

Original Research Article

PREDICTORS OF COMMON BILE DUCT STONES IN PATIENTS WITH SYMPTOMATIC CHOLELITHIASIS UNDERGOING CHOLECYSTECTOMY

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ABSTRACT

Background: Common bile duct (CBD) stones coexist with gallbladder stones in a substantial minority of patients and complicate cholecystectomy. Pre-operative imaging to detect them is costly, invasive or not universally accessible. We evaluated clinical, biochemical and ultrasonographic predictors of CBD stones in patients with symptomatic cholelithiasis.

Materials and Methods: In this single-centre cross-sectional diagnostic accuracy study (March 2024 to August 2025), 90 patients with symptomatic cholelithiasis scheduled for cholecystectomy were enrolled. Index tests were sex, age, right upper quadrant (RUQ) pain, fever, history of jaundice or cholangitis within 6 months, serum total bilirubin, AST, ALT, ALP, GGT, amylase, lipase and ultrasonographic CBD diameter. Magnetic resonance cholangiopancreatography (MRCP) was the reference standard; stones were cleared by endoscopic retrograde cholangiopancreatography (ERCP). Sensitivity, specificity, predictive values, accuracy and area under the curve (AUC) were calculated, with Fisher's exact or chi-square tests and multivariable logistic regression.

Results: Mean age was 46.0 ± 14.1 years and 77.8% were women. MRCP showed CBD stones in 44 patients (48.9%; 95% CI 38.2–59.7). Stones were more frequent in men (70.0% vs 42.9%; $p = 0.032$) and were not associated with age. Total bilirubin >1.3 mg/dL had sensitivity 95.5%, specificity 95.7%, AUC 0.96 and accuracy 95.6%. ALP >126 U/L and GGT >73 U/L each had sensitivity 97.7%, specificity 84.8% and AUC 0.91. CBD diameter >5 mm had sensitivity and negative predictive value of 100% with specificity 76.1%. History of jaundice had specificity 97.8% and sensitivity 63.6%. Fever, cholangitis history, male sex, AST/ALT, amylase and lipase showed low sensitivity, and RUQ pain (present in all patients) was non-discriminatory. On multivariable analysis only bilirubin remained significant (odds ratio 16.0; 95% CI 1.18–217.1; $p = 0.037$), with very wide intervals. ERCP clearance with stenting succeeded in 43 of 44 patients.

Conclusion: In this cohort, serum bilirubin, ALP, GGT and ultrasonographic CBD dilatation were the most accurate pre-operative predictors of CBD stones. The very high accuracy and unstable multivariable estimates reflect a small, high-prevalence sample and need prospective, multicentre validation before clinical use.

Keywords: choledocholithiasis; common bile duct stones; cholelithiasis; cholecystectomy; bilirubin; alkaline phosphatase; MRCP; diagnostic accuracy

INTRODUCTION

Gallstone disease is the most prevalent disorder of the biliary system.^[1,2] It affects an estimated 10–15% of people in Western societies, is asymptomatic in more than 80% of those affected, and yet 1–2% per year develop symptoms that require surgery, which makes cholecystectomy one of the most commonly performed operations.^[3,4] Established risk factors include female sex, increasing age, family history and genetic predisposition, obesity, metabolic syndrome, diabetes mellitus, dyslipidaemia, reduced physical activity, diet, certain drugs (ceftriaxone, octreotide, thiazide diuretics and exogenous hormones) and underlying disease such as cirrhosis or Crohn's disease.^[1,2] Prevalence and risk profile vary between populations.^[3]

The high prevalence of gallstones produces a correspondingly high burden of common bile duct (CBD) stones (choledocholithiasis). About 11% of patients with cholelithiasis, and up to 18% in some series, have CBD stones at the time of cholecystectomy, and 20–25% of initially asymptomatic CBD stones eventually cause symptoms and need treatment.^[5] CBD stones are classed as primary, when they form de novo in the duct, or secondary, when they migrate from the gallbladder. Primary stones are typically brown pigment stones, are common in Asian populations, and arise from biliary stasis and bacterial infection, in which bacterial enzymes hydrolyse bilirubin glucuronides and the free bilirubin precipitates.^[6] Secondary stones predominate in Western series.^[6] Many CBD stones are clinically silent. When symptomatic they range from biliary colic to obstructive jaundice, with dark urine, scleral icterus and pale stools.^[5,6] Jaundice caused by choledocholithiasis is more likely to be painful when obstruction is acute, because rapid ductal distension activates pain fibres. Ascending cholangitis, first described by Charcot in 1877, produces fever, right upper quadrant pain and jaundice (Charcot's triad) and may progress to septic shock with hypotension and altered mental status (Reynolds' pentad), which carries a high mortality unless treated promptly.^[7,8] Choledocholithiasis may also precipitate biliary pancreatitis and sepsis.^[7]

Pre-operative detection of CBD stones therefore matters, but every available test has limitations. Ultrasonography is the first-line investigation but is operator dependent. MRCP is non-invasive and gives images comparable to those of ERCP, but it is purely diagnostic, is expensive, may involve long waiting lists, and is not available everywhere.^[9,10] Its performance in routine practice may be lower than that reported in meta-analyses,^[11,12] and small stones (<5 mm) can be missed.^[13] ERCP is both diagnostic and therapeutic but is invasive and carries risks of morbidity and mortality.^[9,10] Imaging every patient scheduled for cholecystectomy is neither efficient nor feasible, so a reliable pre-test estimate of the

likelihood of CBD stones is needed to select patients for further imaging or ERCP.

