A Nomogram-Based Model to Predict Neoplastic Risk For Patients With Gallbladder Polyps

Xudong Zhang
Nanjing Medical University
Jin-Cheng Wang (1057770573@qq.com)
Nanjing Medical University https://orcid.org/0000-0001-9345-2388
Baoqiang Wu
Nanjing Medical University
Tao Li
Nanjing Medical University
Lei Jin
Nanjing Medical University
Yong Wu
Nanjing Medical University
Peng Gao
Nanjing Medical University
Zhen Zhang
Nanjing Medical University
Xihu Qin
Nanjing Medical University
Chunfu Zhu
Nanjing Medical University

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Abstract

Background: Gallbladder polyps (GBPs) assessment seeks to identify early-stage gallbladder carcinoma (GBC). Many studies have analyzed the risk factors for malignant GBPs, and we try to establish a more accurate predictive model for potential neoplastic polyps in patients with GBPs.

Methods: This retrospective study developed a nomogram-based model in a training cohort of 233 GBP patients. Clinical information, ultrasonographic findings, and blood tests were retrospectively analyzed. Spearman correlation and logistic regression analysis were used to identify independent predictors and establish a nomogram model. An internal validation was conducted in 225 consecutive patients. Performance of models was evaluated through the receiver operating characteristic curve (ROC) and decision curve analysis (DCA).

Results: Age, cholelithiasis, CEA, polyp size and sessile were confirmed as independent predictors for neoplastic potential of GBPs in the training group. Compared with other proposed prediction methods, the established nomogram model presented good discrimination ability in the training cohort (area under the curve [AUC]: 0.845) and the validation cohort (AUC: 0.836). DCA demonstrated the most clinical benefits can be provided by the nomogram.

Conclusions: Our developed preoperative nomogram model can successfully evaluate the neoplastic potential of GBPs based on simple clinical variables, that maybe useful for clinical decision-making.

Introduction

Gallbladder polyps (GBPs) are elevated lesions projecting from the gallbladder wall into the lumen, with prevalence of 5–10% in general population [1]. In recent years, the diagnosis of GBPs has been increasing due to widespread use of abdominal ultrasonography [2]. GBPs can be broadly classified as non-neoplastic (pseudopolyps) and neoplastic polyps (true polyps). 70% of GBPs are benign pseudopolyps (without maglignant tendencies), consisting of cholesterol, focal adenomyomatosis or inflammatory polyps[3]. True polyps can be benign (most commonly adenomas) or malignant (i.e. adenocarcinomas). However, only estimated 3% of GBPs are true polyp adenomas with malignant potential [4].

There are a variety of imaging modalities for assessment such as endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and computed tomography (CT). However, preoperative diagnosis of malignant polyp still remains difficult [5]. Due to the lack of clinical trials, there are still no universally convincing indications for surgery. Considering the rapid progression and poor prognosis of gallbladder carcinoma (GBC), cholecystectomy was generally suggested for malignant potential GBPs. Current guidelines for management of GBPs mainly focused on polyp size in which the diameter of more than 10 mm is generally considered as an indication for cholecystectomy [6]. However, polyp number, shape, patient age, and sessile features also have been demonstrated as the high-risk clinical factors in previous studies [7] [8]. In addition, a considerable part of patients who underwent cholecystectomy according to the guidelines proved to be non-neoplastic polyps, and these patients bared unnecessary surgical risks

and economic burdens [9]. Moreover, incidental gallbladder carcinoma in cases with polyps less than 10mm were frequently reported [10] [11].

Therefore, it is necessary to analyze other preoperative clinical information (e.g. clinical characteristics and ultrasound findings) and integrate variables with predictive values. [12]. The aim of this study is to develop a noninvasive preoperative prediction model for assessing the malignancy risk of GBPs.

Materials And Methods

Patients

A total of 573 patients diagnosed with GBPs on ultrasonography in our hospital between January 2015 and September 2020 were retrospectively reviewed. After excluding conditions such as incomplete data and no surgical treatment, 458 cases were included in this study (**Fig.1**). 233 patients between January 2015 and June 2018 were allocated into the training cohort, and the rest 225 from July 2018 to September 2020 were for validation. This retrospective study was approved by the institutional review board of Affiliated Changzhou NO.2 People's Hospital of Nanjing Medical University (Jiangsu, China) ([2017]KY013-01). All patients were informed of the guideline and possible surgical risks. The requirement for written informed consent was waived due to its retrospective nature.

Clinical characteristics (i.e. age, gender, body mass index (BMI), hypertension, diabetes mellitus, fatty liver, viral hepatitis), laboratory parameters (White blood cell (WBC), Alanine transaminase (ALT), Total bilirubin (TBil), Direct bilirubin (DBil), Triglyceride, Total cholesterol (TCH), bile acid (TBA), γ-glutamyltransferase (GGT), lactic dehydrogenase (LDH), D-dimer (DD)) and pathological diagnosis were collected retrospectively from medical records. We also included variables that have been reported associated with malignancy, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) [13]. The pathological diagnosis was classified as carcinoma (n=41), adenoma with atypical hyperplasia(n=15), adenoma (n=38), inflammatory polyps (n=4), cholesterol polyp (n=313), adenomyomatosis (n=36) or mixed pseudopolyps (n=11). According to the guidelines and the malignant risk of adenomas, we classified patients diagnosed with neoplastic polyps (carcinoma, adenoma with atypical hyperplasia and adenoma) into the group with indications for surgery in this study.

