ORIGINAL ARTICLE

CONTENTS

# Diagnostic criteria for oligosymptomatic choledocholithiasis in patients with acute calculous cholecystitis

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## ABSTRACT

**Aim:** To identify clinically significant diagnostic criteria for oligosymptomatic choledocholithiasis and determine their diagnostic value in patients with acute calculous cholecystitis (ACC) based on instrumental and laboratory examination data.

**Materials and Methods:** The study included 129 patients divided into two groups: the study group (I) and the comparison group (II). The study group included patients with ACC and oligosymptomatic choledocholithiasis (n=83), while the comparison group included patients with ACC without OCL (n=46).

**Results:** A univariate analysis using logistic regression identified nine factors with prognostic value for determining the presence of OCL. A high quality of OCL prediction was observed (AUC=0.99). The optimal decision threshold for diagnosing OCL was 0.5. Sensitivity at the established threshold was 100%, specificity was 88.90%, and accuracy was 96.88% ($p<0.001$). a multivariate regression model based on six factors was developed to enhance the clinical applicability of OCL prediction in ACC. This model also demonstrated a high predictive quality (AUC=0.98) compared to the nine-factor model. The decision threshold for the presence or absence of OCL was 0.6. The sensitivity of this model was 95.65%, specificity was 88.90%, and accuracy was 93.75%.

**Conclusions:** The diameter of the common bile duct, the activity of ALT, AST, alkaline phosphatase, total bilirubin levels, as well as the expression levels of miR-122 and miR-21 in serum and bile, serve as reliable diagnostic criteria associated with the presence of oligosymptomatic choledocholithiasis.

**KEYWORDS:** acute calculous cholecystitis, oligosymptomatic choledocholithiasis, miR-122, miR-21

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## INTRODUCTION

Choledocholithiasis is a common complication in surgical practice observed in patients with gallstone disease. The clinical presentation of gallstones in the common bile duct (CBD) can vary widely, ranging from asymptomatic incidental findings to severe complications such as obstructive jaundice, acute cholangitis, and pancreatitis [1, 2].

The presence of CBD stones in patients with acute calculous cholecystitis (ACC) requires comprehensive surgical treatment to prevent further complications. According to meta-analysis data, the incidence of choledocholithiasis in ACC patients is 13.7% (95% confidence interval 11.8–15.9) [3]. However, in the absence of overt clinical signs of choledocholithiasis, surgical interventions in such patients often do not include a CBD revision [4, 5].

The diagnosis of choledocholithiasis is based on clinical assessment, blood biochemistry, and imaging techniques [6, 7]. Traditionally, indicators of cholestasis in blood biochemistry (direct bilirubin, alkaline phosphatase, gamma-glutamyl transferase) have significant diagnostic value in choledocholithiasis [8]. However, changes in biochemical blood markers, as well as clinical symptoms, indicate only bile flow disturbances rather than their cause. Moreover, ACC itself, regardless of choledocholithiasis, may be associated with elevated cholestasis markers, reducing the diagnostic value of liver function tests [9].

Transabdominal ultrasonography (TAUS) allows for the detection of gallstones, changes in wall thickness and CBD diameter, and inflammatory changes in acute cholecystitis. However, the accuracy of TAUS in detecting choledocholithiasis is only 50-70% since gallstones may lack acoustic shadows or be located in the distal CBD, obscured by bowel gas and duodenal contents [9]. Additionally, the accuracy of the examination largely depends on the specialist's experience and the adequacy of patient preparation, which is not always feasible in acute surgical conditions [4].

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most informative diagnostic tech-

niques for choledocholithiasis; however, it is an invasive procedure with potential complications and is therefore not recommended for diagnostic purposes alone [10].

The use of other highly informative imaging techniques, such as magnetic resonance cholangiopancreatography (MRCP), various types of computed tomography (CT), and endoscopic ultrasonography (EUS), for all patients with gallstone disease is problematic in emergency surgery settings and financially unjustifiable, especially in the presence of ACC [3, 4].