Guidelines stratify patients into low, intermediate and high risk using clinical, biochemical and ultrasonographic criteria,^[9,10] and a meta-analysis has ranked individual indicators by likelihood ratio.^[14] Observational studies and scoring systems have identified bilirubin, GGT, ALP, aminotransferases, CBD diameter, age and sex as predictors, but the thresholds, populations and reference standards differ and the results are inconsistent.^[15–20] Local data are valuable because disease epidemiology, referral patterns and access to imaging differ between settings. We therefore studied the predictors of CBD stones in patients with symptomatic cholelithiasis undergoing cholecystectomy at a hospital in New Delhi, using MRCP as the reference standard.

Aim and objectives

Aim: to study the predictors of CBD stones in patients with symptomatic cholelithiasis undergoing cholecystectomy.

Objectives:

- To compare the sensitivity and specificity of predictors of CBD stones.
- To determine the prevalence and distribution of CBD stones by sex and age group.
- To examine the correlation between liver enzyme levels and CBD stones.
- To examine the correlation between clinical signs and symptoms and CBD stones.
- To identify the most sensitive and accurate predictor(s) of CBD stones.

MATERIALS AND METHODS

Study design and setting: This was a single-centre, cross-sectional diagnostic accuracy study conducted in the Department of General and Minimal Access Surgery, Jaipur Golden Hospital, Sector 3, Rohini, New Delhi, over 18 months from March 2024 to August 2025. The study is reported in line with the STARD 2015 recommendations for diagnostic accuracy studies.²² The study population, index tests, reference standard and patient flow are summarised in [Figure 1].

Ethical approval and consent: The study protocol was reviewed and approved by the Institutional Ethics Committee of Jaipur Golden Hospital, which is registered with the Department of Health Research, Government of India (meeting of 17 January 2024; reference JGH/DNB/MD/2024/). Participants received a participant information sheet and gave written informed consent in a language they understood. They were told that participation carried no additional risk, would not add to their expenses, and that they could withdraw at any time without any effect on their treatment.

Participants: All patients with symptomatic cholelithiasis who were scheduled to undergo cholecystectomy and who met the eligibility criteria were enrolled. We excluded (i) patients with

asymptomatic cholelithiasis undergoing cholecystectomy, (ii) patients already known to have CBD stones, (iii) patients with retained CBD stones after previous cholecystectomy, and (iv) patients with known gallbladder cancer.

Sample size: Published series and local experience suggest that 10–15% of patients with symptomatic gallstones have CBD stones.^{18,21} Taking an expected proportion (P) of 0.15, a 95% confidence level ($Z\alpha/2 = 1.96$) and an absolute precision (δ) of 50% of P (0.075), the required sample size was $n = Z\alpha/2^2 \times P(1 - P) / \delta^2 = (1.96)^2 \times 0.15 \times 0.85 / (0.075)^2 \approx 88$. We recruited 90 patients.

Index tests (candidate predictors): Demographic, clinical and laboratory data were recorded on a case record form and transferred to an electronic database. Each predictor was dichotomised using the cut-offs in [Table 1]. Biochemical tests were total serum bilirubin, aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum amylase and serum lipase. CBD diameter was measured on transabdominal ultrasonography, and a diameter above 5 mm was defined as dilated. Clinical predictors were sex, age, RUQ pain, fever and a history of jaundice or cholangitis in the preceding 6 months.

Table 1: Candidate predictors and the cut-offs used to define a positive result.

Predictor	Definition of a positive result	Domain
Male sex	Male (reference: female)	Demographic
Age	Analysed in 10-year groups (18–30 to 71–80 years)	Demographic
RUQ pain	Present	Clinical
Fever	Present	Clinical
History of jaundice	Within the preceding 6 months	Clinical
History of cholangitis	Within the preceding 6 months	Clinical
Serum total bilirubin	>1.3 mg/dL	Biochemical
AST (SGOT)	>59 U/L	Biochemical
ALT (SGPT)	>50 U/L	Biochemical
ALP	>126 U/L	Biochemical
GGT	>73 U/L	Biochemical
Serum amylase	>110 U/L	Biochemical
Serum lipase	>300 U/L	Biochemical
CBD diameter on ultrasonography	>5 mm	Imaging

RUQ, right upper quadrant; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CBD, common bile duct.

Reference standard and patient management: All 90 patients underwent MRCP. The presence of a CBD stone on MRCP defined the target condition. Patients with a stone on MRCP were managed by ERCP with stone extraction and stenting before cholecystectomy; if ERCP failed, the protocol was laparoscopic or open CBD exploration together with cholecystectomy. Patients without a stone on MRCP proceeded to cholecystectomy [Figure 1].

Statistical analysis: The primary outcome was the proportion of patients with MRCP-confirmed CBD stones, reported with an exact (Clopper–Pearson) 95% confidence interval. Categorical variables are given as frequencies and percentages, and continuous variables as mean $\pm$ standard deviation (SD) and median (25th–75th percentile). The proportion of patients with stones was compared between categories using Fisher’s exact test (age subgroups, clinical and laboratory predictors) and the chi-square test (sex). For each dichotomised predictor we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy and area under the receiver operating characteristic curve (AUC) against MRCP, with exact 95% confidence intervals for proportions. Positive and negative likelihood ratios were derived from sensitivity and specificity. Variables were entered into a multivariable logistic regression model to identify independent predictors, and adjusted odds ratios (aOR) with 95% confidence intervals are reported. A two-sided p value below 0.05 was considered significant.

