

# Scoring System Development and Validation for Prediction Choledocholithiasis before Open Cholecystectomy

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## SUMMARY

**Introduction** Accurate precholecystectomy detection of concurrent asymptomatic common bile duct stones (CBDS) is key in the clinical decision-making process. The standard preoperative methods used to diagnose these patients are often not accurate enough.

**Objective** The aim of the study was to develop a scoring model that would predict CBDS before open cholecystectomy.

**Methods** We retrospectively collected preoperative (demographic, biochemical, ultrasonographic) and intraoperative (intraoperative cholangiography) data for 313 patients at the department of General Surgery at Gornji Milanovac from 2004 to 2007. The patients were divided into a derivation (213) and a validation set (100). Univariate and multivariate regression analysis was used to determine independent predictors of CBDS. These predictors were used to develop scoring model. Various measures for the assessment of risk prediction models were determined, such as predictive ability, accuracy, the area under the receiver operating characteristic curve (AUC), calibration and clinical utility using decision curve analysis.

**Results** In a univariate analysis, seven risk factors displayed significant correlation with CBDS. Total bilirubin, alkaline phosphatase and bile duct dilation were identified as independent predictors of choledocholithiasis. The resultant total possible score in the derivation set ranged from 7.6 to 27.9. Scoring model shows good discriminatory ability in the derivation and validation set (AUC 94.3 and 89.9%, respectively), excellent accuracy (95.5%), satisfactory calibration in the derivation set, similar Brier scores and clinical utility in decision curve analysis.

**Conclusion** Developed scoring model might successfully estimate the presence of choledocholithiasis in patients planned for elective open cholecystectomy.

**Keywords:** scoring system; choledocholithiasis; open cholecystectomy

## INTRODUCTION

Gallstone disease is one of the most common problems in Europe and North America [1]. Surgical cholecystectomy (laparoscopic or open) is the usual method of treatment of patients with symptomatic gallstones. However, the risk that a patient has asymptomatic concurrent common bile duct stones (CBDS) is the key factor in determining diagnostic and treatment strategies [2]. CBDS can cause serious morbidity or mortality, and evidence for them should be sought in all patients with symptomatic gallstones undergoing cholecystectomy. However, preoperative identification of asymptomatic CBDS is a challenge for all surgeons in order to decrease operative risks and health care costs.

The standard preoperative methods used to diagnose patients with gallstones (liver function tests and abdominal ultrasound [US]) are often not accurate enough to establish a firm diagnosis of CBDS [3]. Risk factors for CBDS include abnormal liver chemistry jaundice, and abdominal ultrasound evidence of bile duct dilation (BDD). Also, several different diagnostic studies have been proposed to

make the diagnosis including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (ERCP), spiral computed tomography cholangiography, before any therapeutic intervention and intraoperative cholangiography (IOC), endoscopic ultrasound and laparoscopic common bile duct exploration at the time of surgery. Despite their good results, these imaging modalities cannot be anticipated as routine due to high costs, limited availability and technical difficulties in performing laparoscopic exploration of the common bile duct.

Several recent studies have demonstrated that multivariate models are more accurate than most informative single predictors. Consequently, clinical prediction has evolved from physician judgment alone to risk group stratification, to prediction models (predictive scores) based on multivariate regression [2, 4, 5, 6] or discriminant functions [7], to artificial neural network in predicting CBDS or the need for therapeutic ERCP in patients with suspected choledocholithiasis [8, 9]. Many of these scoring systems were validated and were able to predict CBDS in 80–100% of the patients in both the training and test sets [2, 5, 8, 9]. However,

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discriminative ability is not sufficient for a model to be clinically useful, and not all authors demonstrated their clinical usefulness [10]. Furthermore, unfortunately, such models do not always perform well for patients other than those from whose data the models were derived.

Based on these considerations, the objective of the study was to assess whether pre-treatment clinical and biochemical parameters expressed in our scoring system could improve the prediction of choledocholithiasis in patients scheduled for open cholecystectomy because of symptomatic cholelithiasis.

