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The Preoperative Prediction and Management of Choledocholithiasis before Planned Laparoscopic Cholecystectomy based on Individual Risk of Choledocholithiasis

SUMMARY OF DOCTORAL DISSERTATION

Medicine and Health Sciences,
Medicine (M 001)

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This dissertation was written between 2016 and 2020 at Vilnius University.

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Individualia tulžies latakų akmenligės rizika pagrįstas priešoperacinis ištyrimas ir tulžies latakų akmenligės gydymas prieš planuojamą laparoskopinę cholecistektomiją

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ABBREVIATIONS

ASA – American Society of Anesthesiologists
ASGE – American Society for Gastrointestinal Endoscopy
CBD – common bile duct
CI – confidence interval
ERCP – endoscopic retrograde cholangiopancreatography
EUS – endoscopic ultrasound
IOC – intraoperative cholangiography
IQR – interquartile range
LC – laparoscopic cholecystectomy
MRCP – magnetic resonance cholangiopancreatography
OR – odds ratio
PST – papilosphincterotomy
Q_1, Q_3 – first and third quartiles
SD – standard deviation
VUHI – Vilnius university hospital index

1. INTRODUCTION

Choledocholithiasis is a common complication of cholecystolithiasis occurring for 5–21% of people undergoing cholecystectomy (1–3). Common bile duct (CBD) obstruction by stones can lead to acute biliary pancreatitis, mechanical jaundice, acute ascending cholangitis, and even to fatal outcomes (4). In most cases, choledocholithiasis can be predicted from clinical signs, biochemical tests and imaging studies' findings, but sometimes it can be asymptomatic and does not appear on laboratory blood tests results. Up to 30% of CBD stones evacuate spontaneously, but it to prognose precisely which patients will pass their stones and whether it will happen at all is impossible.

Gallstone disease can be managed by classical and newer treatment methods. They include open surgery, laparoscopy and endoscopy (5–7). The traditional method for treating choledocholithiasis which had been used for many years includes intraoperative cholangiography (IOC), lithectomy and T-tube insertion to CBD. However, this method accounts for a 10–15% rate of complications and side effects, a 1% rate of mortality (patients over 65 years of age), and a failure rate of up to 6% of unsuccessful procedures (8).

With the development of laparoscopic cholecystectomy (LC) – the new gold standard in the treatment of gallstone disease – the assessment of bile ducts has become more difficult: it is not possible to palpate the ducts and detect stones in them during the operation. Therefore, the importance of the preoperative diagnostics of choledocholithiasis has increased significantly, as the detection of CBD stones changed the treatment strategy. Advances in minimally invasive surgery and endoscopy have expanded the treatment options for choledocholithiasis. Currently, the treatment of concomitant cholecystolithiasis and choledocholithiasis can be administered according to a single-stage or two-stage protocol. A single-stage method involves LC and an intraoperative examination of the bile ducts (cholangiography) and the removal of stones. The two-stage

method involves separate endoscopic retrograde cholangiopancreatography (ERCP) with therapeutic interventions such as endoscopic papillosphincterotomy or sphincteroplasty and the removal of stones, followed by LC (8).

The use of ERCP as a diagnostic tool should be minimized, as it, together with additional interventions, carries a considerable risk (5–10%) of post-procedural complications: acute pancreatitis (1.3–6.7%), bleeding (0.7–2%), acute cholangitis (0.5–5%), duodenal perforation (0.3–1%), and a mortality rate that can be as high as 0.5% (9–11). It is noticed that adverse events occur more often in patients with a low risk of choledocholithiasis (9). This increases the duration of hospitalisation, costs of treatment, and worsens the patient's quality of life. Therefore, a scrutinized selection of patients for ERCP is advised, as well as avoiding its usage for purely diagnostic purposes; non-invasive diagnostic methods should be applied for lower risk patients.

The advantage of single-stage treatment is the lower number of procedures including anesthesia, but this strategy requires additional equipment and skills of the surgeon, so it is recommended to choose choledocholithiasis treatment tactics based on the patient's condition, the operator's experience, and the available tools (12). Meta-analyses revealed no significant differences between single- and two-stage treatments in comparing the incidence of complications, mortality, remaining stones, and failure rates (13,14). A consensus has not yet been reached on the ideal treatment for gallbladder and CBD stones. It is being considered whether an intraoperative radiological assessment of bile ducts should be performed in all patients or only in those with suspected choledocholithiasis. There is also a discussion about whether it is better to remove bile duct stones endoscopically before cholecystectomy or during LC, also additionally performing cholangiography.

At Vilnius University Hospital Santaros Klinikos, patients with cholecystocholedocholitihiasis are usually treated using a two-stage strategy, i.e., preoperative ERCP and then LC. Each year about 600

patients at the Abdominal Surgery Center undergo LC, and about 100 of them have ERCP before their surgeries due to the high risk of concomitant choledocholithiasis. CBD stones are detected in only about 60% of the ERCP patients; other pathologies of the bile ducts (strictures, tumours) are diagnosed in 10% of cases, while no pathologies are detected for the remaining cases. The fact that about 30% of patients turn out to be unnecessarily tested after the ERCP may be partially explained by the lack of effective patient selection.

At Vilnius University Hospital Santaros Klinikos, an original prognostic index (Vilnius University Hospital Index (VUHI)) has been used for evaluating the risk of choledocholithiasis before planned LC since 1999 (15). It is calculated by the formula $VUHI=A/30 + 0.4\times B$, where A – total bilirubin concentration (μmol/l), B – CBD diameter measured with ultrasound (US). When the value of the VUHI is equal to or higher than 4.7, the risk for choledocholithiasis is considered high, while VUHI up to 4.7 is associated with a low risk. Considering the diagnostic possibilities available two decades ago, ERCP before LC was the management of choice for high risk patients and patients of the low risk group had LC done without any additional interventions (16,17).

Over the last decade, other effective, less invasive, and safer for the patient investigation methods of the biliary tree (magnetic resonance cholangiography (MRCP) and endoscopic ultrasound (EUS)) have become popular in global practice. These have led to the development of various choledocholithiasis risk stratification algorithms (18–26). However, there is no fully accurate choledocholithiasis prediction model yet, and no clear indications have been established for which patients should be subjected to additional testing prior to LC, depending on the degree of risk of choledocholithiasis.

To achieve more effective diagnostics of concomitant choledocholithiasis before LC, i.e., to reduce the proportion of diagnostic ERCP procedures, it is necessary to improve patient selection for biliary tree examinations. To achieve this goal, we

planned to evaluate the choledocholithiasis prediction index (VUHI) used in Santaros Klinikos and to determine a new set of values for it by classifying patients into high, intermediate, and low risk groups. With the introduction of this trinary choledocholithiasis forecasting model, for our next step we tried to confirm its accuracy in a prospective study.

Aim of the study

The aim of this dissertation is to optimize the choledocholithiasis risk prediction system before forthcoming LC and to determine which diagnostic tactics – preoperative EUS or IOC – are most effective in patients with gallstone disease and with an intermediate risk of choledocholithiasis.

Tasks of the study

The tasks of the dissertation are:

- To evaluate the effectiveness of the Vilnius University Hospital Index (VUHI) and compare it with a choledocholithasis prediction model recommended by other guidelines.
- To establish new VUHI thresholds for describing different choledocholithiasis risk categories.
- To evaluate and compare the effectiveness of different choledocholithiasis investigation and treatment tactics (single-stage and two-stage) – diagnostic accuracy, duration of operations and treatment, frequency of complications, costs.
- To validate the threshold values of the newly defined VUHI model and evaluate its diagnostic parameters.

- To evaluate the predictors of choledocholithiasis and develop a regression-based model for the diagnosis of CBD stones.

Novelty of the study

- VUHI, the prognostic index of Santaros Klinikos used as a binary model (low-high risk) already exceeds the diagnostic parameters of the most widely used choledocholithiasis risk assessment system offered by ASGE in 2010. Based on the results of the performed retrospective and prospective studies, new VUHI threshold values were determined that define a trinary model (low-intermediate-high risk) and further improve its forecasting efficiency. A new algorithm for the diagnosis and treatment of choledocholithiasis is proposed.
- A prospective study compares intraoperative cholangiography and preoperative endoscopic sonoscopy. No previous clinical trials comparing these diagnostic methods have been found.

Practical significance

A more precise selection of patients may reduce the amount of diagnostic ERCP, reserving this procedure for cases where there is a high probability of the need for therapeutic interventions. Simultaneously, the incidence of ERCP complications is reduced. Both treatment tactics (EUS and ERCP on demand, followed by LC vs. LC with IOC and intra- or postoperative ERCP on demand) are adequate in terms of safety and accuracy, and can be chosen depending on local resources and capabilities.

Statements to be defended

- For patients with an intermediate risk of choledocholithiasis, it is optimal to choose single-stage treatment for concomitant cholecystocholedocholithiasis.
- The VUHI trinary model can reduce the number of ERCPs performed for diagnostic purposes, as well as their potential complications.