Cholelithiasis consists of gallbladder stones and bile duct stones. Clinical symptoms including abdominal pain, bile reflux gastritis and jaundice were recorded. Ultrasonography and laboratory analysis via routine blood tests were performed within 1 week before surgery. Polyp characters were scored according to the abdominal ultrasonography which describe the gallstones, the size and sessile of the polyps. The number of polyps was categorized as either single or multiple, and in multiple polyps, the size of the largest one was recorded. The shape of the polyp was classified as sessile or pedunculated. The thickening of gallbladder wall (GBWT) was demarcated by 5mm [14]. Ultrasonic diagnosis was derived from the preoperative diagnosis report of experienced sonologists.

Clinical factors selection and model establishment

We performed spearman correlation analysis to screen out the variables with significant correlation (P < 0.05) for subsequent multivariate logistic regression analysis. Variables with a P-value less than 0.05 in above analysis were identified as independent factors. Based on the β coefficient of each variable, the prediction model was shown by the understandable nomogram.

Validation

The performance of model was subsequently tested in the independent validation cohort by using the formula and cutoff values derived from the training cohort. And the performance would be compared with Ultrasonic report diagnosis (US-reported) [15], guidelines of Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) [16], European Society of Gastrointestinal and Abdominal Radiology (ESGAR) [7], Chinese Committee of Biliary Surgeons (CCBS) [17], and congeneric scoring system (Korean model) [18]. Details of guidelines are described in Supplement Materials and Methods.

Statistical analysis

Categorical and continuous variables were compared with $\chi 2$ test and the Mann-Whitney U test, respectively. All statistical analyses were performed by R software (version 3.5.1, http://www.r-project.org). The diagnostic performance of models was evaluated by the receiver-operating characteristic curve (ROC) and the area under the curve (AUC). Delong test was used to compare AUC values. Decision curve analysis (DCA) was performed to calculate the net benefit from the use of model at different threshold probabilities [19]. P <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of patients in the training and validation groups were shown in **Table 1**. There was no significant difference between these groups in pathologic records (P = 0.514). The incidence with actual neoplastic potential was 19.3% and 21.8% in two cohorts, respectively. This rate partly suggests that there is considerable nonessential surgery based on guidelines for surgical procedures. No significant difference was found in clinical-ultrasonic characteristics(P>0.05).

Risk Factors for Neoplastic GBPs

In the training cohort, the results showed that age, diabetes, cholelithiasis, CEA, CA199, ultrasonic diagnosis, polyp size, number, sessile and clinical symptoms were simultaneously significant predictive clinical and imaging variables for neoplastic polyps (P < 0.05 for all) (**Table 2**). Then, the multivariable conditional logistic regression analysis identified age, cholelithiasis, CEA, polyp size and sessile as independent factors (**Table 3**). According to the ROC curve analysis, we determined the optimal cut-off value of age and CEA as 58 years and 1.56 ng/ml. Considering most guidelines divided 10mm as the positive value of polyp diameter, and the ROC-induced cutoff value was 15 mm, we defined the 10mm and 15mm in polyp size as cutoff points for three-way classification.

Development and validation of the prediction nomogram

According to the results of the univariate and multivariate analyses, we developed a nomogram incorporating predictive variables to predict neoplastic risk in patients with GBPs preoperatively.

As shown in **Fig. 2A**, age (0, ≤ 58 years; 1, >58 years), cholelithiasis (0, negative; 1, positive), CEA (0, ≤1.56 ng/ml; 1, > 1.56 ng/ml), polyp size (0, <10 mm; 1, ≥ 10 mm and ≤ 15 mm; 2, >15 mm) and sessile (0, pedunculated; 1, sessile). The formula of the weighted value was: Y = 1.194 × [Age] +1.177 × [Cholelithiasis] +1.171 × [CEA] +1.112 × [Polyp size] +1.066 × [Sessile] -3.944.

The nomogram achieved the overall accuracy rate of 84.1%, with a sensitivity of 68.1% and a specificity of 88.2%. Among the 30 false negative cases, only 1 case was GBC. We plotted the ROC curve to compare the discrimination ability of our model to the US-reported, three different kinds of guidelines, and comparable score (Korean model) [18]. As shown in **Fig.2B** and summarized in **Table 4**, the nomogram model obtained the best discrimination ability with the AUC value of 0.846 (95% CI: 0.779, 0.913) in the training cohort. In the validation cohort, our model also yielded the highest AUC of 0.835 (95% CI: 0.765,0.905) compared with the US-reported alone (AUC: 0.659; 95% CI: 0.603, 0.716; $P < 0.001$), JSHBPS guideline (AUC: 0.635; 95% CI: 0.569, 0.702; $P < 0.001$), ESGAR guideline (AUC: 0.617; 95% CI: 0.561, 0.672; $P < 0.001$), CCBS guideline (AUC: 0.658; 95% CI: 0.598, 0.717; $P < 0.001$) and Korean model (AUC: 0.746; 95% CI: 0.663, 0.828; $P < 0.001$).