RESULTS

Study population: Ninety patients were included [Figure 1]. The mean age was 45.99 ± 14.1 years (median 44; interquartile range 35.5–56; range 18–77). The largest group was aged 31–40 years (26.7%),

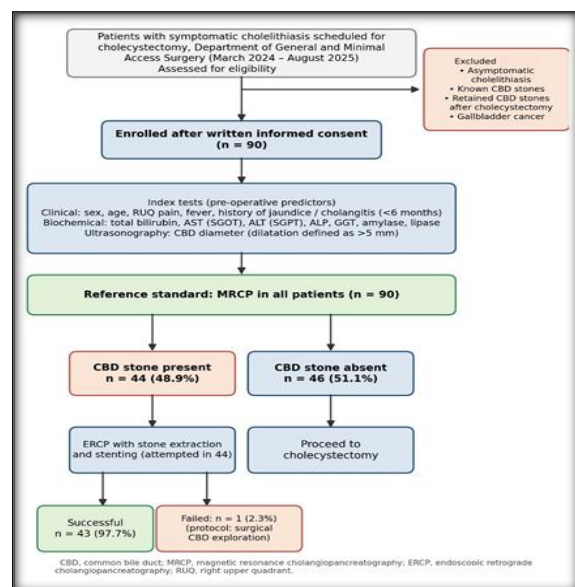


Figure 1: Flow of participants through the study.

and women predominated (70 of 90; 77.8%) [Table 2, Figure 2]. All patients had RUQ pain. A history of jaundice within 6 months was present in 29

patients (32.2%), fever in 13 (14.4%) and a history of cholangitis within 6 months in 10 (11.1%).

Table 2: Demographic and clinical characteristics of the study population (n = 90).

Characteristic	n	%
Age group (years)		
18–30	12	13.3
31–40	24	26.7
41–50	21	23.3
51–60	16	17.8
61–70	11	12.2
71–80	6	6.7
Mean ± SD; median (IQR); range	45.99 ± 14.1; 44 (35.5–56); 18–77	
Sex		
Female	70	77.8
Male	20	22.2
Clinical features		
RUQ pain	90	100
Fever	13	14.4
History of jaundice <6 months	29	32.2
History of cholangitis <6 months	10	11.1

SD, standard deviation; IQR, interquartile range; RUQ, right upper quadrant.

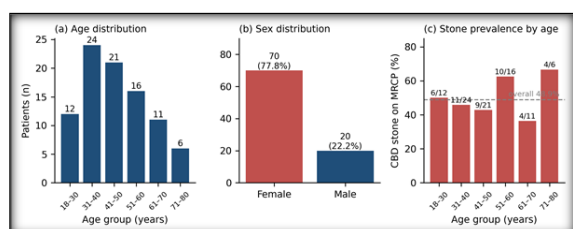


Figure 2: Characteristics of the study population: (a) age distribution; (b) sex distribution; (c) proportion of patients with MRCP-confirmed CBD stones by age group (numbers above bars are patients with stones / patients in the group).

Biochemical and ultrasonographic findings: Total bilirubin exceeded 1.3 mg/dL in 44 patients (48.9%), ALP exceeded 126 U/L and GGT exceeded 73 U/L in 50 patients each (55.6%), and CBD diameter exceeded 5 mm in 55 patients (61.1%). AST and ALT were raised in only 5 patients each (5.6%), and amylase and lipase in 6 patients each (6.7%). The aminotransferase, amylase and lipase distributions were strongly right-skewed (maximum values 1400, 2000, 1800 and 8000 U/L respectively), so the medians describe these variables better than the means [Table 3].

Table 3: Biochemical and ultrasonographic findings (n = 90).

Parameter	Mean ± SD	Median (IQR)	Range	Above cut-off, n (%)
Total bilirubin (mg/dL)	1.78 ± 1.03	1.3 (0.925–2.75)	0.6–4.6	44 (48.9)
AST (U/L)	77.09 ± 152.37	51 (48–55)	36–1400	5 (5.6)
ALT (U/L)	80.88 ± 222.12	43 (39–47)	25–2000	5 (5.6)
ALP (U/L)	206.0 ± 102.24	190 (112.25–297.5)	40–430	50 (55.6)
GGT (U/L)	194.03 ± 130.37	200 (67–300)	40–500	50 (55.6)
Amylase (U/L)	175.44 ± 338.85	97 (89–102)	67–1800	6 (6.7)
Lipase (U/L)	404.28 ± 918.98	235 (198.25–269.75)	98–8000	6 (6.7)
CBD diameter >5 mm	–	–	–	55 (61.1)

Cut-offs are those in [Table 1]. IQR, interquartile range.

Prevalence of CBD stones and outcome of ERCP: MRCP showed CBD stones in 44 of 90 patients (48.9%; 95% CI 38.2–59.7%) and no stones in 46 (51.1%). Stone extraction with stenting was achieved at ERCP in 43 of the 44 patients (97.7%); it failed in one patient (2.3%) [Figure 1].