Recently, the role of small RNA molecules (microRNAs) in liver disease diagnostics has been actively studied. MicroRNA expression is tissue-specific, and changes in the concentration levels of various molecules may accompany pathological processes in corresponding organs and tissues [11, 12]. MiR-122 is a widely distributed liver-specific microRNA [13, 14], constituting approximately 52% of the total hepatic microRNA in humans, with minimal expression in other cell types. Increasing evidence suggests the crucial role of miR-21 in liver diseases [15], particularly its association with the pathogenesis of cholestatic liver injury [11, 13]. Therefore, studying microRNA involvement in the etiology, pathogenesis, and diagnosis of hepatobiliary disorders, including choledocholithiasis, is becoming increasingly relevant. MicroRNA levels are stable and easily detectable in blood plasma, making them superior biomarkers for diagnosing, predicting, and assessing liver diseases compared to traditional markers [14, 16].

Thus, considering the growing importance of diagnosing oligosymptomatic choledocholithiasis (OCL), its diagnostic techniques require further improvement with detailed justification. In emergency settings, determining an adequate minimal scope of examinations is crucial to avoid treatment delays and prevent complications. This prompted us to explore the feasibility of using a combination of biochemical markers and microRNA expression levels for the diagnosis of OCL in ACC patients by developing a regression-based mathematical model.

## AIM

To identify clinically significant indicators of oligosymptomatic choledocholithiasis and determine their diagnostic value in patients with acute calculous cholecystitis based on instrumental and laboratory examination data.

## MATERIALS AND METHODS

The study included 129 patients who underwent treatment at the Department of Surgery No. 1 of Lviv National Medical University from 2016-2023. Patients were divided into two groups: the study group (I) and the comparison group (II). The study group included patients with ACC and OCL (n=83), and the comparison group included ACC patients without OCL (n=46). The first group consisted of 61 females (73.49%) and 22 males (26.51%), with a mean age of 56±14.4 years. Patients in group II were matched by age and gender. The gender distribution was reciprocal. An additional control group (III) included conditionally healthy individuals (volunteers, n=20) of corresponding age and gender. All patients underwent TAUS of the liver, gallbladder, and bile ducts, as well as blood biochemistry and the detection of miR-122 and miR-21 expression levels in blood serum and bile.

The criteria for inclusion in group I were confirmed by the diagnosis of ACC, lack of a clear clinical picture of choledocholithiasis, the absence of direct signs of choledocholithiasis during TAUS (absence of echogenic mass with acoustic shadow in the lumen of the common bile duct), diameter of common bile duct in TAUS was less than 10 mm; no jaundice (total bilirubin less than 34.5 μmol/L). The exclusion criteria for patients in group I were as follows: no confirmation of ACC diagnosis; the presence of jaundice; direct signs of choledocholithiasis according to TAUS; diameter of the common bile duct in TAUS was more than 10 mm; total bilirubin exceeding 34.5 μmol/L.

In the study group (83 patients) and the comparison group (46 patients), quantitative determination of miR-122 and miR-21 was performed using real-time polymerase chain reaction (PCR) in blood serum and bile. In the control group (20 volunteers), it was conducted only in serum.

A two-stage study was used according to the manufacturer's protocol to study the expression level of miR-122 and miR-21 in serum and bile. Initially, RNA was extracted from serum and bile using a Trizol RNA-prep kit (Isogen) to isolate total RNA. The method is based on the use of Trizol reagent.

Reverse transcription was performed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA), specific loop primers to reach the maturation of each miRNA and 10 ng of total RNA. Real-time quantitative PCR was performed using TaqMan MicroRNA Assays (Applied Biosystems, USA): hsa-miR-122, hsa-miR-21, and U6 snRNA as endogenous control. Temperature mode: initial denaturation 95°C – 10 minutes; 45 cycles of 95°C – 15 seconds and 60°C – 60 seconds. The miRNA level was calculated by the formula ($2\Delta Ct \times 100$), normalized to U6 snRNA and represented in relative units (RU). Amplification was performed with 7500 Fast Real-time PCR (Applied Biosystems, USA). The

