Non-invasive assessment of choledocholithiasis in patients with gallstones and abnormal liver function

Bilal O Al-Jiffry, Abdeen Elfateh, Tariq Chundrigar, Bassem Othman, Owaid AlMalki, Fares Rayza, Hashem Niyaz, Hesham Elmakhzangy, Mohammed Hatem

Bilal O Al-Jiffry, Owaid AlMalki, Fares Rayza, Mohammed Hatem, Department of Surgery, College of Medicine and Medical Sciences, Taif University, Taif 21947, Saudi Arabia
Bilal O Al-Jiffry, Abdeen Elfateh, Tariq Chundrigar, Bassem Othman, Department of Surgery, Al-Hada Military Hospital, Taif 21947, Saudi Arabia
Hashem Niyaz, Hesham Elmakhzangy, Department of Gastroenterology, Al-Hada Military Hospital, Taif 21947, Saudi Arabia
Hesham Elmakhzangy, Department of Tropical Medicine, Faculty of Medicine, Cairo University, Cairo 11956, Egypt

Author contributions: Al-Jiffry BO designed the study and supervised the collection of all the data for 4 years; Elfateh A co-designed the study and co-supervised the collection of data; Chundrigar T contributed patient data and helped to draft the manuscript; Othman B, AlMalki O and Rayza F carried out data collection for one year; Niyaz H performed ERCP on the patients in this study and analyzed data; Elmakhzangy H performed ERCP on the patients along with Niyaz H and helped in analyzing the data; Hatem M contributed patient data and helped to draft the manuscript.

Correspondence to: Bilal O Al-Jiffry, MD, Department of Surgery, College of Medicine and Medical Sciences, Taif University, PO Box 888, Taif 21947, Saudi Arabia. jiffrybilal@hotmail.com
Telephone: +966-50-5924635 Fax: +966-27-541234
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Abstract

AIM: To find a non-invasive strategy for detecting choledocholithiasis before cholecystectomy, with an acceptable negative rate of endoscopic retrograde cholangiopancreatography.

METHODS: All patients with symptomatic gallstones were included in the study. Patients with abnormal liver functions and common bile duct abnormalities on ultrasound were referred for endoscopic retrograde cholangiopancreatography. Patients with normal ultrasound were referred to magnetic resonance cholangiopancreatography. All those who had a negative magnetic resonance or endoscopic retrograde cholangiopancreatography underwent laparoscopic cholecystectomy with intraoperative cholangiography.

RESULTS: Seventy-eight point five percent of patients had laparoscopic cholecystectomy directly with no further investigations. Twenty-one point five percent had abnormal liver function tests, of which 52.8% had normal ultrasound results. This strategy avoided unnecessary magnetic resonance cholangiopancreatography in 47.2% of patients with abnormal liver function tests with a negative endoscopic retrograde cholangiopancreatography rate of 10%. It also avoided unnecessary endoscopic retrograde cholangiopancreatography in 35.2% of patients with abnormal liver function.

CONCLUSION: This strategy reduces the cost of the routine use of magnetic resonance cholangiopancreatography, in the diagnosis and treatment of common bile duct stones before laparoscopic cholecystectomy.

Key words: Magnetic resonance cholangiopancreatography; Endoscopic retrograde cholangiopancreatography; Choledocholithiasis; Liver function tests; Laparoscopic cholecystectomy; Obstructive jaundice

Core tip: This strategy reduces the cost of the routine use of magnetic resonance cholangiopancreatography, in the diagnosis and treatment of common bile duct stones before laparoscopic cholecystectomy.
INTRODUCTION

Gallstone disease is one of the most common surgical problems worldwide. Both environmental and genetic factors are known to contribute to susceptibility to the disease. It has been reported that in Saudi Arabia there is an increasing incidence of gallstone disease, especially in the high altitude provinces in the Asir and Taif regions, and similar findings have been reported for other countries that have similar environmental and nutritional factors. Complications of gallstone disease vary from simple recurrent biliary colic to life-threatening conditions such as ascending cholangitis and pancreatitis. In addition, the disease is thought to be a risk factor for developing pancreaticobiliary cancer, particularly in patients with choledocholithiasis (common bile duct stones [CBDS]), approximately 10% of patients with symptomatic gallstones.

Since symptomatic gallstone is a common indication for surgery, an accurate preoperative detection of CBDS is imperative in order to decrease operative risks and health care costs. Better detection and treatment of CBDS before laparoscopic cholecystectomy (LC) would help deliver an appropriate, fast, and cost-effective approach for stone removal, followed by LC. Liver function tests (LFTs) and abdominal ultrasonography (USG), combined with medical history and clinical examinations are currently the standard preoperative methods used to diagnose patients with gallstones. However, this approach is often not accurate enough to establish a firm diagnosis of CBDS.

Imaging tests are routinely used to confirm a choledocholithiasis diagnosis. While abdominal USG is the most commonly used screening modality, other imaging tests used for this purpose include endoscopic and laparoscopic USG, magnetic resonance cholangiopancreatography (MRCP), intraoperative cholangiography (IOC), and endoscopic retrograde cholangiopancreatography (ERCP).