2. METHODOLOGY OF THE STUDY

To improve the risk prediction of choledocholithiasis and to identify more effective tactics for its diagnosis and treatment, we conducted two biomedical trials. First, a retrospective trial was performed – an analysis evaluating the effectiveness of the index (VUHI). Based on its data, new thresholds were established to divide patients according to the degree of risk of choledocholithiasis into three groups – low, intermediate, and high risk. Next, a prospective trial was conducted to evaluate the effectiveness of two different management tactics in the intermediate choledocholithiasis risk group. The methodology of both trials is described below.

Retrospective trial

To evaluate the effectiveness of choledocholithasis diagnosis and management, we performed a retrospective trial "Retrospective analysis of choledocholithiasis risk assessment before planned cholecystectomy and selection of treatment tactics." The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2016, permission No. 158200-16-870-395. To identify study participants, we reviewed all the case records in our institution's reporting database that had included keywords "laparoscopic cholecystectomy" in their operation protocols. The data were collected from January 2012 to December 2015. Written

informed consent for the procedures was obtained from each patient included in the trial.

Inclusion criteria:

- Age 18 years and older;
- LC for gallstone disease during this hospitalization;
- Additional preoperative, preoperative, or postoperative examinations for suspected TLA: computed tomography (CT), MRCP, IOC, EUS, or ERCP.

Exclusion criteria:

- surgically altered anatomy (Billroth II, Roux-en-y anastomosis, gastric bypass);
- a history of biliary surgery or stenting;
- suspected or known hepatopancreatobiliary malignancy;
- other known liver or biliary diseases.

Calculation of the sample size

Based on the literature, the ASGE guidelines state that choledocholithiasis was detected in > 50% of patients at high risk and in 10–50% of patients at the intermediate risk category. For the calculation of the sample size, we assumed a choledocholithiasis rate of 75% in the high risk group and 50% in the intermediate risk group. To find a 15% difference between different risk groups, type I error (α) is chosen to be 0.05, type II error (β) to be 0.2. Taking the statistical test significance level $\alpha = 0.05$, statistical test power $1-\beta = 0.80$, the required sample size is 349 patients, allowing to determine the effect size of 0.15. With $\alpha = 0.05$, a statistical test power of $1-\beta = 0.95$, the required sample size is 342 patients, allowing to determine the effect size of 0.195.

Collected data

The following data were collected for each eligible participant: sex; age at the time of admission; duration from admission to intervention (IOC or ERCP) in days; total bilirubin concentration; CBD diameter and stones if seen on ultrasound (US), CT or MRCP; diagnosed acute cholecystitis, acute ascending cholangitis or acute biliary pancreatitis prior to ERCP; value of VUHI; physical status assessment according to the American Society of Anesthesiologists (ASA) classification; which investigation method of bile ducts was chosen first (ERCP or IOC), its results and outcome; type of cholecystectomy; adverse events of ERCP and their management; surgical complications (Clavien-Dindo classification); ERCP performed after cholecystectomy and its results; length of hospital stay. Jaundice was stated at a total bilirubin level of 34 μmol/l and higher (27). A diagnosis of acute biliary pancreatitis was acknowledged when stated in medical records or when lipase or amylase activity was at least three times higher than the upper limit of normal. A diagnosis of acute cholangitis was declared when stated in medical records. A diagnosis of acute cholecystitis was declared when suspected by clinical findings and confirmed histologically. A CBD stone was considered detected when it was found and removed during ERCP, IOC or choledochotomy. A CBD stone at cholangiography (IOC or ERCP) was suspected when there was a filling defect seen on a radiogram, or if a delayed passage of contrast material into the duodenum was observed.

Prospective trial

Based on the retrospective trial described above, we established new threshold values for VUHI. We newly identified an intermediate risk group for which, according to global guidelines, additional testing is beneficial to determine the indications for therapeutic ERCP. Thus, we conducted a prospective randomized trial “Comparison of Endoscopy First and Laparoscopic Cholecystectomy First Strategies

for Patients with Gallstone Disease and Intermediate Risk of Choledocholithiasis." The main aim of the trial was to determine which examination and treatment tactics are most effective for patients with an intermediate risk of CBD stones and allow the abandonment of ERCP for diagnostic purposes only. Preoperative EUS and IOC were chosen as diagnostic procedures; therefore, this study allows us to compare not only diagnostic interventions, but also single- and two-stage treatment tactics.

Data from patients evaluated for eligibility for the prospective study (both included in the study and not meeting the inclusion criteria) were used to validate the threshold values of the VUHI trinary model.

The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2017, permission No. 158200-17-978-473.

The trial was registered in the ClinicalTrials.gov database, identification No. NCT03658863.

Inclusion Criteria

- Age 18–80 years;
- Symptomatic cholecystolithiasis (stones in the gallbladder seen on imaging studies and causing episodes of biliary colic);
- Intermediate risk of choledocholithiasis (Vilnius University Hospital Index 2.6-6.9 and one of the following predictors: dilated common bile duct >6 mm, elevated total bilirubin >21 μmol/L, or suspected stone in the common bile duct [CBD] on ultrasound).

Exclusion Criteria

- Acute cholangitis, as defined in the Tokyo guidelines 2013 (28);

- Moderately severe or severe biliary pancreatitis, as defined in the revised Atlanta classification (29);
- Acute cholecystitis (degree II-III), as defined in the Tokyo guidelines 2013 (30);
- Anastomosis in the upper gastrointestinal tract;
- Known cholestatic hepatopancreatobiliary disease (primary biliary cholangitis, primary sclerosing cholangitis, secondary biliopathy, tumour of the head of the pancreas or major papilla, or benign or malignant CBD stricture);
- Known or suspected hepatitis (viral, toxic, alcoholic, etc.) or liver cirrhosis;
- Contraindications for general anaesthesia or surgery;
- IV-VI class of the American Society of Anesthesiologists physical status classification;
- Morbid obesity (BMI > 40);
- Pregnancy;
- Patient refusal to participate in the study.

Elimination from the Trial

Patients will be omitted from the trial if their medical circumstances become incompatible with the trial protocol. This can happen because of the following reasons: a neoplastic condition is found at the time of management; the general status of the patient worsens owing to other health issues not related to cholelithiasis (e.g., myocardial infarction) and they require urgent interventions not included in the trial protocol; LC is converted to open cholecystectomy before IOC in the “cholecystectomy first” arm. Additionally, if the patient refuses to further participate in the trial, all the patient’s data are eliminated, and further follow-up is not carried out. Informed consent was obtained from all study participants.

Randomization and Data Protection

Eligible patients who provide informed consent will be assigned to the groups “endoscopy first” or “cholecystectomy first” randomly, according to a premade sequence. The sequence is generated by a randomization website (random.org). The sequence is created using a block randomization of two elements A and B (“endoscopy first” and “cholecystectomy first”) in a ratio of 1:1. According to the sequence, sheets with group names are enclosed in opaque envelopes. Envelopes are numbered, and the envelope number is the patient number in the trial. When a new participant is enrolled, the topmost envelope is opened by one of the investigators and the participant is randomized into the specified group.

All collected data are coded, meaning every case receives an individual number. Only coded data will be employed for statistical analysis and publishing. Uncoded data are available only for researchers of the trial and, on special and reasonable request, for the coordination center for biomedical research of the institution and the Biomedical Research Ethics Committee. Data are processed and stored in a digital database, while physical (“paper”) copies are stored at the trial centre in accordance with procedures established by law.

Procedure

The participants of the trial undergo CBD evaluation depending on the group assignment. For the group “endoscopy first,” EUS is used to evaluate bile ducts. If stones are seen in the extrahepatic bile ducts, ERCP and CBD stone removal are performed during the same general endotracheal anesthesia. LC is performed after endoscopic procedures as soon as possible.

In the group “cholecystectomy first,” LC with IOC is performed. If stones are found, postoperative ERCP with CBD stone removal is applied (during cholecystectomy if the CBD is completely blocked, or as soon as possible). EUS is performed with linear or radial Olympus ultrasound endoscopes. The CBD, pancreatic head, and adjacent

structures are visualized from the duodenal bulb and descending duodenum. EUS is considered positive for a CBD stone when a constant hyperechogenic lesion with acoustic shadowing is seen in CBD projection. ERCP procedures are performed by experienced endoscopists (each has more than 5 years of experience in ERCP and has done more than 500 procedures). Olympus side-viewing endoscopes (TJF-160VR) are used. Primary deep selective cannulation of the CBD is performed with a sphincterotome or cannula and guidewire technique. Diatrizoate (Urografin, Bayer) and iohexol (Omnipaque, GE Healthcare) are used as contrast media. Endoscopic sphincterotomy is performed over a guidewire technique with an Olympus pull-type sphincterotome. Papillary balloon dilation using a through-the-scope balloon catheter is applied when a stricture is indicated. Stones are removed using a retrieval balloon catheter and/or a Dormia basket. Complete clearance of the CBD is documented with a balloon catheter cholangiogram at the end of the procedure. ERCP is considered positive when a filling defect is seen in the cholangiogram and/or a stone is evacuated from the CBD. ERCP is considered unsuccessful when the cannulation of bile ducts is technically impossible.

