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Establishing a preoperative predictive model for gallbladder adenoma and cholesterol polyps based on machine learning: a multicentre retrospective study

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Abstract

Background With the rising diagnostic rate of gallbladder polypoid lesions (GPLs), differentiating benign cholesterol polyps from gallbladder adenomas with a higher preoperative malignancy risk is crucial. This study aimed to establish a preoperative prediction model capable of accurately distinguishing between gallbladder adenomas and cholesterol polyps using machine learning algorithms.

Materials and methods We retrospectively analysed the patients' clinical baseline data, serological indicators, and ultrasound imaging data. Using 12 machine learning algorithms, 110 combination predictive models were constructed. The models were evaluated using internal and external cohort validation, receiver operating characteristic curves, area under the curve (AUC) values, calibration curves, and clinical decision curves to determine the best predictive model.

Results Among the 110 combination predictive models, the Support Vector Machine + Random Forest (SVM + RF) model demonstrated the highest AUC values of 0.972 and 0.922 in the training and internal validation sets, respectively, indicating an optimal predictive performance. The model-selected features included gallbladder wall thickness, polyp size, polyp echo, and pedicle. Evaluation through external cohort validation, calibration curves, and clinical decision curves further confirmed its excellent predictive ability for distinguishing gallbladder adenomas from cholesterol polyps. Additionally, this study identified age, adenosine deaminase level, and metabolic syndrome as potential predictive factors for gallbladder adenomas.

Conclusion This study employed the machine learning combination algorithms and preoperative ultrasound imaging data to construct an SVM + RF predictive model, enabling effective preoperative differentiation of gallbladder

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adenomas and cholesterol polyps. These findings will assist clinicians in accurately assessing the risk of GPLs and providing personalised treatment strategies.

Keywords Machine learning, Predictive model, Gallbladder polyps, Gallbladder adenoma

Introduction

Gallbladder polypoid lesions (GPLs) are locally raised lesions that occur on the inner wall of the gallbladder and can present as benign, potentially malignant, or malignant lesions [1–3]. The detection rate of GPLs in adults is approximately 0.3–12.3%; however, with advancements in imaging technology, especially the widespread use of ultrasound examinations, the detection rate of GPLs is gradually increasing [4–6]. Although most GPLs are benign conditions (such as cholesterol polyps), some, particularly larger polyps (such as adenomas), carry a higher risk of malignant transformation to gallbladder cancer [7–9].Therefore, accurate differential diagnosis and appropriate management strategies for GPLs are crucial for preventing gallbladder cancer.

The 2022 European GBP management guidelines indicate that gallbladder polyps (GBPs) ≥ 10 mm in diameter require cholecystectomy. For polyps with a diameter of 6–9 mm, it is recommended to evaluate risk factors for gallbladder malignancy, including age, solitary polyps, primary sclerosing cholangitis, Indian ethnicity, and pedunculated polyps [3]. However, the use of 10 mm as a surgical indication for GBPs is relatively broad, and deciding whether surgery is needed solely based on polyp size has drawbacks. First, this approach may lead to the erroneous removal of benign GBPs, thereby increasing surgical trauma and wasting medical resources. Second, gallbladder adenomas with a diameter < 10 mm might be overlooked, potentially increasing the risk of malignant transformation to gallbladder cancer [10]. Hence, accurate preoperative differentiation between gallbladder cholesterol polyps and gallbladder adenomas is particularly important, as it helps avoid unnecessary cholecystectomy while improving the diagnosis and treatment efficiency of gallbladder adenomas, thus saving medical resources and alleviating patient suffering. Therefore, it is essential to accurately distinguish between gallbladder cholesterol polyps and adenomas before surgery to implement individualised and differentiated treatment plans.

In recent years, with the development of imaging technologies, such as abdominal ultrasonography, contrast-enhanced ultrasonography (CEUS), computed tomography (CT), and magnetic resonance imaging, the accuracy of preoperative imaging examinations has improved [11–14]. Considering the trauma and examination costs, the evaluation of benign gallbladder lesions is mainly based on abdominal ultrasound examination. However, it is currently challenging to effectively differentiate between gallbladder adenomas and cholesterol polyps preoperatively in clinical practice [15]. Therefore, a precise and effective evaluation method is required. Moreover, existing studies have mostly focused on predicting the risk factors for malignancy of GBPs, while there is limited research on differentiating and predicting cholesterol polyps and gallbladder adenomas. Hence, based on our centre's previous research results [16], this study aimed to establish a preoperative prediction model capable of accurately distinguishing between gallbladder adenomas and cholesterol polyps through retrospective analysis of patients' baseline data, serological indicators, and ultrasound imaging data using machine learning (ML) algorithms. The predictive performance of this model will be evaluated through internal and external validation to provide clinicians with a more comprehensive and accurate method for differentiation, achieve individualised treatment, and avoid unnecessary cholecystectomy. The innovations of this study are summarised as follows:

- We applied 12 machine learning algorithms to develop 110 prediction models. The results demonstrated that machine learning can be effective in constructing predictive models for this condition.
- By including patients' baseline data, serological indicators, and ultrasound imaging data, we discovered potential new predictive factors, including adenosine deaminase (ADA) and metabolic syndrome, which have not been well addressed in previous studies.

