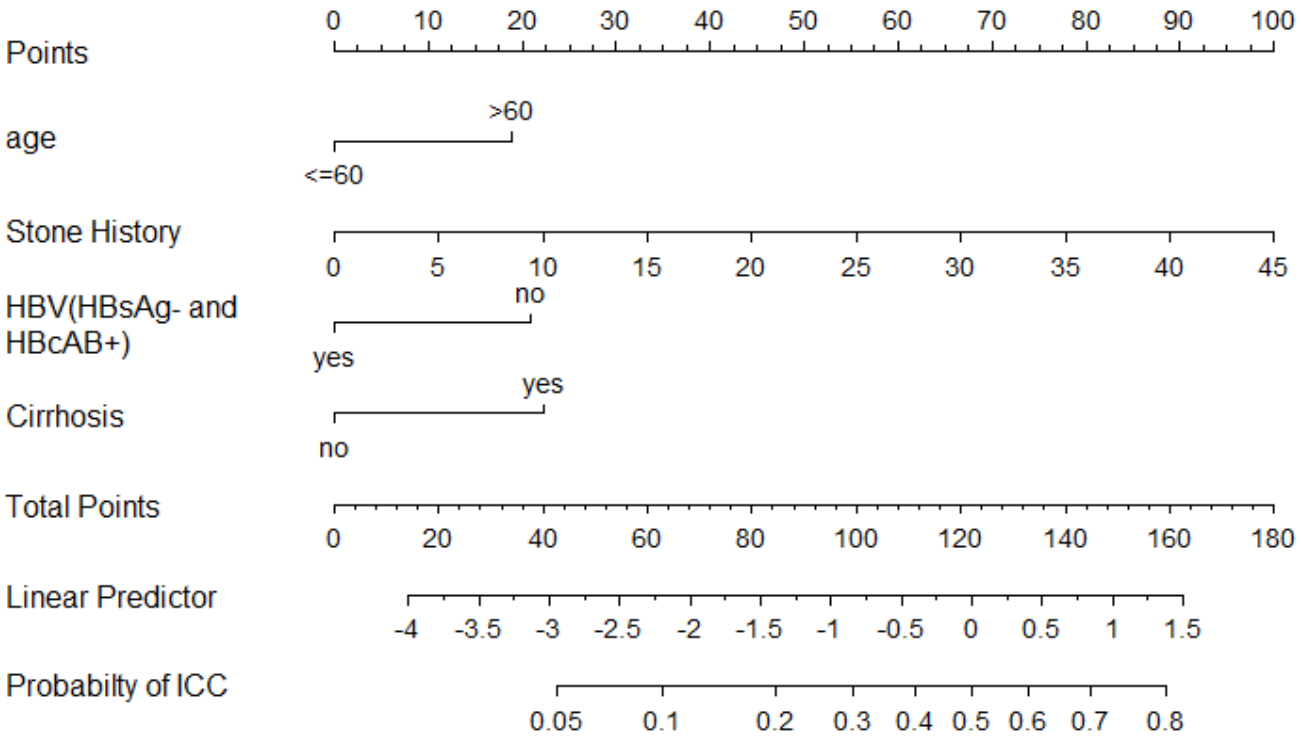

Figure 3

A nomogram predicting the risk of ICC in patients undergoing previous stonegallstone surgery. Note: The preoperative nomogram is was based on four potential independent predictors, which are were determined by multivariate logistic regression analysis, including such as the patient's age (≤ 60 years old, or > 60 years old), liver cirrhosis, stonegallstone course and previous hepatitis B infection (HBsAg- and HBcAb+)..