All patients will undergo a standard four-port LC (a 10-mm port at the umbilicus, a 10-mm port at the subxyphoid, a 5-mm port at the bottom of the gallbladder, and a 5-mm port at the right epigastrium). A 30-degree laparoscope is used for intra-abdominal visualization. After the exposure and identification of the elements of the hepatocystic triangle, a small transverse cut is made in the cystic duct close to the gallbladder infundibulum using laparoscopic scissors. A 4-French cholangiogram catheter is placed in a 5-mm cholangiography fixation clamp and then inserted into the cystic duct. After verifying the absence of leakage at the catheter insertion site, contrast medium (Urografin) diluted in NaCl 0.9% solution (1:1 ratio) in a 20-mL syringe is injected under fluoroscopic vision (C-arm, Siemens GmbH). Cholangiograms are assessed by the operating

surgeon and radiologist. IOC is considered positive when there is a filling defect or lack of contrast evacuation to the duodenum.

Follow-Up

Participants are followed as treated inpatients after LC (short-term surveillance) and for 6 months after hospitalization (long-term surveillance). In the short-term surveillance period, postprocedural adverse events, signs of cholestasis, and need for repeated procedures are recorded. In the long-term surveillance period, participants are encouraged to contact the investigators if any symptoms of recurrent cholelithiasis are suspected. Participants will be contacted via phone or email 6 to 12 months later. Their health status will be evaluated using a questionnaire on the possible symptoms of choledocholithiasis. If any symptoms of possible gallstone disease are observed, the participant is invited for additional investigation (biochemical blood tests, transabdominal ultrasound, and MRCP on demand).

Sample size calculation

The sample size was calculated in reference to collected data on the management of choledocholithiasis at the trial center, Vilnius University Hospital Santaros Klinikos (31). In our previous study, the mean treatment durations for different management strategy groups (LC-IOC first and ERCP first) were 5.37 and 7.13 days, with SDs of 2.5 and 2.8, respectively, and these findings were used to calculate the requested sample size. G*Power version 3.1.9.2 software was used for calculations. The sample size was calculated for a two-tailed t test for means of two independent groups. The significance level was selected to be .05, with a power of 0.8. The required sample size is 74 (37 valid participants in each of the two groups).

Statistical analysis

Statistical analysis was performed using R statistical software package Version 4.0.2 (© The R Foundation for Statistical Computing), Rstudio Version 1.3.959 (© 2009-2020 RStudio, Inc.), IBM SPSS Statistics V.23, and G*Power V. 3.1.9.4 Universität Düsseldorf, Germany.

Interval and ratio variables were defined by minimum and maximum values [Min; Max], means (Mean), their standard deviations (SD), medians (Median), first (Q1) and third (Q3) quartiles, and the distance between these quartiles (IQR 75%). The Kolmogorov-Smirnov criterion and the Shapiro-Wilk criterion were used to test hypotheses about the normality of the distribution of interval variables. In case of disagreement, the Shapiro-Wilk criterion (more appropriate for small samples) was used. Nominal variables were defined by their multiplicity and percentage of the relevant subsample.

We used the Chi-squared (χ^2) test to determine the statistical significance of the association between the respective nominal variables. Fisher's Exact test was used when the multiplicity of the variables concerned was very low. A statistically significant association was declared if the p-value was less than the 0.05 significance level, and the confidence interval (CI) was calculated for a 95% confidence level.

For normally distributed interval variables, the t-test for independent samples was used.

The Mann-Whitney U test was used to compare interval variables in 2 independent samples when the distribution is not normal. The Kruskal-Wallis test is an extension of the Mann-Whitney U test for comparing more than 2 independent groups of subjects and was used to compare interval variables in more than 2 independent groups when the distribution is not normal. Since the results of the Kruskal Wallis test for two groups are consistent with the results of the Mann-Whitney U test, we used the Kruskal-Wallis rank sum test and the effect size

eta2 [H] (eta squared, based on the H-statistic) to assess the dependence of the samples of the two or more independent variables, whether they are interval variables or rank variables. It is assumed that when eta2 [H] is in the range (0.01 - 0.06) we have a small effect, when in the range (0.06 - 0.14) we have a moderate effect and when eta2[H] ≥ 0.14 we have a large effect.

A binary logistic regression model was constructed to predict the average risk of choledocholithiasis in the group of detected CBD stones. The logistic regression is expressed by the equation:

$$z = \ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 \times X1 + \beta_2 \times X2 + \cdots + \beta_n Xn$$

Here p denotes the probability of detecting or possessing a given attribute (in this case, stones in the CBD); β_0 is intercept term (shift in the ordinate axis), β_1, β_2 ... β_n - coefficients of the regression equation, calculated from the data of the sample of the study, indicating changes in the variables; X1, X2 ... Xn - independent variables.

The maximum likelihood estimation (MLE) method was used to calculate standard errors.

To assess the goodness of fit to the data (accuracy) of models based on polynomial logistic equations, we used the following indicators:

Cragg-Uhler and McFadden coefficients of determination;

the Kappa coefficient, used to determine the consistency between the conclusions of two experts (in our case, a blind guess and the model's result) evaluating the same object or phenomenon.

For statistically significant/non-significant relationships between observed and model-derived results, we used McNemar's test.

The relationships between the nominal variables were assessed as statistically significant when the significance of the statistical tests was $\alpha = 0.05$ (p-value < 0.05) and the power of the statistical tests was $1-\beta = 0.95$

Predictive values of the diagnostic tests were calculated according to the following formulae:

Sensitivity = true positives / (true positives + false negatives) × 100;

Specificity = true negatives / (false positives + true negatives) × 100;

Positive predictive value = true positives / (true positives + false positives) × 100;

Negative predictive value = true negatives / (false negatives + true negatives) × 100;

Accuracy = (true positives + true negatives) / (all cases) × 100;

Positive likelihood ratio = sensitivity / (1 - specificity);

Negative likelihood ratio = (1 - sensitivity) / specificity.

We evaluated the classification performance of the fitted model using the ROC (Receiver Operating Characteristics) curve. The ROC curve was evaluated according to the following criteria: area under the curve (AUC): 0.90-1.0 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair, 0.60-0.70 = poor, 0.50-0.60 = bad.

3. RESULTS OF THE STUDY

Retrospective trial

Patient characteristics and differences between patients with and without CBD stones

During the study period 2313 patients had a cholecystectomy performed at Santaros Klinikos. Among them 350 patients (63.4% female, mean age 65.2 years, SD 17.89) were eligible for the study.

CBD stones were found in 226 cases (9.8% of all patients undergoing cholecystectomy); no stones were detected in 124 cases. Basic characteristics of the entire study population and differences between patients with and without CBD stones are summarized in Table 1.

Patients' age and sex distribution did not differ significantly statistically. Patients in the stone-positive group had a significantly higher total bilirubin concentration and CBD diameter and more cases

of acute cholangitis (19.9% vs. 8.9%) but fewer cases of acute biliary pancreatitis (13.2% vs. 26.6%) as compared with the stone-negative group.

A total of 111 (31.71%) patients were classified as having a low risk for choledocholithiasis (VUHI <4.7), and 239 (68.29%) patients were assigned to a high risk group (VUHI ≥4.7).

Table 1. Characteristics of patients with and without CBDS

Variable	All patients n=350	CBDS (+) n=226	CBDS (-) n=124	Odds ratio (95% CI)	P-value
Demographic					
Age (year), mean (SD)	65.2 (17.9)	66.3 (17.7)	63.3 (18.1)	-	0.130
Female; n (%)	222 (63.4)	135 (59.73)	87 (70.16)	0.63 (0.4-1.0)	0.053
Clinical					
Jaundice, n (%)	242 (69.1)	165 (73.0)	77 (62.1)	1.65 (1.04-2.63)	**0.035**
Acute biliary pancreatitis, n (%)	63 (18)	30 (13.2)	33 (26.6)	0.42 (0.24-0.73)	**0.002**
Acute cholangitis, n (%)	56 (16)	45 (19.9)	11(8.9)	2.5 (1.24-5.04)	**0.002**
Acute cholecystitis, n (%)	101 (28.9)	60 (26.5)	41 (33.1)	0.73 (0.45-1.18)	0.198
Radiological					
Diameter of CBD (mm), mean (SD)	10.17 (4.2)	11.35 (4.11)	7.94 (3.28)	-	**<0.001**
CBDS seen on US, n (%)	137 (39.1)	112 (49.6)	25 (20.2)	5.81 (3.29-10.26)	**<0.001**
Biochemical					
Total bilirubin (μmol/l), mean (SD)	74.8 (63.3)	82.1 (65.7)	61.4 (56.4)	-	**0.002**

Predictors of choledocholithiasis

Performance characteristics of separate predictors: elevated bilirubin concentration, dilated CBD (diameter >6 mm) and CBD stones seen or suspected by US were evaluated.