Methods

Study participants

This study adhered to the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Qingdao University (reference number: QYFY WZLL 28152). As this study involved previously collected anonymous data and posed no direct risk of personal privacy disclosure, the ethics committee waived the requirement for obtaining informed consent.

This retrospective study used data from two cohorts. The primary study cohort comprised data on 1,582 patients with GBPs retrieved from the Affiliated Hospital of Qingdao University between January 2015 and December 2022. The external validation cohort included data on 315 patients with GBPs retrieved from two centres: the Affiliated Hospital of Weifang Medical University and Yantaishan Hospital, between January 2020 and

December 2023. The inclusion criteria were as follows: (1) patients who underwent cholecystectomy with a postoperative pathological diagnosis of gallbladder cholesterol polyps or adenomas and (2) patients with complete clinical and imaging baseline data. The exclusion criteria were (1) acute cholecystitis, (2) gallstones and hepatolithiasis, (3) IgG4-related sclerosing cholangitis and hyperbilirubinemia, and (4) other malignant diseases. Based on these inclusion and exclusion criteria, 1,148 patients were included in the study (Fig. 1), of which 1,009 were included in the primary study cohort. Using the train_test_split algorithm, they were randomly divided into a training set (706 patients) and an internal validation set (303 patients) in a 7:3 ratio for model construction and validation, respectively. The external validation cohort included 139 patients.

Data description and preprocessing

This study evaluated the following indicators: (1) baseline data, including sex, age, smoking history, alcohol consumption history, hypertension, and diabetes; (2) ultrasonographic data, including gallbladder wall thickness, polyp size, echo characteristics, and pedicle condition (Supplementary Figure); and (3) serological data, including metabolic syndrome, carcinoembryonic antigen, CA242, lactate dehydrogenase, ADA, and glucose. All data had missing values of < 30%. To ensure data quality, the K-Nearest Neighbours (KNN) imputation was used to fill in the missing values.

ML model development

Twelve ML algorithms were employed to develop the predictive models: Logistic Regression (LR), Support Vector Machine (SVM), Decision Tree (DT), Random Forest (RF), KNN, Multilayer Perceptron (MLP), Gradient Boosting Tree (GBT), Least Absolute Shrinkage and Selection Operator (LASSO), XGBoost (XGB), LightGBM (LGB), Backpropagation Neural Network (BPNN), and Stepwise Regression [17–19]. Based on these algorithms, 110 combinations were used to fit the predictive models. We used hyperparameter tuning to improve the generalisation ability of the models [20] and prevent overfitting and underfitting and evaluated the performance of different hyperparameter combinations using 5-fold cross-validation to select the best hyperparameter combination(Supplementary text).

Statistical analysis

All statistical analyses were performed using Python version 3.11.5. Continuous variables are expressed as mean ± standard deviation (SD), and categorical data are expressed as counts (percentages). The best predictive model was trained using the above algorithm combinations and then validated using an external validation set. Feature importance was displayed using feature weight plots, and the accuracy of the predictive models was evaluated using ROC, AUC, calibration curves, clinical decision curves, clinical impact curves, and learning curves. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

This study included 1,148 patients across three cohorts: D1 (training set), D2 (internal validation set), and D3 (external validation set). The baseline patient characteristics are presented in Table 1. This study included 769

