A Nomogram-based Model to Predict Neoplastic Risk for Patients with Gallbladder Polyps

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Received: 23 February 2021  |  Revised: 14 May 2021  |  Accepted: 2 June 2021  |  Published: 30 June 2021

Abstract

Background and Aims: Gallbladder polyp (GBP) assessment aims to identify the early stages of gallbladder carcinoma. Many studies have analyzed the risk factors for malignant GBPs. In this retrospective study, we aimed to establish a more accurate predictive model for potential neoplastic polyps in patients with GBPs. Methods: We developed a nomogram-based model in a training cohort of 233 GBP patients. Clinical information, ultrasonographic findings, and blood test findings were analyzed. Mann-Whitney U test and multivariate logistic regression analyses were used to identify independent predictors and establish the nomogram model. An internal validation was conducted in 225 consecutive patients. Performance and clinical benefit were compared with the five other methods.

Results: Age, cholelithiasis, carcinoembryonic antigen, polyp size, and sessile shape were confirmed as independent predictors of GBP neoplastic potential in the training group. Compared with five other proposed prediction methods, the established nomogram model presented better discrimination of neoplastic GBPs in the training cohort (area under the curve [AUC]: 0.846) and the validation cohort (AUC: 0.835). DCA demonstrated that the greatest clinical benefit was provided by the nomogram compared with the other five methods.

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

Keywords: Gallbladder polyps; Neoplastic polyp; Preoperative diagnosis; Nomogram model

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AUC, area under the curve; BMI, body mass index; CA199, carbohydrate antigen 199; CCBS, Chinese Committee of Biliary Surgeons; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; DBil, direct bilirubin; DCA, decision curve analysis; DO, D-dimer; ESGAR, European Society of Gastrointestinal and Abdominal Radiology; GBC, gallbladder carcinoma; GBPs, gallbladder polyps; GBWT, gallbladder wall thickening; GGT, γ-glutamyl transferase; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; LDH, lactic dehydrogenase; ROC, receiver-operating characteristic curve; TBA, total bile acid; TBI, total bilirubin; TCH, total cholesterol; US, ultrasonographic imaging.

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This article has been published in Journal of Clinical and Translational Hepatology at https://doi.org/10.14218/JCTH.2021.00078 and can also be viewed on the Journal’s website at http://www.jcthnet.com.

Introduction

Gallbladder polyps (GBPs) are elevated lesions that protrude from the gallbladder wall into the lumen, with a prevalence of 5–10% in the general population.1 In recent years, the diagnosis of GBPs has increased because of widespread use of abdominal ultrasonography.2 GBPs are categorized broadly as non-neoplastic (pseudopolyps) and neoplastic (true) polyps. Approximately 70% of GBPs are benign (without malignant tendencies) and are represented by cholesterol, focal adenomyomatosis, and inflammatory pseudopolyps.3 True polyps can present as benign (most commonly adenomas) or malignant adenocarcinomas or metastases. However, an estimated 3% of GBPs are true polyp adenomas that have malignant potential.4 There are various imaging modalities for GBP assessment, such as endoscopic ultrasonography, magnetic resonance imaging, and computed tomography (CT). However, preoperative diagnosis of malignant polyps remains difficult.5 Because of a lack of clinical trials, there are no universally convincing indications for surgery. Considering the rapid progression and poor prognosis of gallbladder carcinoma (GBC), cholecystectomy is generally suggested for GBPs with malignant potential. Current guidelines for management of GBPs mainly focus on polyp size, and cholecystectomy is recommended when polyp diameter is >10 mm.6 However, previous studies have demonstrated that polyp number and shape, patient age, and sessile features are also high-risk factors for GBP malignancy.7,8

A considerable number of patients who underwent cholecystectomy in accordance with GBP management guidelines were shown to have non-neoplastic polyps.9 These patients experienced unnecessary surgical risks and economic burdens. Moreover, incidental GBC in cases with polyps <10 mm have been reported.10,11 Therefore, it is necessary to...
analyze other preoperative clinical characteristics and ultrasound findings that may be used to integrate variables with greater predictive value for GBP management. The aim of this study was to develop a noninvasive, preoperative prediction model for assessing the malignancy risk of GBPs.