In the stone-positive group, bilirubin was elevated above the upper limit of normal value in 189 cases (83.6% of patients with CBD stones), dilated CBD was found in 209 cases (92.5%) and CBD stones on US were seen in 112 cases (49.6%). In the stone-negative group, concentration of bilirubin was abnormal in 94 cases (75.8% of patients without CBD stones), CBD was dilated in 84 cases (67.7%) and CBD stones on US were seen or suspected in 18 cases (14.5% of US performed).

An evaluation of different criteria showed that dilated CBD and CBD stones on US were stronger predictors than elevated total bilirubin (Table 2). The elevation of bilirubin above the upper limit of normal value (20 μmol/l) was not significantly different between the two groups, but its increase above 34 μmol/l, as a previously defined cut-off value for suspected choledocholithiasis, was found to be a significant predictor. Dilated CBD had the highest sensitivity (92.5%), although its specificity was low (32.2%). CBD stones found by US had low sensitivity (51.3%), despite high specificity (84.6%).

Table 2. Prognostic values of different CBDS predictors and VUHI

Predictors	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	Odds ratio (95% CI)	P-value
Total bilirubin							
Cut-off >20 µmol/l	83.6	24.2	66.8	44.8	62.6	1.63 (0.95-2.8)	0.075
Cut-off >34 µmol/l	73	37.9	68.2	43.5	60.6	1,65 (1,04-2,63)	**0,035**
CBD > 6 mm	92.5	32.2	71.3	70.2	71.1	5.85 (3.15-10.9)	**<0.001**
CBD stones on US	51.3	84.6	86.2	48.3	63.0	5.81 (3.3-10.26)	**<0.001**
VUHI >=4.7	80.5	54.0	76.1	60.4	71.1	4.86 (3.00-7.88)	**0.000**

Evaluation of VUHI

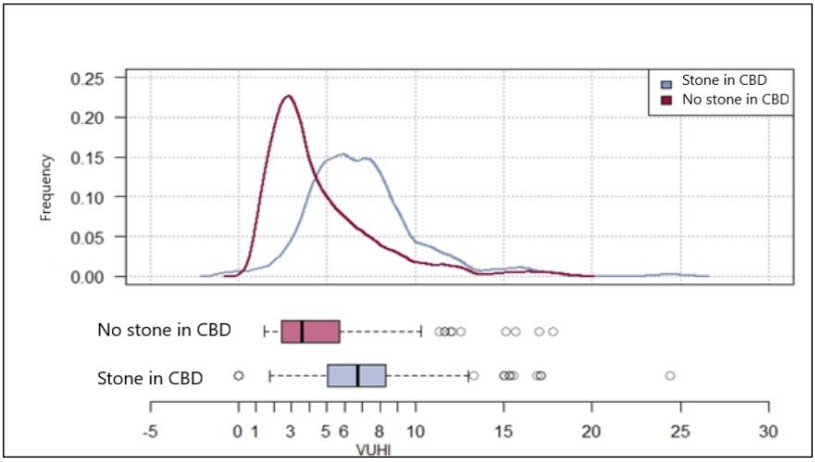
VUHI ≥4.7 was found to be associated with more than a four-fold greater risk of having CBDS than VUHI <4.7 (OR 4.86) (Table 2). When counting CBD stones on US as an additional factor for the higher-risk group ('VUHI ≥4.7 or CBD stones on US') OR and performance rates improved, except specificity (OR 7.07).

Additionally, we included benign CBD strictures (n=14) as a positive outcome, presuming these patients would also benefit from ERCP. This modification raised the OR to 6.09 and overall accuracy to 74.0%.

In the higher risk group ERCP was scheduled for 205 patients; no pathology was detected (i.e., the ERCP was performed unnecessarily) in 20 (9.76%) cases.

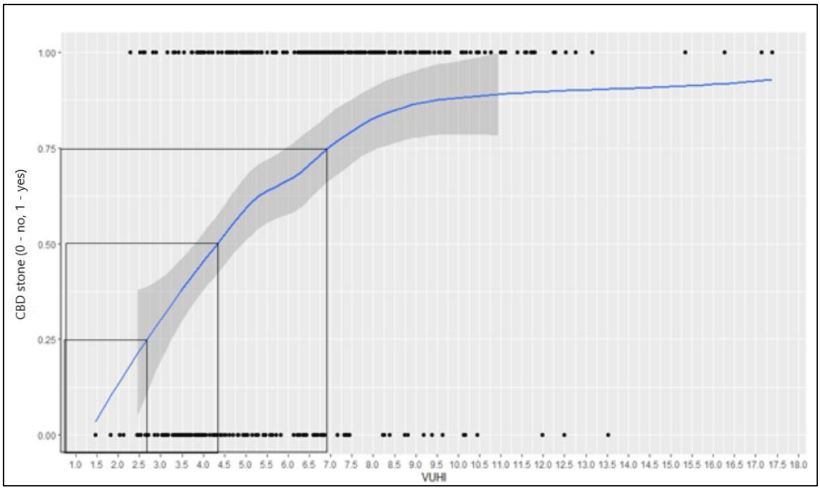
The dependence of the relative frequency (density) of confirmed and denied CBD stones on the VUHI values and the distribution of the VUHI are shown in Figure 1.

Figure 1. Stones in CBD depending on VUHI values



We used a non-parametric smooth spline data visualization method based on the density estimation of the observed values to determine the VUHI thresholds. Since the resulting curve is not easy to describe by a mathematical function, and since it is difficult to expect the resulting function to describe it accurately, we obtained reasonably accurate results by plotting a smooth spline curve describing the dependence of the risk of CBD stone presence on the VUHI and visually identifying the VUHI values and their ranges for the risks of interest (Figure 2).

Figure 2. CBD stone presence risk dependence on VUHI values.



From the smooth spline curve, we have identified new threshold values for three index ranges defining different risk groups:

low (<25%) risk of choledocholithiasis – VUHI <2.6,

intermediate (25-75%) risk of choledocholithiasis – VUHI 2.6-6.9,

high (>75%) risk of choledocholithiasis – VUHI >6.9.

Comparison of different management approaches

Two different choledocholithiasis management strategies were applied for this sample of patients. A total of 118 patients first underwent the LC with intraoperative cholangiography (LC-IOC-first) and then ERCP on demand in a single session (n=18) or the next day (n=10) depending on availability of the endoscopy unit. The other 232 patients had the two procedures in separate sessions: first, ERCP with sphincterotomy and necessary therapeutic interventions were performed and then cholecystectomy followed (ERCP-first). For high-risk patients (VUHI ≥4.7), the ERCP first strategy was chosen in 205 cases and the LC-IOC first strategy in 34 cases. For patients with low risk for choledocholithiasis (VUHI <4.7), LC-IOC as the first intervention was chosen in 84 cases and ERCP as the first strategy in 27 cases, mostly when CBDS were seen on US/CT or when other signs of possible choledocholithiasis were present (e.g., intrahepatic cholestasis).

Patients' age, sex, physical status according to ASA grade and waiting time for the first intervention did not differ significantly between the different strategy groups. The duration from admission to the hospital to first intervention was less than two days (mean 1.34 days, 1.43 in the LC-IOC-first group and 1.29 in the ERCP-first group, p=0.538). Values of separate predictors and VUHI were higher for ERCP-first patients. Acute cholecystitis was more frequent for the LC-IOC first group, as a likely indication for urgent LC.

The duration of hospital stay, both total and post-procedural, was longer in the ERCP-first group. No significant differences were found for ERCP success rates and the percentage of applied interventions between both groups. ERCP was successful at the first attempt for 93% of all patients (90.3% in LC-IOC-first, 93.3% in ERCP-first). Endoscopic treatment was unsuccessful for four (1.5%) patients, all of them belonging to the ERCP-first group. The complication rate was higher in the ERCP-first strategy group (14 vs. 1). ERCP showed significantly better diagnostic performance than IOC, although

diagnostic accuracy was very similar. When ERCP was evaluated just as a diagnostic procedure (cholangiography), it had 95.9% sensitivity, 78.8% specificity and 93.5% accuracy (eight false-negative and seven false-positive cases were found). All the ERCP patients had sphincterotomy and CBD revision performed as a standard procedure that allows detecting false-negative cases. This reduced missed CBDS count to one. Meanwhile, IOC had 90.6% sensitivity, 95.3% specificity and 94.1% accuracy, but another intervention (ERCP) was needed to detect "falses." There was no significant difference in conversion to open operation rate, CBD stenting or surgical complications (Clavien-Dindo classification) between the two groups (Table 3).