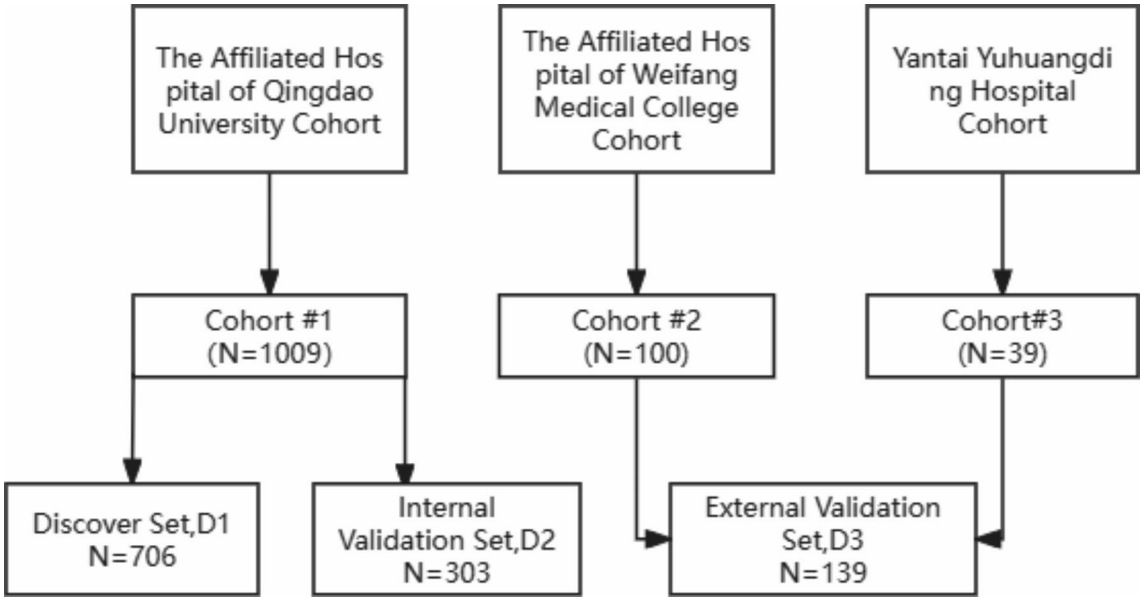

Fig. 1 Screening process for the selection of study participants

Table 1 Baseline data of all included patients

Baseline data	Training Group (*n* = 706)	Internal Validation group (*n* = 303)	External validation group (*n* = 139)
Gender (%)			
Male	246 (0.35)	110 (0.36)	43(0.31)
Female	460 (0.65)	193 (0.64)	96(0.69)
Age (years)	52.98 ± 13.63	53.91 ± 13.21	51.38 ± 9.68
Drinking (%)			
No	625(0.89)	263(0.87)	124(0.89)
Yes	81(0.11)	40(0.13)	15(0.11)
Metabolic syndrome (%)			
No	634(0.90)	261(0.86)	122(0.88)
Yes	72(0.10)	42(0.14)	17(0.12)
Gallbladder wall thickness (cm)	0.28 ± 0.08	0.29 ± 0.09	0.28 ± 0.11
Polyp size (cm)	1.43 ± 0.58	1.41 ± 0.52	1.31 ± 0.62
Polyp echo (%)			
Low and moderate echo	306(0.43)	121(0.40)	23(0.17)
High-level echo	400(0.57)	182(0.60)	116(0.83)
Pedunculation (%)			
No	656(0.93)	289(0.95)	128(0.92)
Yes	50(0.07)	14(0.05)	11(0.08)
LDH (U/L)	167.50 ± 34.46	170.77 ± 41.18	165.3 ± 51.09
ADA (U/L)	9.72 ± 3.21	10.17 ± 3.48	12.56 ± 2.84
Glu (mmol/L)	5.22 ± 1.22	5.24 ± 1.31	5.5 ± 1.65
CEA (ng/ml)	1.81 ± 0.98	1.87 ± 1.30	2.3 ± 1.11
CA242 (IU/ml)	6.07 ± 3.11	6.08 ± 3.68	6.57 ± 4.03

LDH, lactate dehydrogenase; ADA, adenosine deaminase; Glu, glucose; CEA, carcinoembryonic antigen

patients with GBPs and 379 with gallbladder adenomas. The incidence was higher in females than in males (749 [65.24%] vs. 399 [34.76%]). The average age was 52.94 ± 13.42 years, average polyp size was 1.37 ± 0.58 cm, and average gallbladder wall thickness was 0.29 ± 0.1 cm. The correlation matrix of the variables is shown in Fig. 2h. There were no significant differences in the key indicators between D1 (706 patients) and D2 (303 patients), which were randomly split according to proportion, indicating comparability between the two groups (Table 2).

Model application and performance

In this study, we constructed 110 predictive models based on 12 ML algorithms (Fig. 2a). In the training cohort, the SVM + RF model had the highest AUC value, followed by DT + XGB, LASSO + XGB, LGB + RF, and XGB + RF. The average AUC and F1 scores of the five models are shown in Fig. 3. The SVM + RF model with the highest AUC value was selected for this study. The features selected by SVM were gallbladder wall thickness, polyp size, polyp echo, and pedunculation. The feature importance is shown in Fig. 2b. The AUC values for D1 and D2 in this model were 0.972 and 0.922, respectively. The calibration curves are shown in Fig. 3. Overall, the calibration curves for D1 and D2 fluctuated around the ideal curve, indicating the good predictive performance of the model. The confusion matrices (Fig. 2c, d) indicated diagnostic accuracies of 90.08% and 84.16% for D1 and D2, respectively, indicating good diagnostic efficacy. The sensitivities and specificities for D1 and D2 were 85.52% and 97.73% and 89.47% and 81.73%, respectively. Moreover, the clinical decision curve (Fig. 2e) shows that the predictive model curve is above the net benefit line for most thresholds, indicating that the model provides net benefits over random guessing and, thus, has good clinical utility. The clinical impact curve (Fig. 2f) illustrates the trade-off between the number of true positives and false positives at different threshold probabilities. Choosing an appropriate threshold probability can balance the number of false positives and true positives, thereby optimising the sensitivity and specificity of diagnostic or therapeutic decisions. The learning curve in Fig. 2g showed that the training score (blue line) remained relatively stable as the training set size increased, generally remaining at a high level, indicating a good fit for the training data. The cross-validation score (green line) increased and stabilised to some extent with an increase in the training set size, with slight fluctuations, indicating a good generalisation ability for unseen data. The gap between the two curves was not very large, suggesting that the model did not overfit. Additionally, among the 110 models, 50 identified age as a risk factor for gallbladder adenomas, 60 identified ADA levels, and 30 identified metabolic syndrome, with all models achieving AUC values greater than 0.8, demonstrating good predictive performance. This suggests that these factors may also be potential predictors for distinguishing gallbladder adenomas.