## OBJECTIVE

Based on these considerations, the objective of the study was to assess whether pre-treatment clinical and biochemical parameters expressed in our scoring system could improve the prediction of choledocholithiasis in patients scheduled for open cholecystectomy because of symptomatic cholelithiasis.

## METHODS

We retrospectively collected preoperative and intraoperative data of consecutive patients considered for open cholecystectomy for symptomatic gallstones at the department of General Surgery at General Hospital in Gornji Milanovac, Serbia, in the course of five years, from January 2003 through August 2007. The study was approved by the local committee on human research, and all patients gave written informed consent.

For each patient, comprehensive clinical, current biochemical tests, and abdominal US findings (General ELECTRIC® Logiq 3 Pro, USA) were collected as regards precholecystectomy assessment. The clinical data included the patients' sex and age, the presence of acute biliary colic and history of previous acute biliary pancreatitis or jaundice. The biochemical data included preoperative liver function tests (serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, amylase,  $\gamma$ -glutamyl transpeptidase and white blood cell count. Each ultrasound finding included a description of the common bile duct (CBD) appearance (for stones and BDD in millimeters), and number and dimension of gallstones. Gallstones were classified as dangerous or not dangerous as described previously [4]. Briefly, multiple gallstones were classified as dangerous when they were micro (<3 mm), small (3–5 mm), or heterogeneous in size; multiple gallstones were considered not dangerous when they were medium (5–10 mm) or large (>10 mm) sized; and a single stone, irrespective of dimension.

The patients were operated on using technique of open cholecystectomy, under general endotracheal anesthesia. Biliary tree anatomy and the presence of stones in the common bile duct were checked by using IOC. Suspicion of choledocholithiasis was based upon the following: (i) deranged liver function tests (past or present); (ii) history

of jaundice (past or present) or acute pancreatitis; (iii) a dilated CBD or demonstration of CBDS on imaging; or (iv) a combination of these factors [11]. In situations when cholangiogram was positive, choledochotomy with extraction of calculi was performed. Complete clearance was finally checked using proximal and distal fluoroscopic cholangiography. In all patients T-tube insertion was left. T-tube removal after check cholangiography was performed after a minimum of two weeks. Demonstrable CBDS was considered the "gold standard" for the presence of CBDS. It was defined as CBDS visually and was extracted, during surgery or ERCP. After hospital discharge, patients were checked after a week, then once a month as the outpatients, and after a year using the telephone calls checking whether they had pain under the right rib cage, which would resemble those before operations, whether they had to consult their general practitioner or surgeon due to jaundice or other symptoms from the digestive system.

## Derivation and validation sets

The patients were randomized into a derivation set (two-thirds of the patients) and a validation set (one-third of the patients) by random sampling. The validation set was not used until after the multiple logistic regressions model and the scoring system had been created.

## Statistical analyses

Univariate and multivariate LR was used to identify and quantify the independent predictors of CBDS. The results of regressions were expressed in odds ratios with 95% confidence intervals. The resultant beta coefficients for each variable were reported and used to develop an integer based weighted point system for CBDS. The B coefficient for each variable was divided by nine. Individual scores were assigned to each patient discharge record by summing the individual risk factor points. The Hosmer–Lemeshow goodness-of-fit test was performed. Non-significant p-values on this test imply good fit.

For scoring system in the testing and validation sets we calculated the area under the receiver operating characteristic curve (AUC) analysis, sensitivity, specificity, positive (PPV), negative predictive value (NPV), accuracy, calibration plots, Hosmer–Lemeshow statistic, and the Brier score. In order to examine the generality of the constructed models, data of an independent cohort of 100 patients were used for validation.