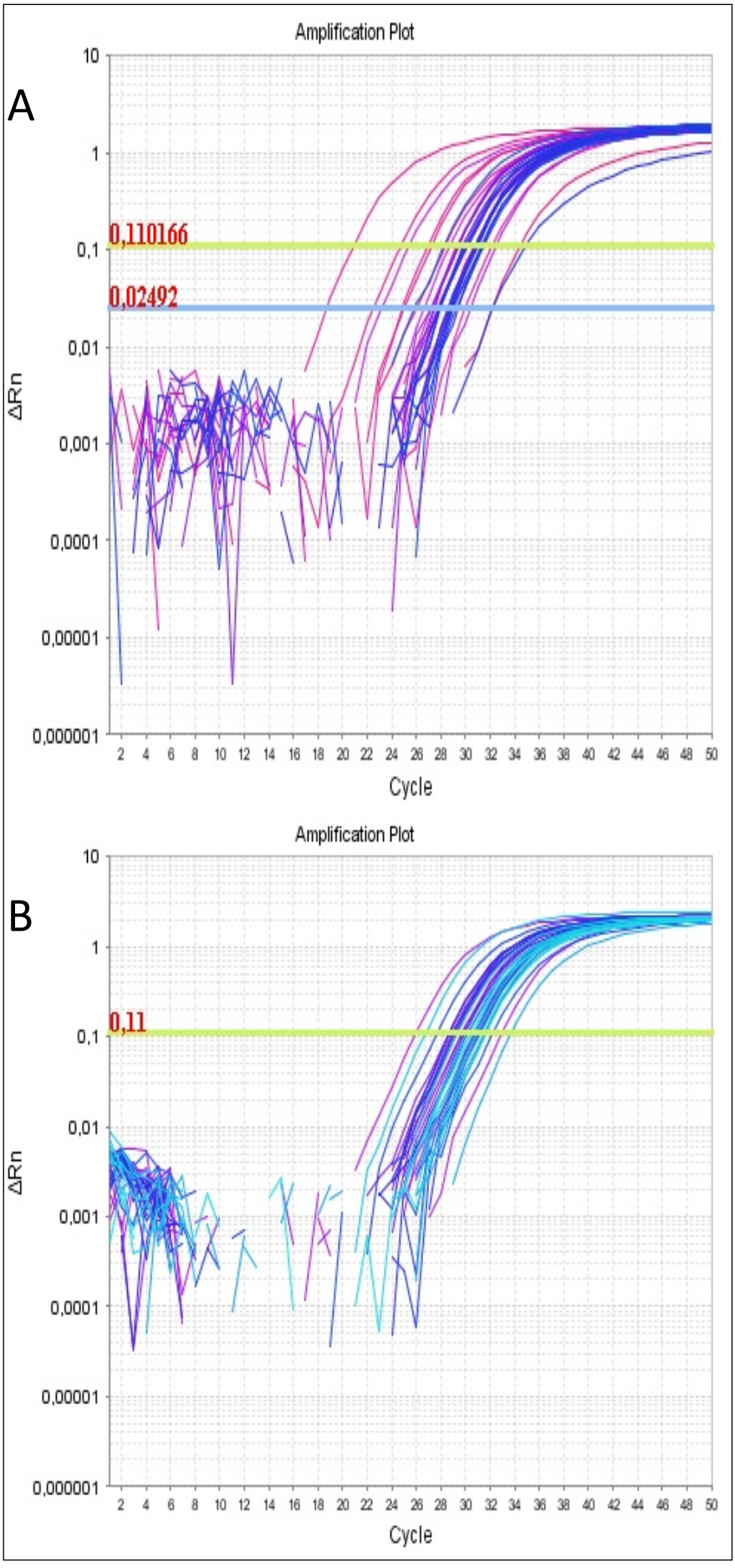


**Fig. 1.** Graph of the increase in fluorescence intensity during real-time PCR. A – miR-122, B – miR-21
*Picture taken by the authors*