Table 3. Results of diagnosing and managing CBD stones and treatment outcomes in different strategy groups.

	LC-IOC-first n=118	ERCP-first n=232	P-value
Cholangiography positive for CBDS, n (%)	33 (28.0%)	198 (85.3%)	**0.000**
True positive for CBDS, n (%)	29 (87.8%)	191 (96.5%)	**0.032**
Success rates of ductal stone clearance (all methods)	28 (96.6%)	189 (99.0%)	0.298
Missed CBDS	3 (10.3%)	1 (0.05%)	**0.000**
Incomplete stone clearance	1 (3.45%) *	0	**0.01**
Conversion to open surgery	2 (1.7)	6 (2.6)	0.597
Choledochotomy	1 (0.8)	4 (1.7)	0.513
Biliary stent placement	1 (0.8)	10 (4.3)	0.079
Failure of CBD clearance	0	2 (0.9)	0.311

	LC-IOC-first n=118	ERCP-first n=232	P-value
Clavien – Dindo			
1-3	12 (10.2)	44 (19.1)	0.472
4-5	1 (0.8)	8 (3.4)	
Mortality**	1 (0.8)	3 (1.3)	0.711

*Endoscopic plastic stent insertion followed by postoperative ERCP after 2 days (n = 1)

**Fatal outcomes were due to poor physical status, septic course of the disease and exacerbation of chronic illnesses. No deaths were caused by complications of surgical or endoscopic treatment.

Complications of interventions to CBD

ERCP-related complications occurred in 15 cases; the overall complication rate for 262 patients who underwent ERCP was 5.7%, being 4.5% (10 out of 221) in the stone-positive group and 12.2% (5 out of 41) in the stone-negative group, p=0.052. The most common adverse event for all patients was post-ERCP pancreatitis (nine cases (4.1%, six in the stone-positive group, three in the stone-negative group) and this was followed by bleeding from the sphincterotomy site (three cases (1.4%)), perforation (two cases (0.9%)) and post-ERCP pancreatitis plus bleeding (one case (0.5%)). All complications were treated conservatively or endoscopically; no surgical treatment was necessary.

There were no complications of IOC reported.

Comparison with other guidelines

We performed an analysis of seven different trials evaluating accuracy of the ASGE guidelines (31). Altogether, 4613 patients were

included in these trials; 2166 (46.95%) of them were classified as having a high risk for choledocholithiasis.

Predictive values of high-risk criteria were evaluated: general sensitivity was found to be 52.4%, specificity 60.8%, positive predictive value 65.6%, negative predictive value 47.4%, accuracy 55.9%.

Our prognostic score shows comparable and, at some parameters, superior performance for predicting choledocholithiasis.

Prospective trial

Main characteristics of patients

During the period of January 2018 to January 2021 a total of 2045 LC were scheduled at Vilnius University Hospital Santaros Klinikos, and in 448 cases these patients were investigated for possible choledocholithiasis. A total of 74 patients were included and stayed in the trial; 74.3% of the valid participants were women, the gender proportion in both groups was similar. the age median in the group "Cholecystectomy first" was higher but it was not statistically significant. Distribution in both groups was also analogous based on physical status and main clinical criteria – total bilirubin concentration, CBD diameter and CBD stones suspected on ultrasound, VUHI, acute cholecystitis (Table 4).

Table 4. Main characteristics of trial participants

Parameter	Value	"Cholecystectomy first" (N=38)	"Endoscopy first" (N=36)	Total (N=74)	p value (Fisher)
Sex	Female, n (%)	28 (73.7)	27 (75.0)	55 (74.3)	1
	male, n (%)	10 (26.3)	9 (25.0)	19 (25.7)	
Age	Median (IQR)	63.0 (30.8)	41.5 (40.2)	55.5 (37.5)	0.103
Physical status	Good (ASA class I-II), n (%)	27 (71.1)	28 (77.8)	55 (74.3)	0.599
	Poor (ASA class III), n (%)	11 (28.9)	8 (22.2)	19 (25.7)	
Total bilirubin	Median (IQR)	38.0 (42.5)	40.5 (40.2)	38.6 (41.6)	0.713
CBD diameter, mm	Median (IQR)	8.0 (3.0)	8.0 (3.2)	8.0 (3.5)	0.708
Suspected CBD stone on US	No, n (%)	34 (89.5)	31 (86.1)	65 (87.8)	0.732
	Yes, n (%)	4 (10.5)	5 (13.9)	9 (12.2)	
VUHI	Median (IQR)	4.6 (1.3)	4.7 (1.7)	4.7 (1.4)	0.387
Acute cholecystitis	No, n (%)	21 (55.3)	27 (75.0)	48 (64.9)	0.092
	Yes, n (%)	17 (44.7)	9 (25.0)	26 (35.1)	

In evaluating management parameters, we did not find a statistically significant difference between the groups by comparing positive and negative main diagnostic procedures (EUS and IOC), true positive diagnoses of CBD stones, the duration of waiting (time from a patient's inclusion to the trial to the first procedure), duration of LC (either with or without IOC), and total duration of anaesthesia of all procedures. We found significantly a shorter duration of endoscopic procedures and the total duration of management in "Cholecystectomy first" group (Table 5).

Table 5. Management performance data.

Parameter	**Value**	**"Cholecyst-ectomy first" (N=38)**	**"Endoscopy first" (N=36)**	**Total (N=74)**	**p value (Fisher)**
Diagnostic procedure (EUS / IOC)	Negative, n (%)	23 (60.5)	18 (50.0)	41 (55.4)	0.483
	Positive, n (%)	15 (39.5)	18 (50.0)	33 (44.6)	
Confirmed CBD stones	No. n (%)	25 (65.8)	20 (55.6)	45 (60.8)	0.476
	Yes, n (%)	13 (34.2)	16 (44.4)	29 (39.2)	
Duration from inclusion till first procedure, days	Median (IQR)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.702
Duration of endoscopic procedures, minutes	Median (IQR)	0 (20.0)	25 (15.0)	20 (25.0)	0.000
Duration of LC, minutes	Median (IQR)	85 (47.5)	80 (42.5)	80 (50.0)	0.109
Total duration of anaesthesia, minutes	Median (IQR)	132.5 (53.8)	142.5 (66.2)	137.5 (57.5)	0.488
Total duration of management, days	Median (IQR)	4.0 (3.8)	6.0 (4.0)	5.0 (4.8)	0.044

Duration of management and impacting factors

Duration of management was chosen as a primary outcome of the trial. For some patients, LC was postponed to a second hospitalization. In these cases, the duration of both hospitalizations was summed up. In our sample we identified a statistically significant dependence between management strategy and duration – the median of management duration is two days shorter for the strategy "Cholecystectomy first" (Table 6). An effect size based on H statistics was calculated for the Kruskal-Wallis test. The value of the obtained effect size: eta2 [H] = 0.04 indicates a small effect size.

Table 6. Duration of management in different groups.

	Group	**Median (IQR)**	**p value (Fisher)**
All sample (n=74)	Both groups	5.0 (4.8)	
	"Endoscopy first"	6.0 (4.0)	0.044
	"Cholecystectomy first"	4.0 (3.8)	
Stones in CBD found (n=29)	Both groups	6.0 (5.0)	
	"Endoscopy first"	6.0 (4.0)	0.399
	"Cholecystectomy first"	4.0 (4.0)	
No stones in CBD (n=45)	Both groups	5.0 (4.0)	
	"Endoscopy first"	6.0 (4.0)	0.084
	"Cholecystectomy first"	4.0 (3.0)	

We presumed that patients with comorbidities could need longer hospitalization. For statistical analysis, we defined categories "good" physical status (I and II class according to the ASA classification system) and "poor" physical status (III ASA class, lower classes were not included to the trial). To evaluate the duration of management dependency from a participant's physical status, we used the Mann – Whitney U rank sum test, and its $\chi 2 = 3.5$, df = 1, p value = 0.06. A statistically significant dependency between patient's physical status and duration of management does not exist with a significance level

of $\alpha = 0.05$, but it can be counted significant if we choose a higher significance level ($\alpha > 0.06$).

Exploitation of operating rooms

We chose the total duration of anaesthesia for all endoscopic and surgical interventions summed up as an indirect indicator of the duration of busyness of the operating room. It did not differ significantly between the two trial groups (Table 4). Depending on whether the CBD stones were confirmed or denied, there was also no statistically significant difference between the duration of anaesthesia. With a less strict significance level of $p = 0.1$, the total duration of anaesthesia was statistically significantly shorter in the "Cholecystectomy first" group when there were no stones in CBD, which means the patient did not need a second procedure – ERCP with stone removal (Table 7).

Table 7. Duration of anaesthesia in different trial groups.