To evaluate prediction models, we presented the for our model, US-reported, JSHBPS guideline, ESGAR guideline, CCBS guideline and Korean model in **Fig. 3**. Across the reasonable threshold probability ranges in both training and validation groups, DCA graphically showed that the nomogram provided more clinical benefits in predicting malignancy in patients with GBPs than the other methods.

Discussion

This study established and validated a nomogram model to predict neoplastic polyps in patients with GBPs. Age, cholelithiasis, CEA, polyp size and sessile were confirmed as independent predictors for neoplastic risk and were integrated into the nomogram model. Subsequently, our model achieved significantly better diagnostic performance and provided more clinical benefits in comparation of ROC and DCA curve with US-reported, guidelines and Korean model.

Through the data, we found that less than 20% of polyp patients actually need surgery. Considering the selective deviation of admitted patients, the incidence of malignant polyps may be lower than observed. More than 50% of patients included in our study have indications for surgery following the guidelines. Metman et al. found that the prevalence of neoplastic polyps was much lower than reported, and questioned the broad recommendations of guidelines through retrospective study [20]. Consequently, preoperative assessment of GBPs is necessary.

By contrast of the abovementioned AUC and DCA curves, we found that the effectiveness of the three guidelines (JSHBPS, ESGAR and CCBS) for predicting were similar, and Korean model was better than these guidelines but slightly less than our model. Our nomogram model achieved satisfactory accuracy, good reliability and reproducibility. The included factors in our final model such as age, cholelithiasis, polyp size and sessile have been reported as risk factors for gallbladder cancer in many studies [21] [22] [23]. The predictive effects of CEA and CA199 have also been demonstrated [24]. We first established the prediction system in a nomogram way that integrates ultrasonics signature, physiological index and tumor marker. Our model achieved significantly better diagnostic performance and provided more clinical benefits. In recent years, clinical studies on gallbladder polyps have upsurged. For instance, Velidedeoğlu et al. doubt about the necessity of cholecystectomy in patients with symptomatic GBPs [25]. Xiaofang Zhao considered dyslipidaemia is associated with GBPs formation, and found non-high density lipoprotein cholesterol ratio is an independent factor to the risk of GBP formation in China's cohort [26]. Meanwhile, fatty liver was also found to be an independent risk factor for gallbladder polyps grow [27]. As for the preoperative evaluation of GPBs, Shinji Onda et al. developed a scoring system for GBC based on age, gallstones, polyp size, solitary and sessile polyp through ultrasonography and CT [28]. In comparison with serum biomarker, although enhanced CT is more sensitive to tumors, but its expensive price and radiation make it not a good choice for follow-up indicators. We hope to develop a non-invasive and user-friendly model for predicting malignant polyps based on easily available data. Not only diagnostic performance but also cost and applicability should be considered. All the indicators included in our model can be obtained through physical examination of outpatient. Modelling by using nomograms has been used in a number of studies and has been shown to be effective [29] [30]. We recommend that patients who are judged to be at high risk through our diagnostic model could be supplemented with CT scans before surgery to further confirm the diagnosis and rule out gallbladder cancer abdominal metastasis. In addition, compared to artificially assigning risk factors, assigning corresponding weights to variables through statistical methods could get more objectively extract information from clinical data.

Unlike the adenoma–carcinoma sequence that is well described for colonic polyps, the adenoma–carcinoma sequence in the gallbladder is less well understood. However, studies have also shown a link between these two polyps of different tissue sources [31]. The evidence suggests that at least some gallbladder adenocarcinomas have arisen in pre-existing adenomas, therefore, some scholars believe that atypical hyperplasia of gallbladder adenoma is a precancerous lesion [32]. If GBC is confined to the connective tissue of gallbladder wall (stage I and II), the 5-year survival rates are much more favorable at 57–92% [33]. Therefore, it is important to early detect and manage GBC. Considering the malignant tendency of gallbladder adenoma and the recommendations of the guidelines, we include adenoma into the recommended cholecystectomy group in our model. Consequently, most cases in the false-negative group detected by our model were adenomas. Before the malignant transformation of gallbladder adenoma, their growth characteristics are different from that of malignant polyps. Currently, the diagnosis can only be confirmed by postoperative pathology. If the number of cases is further expanded, attempts can be made to distinguish the polyps with early malignant and adenoma. Although their

coping methods are both surgical treatments, the accuracy of the system can be improved and is also a good way to study the progress of GBPs malignant transformation.