External validation of the model

The established optimal prediction model, SVM + RF, was validated using the external validation cohort D3. The ROC and calibration curves are shown in Fig. 4a and b, respectively. The AUC value was 0.78, with a specificity and sensitivity of 85.52% and 97.73%, respectively, and diagnostic accuracy of 90.08%. With an increase in the probability threshold, the false-positive rate continuously decreased, and the diagnostic accuracy continuously increased (Fig. 4c). The learning curve in Fig. 4d showed that the training score remained consistently high and slightly decreased with increasing sample size. The cross-validation score was relatively low initially but increased with the sample size, indicating that the model's generalisation ability when faced with unseen data improved. There was a gap between the training and cross-validation scores. However, this gap narrowed as the sample size increased, indicating that the overfitting

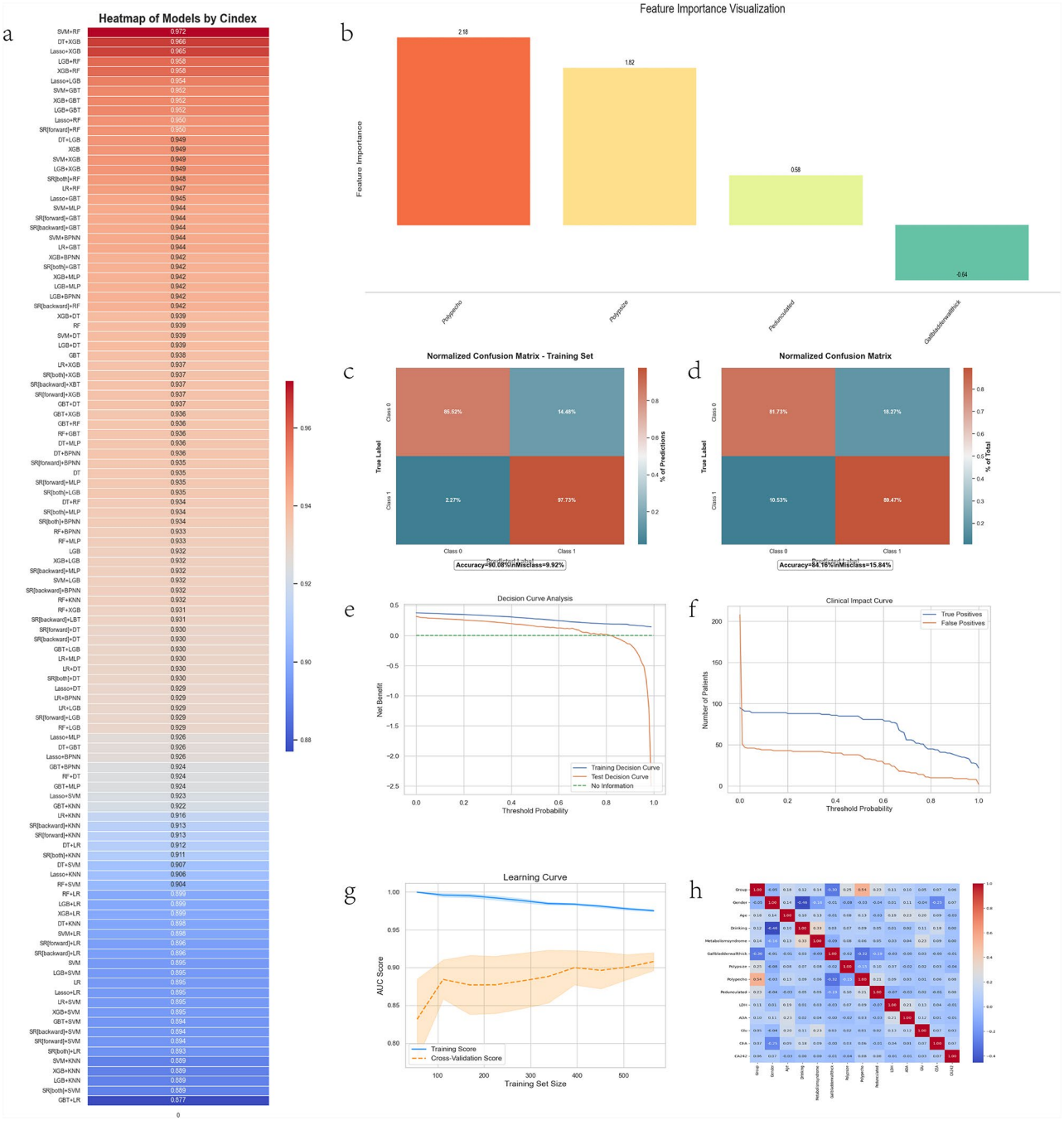

Fig. 2 Results of 110 prediction models. **(a)**Average auc value ranking of the 110 prediction models; **(b)** feature importance of the SVM model; **(c)** confusion matrix for D1; **(d)** confusion matrix for D2; **(e)** clinical decision curve of the SVM model; **(f)** clinical impact curve of the SVM model; **(g)** learning curve of the SVM model; **(h)** correlation matrix of variables in the SVM model, SVM, Support Vector Machine; D1, training set; D2, internal validation set

phenomenon of the model decreased and demonstrating that the model has a good discriminatory diagnostic value.

The predictive model of this research has been deployed at a web address and can be accessed for use at http://123.56.229.150:1000/.

Discussion

This study developed a model based on the machine learning ensemble algorithms, featuring simple, non-invasive, and easily accessible ultrasound imaging metrics with good interpretability, facilitating clinical application and dissemination. Screening 110 models to identify the optimal prediction model not only improved diagnostic accuracy but also provided strong support for

Table 2 Comparison of general baseline data between the training and internal validation groups

Baseline data	Training Group (*n* = 706)	Internal Validation group (*n* = 303)	Value	*P*
Gender (%)			χ2 = 0.14	0.71
Male	246 (0.35)	110 (0.36)		
Female	460 (0.65)	193 (0.64)		