	Group	**Median (IQR)**	**p value (Fisher)**
All sample (n=74)	Both groups	137.5 (57.5)	
	"Endoscopy first"	142.5 (66.2)	0.488
	"Cholecystectomy first"	132.5 (53.8)	
Stones in CBD found (n=29)	Both groups	140.0 (60.0)	
	"Endoscopy first"	130.0 (51.2)	0.13
	"Cholecystectomy first"	155.0 (40.0)	
No stones in CBD (n=45)	Both groups	135.0 (55.0)	
	"Endoscopy first"	147.5 (66.2)	0.074
	"Cholecystectomy first"	120.0 (50.0)	

Diagnostic procedures: EUS vs. IOC

We included 36 patients into the group "Endoscopy first" and 38 – into "Cholecystectomy first." The distribution of participants according to the results of diagnostic procedures and final findings is

shown in Figure 3. There were 5 unsuccessful IOCs in the "Cholecystectomy first" group: 2 cannulations were impossible due to an inflammatory infiltration in the subhepatic space, 1 – a cystic duct stone was suspected, 1 – due to bleeding from a cystic artery, and 1 – due to a lesion of the common hepatic duct. Four of them had acute cholecystitis diagnosed.

Figure 3. Findings of diagnostic procedures

<table>
<tr><td rowspan="10">All sample n = 74</td><td rowspan="4">"Endoscopy first" n=36</td><td rowspan="2">EUS positive n=18 (50%)</td><td>Stones in CBD found n=15</td></tr>
<tr><td>No stones in CBD n=3</td></tr>
<tr><td rowspan="2">EUS negative n=18 (50%)</td><td>Stones in CBD found n=1</td></tr>
<tr><td>No stones in CBD n=17</td></tr>
<tr><td rowspan="6">"Cholecystectomy first" n=38</td><td rowspan="2">IOC positive n=15 (39.5%)</td><td>Stones in CBD found n=13</td></tr>
<tr><td>No stones in CBD n=2</td></tr>
<tr><td rowspan="2">IOC negative n=18 (47.3%)</td><td>Stones in CBD found n=0</td></tr>
<tr><td>No stones in CBD n=18</td></tr>
<tr><td rowspan="2">IOC unsuccessful n=5 (13.2%)</td><td>Stones in CBD found n=0</td></tr>
<tr><td>No stones in CBD n=5</td></tr>
</table>

The prognostic values of both diagnostic procedures in our sample were very similar (Table 8). Because there were no false-negative IOCs in the "Cholecystectomy first" group, the sensitivity and negative prognostic value of this test were 100%. Increasing the sample probably could narrow the confidence intervals.

Table 8. Prognostic values of diagnostic procedures (EUS, IOC)

Prognostic value	**EUS**		**IOC**	
	Value	**95% CI**	**Value**	**95% CI**
Sensitivity	93.75%	69.77 - 99.84%	100.00%	75.29 - 100.00%
Specificity	85.00%	62.11 - 96.79%	90.00%	68.30 - 98.77%
Positive prognostic value	83.33%	63.61 - 93.46%	86.67%	63.58 - 96.03%
Negative prognostic value	94.44%	71.64 - 99.13%	100.00%	
Positive likelihood ratio	6.25	2.19 - 17.88	10.00	2.69 - 37.24
Negative likelihood ratio	0.07	0.01 - 0.49	0.00	
Accuracy	88.89%	73.94 - 96.89%	93.94%	79.77 - 99.26%

Complications, post-operative morbidity

Ten of the 36 participants (27.8%) in the “Endoscopy first” group did not undergo LC during the same hospitalization but were delayed due to a more intense inflammation and possible infiltrate or patient request. The median time to deferred LC was 80.5 days. None of the subjects with delayed LC had a relapse of choledocholithiasis.

As our trial’s sample is too small to compare rare events such as treatment complications, we cannot compare them between the groups and provide descriptive statistics.

According to the Clavien-Dindo classification of surgical complications, 68 patients (91.9%) were assigned to class 0, three to class I (all in the group “Cholecystectomy first”), two to class II (one in each group), one to class III (group “Cholecystectomy first”). Two intraoperative complications were recorded: non-IOC CBD damage (according to ATOM classification D2, type E-1; fixed by ERCP and CBD stenting) and vascular damage (right hepatic artery ruptured

while dividing inflammatory infiltrate, surgery converted to open, blood vessel sutured).

Complications of ERCP in this sample were as follows: bleeding from a papillosphincterotomy (PST) site was observed in 2 patients (one in each group): one was suspected 12 days after ERCP and PST (the patient received dual antiplatelet therapy and low molecular weight heparin due to cardiological pathology), fixed by combined endoscopic haemostasis (injection and electrocoagulation); for another – clinical signs of bleeding 2 days after ERCP and PST, endoscopically no active bleeding was detected, hemostasis was not indicated. No other complications (post-ERCP pancreatitis, gastrointestinal perforation) occurred in the sample.

In the long-term surveillance period of 6–12 months after treatment, the patients were contacted and a survey was conducted on the possible recurrence of choledocholithiasis. Five patients could not be reached, 51 (77.3%) did not experience any symptoms after surgery, 1 patient had symptoms (abdominal pain on the right side, jaundice, unspecified fever) but did not seek medical attention, a choledocholithiasis relapse was ruled out later; 8 patients had complained after LC and sought medical attention, but a relapse of TLA was rejected. One patient died of concomitant causes (lung carcinoma) during long-term follow-up. For 8 patients, the long-term follow-up period at the time of calculating the results has not yet expired.

Prediction of choledocholithiasis in the intermediate risk group

We compared the possible predictors of choledocholithiasis in the intermediate risk group (trial sample) between patients who had confirmed stones in CBD and who had not (Table 9). The only statistically significant predictor was a suspected CBD stone on US at primary investigation.

Table 9. Predictors of choledocholithiasis in the intermediate risk group for patients with and without CBD stones.

Parameter	Value	Stone in CBD	No stones in CBD	Total	p value (Fisher)
Sex	Female, n (%)	21 (72.4)	34 (75.6)	55 (74.3)	0.79
	Male, n (%)	8 (27.6)	11 (24.4)	19 (25.7)	
Age	Median (IQR)	61.0 (41.0)	52.0 (34.0)	55.5 (37.5)	0.438
Physical status	Good, n (%)	19 (65.5)	36 (80.0)	55 (74.3)	0.183
	Poor, n (%)	10 (34.5)	9 (20.0)	19 (25.7)	
Total bilirubin, μmol /l	Median (IQR)	30.0 (44.4)	45.1 (41.2)	38.6 (41.6)	0.28
CBD diameter	Median (IQR)	8.0 (3.0)	8.0 (3.0)	8.0 (3.5)	0.223
Suspected CBD stone on US	No, n (%)	22 (75.9)	43 (95.6)	65 (87.8)	0.024
	Yes, n (%)	7 (24.1)	2 (4.4)	9 (12.2)	
VUHI	Median (IQR)	4.8 (1.4)	4.5 (1.4)	4.7 (1.4)	0.607
Acute cholecystitis	No, n (%)	21 (72.4)	27 (60.0)	48 (64.9)	0.325
	Yes, n (%)	8 (27.6)	18 (40.0)	26 (35.1)	

To estimate which of the variables or their combinations predict choledocholithiasis the best, we applied the binary logistic regression method. The dependent variable was CBD stones or choledocholithiasis: the probability value of the event is 1 when stones are identified in CBD, 0 – when they are not found. The assessed independent variables were gender, age, physical condition (categories "good," ASA class I-II and "poor," ASA class III), total bilirubin concentration, BTL diameter in millimetres, suspected CBD stone on US (yes / no), VUHI value, diagnosis of acute cholecystitis (yes / no). Correlating variables were not added to a single model.

The optimal binary logistic regression equation was obtained including the values of physical status, CBD diameter, suspected CBD

stone on US and diagnosis of acute cholecystitis. The coefficients of these predictors, except for the CBD diameter, are statistically reliable according to the Wald criterion; the AIC (Akaike information criterion) was the lowest of all possible equations (95.16); the Cragg-Uhler coefficient of determination R2 = 0.23 (CBD diameter was not removed because this would lower the Cragg-Uhler coefficient to 0.14).

In the obtained logistic equation, the coefficient of the physical status variable was 1.04, the coefficient of the CBD diameter was 0.18, the coefficient of the suspected CBD stone on US was 2.5, and the coefficient of the acute cholecystitis was -0.82. Intercept was -2.21. The odds ratios of the variables of this applied model are shown in Figure 4.