Methods

Patients

We reviewed the medical records of 573 patients diagnosed with GBPs by ultrasonography in our hospital between January 2015 and September 2020. Exclusion criteria were: (1) preoperative diagnosis of GBC with liver metastasis (n=31); (2) non-recent examination results (>3 months) (n=8); (3) non-operative treatment (n=32); (4) lack of tumor markers (n=19); (5) lack of polyp characteristics (n=15); (6) lack of lipid tests (n=2); and (7) patients who received emergency surgery (e.g., for acute purulent cholecystitis and severe jaundice) (n=8). After exclusions, 458 cases were included in this study (Fig. 1), and 233 of these patients from between January 2015 and June 2018 were allocated to the training cohort. The remaining 225 patients from July 2018 to September 2020 were included in the validation cohort.

This retrospective study was approved by the Institutional Review Board of The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University, Jiangsu, China (approval number [2020]KY222-01). The requirement for written informed consent from the patients was waived because of the retrospective nature of this study. However, at the time of treatment, all patients were informed of the GBP management guidelines and possible surgical risks.

Clinical data and pathological diagnoses were collected from medical records. Clinical characteristics included age,
sex, body mass index, and the presence of hypertension, diabetes mellitus, fatty liver, or viral hepatitis. Laboratory measurements included white blood cell counts and blood levels of alanine transaminase, total bilirubin, direct bilirubin, triglycerides, total cholesterol, total bile acids, γ-glutamyl transpeptidase, lactate dehydrogenase, and D-dimer. We included other blood measurements that are associated with malignancy, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19–9 (CA19–9).13 The pathological diagnoses were categorized as carcinoma (n=41), adenoma with atypical hyperplasia (n=15), adenoma (n=38), inflammatory polyps (n=4), cholesterol polyps (n=313), adenomyomatosis (n=36), or mixed pseudopolyps (n=11). In accordance with the guidelines and malignant risk of adenomas, we classified patients who were diagnosed with neoplastic polyps (carcinoma, adenoma with atypical hyperplasia, and adenoma) into the group with indications for surgery. Ultrasonography and laboratory analysis of routine blood tests were performed within 1 week before surgery. Clinical symptoms of cholelithiasis were recorded, including abdominal pain, bile reflux gastritis, and jaundice. Polyp characteristics were scored according to the abdominal ultrasonography, which identified gallstones and size and shape of the polyps. The number of polyps was categorized as either single or multiple. For multiple polyps, the size of the largest was recorded. The shape of the polyp was classified as sessile or pedunculated. The threshold for thickening of the gallbladder wall was set at 5 mm.14 Ultrasonic diagnoses were derived from the preoperative diagnosis reports from experienced sonographers.

Validation

The performance of the model was subsequently tested in the independent validation cohort by using the former and cutoff values derived from the training cohort. Model performance was compared with the ultrasonic report diagnosis (US-reported),15 guidelines from the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS),16 European Society of Gastrointestinal and Abdominal Radiology (ESGAR),17 and Chinese Committee of Biliary Surgeons (CCBS),18 and the Korean scoring model.19 These methods, derived from guidelines and previous studies, are summarized in Table 1. Details of these guidelines are described in the Supplemental File 1.