**Table 1.** Prognostic Risk Factors for OCL Diagnosis using Logistic Regression (General Model)

| No. | Indicator | Abbreviation | Regression Coefficient ($\beta_i$) |
|---|---|---|---|
| 1 | Constant ($\beta_0$) | | -128.410 |
| 2 | ALP (alkaline phosphatase) | V1 | 1.103 |
| 3 | Common bile duct diameter | V2 | -73.040 |
| 4 | Total bilirubin | V3 | 13.380 |
| 5 | AST (aspartate aminotransferase) | V4 | 772.000 |
| 6 | ALT (alanine aminotransferase) | V5 | 58.530 |
| 7 | miR-21 in serum | V6 | -3.389 |
| 8 | miR-122 in serum | V7 | 0.816 |
| 9 | miR-21 in bile | V8 | -0.539 |
| 10 | miR-122 in bile | V9 | 15.050 |

*Source: compiled by the authors of this study*

**Table 2.** Results of logistic regression for risk factors of oligosymptomatic choledocholithiasis (simplified model)

| No. | Indicator | Abbreviation | Regression Coefficient ($\beta_i$) |
|---|---|---|---|
| 1 | Constant ($\beta_0$) | | -17.440 |
| 2 | ALP | V1 | 0.020 |
| 3 | Common bile duct diameter | V2 | 0.745 |
| 4 | Total bilirubin | V3 | 0.230 |
| 5 | AST | V4 | 10.804 |
| 6 | ALT | V5 | 1.506 |
| 7 | miR-122 in serum | V6 | 0.018 |

*Source: compiled by the authors of this study*

data obtained were analyzed using 7500 Fast Real-time PCR software and displayed using a graph (Fig. 1).

## STATISTICAL CALCULATIONS

Statistical calculations were performed using RStudio software v.1.1.442 and R Commander v.2.4-4. Logistic regression was used to create a mathematical model for the prediction of OCL depending on the microRNA expression level in serum and bile. ROC analysis (The Receiver Operating Characteristic) was used to evaluate the quality of the model. As a result, in addition to the graph of the ROC curve, we analyzed the area under the curve (AUC), and the sensitivity, specificity, and accuracy of the model. Subsequently, the selection of the optimal indicator of the threshold value of decision-making (DM) using the graphs of sensitivity, specificity, and accuracy, as well as analyzing the following calculated DM: DM with equal values of sensitivity and specificity, DM at the maximum values of sensitivity and specificity, DM at the maximum value of Cohen's kappa coefficient, DM at the maximum value of the proportion of available and missing correctly defined cases, optimal DM for a given ROC curve. After determining the optimal DM value, the final values of sensitivity, specificity, and accuracy of the model were calculated.

## ETHICS

This work complies with the principles of the Declaration of Helsinki.

## AI STATEMENT

The author states that no AI tools were used in writing this article.

## FRAMEWORK

The study was approved by the Ethics Committee of the Danylo Halytsky Lviv National Medical University, Ukraine (decision number 6 on 28.09.2020). The article was carried out within the framework of the research theme of the Department of Surgery No. 1 of the Danylo Halytsky Lviv National Medical University state registration number 011511000048.

# RESULTS

The results of TAUS and laboratory tests were used to determine the criteria for diagnosing OCL in patients with ACC. A univariate analysis using logistic regression identified 9 of the 51 indicators that have prognostic value for diagnosing OCL: common bile duct diameter