Logistic regression model:

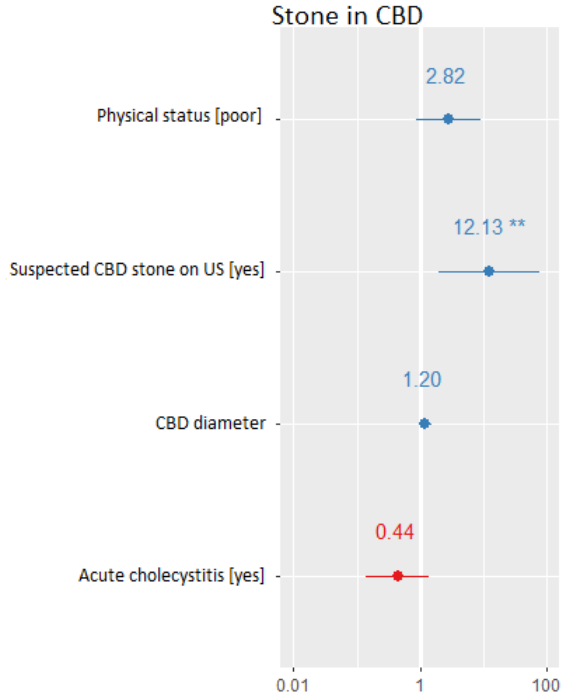
$$\mathrm{Ln}\frac{P(CBD\ \text{stone})}{P(No\ CBD\ stones)} = -2.21 + \begin{cases} 0.0, & \text{suspected CBD stone on US: no} \\ 2.50, & \text{suspected CBD stone on US: yes} \end{cases} +$$

$$+ \begin{cases} 1.04, & physical\ status: poor \\ 0.00, & physical\ status: good \end{cases} + 0.18 \times \text{CBD diameter} -$$

$$\begin{cases} 0.0, & \text{acute cholecystitis: no} \\ 0.82, & \text{acute cholecystitis: yes} \end{cases}$$

Logistic model is eligible, chi square of likelihood ratio is $\chi 2 = 13.94$; $p = 0.01$.

Figure 4. Odds ratios of independent variables for probability to detect CBD stones in the intermediate risk group.



** p <0.01

The efficiency of the model was evaluated by compiling a classification table from the results calculated by the model and determined in reality by drawing an ROC curve. The sensitivity of the model is 48.3%, specificity 86.7%, positive prognostic value 70.0%, negative prognostic value 72.2%, accuracy 71.6%. The results of the blind guess and the model differed statistically significantly in favor of the model (p = 0.035). Kappa test value 0.37, McNemar test p value 0.08 (there is no statistically significant difference between the

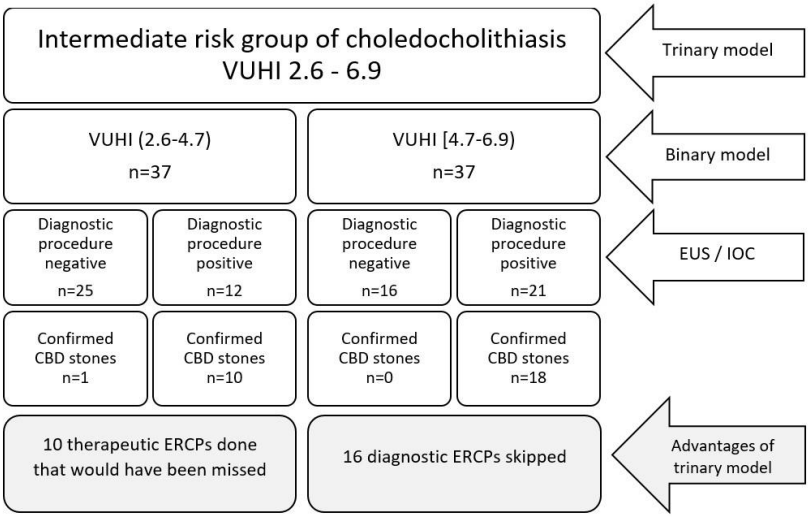
observed values and the values obtained by the model). The area under the ROC curve is 0.733.

Benefits of the updated VUHI system

We evaluated how the diagnostics of choledocholithiasis changed converting from a binary to trinary categorization of VUHI (Figure 5). When patients are categorized according to the older system – into two risk groups – 37 patients of this trial's sample (74 patients) would belong to the high risk group – VUHI ≥ 4,7. After we used the new system and performed additional diagnostic procedures (EUS or IOC), 21 of them had positive diagnostic procedure, while 16 – negative. This means that the application of the new strategy helped prevent diagnostic ERCP almost for every other patient whose VUHI ranges from 4.7 to 6.9.

On the other hand, in the former low-risk group of the binary model, 12 of the 37 patients, after additional investigation (EUS / IOC), had a positive diagnostic procedure and 10 (27%) had CBD stones confirmed by the ERCP, whereas these cases might not have been diagnosed in the past. Thus, the diagnostics of choledocholithiasis were significantly improved using the new trinary categorization model (Figure 5).

Figure 5. Comparison of the binary and trinary VUHI models.



Validation of new VUHI threshold values

Data from 448 patients treated for gallbladder stones during the prospective study period were collected for the validation of newly established VUHI threshold values. In 434 of them, all tests (biochemical blood and abdominal ultrasound tests) necessary to calculate the risk group of choledocholithiasis were performed. This sample was used for further analysis (431 patients were used for binary logistic regression due to missing data for some variables); 61.5% of patients were female and 38.5% were male. The median age of the patients was 69 years (Q1, Q3: 54, 79.25).

In terms of whether CBD stones were confirmed or ruled out, the patient groups differed significantly on age and predictors of choledocholithiasis (table 10).

Table 10. Characteristics of patients depending on presence of CBD stones.

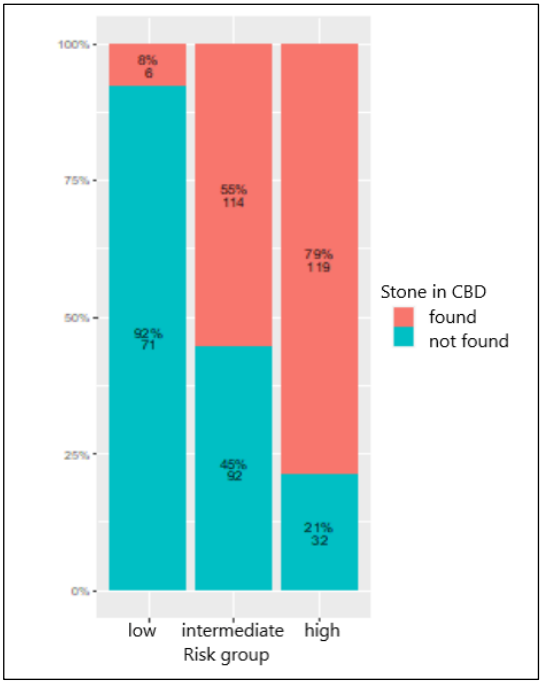
	No stones in CBD N=195	**Stones in CBD found N=239**	**p value**	**All sample**
Female, n (%)	121 (61.7%)	146 (61.3%)	0.934	267 (61.5%)
Age, median [Q1, Q3]	63 [49, 77]	72 [59.75, 81]	**0,000**	69 [54, 79.25]
Total bilirubin, median [Q1, Q3]	21.35 [13, 55.38]	64 [29.6, 114.2]	**0.000**	44.65 [17.37, 94]
CBD diameter, median [Q1, Q3]	6.5 [5, 9.25]	10.3 [8, 13]	**0.000**	9 [6,12]
Suspected CBD stone on US	23 (11.7%)	126 (53.4%)	**0.000**	149 (34.5%)
VUHI, median [Q1, Q3]	3.6 [2.43, 5.72]	6.86 [5.05, 8.35]	**0.000**	5.4 [3.49, 7.7]
Risk group of choledocholithiasis				
low, n (%)	71 (36.0%)	6 (2.4%)	**0.000**	77 (17.2%)
intermediate, n (%)	92 (46.7%)	114 (45.6%)		207 (46.2%)
high, n (%)	32 (16.2%)	119 (47.6%)		151 (33.7%)

The association of confirmed CBD stones with the choledocholithiasis risk group was assessed using Pearson's chi-squared (χ^2) criterion. The result was 0.104, p-value <0.001, concluding that there is a statistically significant dependence between the detected CBD stones and choledocholithiasis risk group according to VUHI. The effect size found was Cramer's V = 0.4894, p value < 0.001, showing the average effect size.

Similarly, a significant dependence between confirmed choledocholithiasis and VUHI was observed: Mann-Whitney U rank sum criterion = 94, p value < 0.001. The effect size was calculated by several methods: Cohen's d = 0.8056, Hedges' g = 0.8042, Cliff's Delta = 0.5386 (p < 0.001), with a large effect size for all criteria.

In the low risk group, 8% of patients had confirmed choledocholithiasis (6 out of 77), respectively – 55% (114 out of 206) in the intermediate risk group and 79% (119 out of 151) in the high risk group. The distribution of confirmed and ruled out CBD stones in the different risk groups is shown graphically in Figure 6.