Age (years)	52.98 ± 13.63	53.91 ± 13.21	t=-1.01	0.31
Drinking (%)			χ2 = 0.45	0.50
No	625(0.89)	263(0.87)		
Yes	81(0.11)	40(0.13)		
Metabolic syndrome (%)			χ2 = 2.48	0.11
No	634(0.90)	261(0.86)		
Yes	72(0.10)	42(0.14)		
Gallbladder wall thickness (cm)	0.28 ± 0.08	0.29 ± 0.09	t=-1.86	0.06
Polyp size (cm)	1.43 ± 0.58	1.41 ± 0.52	t=-0.61	0.52
Polyp echo (%)			χ2 = 0.87	0.35
Low and moderate echo	306(0.43)	121(0.40)		
High-level echo	400(0.57)	182(0.60)		
Pedunculation (%)			χ2 = 1.77	0.18
No	656(0.93)	289(0.95)		
Yes	50(0.07)	14(0.05)		
LDH (U/L)	167.50 ± 34.46	170.77 ± 41.18	t=-1.30	0.19
ADA (U/L)	9.72 ± 3.21	10.17 ± 3.48	t=-1.99	0.05
Glu (mmol/L)	5.22 ± 1.22	5.24 ± 1.31	t=-0.27	0.79
CEA (ng/ml)	1.81 ± 0.98	1.87 ± 1.30	t=-0.88	0.38
CA242 (IU/ml)	6.07 ± 3.11	6.08 ± 3.68	t=-0.03	0.98

clinical decision-making. By incorporating patients' baseline data, serological indicators, and ultrasound imaging data, we identified potential new predictive factors, including gallbladder wall thickness, polyp size, polyp echo, and pedunculation. The SVM + RF model achieving a sensitivity and specificity of 85.52% and 97.73%, respectively, and a diagnostic accuracy of 90.08%, demonstrating excellent diagnostic performance.

Infiltrative gallbladder cancer accounts for approximately 5–10% of tumours that arise from malignant transformation of intra-gallbladder tumours, such as adenomas [21], fitting the 'adenoma-carcinoma sequence' concept. Approximately two-thirds of patients with intra-gallbladder tumours may eventually develop infiltrative cancer. Therefore, timely diagnosis and intervention for potentially malignant gallbladder adenomas are crucial. However, it is challenging to distinguish them from benign cholesterol polyps in clinical practice. This has led to some patients undergoing cholecystectomy as a precaution against gallbladder malignancy, even when the postoperative pathology reveals cholesterol polyps. In particular, the inability to effectively differentiate polyps > 10 mm from gallbladder adenomas increases the risk of unnecessary surgical removal [22–25]. Building on our previous research [16], this study utilised a multicentre retrospective data analysis combined with the latest ML algorithms to establish an effective preoperative prediction model, SVM + RF, aimed at enhancing the ability to differentiate gallbladder adenomas from cholesterol polyps, thereby providing better individualised treatment strategies for patients.