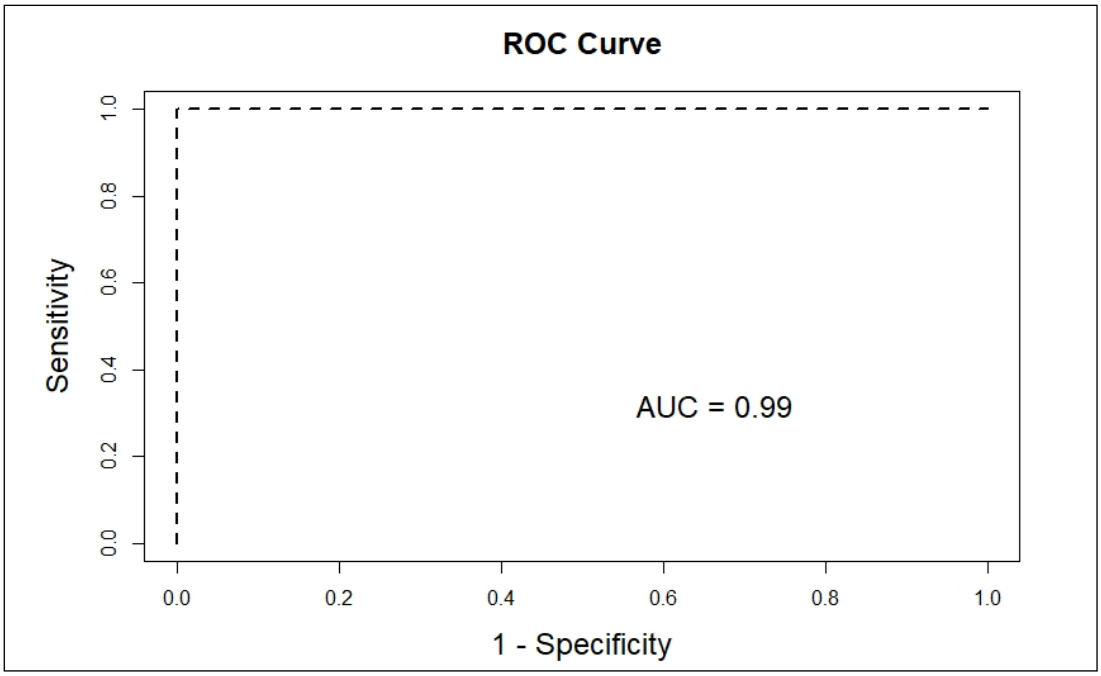


**Fig. 2.** ROC curve of the diagnostic capability of the logistic regression model for oligosymptomatic choledocholithiasis (9-factor model)
*Picture taken by the authors*

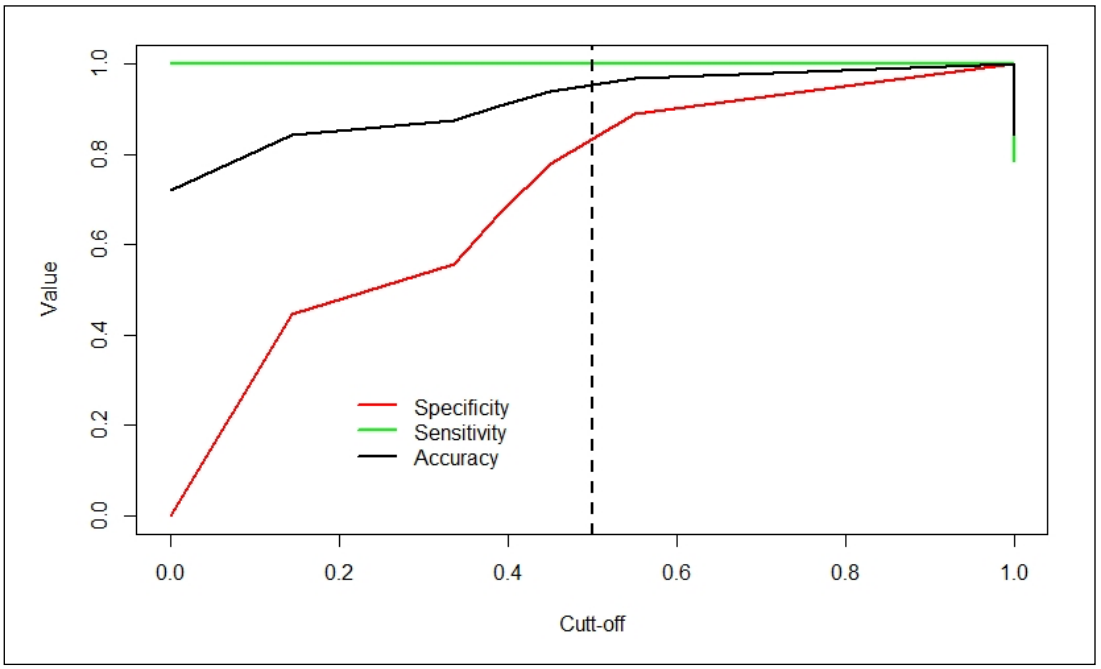


**Fig. 3.** Optimal threshold for decision-making in determining the presence of oligosymptomatic choledocholithiasis (9-Factor Model)
*Picture taken by the authors*

based on TAUS, alkaline phosphatase (ALP) activity, AST activity, ALT activity, total bilirubin level, and the expression levels of miR-122 and miR-21 in blood serum and bile (Table 1).

