



The significance of isolated hyperbilirubinemia in detecting asymptomatic common bile duct stones in patients undergoing laparoscopic cholecystectomy

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ARTICLE INFO

Keywords:

Hyperbilirubinemia
Common bile duct stones
Cholelithiasis
Cholecystectomy

ABSTRACT

Aim: The aim of this study was to evaluate the role of isolated hyperbilirubinemia in the detection of choledocholithiasis.

Methods: A retrospective cohort study focused on adult patients diagnosed with gallstone disease, and undergoing intra-operative cholangiogram for suspected choledocholithiasis. Those presenting with isolated hyperbilirubinemia were investigated for their risk of choledocholithiasis, and were compared with those with normal liver function tests.

Results: Out of the total 1274 patients undergoing intra-operative cholangiogram in the study period, only 18 exhibited isolated hyperbilirubinemia. Among these, four patients were found to have common bile duct (CBD) stones. This indicates that in approximately 22 % of patients, isolated hyperbilirubinemia may be associated with CBD stones. However, it is essential to note that the number of patients in the study with isolated hyperbilirubinemia was relatively small.

Conclusion: Although the incidence of isolated hyperbilirubinemia was limited in our study, the presence of CBD stones in some of these patients suggests a potential association. Isolated hyperbilirubinemia should not be overlooked as a risk factor for CBD stones. Nonetheless, additional investigations with a larger sample size are needed to establish a more definitive understanding of the relationship between isolated hyperbilirubinemia and choledocholithiasis.

Introduction

Cholelithiasis is a common clinical problem in the Western world and is found in 10 %–15 % of adults in America and Europe [1,2]. Complications from cholelithiasis account for a significant burden on health-care systems; the financial burden is estimated to be between £3406 and £12011 per patient in the UK [3], and 6.2 billion dollars in the USA, annually [2]. One of these complications is common bile duct (CBD) stones or choledocholithiasis, which affects approximately 15 % of patients with cholelithiasis and up to 25 % of elderly patients undergoing cholecystectomy [4].

Choledocholithiasis is a significant cause of acute pancreatitis and cholangitis [5]. Due to the high risk to patients from these conditions,

the UK recommends removing common bile duct stones, even if asymptomatic [6]. CBD stones can be removed by endoscopic retrograde cholangiopancreatography (ERCP) or surgical CBD exploration [5,6]. Therefore, it is essential for patients presenting with cholelithiasis to have their risk of having common bile duct stones assessed, to have appropriate investigation if at high risk, and to have treatment for the CBD stones offered if they are identified [5,6]. Patients needing surgical treatment found not to have CBD stones can proceed directly to laparoscopic cholecystectomy [5,6,7]. It is worth noting that clinically silent, asymptomatic CBD stones can be found in about 4 % of cases [8].

The initial investigations for identifying CBD stones are liver function tests (LFTs) and transabdominal ultrasound (USS). Patients with normal LFTs, and no biliary dilatation on USS, are at low risk of CBD

Disclosure This study received no external funding, and the authors declare no conflicts of interest or financial disclosures. The research was conducted independently, with no involvement of any external sources that could influence the study findings or bias the interpretation of the results. This disclosure ensures transparency and underscores the impartiality of the study.

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<https://doi.org/10.1016/j.sipas.2023.100223>

Received 26 September 2023; Received in revised form 6 November 2023; Accepted 6 November 2023

Available online 6 December 2023

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stones [5]. Those patients with abnormal LFTs or biliary dilatation on USS require further investigations, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), intra-operative cholangiography, or ERCP [5,6]. There are significant resource implications in undertaking these further investigations, so an accurate method of predicting the presence of CBD stones using LFTs and USS would be beneficial.

Numerous prior investigations have explored the significance of abnormal liver function tests (LFTs) and biliary dilatation as diagnostic indicators for choledocholithiasis. These studies have aimed to elucidate the potential role of these parameters in identifying the presence of common bile duct (CBD) stones. Both abnormal LFT and CBD dilatation were identified as strong indicators of the presence of CBD stones [5,9]. However, the significance of isolated hyperbilirubinemia is unknown in the absence of biliary dilatation. Other causes of isolated hyperbilirubinemia (especially conjugated fraction) include inherited diseases like Gilbert syndrome, Dubin-Johnson syndrome, Rotor syndrome, progressive familial intrahepatic cholestasis, and benign recurrent intrahepatic cholestasis [10]. We postulated that isolated hyperbilirubinemia, in the presence of gallstones, may not be an indicator of CBD stones; and that the rate of CBD stones found in this group of patients may be no higher than in patients with no identified risk factors (i. e., normal LFTs, and no biliary dilatation).