Clinical usefulness was assessed by using decision curve analyses [12]. These analyses estimate a "net benefit" for prediction models by summing the benefits (true positives) and subtracting the harms (false positives). Assumption is made that the suspicion of CBDS would lead to diagnosis with IOC. Net benefit is plotted against threshold probabilities compared with 'NC for all' and 'NC for none' strategy. The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold

probability should be chosen. Calculations and graphic net benefit were performed in Microsoft Excel using the recommended formula from true- and false-positive count of patients [12]. All other analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at  $p < 0.05$ .

## RESULTS

### Patients' characteristics

The study included 313 patients, the mean  $\pm$  standard deviation (range) patient age at the time of open cholecystectomy was  $55.9 \pm 13.4$  (21–85) years and 225 (71.9%)

patients were female. Of all the patients, in 249 (79.6%) the IOCs were successfully performed. Twenty-two of 249 (8.8%) IOCs were positive for bile duct stones that subsequently underwent open choledochotomy with stone extraction. Retained CBDS were detected in two patients during follow-up evaluation and were treated with ERCP. The patients were divided into the derivation (213) and the validation set (100). Baseline clinical characteristics of the patients in the derivation and validation sets are shown in Table 1. There were no significant differences in these sets (Table 1) except in the presence of acute or chronic cholecystitis.

In a univariate analysis, seven risk factors displayed significant correlation with CBDS (Table 2). During multivariable analysis, three of them sustained their prognostic

**Table 1.** Baseline patients' characteristics in the derivation and the validation set

Characteristics		Derivation set (n=213)	Validation set (n=100)	p-value	
Demographic factor	Age (years)	Mean (SD)	55.8 $\pm$ 13.3	56.1 $\pm$ 13.5	0.820
	Sex (%)	Female	71.8	72.0	0.975
		Male	18.2	28.0	
Laboratory data, median (IQR)	Total bilirubin		16 (13.5)	16 (10)	0.590
	ALT		20 (18)	19 (12.5)	0.550
	AST		18 (11)	18 (10)	0.293
	ALP		76 (35)	70.5 (31)	0.290
	Amylase		51 (19)	52 (24)	0.206
	GGT		24 (19.5)	21 (17)	0.086
	WBC count ( $\times 10^9/L$ )		8 (4)	7 (4)	0.188
Bile duct diameter (mm)		7 (2)	7 (2)	0.498	
Types of biliary calculus (%)	1		17.4	15.0	0.865
	2		68.5	70.0	
	3		14.1	15.0	
"Dangerous" stones (%)	No		31.1	32.9	0.808
	Yes		68.9	67.1	
Clinical finding	Acute/chronic cholecystitis (%)	No	39.9	25.3	0.007
		Yes	60.1	74.7	
	Biliary colic (%)	No	32.4	31.8	1.000
		Yes	67.6	68.2	
	Pancreatitis (%)	No	46.7	31.2	0.257
		Yes	53.3	68.8	
CBDS (%)	No		91.5	94.0	0.504
	Yes		8.5	6.0	
IOC (%)	No		17.8	26.0	0.100
	Yes		82.2	74.0	

All values are reported as mean  $\pm$  SD or median  $\pm$  IQR, and percentage of group.

SD – standard deviation; IQR – interquartile range; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; GGT –  $\gamma$ -glutamyl transpeptidase; WBC – white blood cells; 1/2/3 – bilirubin/cholesterol/ mixed stones; CBDS – common bile duct stones; IOC – intraoperative cholangiography

**Table 2.** The analysis of possible and independent predictors for choledocholithiasis in the derivation set and point value

Factor	Univariate analysis		Multivariable analysis			Point value
	OR (95% CI)	p-value	OR (95% CI)	p-value	B	
Total bilirubin	1.041 (1.020–1.062)	0.000	1.027 (1.008–1.046)	0.005	0.027	0.003
ALT	1.008 (1.004–1.012)	0.000				
ALP	1.015 (1.007–1.022)	0.000	1.018 (1.002–1.034)	0.028	0.018	0.002
GGT	1.007 (1.003–1.011)	0.000				
Bile duct diameter	2.881 (1.941–4.276)	0.000	2.669 (1.739–4.098)	0.000	0.982	0.110
"Dangerous" stones	3.536 (1.124–11.124)	0.031				
Acute/chronic cholecystitis	0.165 (0.037–0.738)	0.018				