In the process of data collection and analysis, we also paid attention to some risk factors that were less concerned before. For instance, Spearman correlation results showed that diabetes and CA199 were risk factors. Systematic review have indicated that compared with non-diabetic individuals, patient with diabetes had an increased risk of GBC and had a higher mortality [34] [35]. Meanwhile, we found that in addition to CEA and CA199 [36], CA724 can also become a biomarker for GBC, but there were too much data missing, which cannot be presented in this article. We are prospectively collecting relevant results and looking forward to obtaining stronger evidence. Given that the system is simple and easy to understand, we have also made the model into a clinical mini electronic software to promote it to the public, so that GBPs patients can follow-up by themselves and receive more accurate and detailed clinical recommendations.

As mentioned before, several limitations in this study should be noted. Firstly, inherent selection biases cannot be avoided due to the retrospective nature of this study. The enrolled patients were those who underwent cholecystectomy due to the possibility of malignancy, thus, many cases thought to have benign polyps and did not undergo surgery were excluded from this study. Moreover, due to the low incidence of GBC, the total number of positive cases included in this article is low. Secondly, the accuracy of ultrasound diagnosis is highly dependent on the professional level of the operator. Incorporating novel specific tumor indicators such as CA724 or texture analysis of ultrasound signals in prospective study can further improve the accuracy of the model. Furthermore, this nomogram was established and validated on the basis of data obtained from a single center. Relatively recognized risk factors such as Indian ethnicity and primary sclerosing cholangitis (PSC) were not involved in this study. We share this model and hope that more scholars may pay attention to this and cooperate in multi-center prospective research to externally validate the model.

Conclusion

To sum up, we proposed an accurate and user-friendly prediction model based on simple clinical variables to evaluate the neoplastic polyps in patients with GBPs. Furthermore, the model helps surgeons and patients to make more accurate surgical decisions and facilitates the early diagnosis and treatment of GBC.

Abbreviations

GBPs, gallbladder polyps; GBC, gallbladder carcinoma; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; CT, computed tomography; WBC, white blood cell; ALT, alanine transaminase; TBil, total bilirubin; DBil, direct bilirubin; TCH, total cholesterol; TBA, bile acid; GGT, γ-glutamyltransferase; LDH, lactic dehydrogenase; DD, D-dimer; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; PSC, primary sclerosing cholangitis; ROC, receiver-operating characteristic

curve; AUC, area under the curve; DCA, decision curve analysis; US-reported, ultrasonic report diagnosis; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; ESGAR, European Society of Gastrointestinal and Abdominal Radiology; CCBS, Chinese Committee of Biliary Surgeons.

Declarations

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Authors Contributions

BQ Wu, XD Zhang, Y Wu, Z Zhang and P Gao collected data; JC Wang and L Tao analyzed data; L Jin, and XH Qin participated in research design; XD Zhang and JC Wang wrote the manuscript; XH Qin supervised the study; CF Zhu revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

This retrospective study was approved by the Hospital research ethics committee ([2017]KY013-01). The requirement for written informed consent was waived due to its retrospective nature.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Author details

1 Department of Hepato-biliary-pancreatic Surgery, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, 213000, P.R. China

2 Nanjing Medical University, Nanjing 210000, P.R. China.

3 Dalian Medical University, Liaoning 116000, P.R. China.

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Tables

Table.1 Baseline Characteristics of patients included in this study.

Baseline Characteristics	Training (n=233)	Validation (n=225)	*P*
Age (years, mean±SD)	49.47±13.53	49.11±14.11	0.781
Gender			0.658
Male	106	107	
Female	127	118	
Physical condition			
BMI (kg/m^2)	24.14±3.13	24.05±3.14	0.763
Hypertension, n (%)	59(25.3)	52(23.1)	0.581
Diabetes, n (%)	21(9)	14(6.2)	0.261
Fatty liver, n (%)	50(21.5)	45(20.0)	0.701
Cholelithiasis, n (%)	53(22.7)	56(24.9)	0.591
Viral hepatitis, n (%)	13(5.6)	8(3.6)	0.301
Laboratory findings			
WBC (10^9/L)	5.89±1.75	6.10±1.85	0.199
DD (mg/L)	0.61±1.78	0.46±0.84	0.257
ALT (U/L)	24.71±21.96	27.60±27.00	0.209
TBil (μmol/L)	13.82±9.49	14.85±19.37	0.470
DBil (μmol/L)	4.66±5.54	5.89±16.22	0.280
Triglyceride(mmol/L)	1.52±1.05	1.64±1.02	0.213
TCH (mmol/L)	4.61±0.98	4.62±0.98	0.852
TBA (μmol/L)	5.47±10.72	5.44±11.89	0.975
GGT (U/L)	33.47±36.65	48.0±115.57	0.068
LDH (U/L)	167.4±55.75	172.67±43.05	0.260
Tumor markers		±	
AFP (ng/ml)	2.81±2.12	2.75±1.63	0.708
CEA (ng/ml)	2.12±2.14	2.22±2.65	0.657
CA199 (U/ml)	20.57±80.89	28.1±109.14	0.401
Ultrasonic diagnosis			0.517
Malignant or suspected, n (%)	56(24.0)	60(26.7)	