Age, sex and CBD stones: The proportion of patients with CBD stones did not differ significantly across age groups, either overall ($p = 0.716$) or within men ($p = 0.487$) or women ($p = 0.68$) [Table 4]. Stones were significantly more frequent in men (14 of 20; 70.0%) than in women (30 of 70; 42.9%) (chi-square $p = 0.032$; Fisher's exact $p = 0.043$).

Table 4: Proportion of patients with MRCP-confirmed CBD stones by age group and sex.

Group	Total, n	CBD stone present, n (%)	p value
All patients, by age group (years)			
18–30	12	6 (50.0)	0.716*
31–40	24	11 (45.8)	
41–50	21	9 (42.9)	
51–60	16	10 (62.5)	
61–70	11	4 (36.4)	
71–80	6	4 (66.7)	
Men, by age group (years)			

18–30	2	2 (100)	0.487*
31–40	3	1 (33.3)	
41–50	7	5 (71.4)	
51–60	2	2 (100)	
61–70	4	2 (50.0)	
71–80	2	2 (100)	
Women, by age group (years)			
18–30	10	4 (40.0)	0.68*
31–40	21	10 (47.6)	
41–50	14	4 (28.6)	
51–60	14	8 (57.1)	
61–70	7	2 (28.6)	
71–80	4	2 (50.0)	
Sex			
Male	20	14 (70.0)	0.032†
Female	70	30 (42.9)	

*Fisher's exact test across age groups. †Chi-square test (Fisher's exact p = 0.043).

Association of clinical, biochemical and ultrasonographic predictors with CBD stones:

Fever, history of jaundice, history of cholangitis, bilirubin, AST, ALT, ALP, GGT and CBD dilatation were each significantly associated with MRCP-confirmed stones, whereas amylase and lipase were not [Table 5, Figure 3]. The associations were strongest for a history of jaundice (96.6% of those with a history had stones vs 26.2% without), raised

bilirubin (95.5% vs 4.3%), raised ALP or GGT (86.0% vs 2.5%) and CBD dilatation (80.0% vs 0%). No patient with a CBD diameter of 5 mm or less had a stone. All patients with a history of cholangitis (10 of 10) or elevated AST or ALT (5 of 5) had stones, but these groups were small. The cross-tabulations for AST and ALT, for ALP and GGT, and for amylase and lipase were identical, meaning that the same patients exceeded both cut-offs in each pair.

Table 5: Association of predictors with CBD stones on MRCP (univariable analysis).

Predictor	Stone present when predictor positive, n/N (%)	Stone present when predictor negative, n/N (%)	p value
Male sex	14/20 (70.0)	30/70 (42.9)	0.032†
Fever	10/13 (76.9)	34/77 (44.2)	0.037
History of jaundice <6 months	28/29 (96.6)	16/61 (26.2)	<0.0001
History of cholangitis <6 months	10/10 (100)	34/80 (42.5)	0.0004
Total bilirubin >1.3 mg/dL	42/44 (95.5)	2/46 (4.3)	<0.0001
AST >59 U/L	5/5 (100)	39/85 (45.9)	0.025
ALT >50 U/L	5/5 (100)	39/85 (45.9)	0.025
ALP >126 U/L	43/50 (86.0)	1/40 (2.5)	<0.0001
GGT >73 U/L	43/50 (86.0)	1/40 (2.5)	<0.0001
Amylase >110 U/L	1/6 (16.7)	43/84 (51.2)	0.203
Lipase >300 U/L	1/6 (16.7)	43/84 (51.2)	0.203
CBD diameter >5 mm	44/55 (80.0)	0/35 (0)	<0.0001

Fisher's exact test unless stated. †Chi-square test. RUQ pain was present in all patients and could not be tested.

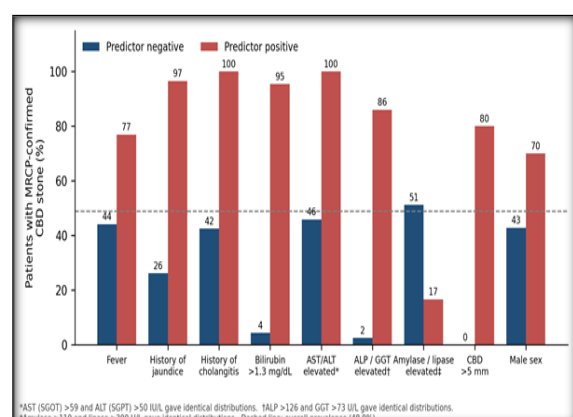


Figure 3: Proportion of patients with MRCP-confirmed CBD stones according to predictor status. Numbers above bars are percentages.

Diagnostic performance of the predictors: Serum total bilirubin above 1.3 mg/dL was the most accurate

single predictor, with sensitivity 95.5%, specificity 95.7%, PPV 95.5%, NPV 95.7%, AUC 0.96 and accuracy 95.6% [Table 6 and 7, Figure 4 and 5]. ALP above 126 U/L and GGT above 73 U/L each had sensitivity 97.7%, specificity 84.8%, AUC 0.91 and accuracy 91.1%. CBD dilatation above 5 mm had sensitivity 100% and NPV 100%, but its specificity was lower (76.1%; PPV 80.0%), giving an accuracy of 87.8%. A history of jaundice in the preceding 6 months had high specificity (97.8%) and PPV (96.6%) but moderate sensitivity (63.6%), with an accuracy of 81.1%.