OR – odds ratio; CI – confidence interval; B – coefficient

**Table 3.** Efficacy measure from model both in the test and the validation set

Efficacy measure	Test set	p-value	Validation set	p-value
AUC (95% CI)	94.3 (90.2–96.9)	<0.001	89.9 (82.2–95)	<0.001
Sensitivity (95% CI)	61.1 (35.7–82.7)		66.7 (22.3–95.7)	
Specificity (95% CI)	98.5 (95.6–99.7)		95.7 (89.3–98.8)	
PPV (95% CI)	78.6 (49.2–95.3)		50.0 (15.7–84.3)	
NPV (95% CI)	96.5 (92.9–98.6)		97.8 (92.3–99.7)	
Accuracy (95% CI)	95.3 (91.5–97.7)		93.9 (87.3–97.7)	
HL test $\chi^2$	2.682	0.953	16.705	0.019
Brier score	0.0357		0.052	

AUC – area under the receiver operating characteristic curve; PPV – positive predictive value; NPV – negative predictive value; HL – Hosmer–Lemeshow;  $\chi^2$  – chi-square

significance (Table 2). The analysis demonstrated that total bilirubin, alkaline phosphatase and bile duct diameter have strong prognostic value for CBDS (Table 2). Critical values of the independent variables were as follows (the limits of normal range are in parentheses): total bilirubin >29  $\mu\text{mol/L}$  (5–21  $\mu\text{mol/L}$ ), alkaline phosphatase >108 U/L (34–104 U/L) and bile duct diameter >8 mm. Also, the resultant beta coefficients and point value for each variable were reported (Table 2). Next, a total score was calculated by summing the points from each variable for each patient. The resultant total possible score in derivation set ranged from 7.6 to 27.9. In the test set in patients with or without CBDS the median (IQR) scoring values were 16.9 (7.6) and 9.8 (2.4), respectively.

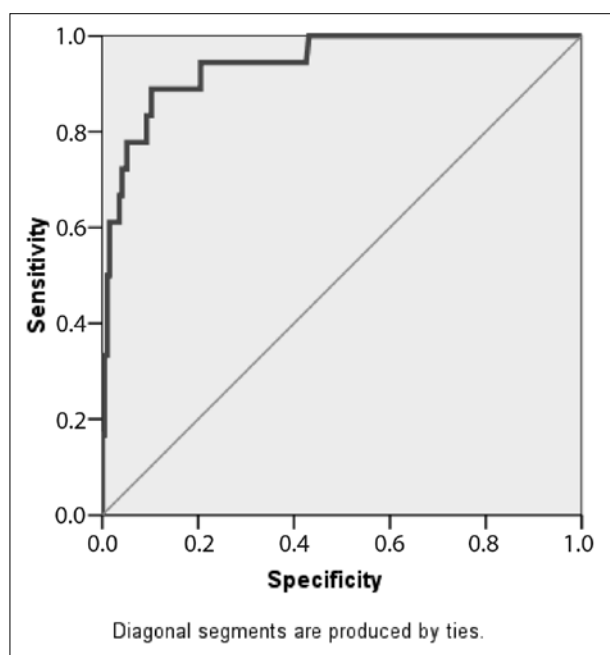
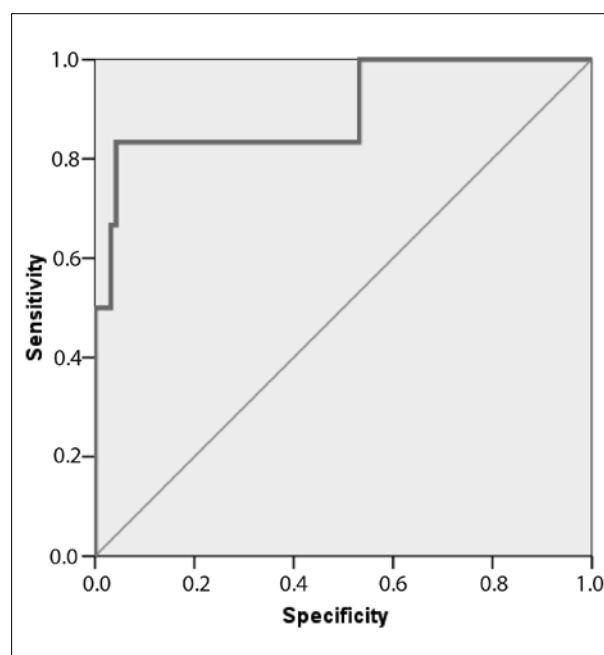
AUC for the scoring system was 94.3 (95% CI, 90.2–96.9), showing the scoring system to have good discriminatory ability (Graph 1). The scoring model retained the performance characteristics (AUC) in the validation set (Graph 2). The estimated AUC, sensitivity, specificity, PPV, NPV, accuracy, Hosmer–Lemeshow tests and Brier scores of the scoring models in the derivation and validation sets are summarized in Table 3. The scoring model was well