Benign, n (%)	177(76.0)	165(73.3)	
Polyp characters			
Polyp size (mm)	9.60±5.10	9.83±6.69	0.679
Single polyp, n (%)	115(49.4)	112(49.8)	0.928
Sessile polyp, n (%)	84(36.1)	83(36.9)	0.852
GBWT, n (%)	87(37.3)	89(39.6)	0.626
Clinical symptoms, n (%)	95(40.8)	76(33.8)	0.122
Neoplastic polyps, n (%)	45(19.3)	49(21.8)	0.514

NOTE: BMI= Body Mass Index, WBC= white blood cell, DD= D-dimer, ALT= Alanine transaminase，TBil= Total bilirubin, DBil= Direct bilirubin, TCH= Total cholesterol, TBA= bile acid, GGT= γ-glutamyltransferase, LDH= lactic dehydrogenase, AFP= alpha-fetoprotein, CEA= carcinoembryonic antigen, CA199= carbohydrate antigen 199, GBWT= gallbladder wall thickening.

Table.2 comparison between neoplastic polyp and pseudopolyps (non-neoplastic).

Characteristics	Neoplastic (n=45)	Pseudopolyps (n=188)	*P*
Age (years, mean±SD)	57.49±13.53	47.55±12.84	*<0.001
Gender			0.875
Male	20(44.4)	86(45.7)	
Female	25(55.6)	102(54.3)	
Physical condition			
BMI (kg/m^2)	24.18±3.32	24.13±3.10	0.829
Hypertension, n (%)	15(33.3)	44(23.4)	0.170
Diabetes, n (%)	8(17.8)	13(6.9)	*0.023
Fatty liver, n (%)	8(17.8)	42(22.3)	0.504
Cholelithiasis, n (%)	23(51.1)	30(16.0)	*<0.001
Viral hepatitis, n (%)	4(8.9)	9(4.8)	0.283
Laboratory findings			
WBC (10^9/L)	6.47±2.31	5.75±1.56	0.172
DD (mg/L)	1.06±2.08	0.52±1.72	0.071
ALT (U/L)	24.39±18.97	24.78±22.66	0.727
TBil (μmol/L)	15.61±14.92	13.38±7.65	0.842
DBil (μmol/L)	6.81±11.61	4.14±2.26	0.162
Triglyceride(mmol/L)	1.64±1.00	1.49±1.06	0.333
TCH (mmol/L)	4.44±0.80	4.65±1.01	0.193
TBA (μmol/L)	8.97±22.96	4.63±3.86	0.626
GGT (U/L)	39.29±47.83	32.07±33.43	0.853
LDH (U/L)	173.98±87.45	165.83±45.19	0.805
Tumor markers		±	
AFP (ng/ml)	3.25±3.31	2.70±1.72	0.511
CEA (ng/ml)	3.61±4.04	1.76±1.10	*<0.001
CA199 (U/ml)	59.82±178.68	11.17±12.11	*0.001
Ultrasonic diagnosis			*<0.001

Malignant or suspected, n (%)	22(51.1)	34(18.1)	
Benign, n (%)	23(48.9)	154(81.9)	
Polyp characters			
Polyp size (mm)	13.93±8.30	8.56±3.24	*<0.001
Single polyp, n (%)	29(64.4)	86(45.7)	*0.025
Sessile polyp, n (%)	31(68.9)	53(28.2)	*<0.001
GBWT, n (%)	18(40.0)	69(36.7)	0.681
Clinical symptoms, n (%)	26(57.8)	69(36.7)	*0.010

NOTE: BMI= Body Mass Index, WBC= white blood cell, DD= D-dimer, ALT= Alanine transaminase，TBil= Total bilirubin, DBil= Direct bilirubin, TCH= Total cholesterol, TBA= bile acid, GGT= γ-glutamyltransferase, LDH= lactic dehydrogenase, AFP= alpha-fetoprotein, CEA= carcinoembryonic antigen, CA199= carbohydrate antigen 199，GBWT= gallbladder wall thickening.

Table.3 Predictive Spearman correlation and multivariate regression model parameters.

Variables	Spearman correlation		Multivarible analysis		ROC analysis	
	R	*P*	β	*P*	AUC	Cutoff
Age	0.253	<0.001	0.042	0.009	0.685	58
Gender	-0.010	0.876	NA	NA		
BMI	-0.140	0.830	NA	NA		
Hypertension	0.090	0.170	NA	NA		
Diabetes	0.150	0.022	NA	0.39		
Fatty liver	-0.044	0.505	NA	NA		
Cholelithiasis	0.331	<0.001	-1.06	0.019	NA	NA
Viral hepatitis	0.071	0.284	NA	NA		
WBC (109/L)	0.090	0.173	NA	NA		
DD (mg/L)	0.119	0.071	NA	NA		
ALT (U/L)	-0.023	0.727	NA	NA		
TBil (μmol/L)	0.013	0.842	NA	NA		
DBil (μmol/L)	0.092	0.163	NA	NA		
Triglyceride(mmol/L)	0.064	0.334	NA	NA		
TCH (mmol/L)	-0.085	0.194	NA	NA		
TBA (μmol/L)	0.032	0.627	NA	NA		
GGT (U/L)	0.012	0.854	NA	NA		
LDH(U/L)	0.016	0.805	NA	NA		
AFP (ng/ml)	0.043	0.513	NA	NA		
CEA (ng/ml)	0.283	<0.001	0.35	0.022	0.707	1.56
CA199 (U/ml)	0.221	0.003	NA	0.573		
Ultrasonic diagnosis	0.285	<0.001	NA	0.436		
Polyp size (mm)	0.287	<0.001	0.15	0.005	0.707	15
Single polyp	-0.148	0.024	NA	0.264		
Sessile polyp	0.335	<0.001	-1.045	0.017	NA	NA
GBWT	0.027	0.683	NA	NA		
Clinical symptoms	0.169	0.011	NA	0.926		