Fever, a history of cholangitis, male sex, AST, ALT, amylase and lipase had low sensitivity (2.3–31.8%) and poor accuracy (46.7–62.2%), even though some had high specificity. RUQ pain, present in every patient, had a sensitivity of 100% and a specificity of 0% and therefore no discriminatory value (AUC 0.50). Likelihood ratios are in [Table 7].

Table 6: Sensitivity, specificity, AUC and accuracy of each predictor for CBD stones on MRCP (% with 95% CI).

Predictor	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Accuracy (%)
Total bilirubin >1.3 mg/dL	95.45 (84.53–99.44)	95.65 (85.16–99.47)	0.96 (0.89–0.99)	95.56
ALP >126 U/L	97.73 (87.98–99.94)	84.78 (71.13–93.66)	0.91 (0.83–0.96)	91.11
GGT >73 U/L	97.73 (87.98–99.94)	84.78 (71.13–93.66)	0.91 (0.83–0.96)	91.11
CBD diameter >5 mm	100.00 (91.96–100.00)	76.09 (61.23–87.41)	0.88 (0.79–0.94)	87.78
History of jaundice <6 months	63.64 (47.77–77.59)	97.83 (88.47–99.94)	0.81 (0.71–0.88)	81.11
History of cholangitis <6 months	22.73 (11.47–37.84)	100.00 (92.29–100.00)	0.61 (0.51–0.71)	62.22
Male sex	31.82 (18.61–47.58)	86.96 (73.74–95.06)	0.59 (0.49–0.70)	60.00
Fever	22.73 (11.47–37.84)	93.48 (82.10–98.63)	0.58 (0.47–0.68)	58.89
AST >59 U/L	11.36 (3.79–24.56)	100.00 (92.29–100.00)	0.56 (0.45–0.66)	56.67
ALT >50 U/L	11.36 (3.79–24.56)	100.00 (92.29–100.00)	0.56 (0.45–0.66)	56.67
RUQ pain	100.00 (91.96–100.00)	0.00 (0.00–7.71)	0.50 (0.39–0.61)	48.89
Amylase >110 U/L	2.27 (0.06–12.02)	89.13 (76.43–96.38)	0.46 (0.35–0.57)	46.67
Lipase >300 U/L	2.27 (0.06–12.02)	89.13 (76.43–96.38)	0.46 (0.35–0.57)	46.67

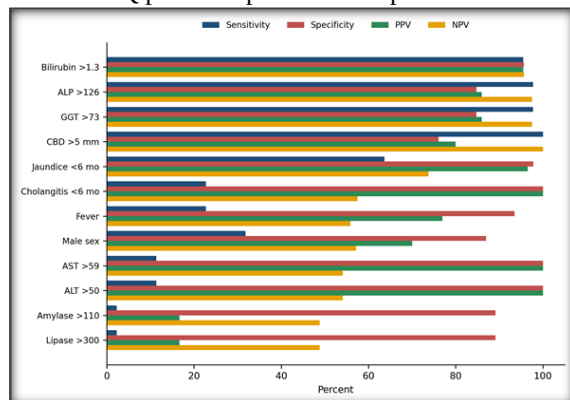
AUC, area under the receiver operating characteristic curve. For a single dichotomous predictor the AUC

equals the mean of sensitivity and specificity. Rows are ordered by AUC.

Table 7: Predictive values and likelihood ratios of each predictor for CBD stones on MRCP.

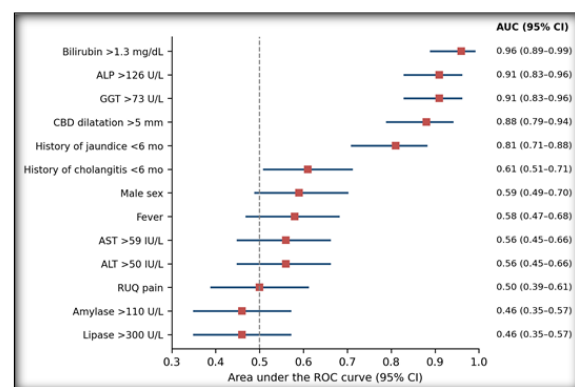
Predictor	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR–
Total bilirubin >1.3 mg/dL	95.45 (84.53–99.44)	95.65 (85.16–99.47)	21.95	0.05
ALP >126 U/L	86.00 (73.26–94.18)	97.50 (86.84–99.94)	6.42	0.03
GGT >73 U/L	86.00 (73.26–94.18)	97.50 (86.84–99.94)	6.42	0.03
CBD diameter >5 mm	80.00 (67.03–89.57)	100.00 (90.00–100.00)	4.18	0.00
History of jaundice <6 months	96.55 (82.24–99.91)	73.77 (60.93–84.20)	29.27	0.37
History of cholangitis <6 months	100.00 (69.15–100.00)	57.50 (45.94–68.49)	n/a‡	0.77
Male sex	70.00 (45.72–88.11)	57.14 (44.75–68.91)	2.44	0.78
Fever	76.92 (46.19–94.96)	55.84 (44.07–67.16)	3.48	0.83
AST >59 U/L	100.00 (47.82–100.00)	54.12 (42.96–64.98)	n/a‡	0.89
ALT >50 U/L	100.00 (47.82–100.00)	54.12 (42.96–64.98)	n/a‡	0.89
RUQ pain	48.89 (38.20–59.65)	not estimable	1.00	n/a
Amylase >110 U/L	16.67 (0.42–64.12)	48.81 (37.74–59.96)	0.21	1.10
Lipase >300 U/L	16.67 (0.42–64.12)	48.81 (37.74–59.96)	0.21	1.10

PPV, positive predictive value; NPV, negative predictive value; LR+/LR–, positive/negative likelihood ratio (derived from sensitivity and specificity). ‡Not defined because specificity was 100%. RUQ pain was present in all patients.