Figure 6. CBD stones in different risk groups

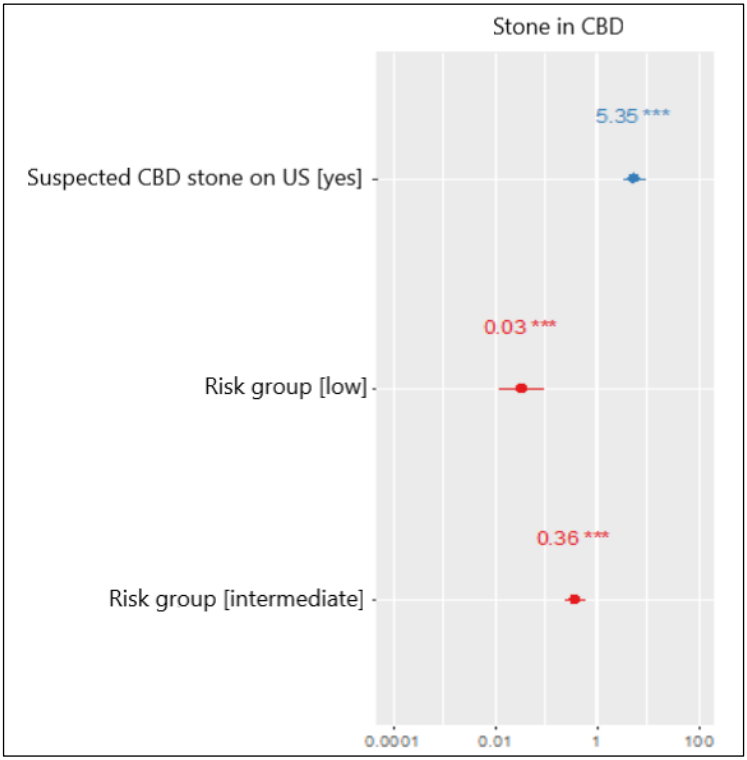


In addition, the prognostic values of the updated VUHI were calculated excluding the intermediate risk group, as it will require additional testing. The high risk group was considered to be a positive test response, and the low risk group – a negative test response. In this case, VUHI had a sensitivity of 95.2% (95% CI 89.85-98.22%), specificity of 68.93% (59.06-77.69%), positive predictive value of

78.81% (73.56-83.25%), negative predictive value of 92.21% (84.28-96.31%) and accuracy of 83.33% (77.85-87.93%).

We used binary logistic regression to assess which variables best predicted choledocholithiasis in all risk groups. The dependent variable was “Stone in CBD”: the probability value of the event is 1 when stones in CBD are found, 0 – when there are no stones in CBD. The independent variables assessed were sex, age, total bilirubin concentration, BTL diameter in millimetres, suspected CBD stone on US, VUHI value, choledocholithiasis risk group, diagnosis of acute cholangitis, biliary pancreatitis, and additional imaging tests (MRCP, EUS). Correlating variables were not included in the model. The chosen optimal model included the following independent variables: “suspected CBD stone on US,” “risk group: low,” and “risk group: intermediate.” The model’s Akaike information criterion was 438.65, Cragg-Uhler coefficient of determination R2 = 0.42. The effect of these variables on the probability of detecting choledocholithiasis is shown in Figure 7.

Figure 7. Effect of the suspected CBD stone on US and risk group on the probability of detecting choledocholithiasis (odds ratios).



The performance of the model was evaluated by compiling a binary classification table of the model's calculated and truly observed results, calculating the model's predictive values and plotting the ROC curve. The model has a sensitivity of 74.6%, specificity of 75.9%, positive predictive value of 78.9%, negative predictive value of 71.2% and accuracy of 75.2%. The results of blind prediction and the model were statistically significantly different in favor of the model ($p < 0.001$). Kappa test value 0.502, McNemar's test p-value 0.246 (no statistically significant difference between the observed values and the values obtained with the model). The area under the ROC curve, in

terms of the sensitivity to specificity ratio of the study/model, was 0.820, which describes the test as good.

The strongest regressor, suspected CBD stone on US, was analyzed separately. Its prognostic values were: sensitivity – 53.75% (95% CI: 47.22-60.19%), specificity – 87.82% (82.42-92.04%), positive prognostic value – 84.31% (78.40-88.84%), negative prognostic value – 60.92% (57.39-64.33%), and accuracy – 69.11% (64.54-73.41%).

CONCLUSIONS

- We determined a statistically significant correlation between choledocholithiasis and VUHI value. The predictive performance of the VUHI binary model (low-high risk) matches and in some cases surpasses the predictive values for choledocholithiasis in other guidelines (compared to ASGE guidelines of 2010, respectively, VUHI binary model sensitivity was 80.5% vs. 52.4%, specificity 54.0% vs. 60.8%, accuracy 71.1% vs. 55.9%).
- Based on the frequency density of stone detection, we calculated the probability of detecting choledocholithiasis depending on the value of VUHI.
- New choledocholithiasis risk categories were defined: low risk of choledocholithiasis – VUHI <2.6, intermediate risk of choledocholithiasis – VUHI 2.6-6.9, high risk of choledocholithiasis – VUHI >6.9.
- Minimally invasive examination methods IOC and EUS did not differ statistically significantly in efficacy or complication rates in the intermediate choledocholithiasis risk group. The total duration of treatment was 2 days shorter in the "Cholecystectomy above" group.
- The newly identified choledocholithiasis risk groups reliably categorized patients according to the rate of choledocholithiasis detection: 8% in the low-risk group, 55% in the intermediate-risk group, and 79% in the high-risk group. In the intermediate-risk group, the use of the trinary model significantly reduced the number of diagnostic ERCPs (using the previous binary model, 48.6% of all indicated ERCPs would have been diagnostic). The sensitivity of the VUHI trinary model (low-intermediate-high risk) is 95.2%, its specificity – 68.93%, and accuracy – 83.33%, with a positive test response considered as a high risk group for

choledocholithiasis and a negative test response considered as a low risk group.

- Using logistic regression, it was found that CBD stone suspected on US is an important additional indicator that increases the probability of detecting choledocholithiasis 5.35 times. When the likelihood of detecting choledocholithiasis is estimated from the model equation, if this predictor is present, the probability of detecting a stone in the BTL is 0.258 in the low risk group and 0.794 in the intermediate risk group.

RECOMMENDATIONS

In patients with gallbladder stones, the risk of choledocholithiasis should be assessed before elective cholecystectomy. We recommend using the prognostic index VUHI as a reliable and simple-to-use tool. The index values: VUHI <2.6 determines low (<25%) risk of choledocholithiasis, VUHI 2.6 - 6.9 – intermediate (25-75%) risk of choledocholithiasis, VUHI >6.9 – high risk of choledocholithiasis (>75%). If a stone in the CBD is suspected on ultrasound examination for a patient in the low risk group (according to the VUHI values), the patient should be considered as intermediate risk. If a stone in the CBD is suspected on US for an intermediate risk patient, this patient should be considered as high risk.

In low choledocholithiasis risk patients, no further investigation before LC is required. In high choledocholithiasis risk patients, ERCP and stone removal are recommended. For patients in the intermediate risk group of choledocholithiasis, additional investigation (MRCP, EUS or IOC) is recommended. The proposed first-line treatment strategy is LC with IOC and, if stones are detected during IOC, ERCP with lithectomy under the same anaesthesia. In patients with a probability of unsuccessful IOC (obesity, suspected inflammatory infiltrate in the subhepatic space), it is recommended to opt for EUS prior to elective LC, and ERCP with lithectomy in case of stones in CBD.

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LIST OF PUBLICATIONS AND PRESENTATIONS

Publications

- Aleknaite A, Simutis G, Stanaitis J, Valantinas J, Strupas K. Risk assessment of choledocholithiasis prior to laparoscopic cholecystectomy and its management options. United European Gastroenterology Journal 2018; 6(3): 428–438.

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Presentations:

- Oral presentation "Prediction of choledocholithiasis prior to laparoscopic cholecystectomy using original prognostic index." 9th Congress of Baltic Association of Surgeons, 2018 05 10-12, Klaipėda.

- Electronic poster "Prediction of choledocholithiasis prior to laparoscopic cholecystectomy using original prognostic index," 5th European Update Congress in Gastroenterology 2018 06 15-16, Praga, Czech Republic.

- Electronic poster "Prediction of choledocholithiasis prior to laparoscopic cholecystectomy using an original prognostic index," "Evolutionary medicine: health and diseases in changing environment" 2018 06 05-08, Vilnius. Abstract published in *Acta medica Lituanica* (supplement to Volume 25, 2018).

- Oral presentation “Tulžies latakų akmenligės diagnostika: skirtingų metodų palyginimas,” international conference *Sisteminės medicinos privalumai chirurgijoje* 2020-09-18, Vilnius.
- Oral presentation “Tulžies akmenligės diagnostikos ir gydymo aktualijos,” 2017-04-28, Druskininkai.
- Oral presentation at the conference of the Lithuanian Society of Gastroenterologists “Gastroenterologija 2018.”
- Oral presentation “Tulžies latakų akmenligės rizikos vertinimas” at the conference of the Society of Surgeons of Klaipėda, 2020-11-20.

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