NOTE: BMI= Body Mass Index, WBC= white blood cell, DD= D-dimer, ALT= Alanine transaminase，TBil= Total bilirubin, DBil= Direct bilirubin, TCH= Total cholesterol, TBA= bile acid, GGT= γ-glutamyltransferase, LDH= lactic dehydrogenase, AFP= alpha-fetoprotein, CEA= carcinoembryonic antigen, CA199= carbohydrate antigen 199，GBWT= gallbladder wall thickening.

Table.4 Diagnostic performances of all methods for GBPs in the training and validation cohort.

	Training (n=233)	Validation (n=225)	Training vs. Validation
Methods	**AUROC (95% CI)**	**AUROC (95% CI)**	**Delong test**
Nomogram model	0.846 (0.779, 0.913)	0.835 (0.765, 0.905)	*P* = 0.826
US-reported	0.639 (0.561, 0.717)	0.659 (0.603, 0.716)	*P* = 0.683
JSHBPS guideline	0.613 (0.544, 0.682)	0.635 (0.569, 0.702)	*P* = 0.642
ESGAR guideline	0.591 (0.513, 0.670)	0.617 (0.561, 0.672)	*P* = 0.606
CCBS guideline	0.632 (0.565, 0.699)	0.658 (0.598, 0.717)	*P* = 0.573
Korean model	0.753 (0.670, 0.836)	0.746 (0.663, 0.828)	*P* = 0.901
Delong test (Comparison of AUR)			
Model vs. US-reported	*P* < 0.001	*P* < 0.001	
Model vs. JSHBPS	*P* < 0.001	*P* < 0.001	
Model vs. ESGAR	*P* < 0.001	*P* < 0.001	
Model vs. CCBS	*P* < 0.001	*P* < 0.001	
Model vs. Korean model	*P* = 0.010	*P* = 0.007	

Note: CI, confidence interval, AUROC, area under the receiver operating characteristic, JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery,

ESGAR, European Society of Gastrointestinal and Abdominal Radiology, CCBS, Chinese Committee of Biliary Surgeons.