Statistical analysis

Categorical and continuous variables were compared using the χ² and Mann-Whitney U tests, respectively. We performed the χ² test or Mann-Whitney U test to determine the variables with significant differences between the training and validation groups, for inclusion in subsequent multivariate logistic regression analysis. Variables with a p-value <0.05 in multivariate logistic regression analysis were identified as independent factors. Based on the β coefficient of each variable, the prediction model was demonstrated by the nomogram. All statistical analyses were performed by R software (version 3.5.1; http://www.r-project.org). The diagnostic performance of the model was evaluated using receiver-operating characteristic (ROC) curve and area under the curve (AUC) analyses. The Delong test was used to compare AUC values. Decision curve analysis (DCA) was performed to calculate the net benefit from the use of the model at different threshold probabilities. A p <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the patients in the training and validation groups are shown in Table 2. There were no significant differences in pathological markers between these two groups. The incidences of GBPs with neoplastic potential were 19.3% and 21.8% in the training and validation cohorts, respectively. These rates suggest that there was considerable nonessential surgery based on the guidelines for GBP surgical management. No significant differences were found for clinical or ultrasonographic characteristics between the two groups.

Risk factors for neoplastic GBPs

In the training cohort, age, diabetes, cholelithiasis, CEA, CA19–9, ultrasonic diagnosis, polyph size, number, sessile shape, and clinical symptoms were predictive clinical and imaging variables for neoplastic GBPs (p<0.05) (Table 3). Multivariate conditional logistic regression analysis identified age, cholelithiasis, CEA levels, polyp size, and sessile shape as independent factors that were associated with neoplastic GBP risk (Table 4). According to ROC curve analysis, we determined that the optimal cut-off values for age and CEA were 58 years and 1.56 ng/mL, respectively. Most of the management guidelines used a polyp diameter of 10 mm as a positive indicator of neoplastic risk. However, our ROC cutoff value for polyp diameter was 15 mm. Therefore, we defined both the 10-mm and 15-mm polyp diameters as

| Guideline or model | Instructions for surgical indications |
|--------------------|---------------------------------------|
| JSHBPS             | Sessile gallbladder polyp and diameter ≥10 mm. |
| ESGAR              | Gallbladder polyps ≥10 mm, polyps <10 mm but patient have symptoms that are attributable to the gallbladder (cholelithiasis or inflammation), polyps 6–9 mm with risk factors (age >50 years, primary sclerosing cholangitis, Indian ethnicity, or sessile) |
| CCBS               | Diameter ≥10 mm, combined gallbladder stones or cholecystitis, single or sessile polyps, with fast growth rate (growth rate >3 mm/6 months), adenomatous polyps |
| US-reported        | Based on the size (>10 mm), gallbladder wall thickening (>4 mm), echo intensity (inhomogeneous), procellaneous gallbladder, shape of the polyp and boundary with the surrounding tissues (irregular), diagnosis made by experienced sonologists. |
| Korean Model       | PS (predictive score) = −7.3633 + 0.0374*[age] + 0.6667*[polyp number] + 1.5784*[sessile] + 0.2189*[polyp size]. Probability of neoplastic GBP = ePS / (1 + ePS), where e = 2.7182. |

Table 1. Methods derived from guidelines and previous studies.
cutoff points for a three-way classification in the nomogram as described below.

**Development and validation of the prediction nomogram**

Using the results of the univariate and multivariate analyses, we developed a nomogram that incorporated the preoperative predictive variables for neoplastic risk in patients with GBPs. The scoring points for the nomogram are shown in Figure 2A for 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 shape (0, pedunculated; 1, sessile). The formula for the weighted value was: $Y=1.194 \times \text{age} + 1.177 \times \text{cholelithiasis} + 1.171 \times \text{CEA} + 1.112 \times \text{polyp size} + 1.066 \times \text{sessile} - 3.944$.

The nomogram achieved an overall accuracy rate of 84.1%, with a sensitivity and specificity of 68.1% and 88.2%, respectively. Among the 30 false negative cases, only 1 case was GBC. We plotted the ROC curves to compare the discrimination abilities among our model, the US-reported model, the JSHBPS, ESGAR, and CCBS guidelines, and the Korean scoring model described above. As shown in Figure 2B and summarized in Table 5, the greatest discrimination ability, as demonstrated by the AUC, was observed in our nomogram.