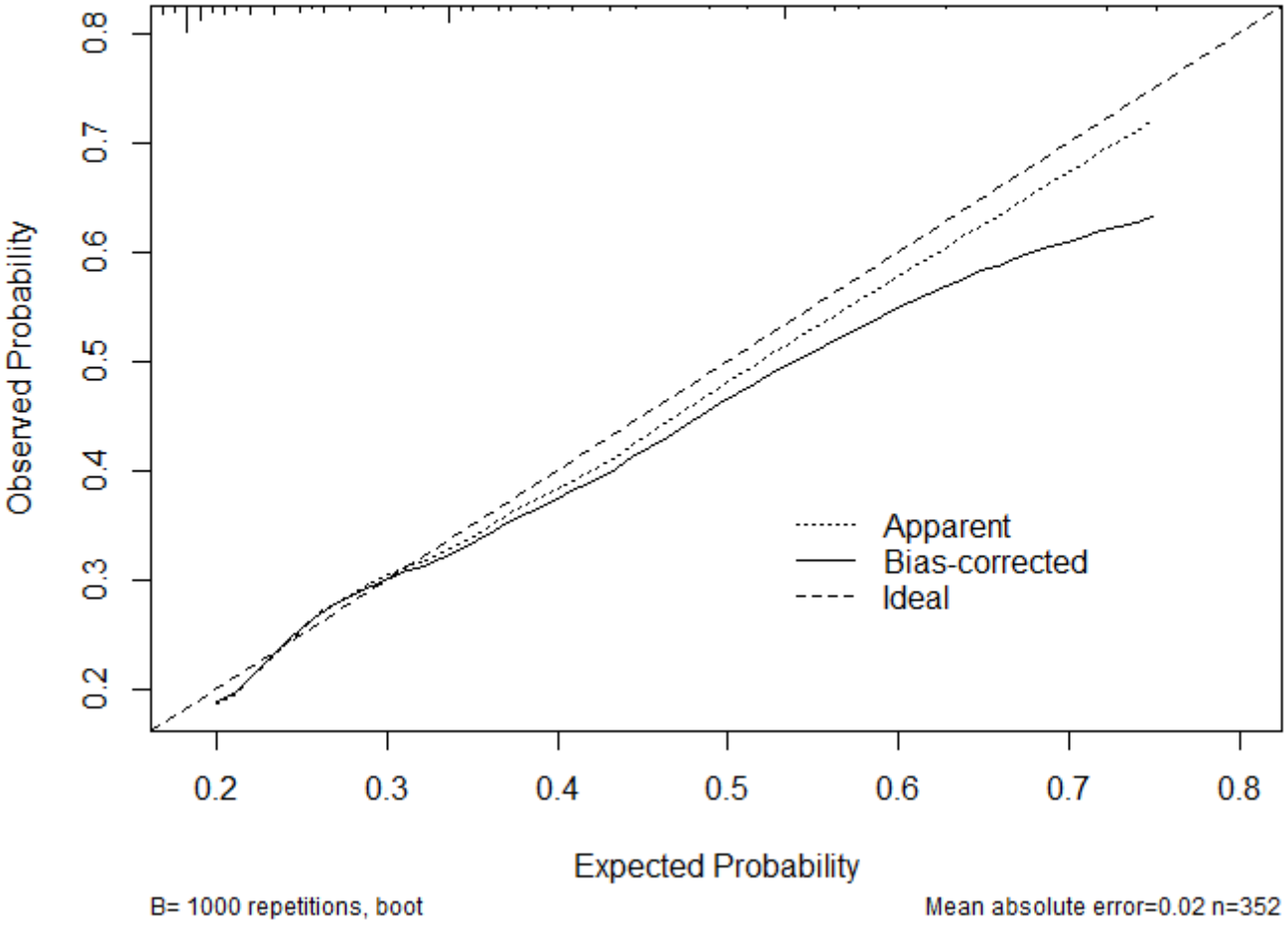

Figure 4

Calibration for predicting the incidence of ICC in patients undergoing previous stone surgery and internal verification with Bootsarap.

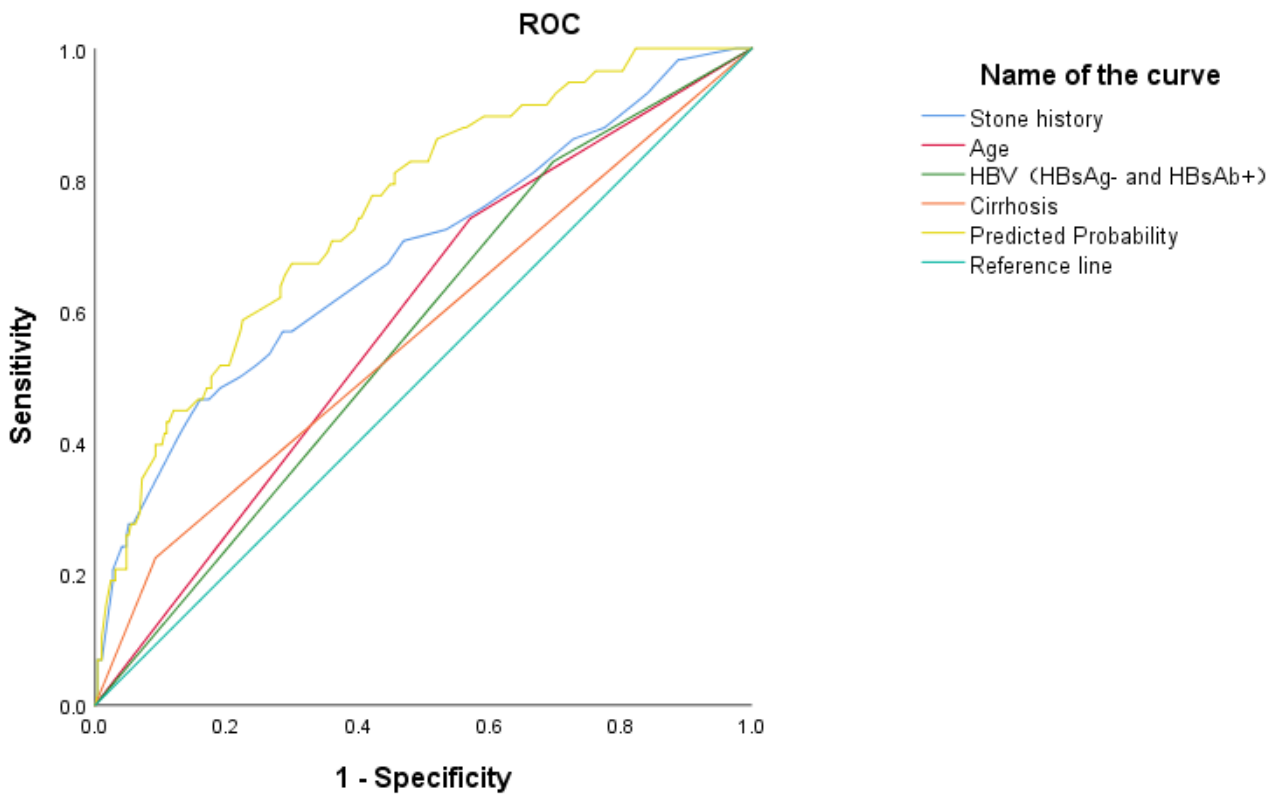

Figure 5

Age, liver cirrhosis, stone history, previous hepatitis B infection and nomogram ROC graph, in which the nomogram AUC was 0.753 (95% CI=0.686-0.818). It is significantly higher than the other four items, and the best cut-off value obtained from the line chart Youden was 0.164. Under this threshold, the sensitivity of the line chart is 70.1%, and the specificity is 67.2%.