Risk factor analysis of gallbladder adenomas is essential for the formulation of individualised treatment strategies. Studies have shown that polyp size is the most common risk factor for gallbladder adenomas [26, 27]. Wang et al. [28] evaluated 89 patients with GBPs measuring 1–2 cm using conventional and contrast-enhanced ultrasonography and found that a maximum diameter of 1.45 cm was the optimal cutoff value for predicting adenomatous polyps. Similar studies have indicated that polyps > 1 cm significantly increase the risk of malignancy [29–31], consistent with our findings. Mellnick et al. [32] reported that adenomas are mostly sessile or pedunculated hypoechoic polyps. Although gallbladder wall thickness and polyp base thickness are considered risk factors for gallbladder cancer, no direct link between gallbladder wall thickness and adenoma formation has been established and requires further research. Through ML analysis of ultrasound imaging features, we identified polyp size, pedunculated hypoechoic polyps, and gallbladder wall thickness as independent risk factors for gallbladder adenomas. In addition to these conventional factors, previous studies have found a correlation between obesity, especially visceral fat accumulation, and an increased risk of GBPs [35, 36]. Yamin et al. highlighted the relationship between dyslipidaemia and GBP formation, particularly in the Chinese population [37], indicating that lifestyle and metabolic factors might play a role in the pathogenesis of GBPs. Our study also found that metabolic syndrome is a potential risk factor for gallbladder adenomas. To date, no study has reported a relationship between ADA and gallbladder adenomas. Only one study by Tounsi et al. [38] on the association between ADA and tumour angiogenesis in patients with gallbladder cancer under nitroxidative stress indicated that ADA influences microvascular density, possibly regulating adenosine levels and affecting immune and endothelial cells, indirectly participating in angiogenesis regulation. A high microvascular density/glutathione ratio is a potential biomarker for gallbladder cancer, suggesting a correlation between ADA levels and tumour progression. Nonetheless, controversy regarding the risk factors for gallbladder adenomas still remains, requiring further research to identify patients needing proactive intervention.

To improve preoperative diagnostic accuracy, various ultrasound imaging-based risk assessment models and prediction tools have emerged in recent years. These