Figures

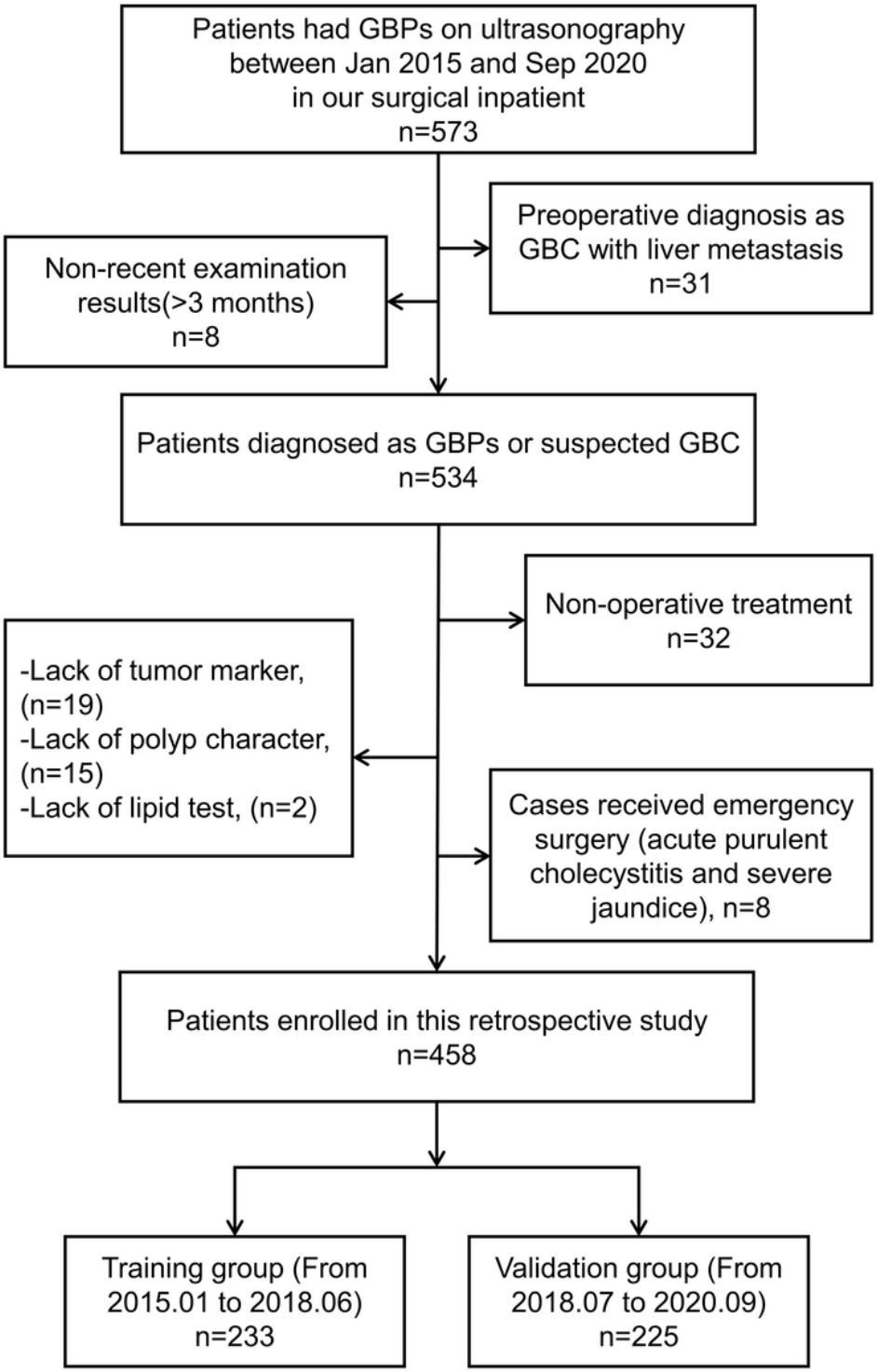

Figure 1

Patient selection flowchart. GBPs, gallbladder polyps; GBC, gallbladder carcinoma.