### Table 2. Baseline characteristics of patients included in this study

| Baseline characteristics | Training, $n=233$ | Validation, $n=225$ | $p$ |
|--------------------------|------------------|---------------------|----|
| Age in years, mean±SD    | 49.47±13.53      | 49.11±14.11         | 0.781 |
| Sex                      |                  |                     |     |
| Male                     | 106              | 107                 | 0.658 |
| Female                   | 127              | 118                 |     |
| Physical condition       |                  |                     |     |
| BMI (kg/m$^2$)           | 24.14±3.13       | 24.05±3.14          | 0.763 |
| 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      |                  |                     |     |
| 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 |
| Triglycerides (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 |
| 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 |

BMI, body mass index; DD, D-dimer; ALT, alanine transaminase; TBil, total bilirubin; TCH, total cholesterol; TBA, total bile acid; GGT, γ-glutamyltransferase; AFP, alphafetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; GBWT, gallbladder wall thickening.
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Table 3. Comparison between neoplastic polyp and pseudopolyps (non-neoplastic) in the training cohort

| Characteristics                        | Neoplastic, n=45 | Pseudopolyps, n=188 | p     |
|----------------------------------------|------------------|---------------------|-------|
| Age in years, mean±SD                  | 57.49±13.53      | 47.55±12.84         | *<0.001|
| Sex                                    |                  |                     | 0.875 |
| Male                                   | 20 (44.4)        | 86 (45.7)           |       |
| Female                                 | 25 (55.6)        | 102 (54.3)          |       |
| Physical condition                     |                  |                     | 0.829 |
| BMI (kg/m²)                            | 24.18±3.32       | 24.13±3.10          |       |
| 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                   |                  |                     |       |
| 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 |
| 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 |
| 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|

BMI, body mass index; DD, D-dimer; ALT, Alanine transaminase; TBil, total bilirubin; TCH, total cholesterol; TBA, total bile acid; GGT, γ-glutamyltransferase; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; GBWT, gallbladder wall thickening.

model in both the training (AUC: 0.846) and validation (AUC: 0.835) cohorts compared with the US-reported alone, the JSHBPS, ESGAR, and CCBS guidelines, and the Korean model. To further evaluate and compare these prediction models or guidelines, we determined the net benefits of each using DCA (Fig. 3). Across a reasonable threshold of probability ranges for both the training and validation groups, DCA graphically showed that the nomogram provided greater clinical benefit for predicting malignancy in patients with GBPs than the other methods.

**Discussion**

This study established and validated a nomogram model for predicting neoplastic polyps in patients with GBPs. Age, cholelithiasis, serum CEA levels, polyp size, and sessile shape were confirmed as independent predictors for neoplastic risk and integrated into the nomogram model. Subsequently, our model achieved significantly better diagnostic performance and provided more clinical benefit, as demonstrated by ROC and DCA curves, compared with the US-reported model, three different management guidelines, and a Korean scoring model. We discovered that less than 20% of GBP patients actually required surgery. There is a selection bias for cases that are chosen for inpatient surgery because many patients have cholesterol polyps that do not require surgical intervention. Therefore, the incidence of malignant polyps may be lower than that observed in our study. Greater than...
Table 4. Factors for the prediction of neoplastic risk for patients with gallbladder polyps