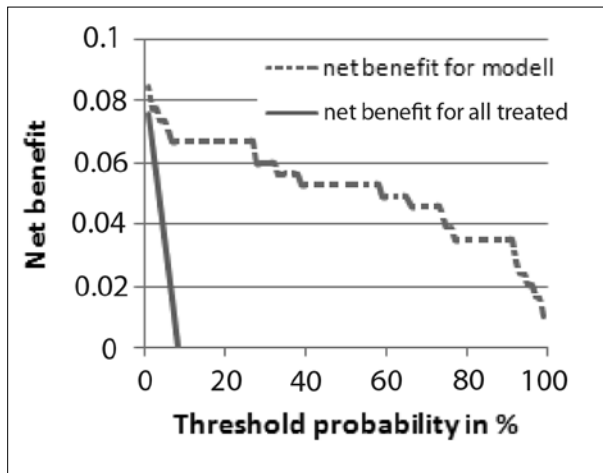
calibrated in the derivation set but did not show satisfactory calibration in the validation set (Table 3). The patients with a score between 15 and 20 have a probability of the presence of CBDS in about 50% of cases, whereas the patients with score over 20 have a probability of the presence of CBDS in about 80% of cases. Results of the Brier score showed to be informative in both the derivation and the validation set (Table 3).

In the decision curve analysis (Graph 3), scoring model provided net benefit throughout the entire range of threshold probabilities as compared to the strategy of treating all patients with IOC, or, alternatively, treating no one.

## DISCUSSION

Pretreatment identification of patients undergoing elective cholecystectomy with asymptomatic concurrent CBDS is key in the clinical decision-making process. In the current study, we have taken a unique approach for prediction of cholelithiasis using clinical and laboratory parameters before open cholecystectomy. The essential

**Graph 1.** Receiver operating characteristic (ROC) curves analyses in the derivation set**Graph 2.** ROC curves analyses in the validation set



Graph 3. Decision curve analyses

results of this study indicated that the prediction models expressed in our scoring system were able to achieve an accuracy of 95.3%. The most useful traits of precystectomy assessment of CBDS were the rise in alkaline phosphatase, elevated total bilirubin and BDD on ultrasonography. The tool showed satisfactory discrimination, calibration, and clinical usefulness in the internal validation.