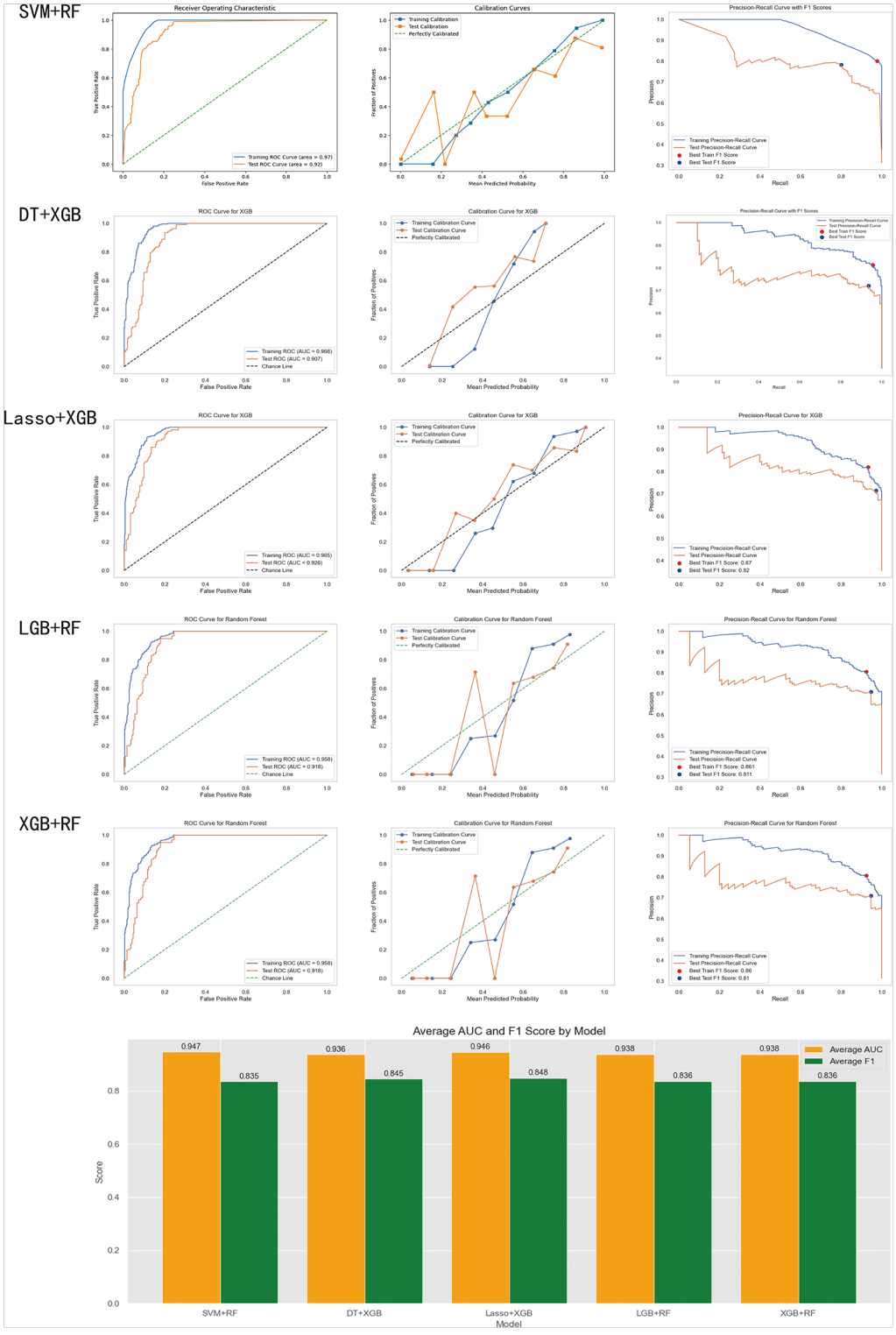

Fig. 3 ROC curves, calibration curves, learning curves, and their respective average AUC and F1 scores for the following five models: SVM + RF, DT + XGB, LASSO + XGB, LGB + RF, and XGB + RF. ROC, receiver operating characteristic

tools aim to combine multiple independent risk factors to predict the malignancy risk of GBPs and guide clinical decisions [16, 39, 40]. For example, Liu et al. [31] retrospectively analysed 423 patients with GBPs and developed a prediction model combining ultrasound imaging features, identifying solitary lesions,

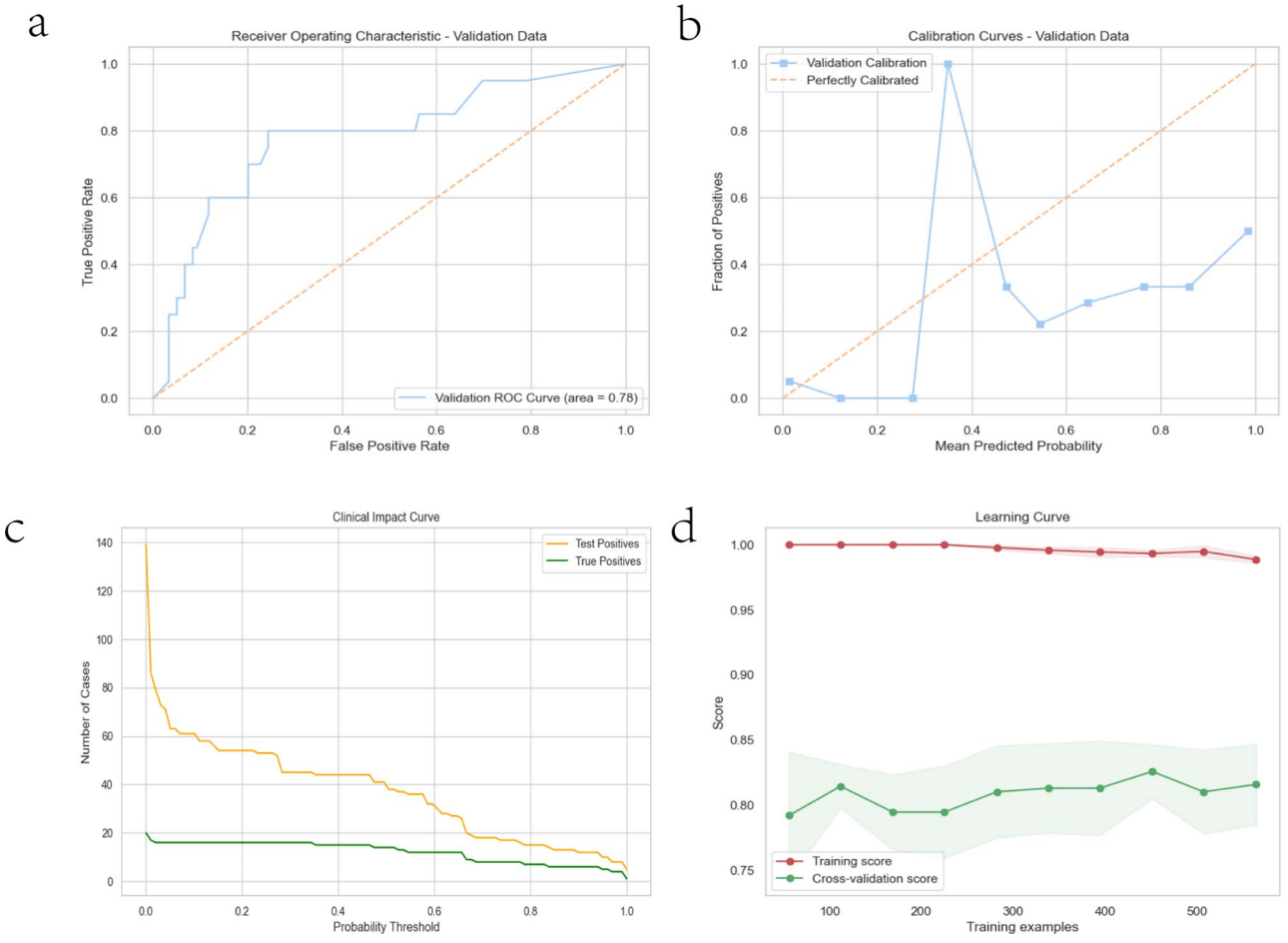

Fig. 4 Results of the external validation cohort. **(a)** ROC curve of the external validation cohort; **(b)** calibration curve of the external validation cohort; **(c)** clinical impact curve of the external validation cohort; **(d)** learning curve of the external validation cohort