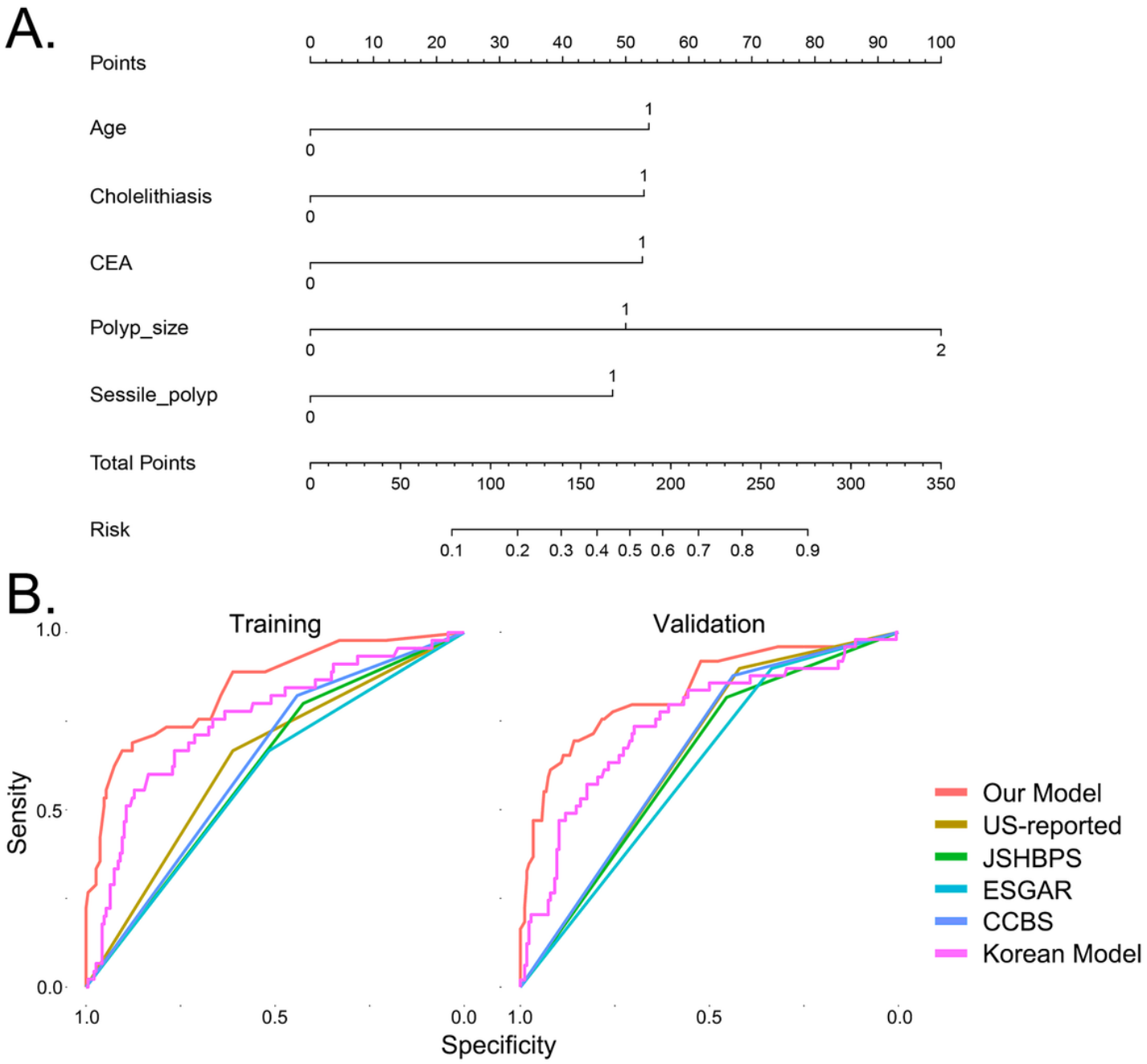

Figure 2

Developed nomogram presented with ROC. A. The nomogram was established due to the training cohort, with age, cholelithiasis, CEA, polyp size and sessile incorporated. B. Comparison of ROC curves between our model, US-reported, JSHBPS guideline, ESGAR guideline, CCBS guideline and Korean model in the training and validation.

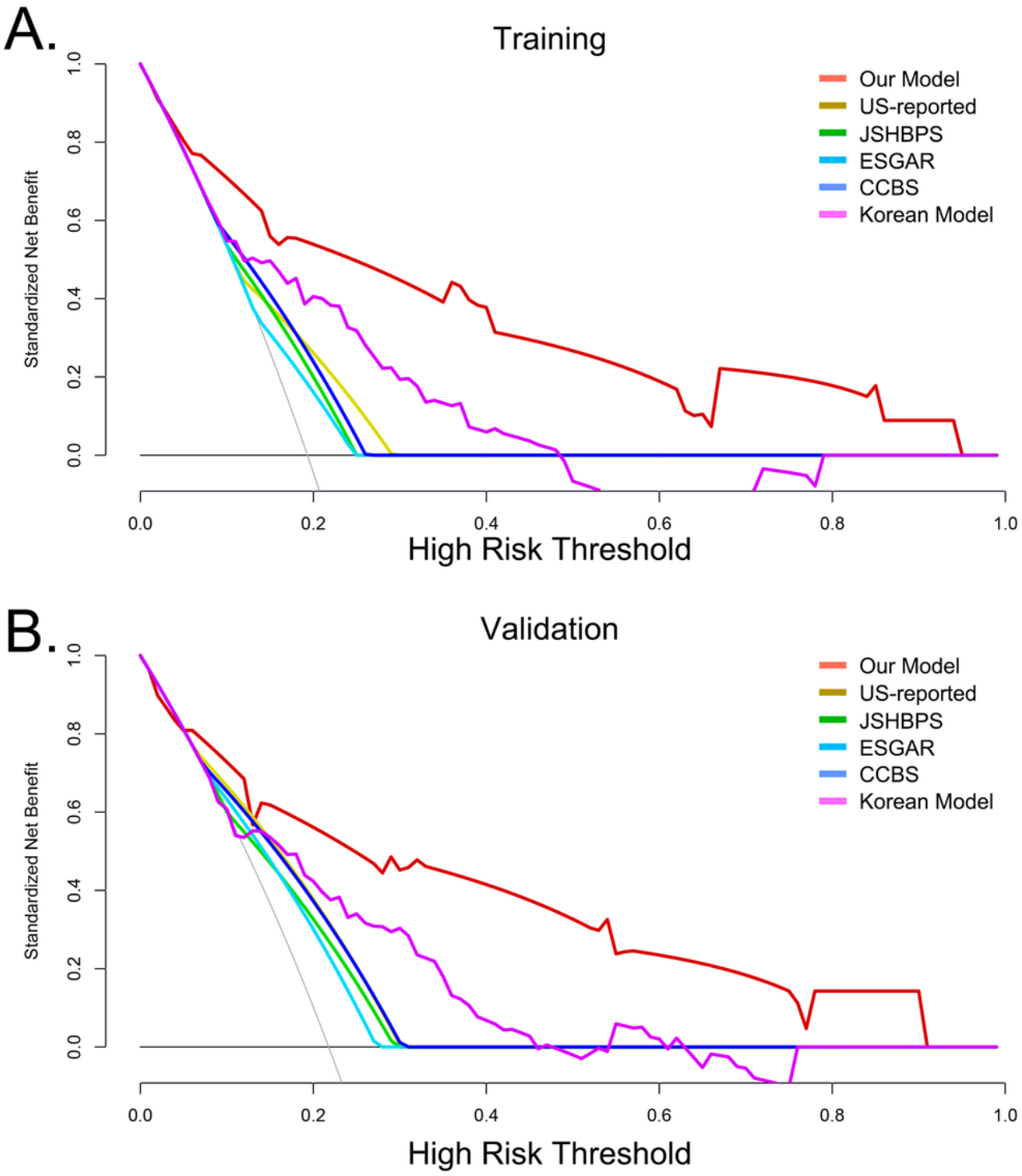

Figure 3

Decision curve analysis for each prediction method in the training (A) and validation (B) dataset. The y-axis measures the net benefit.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementMaterialsandMethods.docx