| Variables            | Multivariate analysis | ROC analysis |
|----------------------|-----------------------|--------------|
|                      | β                     | OR           | p           | AUC (Cutoff) |
| Age in years         | 0.042                 | 1.043 (1.010, 1.077) | 0.009      | 0.685 (598, 0.772) | 58 |
| Diabetes             | NA                    | NA           | 0.39       | NA          | NA          |
| Cholelithiasis       | 1.06                  | 2.887 (1.192, 6.993) | 0.019      | 0.676 (0.581, 0.771) | NA          |
| CEA (ng/mL)          | 0.35                  | 1.420 (1.052, 1.915) | 0.022      | 0.707 (0.62, 0.789) | 1.56             |
| CA199 (U/mL)         | NA                    | NA           | 0.573      | NA          | NA          |
| Ultrasonic diagnosis | NA                    | NA           | 0.436      | NA          | NA          |
| Polyp size (mm)      | 0.15                  | 1.162 (1.047, 1.289) | 0.005      | 0.707 (0.617, 0.797) | 15             |
| Single polyp         | NA                    | NA           | 0.264      | NA          | NA          |
| Sessile polyp        | 1.045                 | 2.843 (1.209, 6.684) | 0.017      | 0.703 (0.617, 0.790) | NA          |
| Clinical symptoms    | NA                    | NA           | 0.926      | NA          | NA          |

OR, odds ratio; AUC, area under the curve; CEA, carcinoembryonic antigen.

Fig. 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, JSHBP guideline, ESGAR guideline, CCBS guideline, and Korean model in the training and validation. ROC, receiver operating characteristic; CEA, carcinoembryonic antigen; US-reported, ultrasonic report diagnosis.
50% of patients included in our study presented with indications for surgery following the guidelines. In a retrospective study, Metman et al.20 determined that the prevalence of neoplastic polyps was much lower than reported and questioned the broad recommendations in the guidelines. From these data, it is clear that more accurate preoperative assessments of GBPs are necessary.

Our nomogram model achieved satisfactory accuracy, good reliability, and reproducibility. The factors included in our final model, such as age, cholelithiasis, polyp size, and sessile shape have been reported as risk factors for gallbladder cancer in other studies.21–23 The predictive effects of serum CEA and CA199 levels have also been demonstrated.24 However, we established a prediction system using a nomogram that integrated a combination of ultrasonic signatures and physiological and tumor markers. The effectiveness of the three guidelines (JSHBPS, ESGAR, and CCBS) for predicting GBP malignancy was similar. The Korean model was more effective than these guidelines but slightly less effective than our model.25

We developed a non-invasive and user-friendly model for predicting malignant GBPs based on easily available data. Not only diagnostic performance but also cost and applicability should be considered. Each of the indicators included in our model can be obtained through an outpatient physical examination. Nomogram modelling has been used effectively in a number of studies.29,30 We recommend that patients who are judged to be at high risk using our diagnostic model should have supplemental CT scans before surgery to confirm the diagnosis and rule-out abdominal metastasis of GBC. Additionally, compared with artificially assigning risk factors, assigning corresponding weights to variables through statistical methods may result in more objective extraction of information from clinical data.

Unlike the adenoma-carcinoma sequence that is well described for colonic polyps, the adenoma-carcinoma sequence for GBPs is not well understood. One study has shown a link between the presence of proximal colon polyps and higher rates of GBPs.31 The evidence suggests that at liver was found to be an independent risk factor for GBPs.27

### Table 5. Diagnostic performances of all methods and independent factors for GBPs in the training and validation cohort

| Methods               | Training, n=233 AUROC (95% CI) | Validation, n=225 AUROC (95% CI) | Delong test (comparison of AUROC) |
|-----------------------|---------------------------------|----------------------------------|----------------------------------|
| Nomogram model        | 0.846 (0.779, 0.913)            | 0.835 (0.765, 0.905)             | p<0.001                          |
| 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                          |
| Age                   | 0.685 (0.598, 0.772)            | 0.720 (0.636, 0.804)             | p=0.569                          |
| Cholelithiasis        | 0.676 (0.581, 0.771)            | 0.693 (0.603, 0.784)             | p=0.755                          |
| CEA                   | 0.707 (0.625, 0.789)            | 0.648 (0.560, 0.736)             | p=0.336                          |
| Polyp size            | 0.707 (0.617, 0.797)            | 0.749 (0.659, 0.839)             | p=0.519                          |
| Sessile polyp         | 0.703 (0.617, 0.790)            | 0.708 (0.624, 0.792)             | p=0.937                          |