Standard methods used to diagnose choledocholithiasis in all patients with symptomatic gallstones are often not perfect [3]. On the other hand, routine use of more sophisticated methods is not cost-effective. Several prognostic models have been developed which basically use scoring system, including independent prognostic predictors obtained by multivariate regression analysis [4, 5, 6, 10, 13]. In previous literature numerous predictors have been identified that related with higher risk of CBDS: age [1, 2, 5, 10], sex [5], history of biliary colic [2, 4, 14], jaundice [1, 5], ascending cholangitis [5], acute cholecystitis [2, 14], acute biliary pancreatitis [14], total bilirubin [1, 6, 10, 15-17],  $\gamma$ -glutamyl transferase [1, 15], alkaline phosphatase [1, 3, 4, 6, 10, 15, 16, 18], aspartate aminotransferase [1, 10], alanine aminotransferase [1, 18], number and size of gallbladder stones [2, 4, 6], CBD diameter on ultrasonography [1-6, 17, 19]. In line with previous studies, several of these predictors have reached statistical significance in the univariate or multivariate analysis in our study. However, many of these parameters did not sustain their independent value. Nevertheless, we found that elevated alkaline phosphatase and total bilirubin were strong independent predictors of CBDS. However, levels of alkaline phosphatase and bilirubin may be deranged by mechanisms that are not related to CBDS (sphincter of Oddi dysfunction, microlithiasis and sludge in the CBD, numerous medical conditions or syndromes) [16, 20]. It was established that alanine aminotransferase and  $\gamma$ -glutamyl transpeptidase, increase progressively with the duration and severity of biliary obstruction [15]. The best agreement between elevated liver function values and presence of CBDS was seen in patients without acute pancreatitis or cholecystitis and operated electively [16] as were our patients. The previous authors suggested that serum total bilirubin on hospital Day 2 best predicts persisting

CBDS in gallstone pancreatitis [21]. Our study also supports findings of previous investigations that dilated CBD at US, or evidence of CBDS is the most powerful preoperative attribute of precystectomy assessment of CBDS [1-6, 13, 17, 19, 22]. Although there is controversy about the cutoff of dilated CBD diameter, our findings are in agreement with others which reported that cystic duct leaks may be considered when dilation of the CBD greater than 8 mm is present on US or computed tomography [14, 23]. Possibility of CBD stones increases in an approximately linear fashion with an increasing CBD diameter [9]). Practical implication of our results that patients with symptomatic gallstones but normal liver function test and US are considered to be at low risk for choledocholithiasis. On the other hand, patients with score from 15 to 20 points, expressed through our scoring system, should be considered to be at intermediate risk of choledocholithiasis and should be further evaluated with preoperative imaging, while a patient with score above 20 points should be considered to be at high risk of CBDS. Similar recommendations can be found in the proposed guideline [24].

It was found that the accuracy of the present models was higher than the accuracy of many earlier models. Incorporating identified factors in our scoring model resulted in an AUC of 94.3%, which is statistically better than many other models (79-88.4%) [9, 10]. Also, the specificity and NPV were similar to other reports (82-100%), but sensitivity and PPV was somewhat worse (61.1% and 78.6%, respectively) [2, 4, 5, 6, 13, 16]. However, it should be emphasized that we included a non-selective population of patients with no clear predictors for synchronous CBDS, unlike other studies, whose proposed scoring systems were effective in identifying symptomatic CBDS. In summary, our model was more able to exclude outcome of interest than confirm it.

However, metrics of accuracy do not address the clinical value of a model. The second advantage of decision curve analysis is that it can be used to compare several different models [12]. In our decision curve analysis we identified almost a whole range of threshold probabilities in which our scoring model was of value. Nevertheless, in the group of CBDS patients there are many unresolved issues regarding the IOC and thus the threshold probability of clinical implementation remains an open question. The primary methods for assessing the CBD for stones during cholecystectomy are IOC and intraoperative US. However, the issue of routine versus selective cholangiography has been long debated. Furthermore, in patients with symptomatic or suspected choledocholithiasis the treatment remains a complex and controversial issue depending on numerous factors (patients' characteristics, surgeon preference, laparoscopic expertise, availability of equipment). Although the era of open cholecystectomy ended in recent years, and the traditional approach to CBD exploration has been supplemented by newer, less-invasive procedures, (open) surgical exploration remains an important treatment option and is still the simple and straight-forward solution for management of choledocholithiasis with an excellent stone-clearance rate, as recommended by the