The overall probability **(*P*)** of OCL in ACC patients can be expressed using the regression equation:

$P=1/(1+e^z)$

$Z=1.03\times V1-73.04\times V2+13.38\times V3+772\times V4+58.53\times V5-3.39\times V6+0.82\times V7-0.54\times V8+15.05\times V9-128.41$

where: *e* is the Euler's number (exponent) equal to 2.718; *Z* is the value of the associated criterion; *V1* is alkaline phosphatase activity (U/L); *V2* is common bile duct diameter (mm); *V3* is total bilirubin level (μmol/L); *V4* is AST activity (U/L); *V5* is ALT activity (U/L); *V6* is miR-21 expression level in serum (RU); *V7* is miR-122 expression level in serum (RU); *V8* is miR-21 expression level in bile (RU); *V9* is miR-122 expression level in bile (RU).

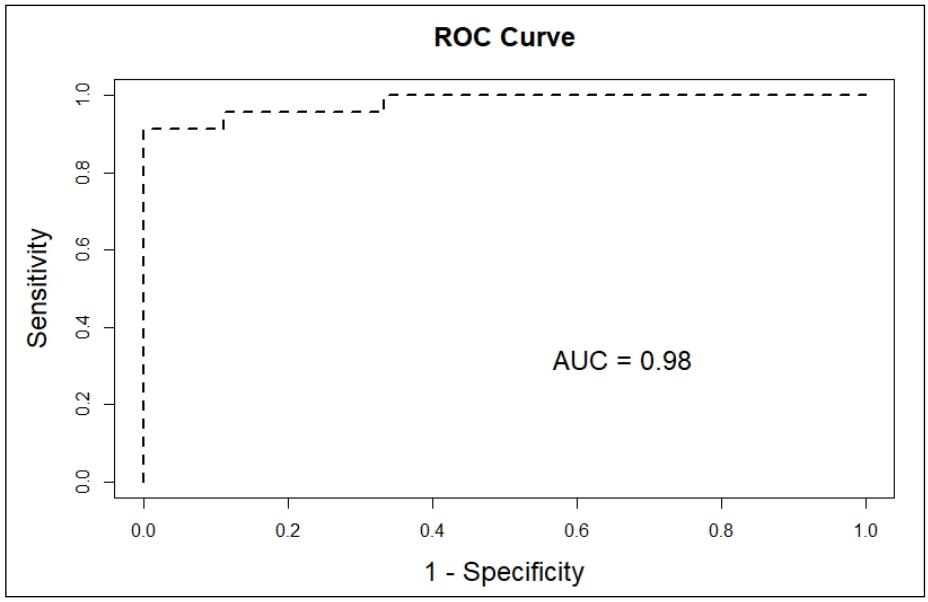


**Fig. 4.** ROC curve of the diagnostic capability of the logistic regression model for oligosymptomatic choledocholithiasis (6-factor model)
*Picture taken by the authors*