AUROC, the area under the receiver operating characteristic; CEA, carcinoembryonic antigen.
least some gallbladder adenocarcinomas may have arisen from pre-existing adenomas and atypical hyperplasia of gallbladder adenoma may be a precancerous lesion.\textsuperscript{32} If GBC is confined to the connective tissue of the gallbladder wall (stage I and II), the 5-year survival rates are more favorable at 57–92\%.\textsuperscript{33} Therefore, early detection and management of GBC is critical. Considering the malignant tendency of gallbladder adenoma and the recommendations of the guidelines, we included adenomas in the recommended cholecystectomy group in our model. Consequently, most of the false-negative cases detected by our model were adenomas. Prior to malignant transformation of gallbladder adenoma, their growth characteristics are different from that of malignant polyps. Currently, the diagnosis of malignancy can only be confirmed by postoperative pathology. If the number of cases is further expanded, attempts can be made to distinguish the polyps that are early malignant adenomas, and the accuracy of GBP management and study of malignant transformation of GBPs may be improved.

In the process of data collection and analysis, we noted certain risk factors for the development of malignant GBPs that have been less recognized. For example, Spearman correlation analysis indicated that diabetes and CA199 were risk factors for malignant GBPs. Systematic reviews have indicated that patients with diabetes had an increased risk of GBC and a higher GBC-mediated mortality compared...
with non-diabetic individuals. In addition to CEA and CA199, we found that CA724 may be a potential biomarker for GBC. However, in this study, there were too many missing data points, and we are prospectively collecting relevant results to obtain stronger evidence for CA724 as a potential biomarker. Given that our model is simple and easy to understand, we have created a clinical electronic software program for the nomogram to promote it to the public (https://smartglass.nextrael.cn/web/h5/psf/tnogop/dev/), so that GB patients can follow-up by themselves and receive accurate and detailed clinical recommendations.

Several limitations in this study should be noted. First, inherent selection biases could not be avoided due to the retrospective nature of this study. The enrolled patients underwent cholecystectomy because of the possibility of malignancy; thus, many patients who were thought to have benign polyps did not undergo surgery and were excluded from this study. Moreover, due to the low incidence of GBC, the total number of positive cases included in this study was low. Second, the accuracy of an ultrasound diagnosis is highly dependent on the experience level of the operator. Incorporating novel specific tumor indicators in a prospective study, such as CA724 or texture analysis of ultrasound signals, may further improve the accuracy of the model. Furthermore, this nomogram was established and validated on the basis of data obtained from a single center. Recognized risk factors, such as Indian ethnicity and primary sclerosing cholangitis, were not examined in this study. We shared this model to increase recognition of risk factors for GBP malignancy and promote cooperation in multi-center prospective research to externally validate our model.

Conclusions
We present an accurate and user-friendly prediction model based on simple clinical variables to improve diagnosis of neoplastic polyps in patients with GBPs. Furthermore, the model facilitates greater accuracy of surgical decisions by both surgeons and patients and may aid in the early diagnosis and treatment of GBC.

Acknowledgments
We thank Xuecun Huang (Department of Ultrasonography, The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University) for his technical consulting service, and Susan Zunino, PhD, from Edanz for editing the language.

Funding
This study was supported by the National Natural Science Foundation of China (81702323 and 81672469), the Changzhou Medical Innovation Team (CCX201807), and the Changzhou Sci & Tech Program (CE20165020).

Conflict of interest
The authors have no conflict of interests related to this publication.

Author contributions
Collected the data (BW, XZ, YW, ZZ, PG), analyzed the data (JW, LT), participated in research design (LJ, XQ), wrote the manuscript (XZ, JW), supervised the study (XQ), and revised the paper (CZ). All authors read and approved the final manuscript.

Ethical statement
This retrospective study was approved by the Hospital Research Ethics Committee. The requirement for written informed consent was waived due to its retrospective nature.

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

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