This study, therefore, investigated the significance of the finding of isolated hyperbilirubinemia in the detection of CBD stones in patients planned for laparoscopic cholecystectomy.

Methods

The initial data were collected prospectively, with a database that included all adult patients who underwent laparoscopic cholecystectomy and intra-operative cholangiogram for symptomatic gallstones suspected of CBD stones between April 2004 and May 2021. All patients had a marker for high risk of CBD stones in their initial investigations, which included dilated CBD on USS, or abnormal LFTs. MRCP was not used routinely for pre-operative identification of CBD stones.

The database was analysed retrospectively to identify those patients whose only marker of suspicion for CBD stones was raised serum bilirubin (isolated hyperbilirubinaemia)

A retrospective cohort study design was employed to evaluate the effectiveness of utilizing elevated bilirubin levels as a standalone indicator in screening for common bile duct (CBD) stones before laparoscopic cholecystectomy. The study encompassed a meticulous statistical analysis to assess key performance measures, including sensitivity, specificity, and positive and negative predictive values.

To determine the capacity of bilirubin as a singular marker for identifying the presence of CBD stones, the receiver operating characteristic (ROC) curve was utilized to calculate the area under the curve (AUC). This quantitative measure provides valuable insights into the overall diagnostic ability of bilirubin as a solitary marker in detecting CBD stones. Through the implementation of this research approach, this investigation aims to contribute to the existing body of knowledge, enhancing our understanding of the diagnostic utility of elevated bilirubin levels in the preoperative screening process for CBD stones before laparoscopic cholecystectomy. [11].

The defining level of hyperbilirubinemia was adopted from the standard followed by the hospital laboratory.

Results and analysis

The statistical analysis resulted in 3 tables and 1 figure, which will be clarified in the following paragraph.

The first table (Table 1) shows the total number of cases and the number of issues that were proven positive or negative regarding CBD stones in the two developed categories. The table (Table 2) demonstrates the statistical value of isolated hyperbilirubinemia in detecting CBD

Table 1

Data analysis of patients undergoing laparoscopic cholecystectomy and Intra-operative cholangiogram.

Intraoperative Cholangiogram	1274	
Isolated Hyperbilirubinemia	+ve IOC 448 (35.16 %)	-ve IOC 826 (64.83 %)
Normal Bilirubin	4 (0.313 %)	14 (1.09 %)
	Normal Bilirubin+ Normal LFTs 127 (9.96 %)	Normal Bilirubin+ Normal LFTs 405 (31.78 %)

Table 2

Calculated sensitivity, specificity, positive and negative predictive value of isolated hyperbilirubinemia.

Sensitivity	3.05 %
Specificity	96.65 %
Positive predictive value	22.22 %
Negative predictive value	76.12 %

ROC Report.

stones in the 550 cases considered for this study. The following figure is the ROC plot for bilirubin as an indicator for CBD stones, and the associated table provides additional analysis of the ROC plot. Table 3.

Discussion

Several investigations are used to predict and diagnose common bile duct stones. However, intra-operative cholangiography (IOC) has a high sensitivity and specificity (93–100 %) for diagnosing CBD stones [9,12,13]. An intraoperative cholangiogram is safe and effective in detecting common bile duct stones even if used routinely with laparoscopic cholecystectomy. Therefore, our study chose it as the gold standard for diagnosing CBD stones [14].

Multiple studies have concluded that liver function tests are good negative predictors for CBD stones but less reliable positive predictors [15]. In this study, we focused on the significance of the bilirubin level as the sole diagnostic factor of Choledocholithiasis.

In their 2019 guidelines update, The American Society for Gastrointestinal Endoscopists (ASGE) reported that patients are considered at high risk for CBD stones, i.e., more than 50 percent, if the serum bilirubin is higher than 68 micromole/l (4 mg/dl), in the presence of CBD dilatation more than 6mm (in patients who still have their gall bladders) or more than 8 mm in patients who have had a cholecystectomy [16,17].

Furthermore, Dauer and Lammert detected choledocholithiasis in about 60 % of patients included in their research with bilirubin levels of more than 51 micromole/l (3 mg/dl) [18]. Still, how many of these patients had isolated hyperbilirubinemia is not recorded.