**Figure 4: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each predictor for CBD stones on MRCP.**

Multivariable analysis: In the multivariable logistic regression model, total bilirubin was the only

variable independently associated with CBD stones (aOR 16.01; 95% CI 1.18–217.11; $p = 0.037$). Male sex, fever, history of jaundice, history of cholangitis, AST, ALP and CBD dilatation were not significant after adjustment (all $p > 0.05$), and their confidence intervals were very wide and crossed unity [Table 8, Figure 6].

**Figure 5: Area under the ROC curve (95% CI) of each predictor. The dashed line marks an AUC of 0.5 (no discrimination).****Table 8: Multivariable logistic regression for independent predictors of CBD stones on MRCP.**

Variable	β	SE	aOR	95% CI	p value
Male sex (vs female)	4.994	2.698	147.53	0.745–29 218.9	0.064
Fever	–5.078	3.384	0.006	0.000–4.730	0.133
History of jaundice <6 months	0.743	1.582	2.10	0.095–46.65	0.639
History of cholangitis <6 months	5.394	3.592	220.18	0.193–251 575.6	0.133

Total bilirubin >1.3 mg/dL	2.773	1.330	16.01	1.181–217.1	0.037
AST >59 U/L	-0.545	1.805	0.58	0.017–19.94	0.763
ALP >126 U/L	3.271	2.087	26.33	0.440–1573.7	0.117
CBD diameter >5 mm	2.791	2.298	16.30	0.180–1472.9	0.225

β , regression coefficient; SE, standard error; aOR, adjusted odds ratio. The very wide confidence intervals indicate an unstable model (see Limitations).

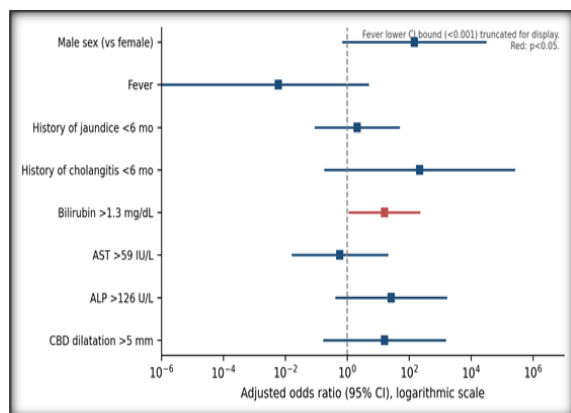


Figure 6: Adjusted odds ratios (95% CI) from the multivariable model on a logarithmic scale. The extreme width of the intervals reflects small numbers and near-complete separation for several variables.

DISCUSSION

Principal findings: In 90 patients with symptomatic cholelithiasis, nearly half (48.9%) had MRCP-confirmed CBD stones. Total bilirubin above 1.3 mg/dL, ALP above 126 U/L, GGT above 73 U/L and ultrasonographic CBD diameter above 5 mm were the most sensitive and accurate predictors, and a history of jaundice was a highly specific one. Male sex and, to a lesser degree, fever and a history of cholangitis were associated with stones but had poor sensitivity. RUQ pain, amylase, lipase and the aminotransferases did not usefully discriminate. Bilirubin was the only independent predictor on multivariable analysis.

Prevalence of CBD stones: The prevalence of 48.9% is far above the 10–15% assumed in the sample size calculation and above the figures usually quoted for unselected patients undergoing cholecystectomy (about 11–18%).^[5] In the largest comparators it was 5% among 986 cholecystectomies¹⁵ and 18.8% among 880 patients,¹⁶ although cohorts selected for ERCP report higher rates (143 of 206, 69%, in one Thai series).^[23] The high prevalence here probably reflects a referral and selection effect, in which patients with biochemical or clinical suspicion were more likely to be admitted or imaged, and the exclusion of asymptomatic patients. It has a direct consequence for interpretation: predictive values depend on prevalence, so the PPVs reported here will be lower, and the NPVs higher, in populations with fewer stones.

Age and sex: Women formed 77.8% of the cohort, as expected for gallstone disease, but stones in the duct were more frequent in men (70.0% vs 42.9%; $p = 0.032$). The difference was modest in statistical

terms, since Fisher's exact test gave $p = 0.043$ and a continuity-corrected chi-square test would be around 0.06, and men numbered only 20. We found no association with age, although many studies report that older age is a risk factor: patients aged over 55 years were more likely to have stones in a Thai series (mean age 61 years),^[23] and age over 50 years in men contributes to the Saudi scoring system.¹⁸ Our small sample, with only 6 patients above 70 years, limits power to detect an age effect.