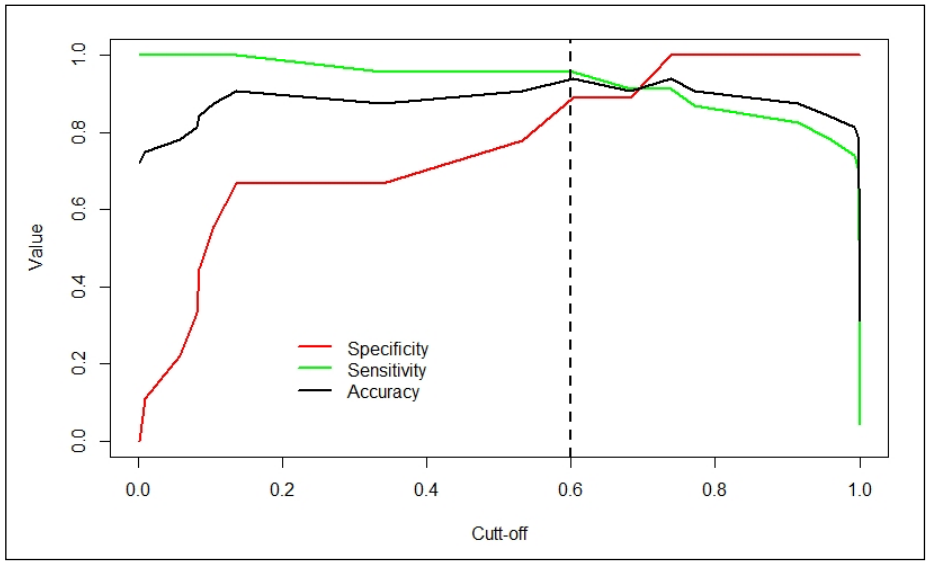


**Fig. 5.** Optimal threshold for decision-making in determining the presence of oligosymptomatic choledocholithiasis (6-factor model)
*Picture taken by the authors*

The associated criterion values were determined for all patients and then entered into ROC analysis to predict the OCL presence (Fig. 2). A high predictive quality for OCL was found (AUC=0.99).

The optimal threshold for decision-making in determining the presence of OCL was 0.5 (Fig. 3). Values above this threshold indicate the presence of OCL, while lower values suggest its absence. Sensitivity at the established threshold was 100%, specificity was 88.90%, and accuracy was 96.88% ($p<0.001$).

From the perspective of broader application in clinical practice for OCL prediction in ACC patients, a multivariate regression model was also developed using six factors: the activity of ALP, ALT, and AST, total bilirubin level, common bile duct diameter according to TAUS, and serum miR-122 expression level (Table 2).

Based on these data, the probability (*P*) of OCL in ACC patients can be expressed using the regression equation:

$P=1/(1+e^{z})$

$Z=0.02\times V1+0.745\times V2+0.23\times V3+10.80\times V4+1.51\times V5+0.018\times V6-17.44$

where: *e* is the Euler's number (exponent) equal to 2.718; *Z* is the value of the associated criterion; *V1* is ALP (U/L); *V2* is common bile duct diameter (mm); *V3* is total bilirubin level (μmol/L); *V4* is AST activity (U/L); *V5* is ALT activity (U/L); *V6* is miR-122 expression level in serum (RU).

Associated criterion values were determined for all patients and then entered into ROC analysis for OCL prediction. A high-quality prediction of OCL (AUC=0.98) was observed, compared to the 9-factor model (Fig. 4).

The threshold for decision-making in determining the presence or absence of OCL was 0.6 (Fig. 5). The sensitivity of the model was 95.65%, specificity was 88.90%, and accuracy was 93.75%. From a practical perspective, this means that in 95.6% of cases, the test will be positive if the patient has OCL.

## DISCUSSION

The evaluation of the probability of choledocholithiasis in ACC patients remains a relevant issue in clinical practice and continues to be a subject of scientific debate to this day [1-3]. According to clinical treatment protocols, patients with symptomatic choledocholithiasis require treatment to remove stones from the bile ducts and ensure adequate bile drainage. However, the clinical management of patients with asymptomatic choledocholithiasis remains controversial, as any intervention, including endoscopic procedures, carries a certain risk of side effects [5].

It is well known that the presence of stones in the common bile duct is associated with a risk of complications. Therefore, during surgical treatment for ACC, it is advisable to simultaneously address choledocholithiasis if present. Diagnosing this condition before surgical intervention is crucial, as removing stones from the bile ducts along with cholecystectomy helps avoid additional future invasive procedures, reducing the risk of complications, lowering treatment costs, and lessening the burden on the healthcare system.

ERCP, previously considered the gold standard for diagnosing common bile duct stones, is associated with a risk of serious complications and is not widely recommended as a diagnostic technique in this clinical scenario [4, 6, 7]. Additionally, the benefit-risk ratio must be determined for therapeutic ERCP to be performed.