Our study concentrated on eighteen patients with isolated hyperbilirubinemia, with no biliary dilatation on USS. We aimed to determine whether isolated hyperbilirubinemia is a clinically significant risk factor for CBD stones or if this patient group can be considered low risk for CBD stones and can proceed directly to laparoscopic cholecystectomy.

In this study, four patients with isolated hyperbilirubinemia had proven CBD stones on IOC, while 14 cases were found to have no stones. Isolated abnormal bilirubin elevation had a negative predictive value of 76.12 %. Within the four positive cases, the highest bilirubin level was 35 micromole/l, while the lowest was 23 micromole/l. The mean value of the positive group is 27.75, and the median value is 27.5. Regarding the opposing group, the mean value is 27.64, and the median value is 27. This was not significantly different from the positive CBD stone group (P value 0.97046). Additionally, it is worth noting that the area under the ROC curve (AUC) (Fig. 1) is <0.6, which translates clinically to a poor screening tool. Although the number of patients in the study was very low, the positive rate for CBD stones (4/18, or 22 %) was higher than expected if isolated hyperbilirubinemia was not considered a risk factor

Table 3
Area under curve analysis (empirical estimation).

Criterion	Count	AUC	Standard Error	Z-Value to Test AUC > 0.5	Upper 1-Sided P-Value	95 % Confidence Limits	
						Lower	Upper
Isolated Bilirubin count	550	0.5876	0.0275	3.181	0.0007	0.5310	0.6390

The criterion is the Criterion Variable containing the scores of the individuals.
 The count is the number of individuals used in the analysis.
 AUC is the area under the ROC curve using the empirical (trapezoidal) approach.
 Standard Error is the standard error of the AUC estimate.
 Z-Value is the Z-score for testing the designated hypothesis test.
 The P-Value is the probability level associated with the Z-Value.
 The Lower and Upper Confidence Limits form the confidence interval for AUC.
 Estimated Prevalence = 131 / 550 = 0.2382

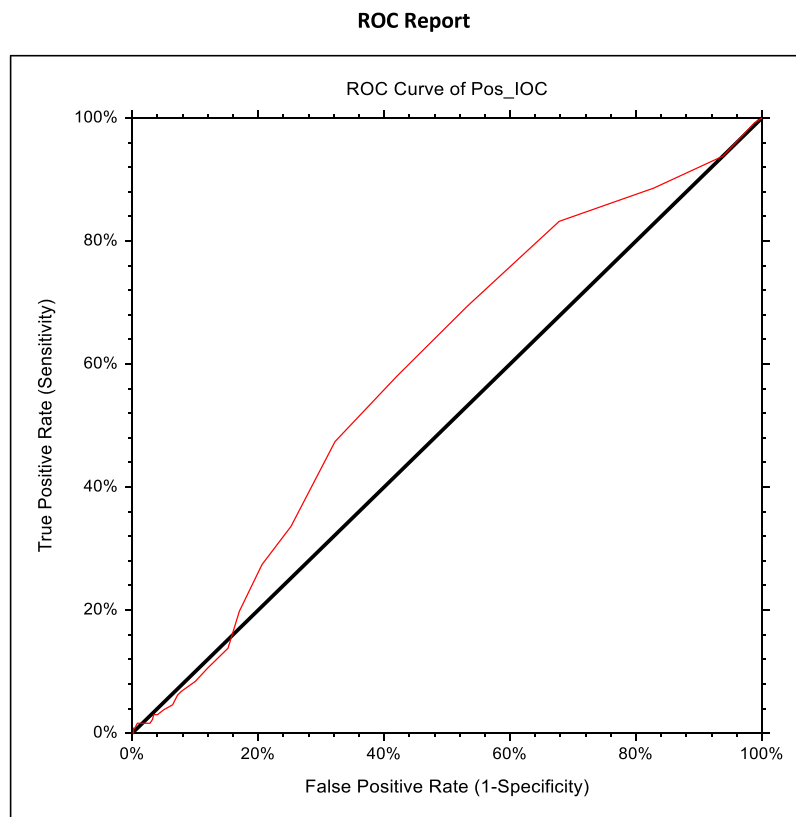


Fig. 1. ROC Plot section.

for CBD stones. It compares very closely with the positive rate in patients with normal LFTs (127/532, or 24 %), most of whom were undergoing IOC due to biliary dilatation on USS.

In conclusion, isolated hyperbilirubinemia may be associated with CBD stones, and while it does not reliably predict choledocholithiasis, this group of patients does need further investigation to exclude CBD stones.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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