Clinical features: A history of jaundice in the previous 6 months was a reliable clinical marker (specificity 97.8%, PPV 96.6%, LR+ 29), whereas fever and a history of cholangitis had specificities of 93.5% and 100% but sensitivities of only 22.7%. This agrees with the meta-analysis of Abboud and colleagues, in which cholangitis, pre-operative jaundice and ultrasonographic duct stones had the highest positive likelihood ratios (10 or more) and most indicators had specificity above 90%.^[14] In an ERCP cohort, jaundice and biliary pancreatitis each had a sensitivity of only 42%,^[24] in line with our modest sensitivity for jaundice. RUQ pain was universal here because it was part of the definition of symptomatic disease, so its accuracy figures reflect study design rather than the symptom itself.

Liver biochemistry: Bilirubin, ALP and GGT were the best laboratory predictors. This is consistent with studies that found bilirubin and GGT to be independent predictors in patients under 70 years and bilirubin alone in older patients,^[15] and with reports that raised ALP and bilirubin are associated with choledocholithiasis,^[17,18] and that a GGT well above the normal range is a strong predictor.^[16,19] GGT also had good sensitivity and specificity in acute cholecystitis,^[25] and liver enzymes aided the diagnosis in patients with biliary colic.^[26] The very high accuracy we observed for bilirubin (95.6%) is, however, higher than most published series, in which hyperbilirubinaemia had a positive likelihood ratio of about 4–7.14. Our LR+ was 22. In the same meta-analysis ALP had a low likelihood ratio (<3),¹⁴ whereas ALP in our cohort had LR+ 6.4 and a very low LR- of 0.03. Differences in thresholds, in the spectrum of patients and in the reference standard probably explain these discrepancies, and the narrow, dichotomised cut-offs we used may have produced optimistic estimates in a sample this small.

Amylase and lipase did not discriminate (sensitivity 2.3%), and only 1 of the 6 patients with raised values had a stone. This is also in line with the low likelihood ratios of hyperamylasaemia in the meta-analysis.^[14] The number of patients with raised enzymes was small, and we did not analyse a history of pancreatitis separately, so we cannot comment on

biliary pancreatitis as an entity. AST and ALT were raised in only 5 patients, all of whom had stones; their specificity was 100% but their sensitivity was only 11.4%, so they are of limited use for ruling out stones. **Ultrasonographic CBD diameter:** CBD diameter above 5 mm detected every stone (sensitivity 100%), and no patient with a CBD of 5 mm or less had a stone (NPV 100%), but 11 patients with a dilated duct had no stone on MRCP (specificity 76.1%). Dilated ducts have also been reported as a good pre-operative predictor in earlier series.^[23,24] The cut-off we used is

lower than the greater than 6 mm often used for a patient with the gallbladder in situ,^[9] which will increase sensitivity at the expense of specificity. Duct diameter alone has, moreover, been considered insufficient in patients with acute cholecystitis, in whom CBD stones were found in 14%, 14% and 39% of those with a duct under 6 mm, 6–9.9 mm and 10 mm or more respectively.^[27] Ultrasonography is operator dependent, so the apparent NPV of 100% may not be reproducible elsewhere.

Table 9: Comparison of the present findings with selected previous studies on the prediction of CBD stones.

Study	Design and population	Principal findings
Alam, ^[24]	Retrospective; 104 patients who had ERCP before laparoscopic cholecystectomy	Ultrasonographic stone detection had sensitivity 75%; dilated duct with deranged LFTs 46%; jaundice and biliary pancreatitis 42% each; dilated duct alone 36%; deranged LFTs without jaundice 22%
Charatcharoenwittaya et al. ^[23]	Retrospective; 206 patients with symptomatic cholelithiasis, ERCP in all	143 (69%) had CBD stones; age >55 years, jaundice, raised ALP and dilated CBD on ultrasonography were predictive
Kondo et al. ^[13]	Prospective; 28 patients	Sensitivity of EUS 100%, MRCP 88%, helical CT cholangiography 88%; false negatives for stones <5 mm with MRCP and CT
Abboud et al. ^[14]	Meta-analysis; 22 studies	Cholangitis, pre-operative jaundice and ultrasonographic duct stones had LR+ ≥10; dilated CBD, hyperbilirubinemia and jaundice LR+ about 4–7; ALP, pancreatitis, cholecystitis and hyperamylasaemia LR+ <3
Kama et al. ^[15]	Prospective database; 986 cholecystectomies	5% had CBD stones; CBD >8 mm or visible stone, bilirubin and GGT were independent predictors under 70 years; bilirubin alone above 70 years
Prat et al. ^[16]	880 patients; EUS as reference	CBD stones in 18.8%; age, bilirubin, AST, ALT, GGT, ALP, jaundice, fever, dilated CBD and pathological gallbladder were associated; GGT >7 × normal plus pathological gallbladder plus dilated duct predicted stones under 70 years
Jovanović et al. ^[19]	203 patients with ERCP; testing (103) and validation (100) groups	GGT, CBD diameter and hyperechoic structures in the duct were associated with stones; a threshold of 0.86 carried a 93.1% probability in the validation group
Al-Jiffry et al. ^[17]	Symptomatic gallstones; selective strategy	Direct laparoscopic cholecystectomy in 78.5%; 21.5% had abnormal LFTs, of whom 52.8% had a normal ultrasound; the strategy avoided unnecessary MRCP in 47.2% and unnecessary ERCP in 35.2% of those with abnormal LFTs
Al-Jiffry et al. ^[18]	Prospective score; validation in 272 patients	CBD diameter, ALP ≥200, bilirubin, ALT ≥220 and male age ≥50 years entered the score; AUC 0.896 in the validation cohort
Boys et al. ^[27]	Retrospective; 248 patients with acute cholecystitis, 48 with stones	CBD stones in 14%, 14% and 39% at diameters <6, 6–9.9 and ≥10 mm; CBD diameter alone insufficient
Present study	Cross-sectional; 90 patients, MRCP reference	CBD stones in 48.9%; bilirubin >1.3 mg/dL (AUC 0.96), ALP and GGT (AUC 0.91) and CBD >5 mm (AUC 0.88) most accurate; bilirubin the only independent predictor