The limited availability of other imaging techniques for diagnosing choledocholithiasis (MRCP, CT, EUS) and their practical unavailability in some cases necessitate the development of simple and effective predictive models for OCL diagnosis. Although some sources highlight the prognostic value of biochemical and instrumental parameters in assessing OCL risk and choosing patient management methods, no universally accepted evaluation system currently exists [6-8, 17].

Choledocholithiasis is typically suspected in patients with signs of cholestasis (elevated bilirubin levels and alkaline phosphatase activity in serum) and confirmed by TAUS. Indeed, in patients with gallstone disease, a total bilirubin level of 3–4 mg/dL (51.3–68.4 μmol/L) is closely associated with choledocholithiasis. Serum ALT, AST, and alkaline phosphatase activity levels are also elevated in bile duct obstruction. However, in cases of OCL in ACC, the prognostic value of elevated liver enzyme levels is limited, as other factors may also contribute to these abnormalities [4, 18].

TAUS is the initial test for patients with suspected choledocholithiasis. Although abdominal ultrasound often reveals only dilation of the bile ducts, its sensitivity for detecting common bile duct stones is relatively low.

Consequently, biochemical tests and TAUS cannot reliably predict the presence of common bile duct stones, and ERCP is not a viable screening tool due to its associated complications.

Recent studies demonstrate the important role of microRNAs in the pathogenesis of liver diseases. The levels of these molecules increase in bile and blood serum in various hepatobiliary disorders. Based on this, miR-122 and miR-21 are suggested as markers for diagnosing cholestatic liver injury and bile duct pathology [14-16].

Our previous research demonstrated the potential of quantifying serum and bile miR-122 and miR-21 expression levels to predict the probability of choledocholithiasis in ACC patients [19]. Additionally, we determined the diagnostic significance of some liver function tests and ultrasound indicators for detecting common bile duct stones. Notably, combining different indicators in multivariate analysis improved the predictive accuracy compared to using individual components.

In this study, we combined nine different indicators into a multivariate model, which demonstrated a high prognostic value in ROC analysis (AUC=0.99), with a decision-making threshold for OCL presence at 0.5. The sensitivity of the method was 100%, and the specificity was 88.9%. From a practical perspective, this method allows for a highly reliable risk assessment of OCL in patients with ACC when the calculated probability exceeds 0.5.

However, the mentioned model includes bile miR-122 and miR-21 expression levels, which cannot be routinely measured in clinical practice. Previous findings indicated that the most sensitive microRNA indicator (according to ROC analysis) is the bile miR-122 level, and increased serum miR-122 and miR-21 expression levels significantly ($p<0.05$) correlated with those in bile [19].

To enhance practical applicability, we developed a regression model based on six widely accessible parameters in routine surgical practice: the activity of alkaline phosphatase, AST, and ALT, total bilirubin level, common bile duct diameter based on TAUS, and serum miR-122 expression.

The analysis of this model showed its high prognostic accuracy (AUC=0.98) compared to the 9-factor model, with a sensitivity of 95.65% and specificity of 88.90%

allowing for a highly confident assessment of OCL risk in ACC patients.

The simplicity and accessibility of determining each indicator make this model feasible for use in routine clinical practice. Since this evaluation system has high prognostic accuracy and broad applicability, it can help avoid unnecessary referrals for MRCP, EUS, and ERCP. This model can serve as a diagnostic tool for predicting OCL in ACC patients.

## CONCLUSIONS

1. The diameter of the common bile duct, the activity of ALT, AST, and alkaline phosphatase, total bilirubin levels, as well as the expression levels of miR-122 and miR-21 in serum and bile, serve as reliable diagnostic criteria for the presence of oligosymptomatic choledocholithiasis.
2. A multivariate model based on six factors (the activity of alkaline phosphatase, AST, and ALT, total bilirubin level, common bile duct diameter assessed via TAUS, and serum miR-122 expression level) demonstrates comparable predictive accuracy and is more practical for routine clinical application. This method can be recommended as a diagnostic test for predicting the presence of OCL in patients with ACC.

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**CONFLICT OF INTEREST**

The Authors declare no conflict of interest

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