larger polyps, and irregular morphology as independent risk factors for gallbladder adenomas, thereby providing more accurate predictions for adenomas > 1 cm. Zhu et al. proposed a new risk-scoring system, the gallbladder reporting and data system (GB-RADS), to explore the risk factors for gallbladder adenomas [33]. This system evaluated the ultrasound imaging features of 136 patients, forming a scoring standard for gallbladder adenomas, including enhancement patterns, wash-out characteristics, and vascularity. Additionally, this system simplifies the assignment of different weights to each risk factor, ultimately calculating the total score and providing a straightforward risk assessment for physicians. Compared with traditional ultrasound imaging methods, the CEUS-based scoring system significantly improves diagnostic accuracy, as confirmed in previous studies [34]. Zhang et al. [41] developed a nomogram prediction model focusing on GBPs measuring 10–15 mm in diameter. By combining clinical and ultrasound imaging features, this model provides a quantitative risk score, allowing physicians to evaluate malignant tendencies and make appropriate treatment decisions. These tools enable a more precise malignancy risk assessment, avoiding overtreatment for low-risk patients while ensuring that high-risk patients receive timely medical intervention.

In recent years, the field of artificial intelligence-based radiomics has developed rapidly, utilising complex mathematical models to process large datasets and uncover patterns unrecognisable via traditional biostatistical methods [42]. For example, Yuan et al. [43] used ultrasound radiomics to analyse the spatial and morphological features of preoperative ultrasound imaging in 99 patients with GBPs, confirming that cholesterol polyps are smaller and more regular in morphology than are gallbladder adenomas, aiding in differentiating true from pseudo polyps. Similarly, Yin et al. [44] proposed a new risk assessment model for the preoperative differentiation of cholesterol and adenomatous GBPs and analysed the CT imaging parameters of 52 patients with polyps. This model served as a prediction model for gallbladder adenomas, showing that arterial phase, portal vein phase and delayed phase CT values and ΔCT values (including ΔCT1 and ΔCT2) can differentiate the nature of gallbladder polypoid lesions, thereby providing objective risk

assessment for physicians. These radiomics models based on high-throughput data are less convenient and generalisable for clinical applications, with unclear indicator significance. Elmasry et al. [45] analysed bile viscosity, bile cholesterol, and age as independent risk factors and established a prediction model for GBPs and adenomas, demonstrating good specificity and sensitivity (80.2% and 90.9%, respectively), with an AUC of 0.845. They concluded that bile viscosity, bile cholesterol, and age are important predictors of tumorous polyps, although the invasive nature of the procedures limits their clinical implementation.

However, the current study has some limitations. Firstly, ultrasound is an examiner-dependent procedure, which may introduce certain biases in the results. Secondly, the sample size is small, and broader clinical validation is needed to verify the effectiveness of the prediction model. Future research should include larger sample sizes to supplement and improve the model. Additionally, future studies should utilise emerging ML algorithms combined with radiomics to explore the risk factors for gallbladder adenomas, further enhancing the model accuracy and reliability.

Conclusion

This study demonstrated that by utilising the latest ML combination algorithms and preoperative ultrasound imaging data, an SVM + RF prediction model was constructed to effectively differentiate between gallbladder adenomas and cholesterol polyps preoperatively. Polyp size, gallbladder wall thickness, polyp echo, and pedicle characteristics were identified as independent risk factors for predicting gallbladder adenomas. Additionally, age, (ADA level, and metabolic syndrome were identified as significant influencing factors that cannot be ignored. These findings will aid clinicians in conducting more accurate risk assessments of GPLs and developing personalised treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03671-y.

Supplementary Material 1

Supplementary Material 2

Author contributions

Yubing Wang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. Chao Qu: Conceptualization, Writing – original draft. Jiange Zeng: Formal analysis, Data curation. Yumin Jiang: Formal analysis, Data curation. Ruitao Sun: Formal analysis, Data curation. Changlei Li: Data curation, Conceptualization. Jian Li: Data curation. Chengzhi Xing: Data curation. Bin Tan: Writing – review & editing, Visualization. Kui Liu: Writing – review & editing, Visualization. Qing Liu: Writing – review & editing, Data curation, Visualization. Dianpeng Zhao: Writing – review & editing, Data curation, Formal analysis, Conceptualization. Jingyu Cao: Writing – review & editing, Conceptualization. Weiyu Hu: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Qingdao University (reference number: QYFY WZLL 28152).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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