guideline [25, 26]. Several limitations also need to be addressed. First, enrolled patients were retrospectively collected in a single center. Second, we included only those variables that we believed might be related to the outcome of interest. Furthermore, a reference standard for diagnosing CBDS, such as IOC, is not always described. In addition, the results of the current study are limited by the short follow-up time that may have resulted in an underestimation of the true positive predictive value. Also, CBDS are encountered in our study in only approximately 8% of unselected population undergoing cholecystectomy, and therefore a very large number of patients is required to achieve a power sufficient to assess the ability of the model to predict CBDS. Finally, there is a so-called data barrier, beyond which mathematical models fail to make reliable predictions in biological systems, which is more of a consequence of the (un)availability of the information in data than a consequence of the imperfection of a particular model. Nevertheless, we have proposed a scoring system that, using noninvasive investigative methods, enables simple screening and identification of patients at low risk for asymptomatic CBDS, and patients at higher risk, who should undergo further common bile duct assessment, and which could allow a significant reduction of the total number of preoperative examinations. Our findings provide a

prognostic tool that relies on information that is regularly or simply collected in clinical practice, should be readily obtainable and may be used as a tool for subsequent choice of diagnostic or therapeutic procedures.

## CONCLUSION

The proposed scoring system that uses preoperative total bilirubin, alkaline phosphatase and common bile duct diameter can successfully estimate presence of cholelithiasis in patients planned for elective cholecystectomy. Developed scoring model may be used as a tool for risk stratification and subsequent choice of diagnostic or therapeutic procedures. However, before recommending its use in clinical practice, a controlled prospective study is required to verify our results.

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## Развој и провера система бодовања за предвиђање холедохолитијазе пре отворене холецистектомије

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### КРАТАК САДРЖАЈ

**Увод** Тачна процена постојања придружене асимптоматске калкулозе заједничког жучног вода пре извођења отворене холецистектомије основа је клиничке одлуке. Стандардне преоперационе методе које се користе у ту сврху често нису довољне.

**Циљ рада** Циљ ове студије је био да развије модел бодовања који би могао предвидети постојање конкремената у заједничком жучном воду пре извођења отворене холецистектомије.

**Методе рада** Ретроспективно су прикупљени и анализирани преоперациони (демографски, биохемијски, ултразвучни) и интраоперациони (интраоперациона холангиографија) подаци о 313 болесника оперисаних од 2004. до 2007. године на Хируршком одељењу Опште болнице у Горњем Милановцу. Болесници су сврстани у тзв. деривациони (213) и валидациони сет (100). За одређивање независних предиктора холедохолитијазе коришћене су једноваријантна и мултиваријантна регресиона анализа. Овако добијени предиктори коришћени су за развијање система бодовања.

Ефикасност овог модела процењивана је на основу: предиктивних вредности, прецизности, површине испод ROC криве (AUC), калибрације и клиничке корисности модела коришћењем криве одлучивања.

**Резултати** Једноваријантна анализа је показала да је седам фактора ризика у корелацији с калкулозом заједничког жучног вода. Као независни предиктори холедохолитијазе означени су укупни билирубин, алкална фосфатаза и ширина холедохуса. Вредности скорa у деривационом сету биле су од 7,6 до 27,9. Прогностички модел показује добру дискриминаторну способност и у деривационом и у валидационом сету (AUC 94,3% и 89,9%), одличну прецизност (95,5%), задовољавајућу калибрацију у деривационом сету, као и сличан Бријеров (Brier) скор и клиничку корист одређену кривом одлучивања.

**Закључак** Приказаним моделом бодовања може се успешно проценити постојање конкремената у холедохусу код болесника планираних за елективну отворену холецистектомију.

**Кључне речи:** скоринг систем; холедохолитијаза; отворена холецистектомија