LFT, liver function test; EUS, endoscopic ultrasonography; LR+, positive likelihood ratio. Findings are as reported in the original publications.

Multivariable findings: Bilirubin remained independently associated with CBD stones (aOR 16.0), while ALP, CBD dilatation, male sex and a history of cholangitis did not. This should not be read to mean that the others carry no information. They are correlated with bilirubin and with each other, the model included eight variables for 44 events, several cells were empty (for example, no stone-free patient had a history of cholangitis and no patient with a non-dilated duct had a stone), and the confidence intervals for several estimates extend over several orders of magnitude. These features indicate sparse-data bias and separation, so the model should be treated as exploratory.

Clinical implications: Within the limits of the data, the findings suggest a way of organising the pre-operative work-up [Figure 7]. A normal ductal diameter on ultrasonography, normal ALP or GGT

and a bilirubin within the normal range were each associated with very few stones (0 of 35, 1 of 40 and 2 of 46 respectively), whereas raised bilirubin, a history of jaundice or cholangitis, and raised ALP or GGT identified groups in which stones were found in 86–100%. Such a framework might allow patients with reassuring features to proceed directly to cholecystectomy and concentrate MRCP and ERCP on those with markers of obstruction. This is hypothesis generating only. Whether the proposed approach is safe cannot be shown by a study in which every patient had MRCP. Selective approaches to cholangiography have been evaluated prospectively elsewhere,^[21] and when stones are found, endoscopic clearance is usually followed by cholecystectomy, with laparoscopic or open duct exploration reserved for failed ERCP.^[28,29] In our cohort ERCP with stenting was successful in 43 of 44 patients (97.7%).

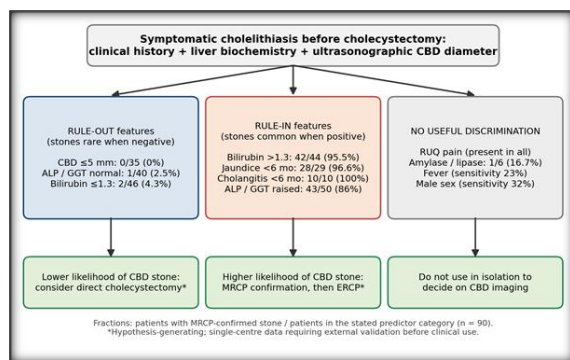


Figure 7: Summary of how each predictor performed in this cohort and a proposed interpretation (hypothesis generating; needs external validation).

Strengths and limitations: Strengths include the uniform application of a single imaging reference standard (MRCP) to all 90 patients, the pre-specified sample size calculation, the assessment of a broad set of clinical, biochemical and ultrasonographic predictors in one cohort, and the reporting of confidence intervals for all accuracy measures.

The study also has important limitations. (1) It is a single-centre study with a modest sample, so estimates are imprecise and the multivariable model is unstable. (2) The prevalence (48.9%) was much higher than assumed, indicating a selected population that limits generalisability and inflates predictive values. (3) MRCP is an imperfect reference standard: small stones and microlithiasis may be missed, 13,30 and patients with a negative MRCP did not undergo a second reference test such as endoscopic ultrasonography or intra-operative cholangiography, so partial verification bias cannot be excluded. (4) Predictors were dichotomised at laboratory reference limits rather than at cut-offs derived from receiver operating characteristic analysis, and no internal or external validation was carried out, so the accuracy of bilirubin in particular may be over-estimated. (5) Many comparisons were made without adjustment for multiple testing. (6) Ultrasonography is operator dependent and the observers and the interval between tests and MRCP were not described. (7) A history of pancreatitis was recorded as a predictor but is not analysed here, and stone size and number were not recorded.

Future directions: Larger prospective multicentre studies with pre-specified cut-offs, ROC-based threshold selection, a validation cohort, and an appropriate reference standard (including endoscopic ultrasonography or intra-operative cholangiography for MRCP-negative patients) are needed to confirm these findings and to develop and validate a simple risk score for use before cholecystectomy in Indian practice.

CONCLUSION

In patients with symptomatic cholelithiasis undergoing cholecystectomy, serum total bilirubin above 1.3 mg/dL was the most accurate predictor of

CBD stones (sensitivity 95.5%, specificity 95.7%, AUC 0.96), followed by ALP, GGT and ultrasonographic CBD dilatation above 5 mm, which had very high sensitivity and negative predictive value. A history of jaundice was a highly specific clinical marker. RUQ pain, amylase, lipase, aminotransferases, fever and male sex were of little value for discrimination. Because the sample was small, highly selected and verified by an imperfect reference standard, these findings should be validated in larger prospective studies before they inform clinical decision-making.

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