ERCP was the gold standard for diagnosing and treating CBDS; however, it is invasive, has associated morbidity and mortality, and has been shown to have a negative rate up to 75% in some studies. Therefore, it was abandoned as a diagnosing method and used only for stone extraction.

MRCP is a noninvasive procedure with no associated morbidity that has become the gold standard in diagnosing CBDS; however, it should only be used when proper indications are observed due to its high cost and limited availability. Many authors have proposed its routine use in all patients with suspected CBDS, however, in high probability patients, its cost and the need for ERCP to remove the stones makes it questionable.

 IOC is particularly valuable in patients with unclear anatomy and those with preoperative predictors of choledocholithiasis but negative findings on MRCP.

Many scoring indices and guidelines have been developed to determine acceptable preoperative indications for IOC, but none so far have proved satisfactory. Therefore, the aim of the current study was to find a non-invasive preoperative approach, using MRCP, ERCP, and IOC, to diagnose and treat CBDS prior to performing LC.

MATERIALS AND METHODS

We conducted a prospective study on all patients with symptomatic gallstones who presented at Al Hada Armed Forces Hospital in Taif, Saudi Arabia from April 2006 to April 2010. Patients not fit for surgery were excluded from the study. In addition, patients who presented with acute pancreatitis were excluded since we have a different protocol for them in our center. The study was approved by the local committee on human research, and all patients gave written informed consent. All patients underwent detailed preoperative evaluations consisting of clinical history, laboratory testing including LFT, (serum bilirubin, alkaline phosphatase, serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase), and USG examination.

An algorithm was designed (Figure 1). Patients with normal LFT and no bile duct abnormalities were referred for LC without further work-up. Patients with abnormal LFT and USG proven CBDS and/or bile duct dilatation greater than 7 mm were referred for ERCP for stone removal, followed by LC. Patients with abnormal LFT and normal bile ducts (detected by USG) were referred for MRCP, and if CBDS were detected, they were referred for ERCP for stone removal, followed by LC. MRCP and ERCP negative cases underwent LC with IOC to detect false negative cases and avoid retained stones. For these patients, intraoperative discovery of CBDS would indicate...
stone removal by ERCP in the same sitting with the LC.

**Statistical analysis**

SPSS 18.0 (SPSS, Chicago Illinois) was used for carrying out statistical analysis. Group differences were further analyzed by $\chi^2$ and difference between means of continuous variables was tested by Student’s $t$ test. Multivariate logistic regression analysis was adopted to control for confounders and level of significance was determined at $P < 0.05$.

**RESULTS**

A total of 896 patients were included in the study. Table 1 shows the patient demographic information. Out of these, 703 (78.5%) patients underwent LC without any further workup. Patients who had abnormal LFTs [193 (21.5%)] were older and there were more males in this group. Table 2 demonstrates the breakdown of all the patients with abnormal LFT. CBD abnormalities were detected on USG in 91 (47.2%) patients and ERCP was used to extract stones in 90% of them. Abnormal LFT results, in which USG found dilatation but no stones were observed in 28 patients. The mean CBD diameter was 8.8 mm in these patients, with stones being extracted by ERCP in 85.7%. In 40 patients with abnormal LFT results and for whom USG detected both dilatation and stones, the mean CBD diameter was 9 mm, with stones being extracted by ERCP in 90%.

Normal bile ducts were detected by USG in 102 (52.8%) patients and ERCP was used to extract stones in 26.5% of them. IOC detected two patients with CBDs in the MRCP negative group (false negative 2.9%) and none in the ERCP negative group. There were seven patients with false positive MRCP where the ERCP did not detect any stones (false positive of 21%). This high percentage could be explained by the time between the MRCP and the ERCP that is about 2-3 d because of which the stones could have passed.

More importantly when looking at this group, 29/102 (28.4%) patients had a total bilirubin > 4 mg/dL which is counted as a high risk in recent guidelines (9); out these 17 (58.6%) patients did not have stones on IOC and ERCP was not conducted in this group of patients.

 Stones were confirmed in 90% of the patients with an abnormal LFT and USG findings. ERCP detected stones in 24.5% of the patients with normal findings. This strategy avoided the use of MRCP in 47.2% of patients with abnormal LFT with a negative rate for the ERCP of 10% only. It also helped avoid unnecessary ERCP in 17 (58.6%) patients with total bilirubin > 4 mg/dL.

Statistical findings are shown in Table 3, where patients with abnormal USG, total bilirubin and alkaline phosphatase had a significant stone prediction in a univariate analysis. After controlling for confounders in multivariate Logistic regression analysis Alkaline phosphatase and USG findings were found to be significant predictors for CBDs. However, total bilirubin was found not to be a significant predictor (Table 4).

Multivariate statistical analysis found that the rise in alkaline phosphatase was a significant predictor for CBDs. It became highly significant when double the normal alkaline phosphatase value. In this case, the probability of stone detection by ERCP increased 30-fold when

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**Table 1 Demographic data n (%)**

| Characteristic                        | Value          |
|---------------------------------------|----------------|
| Total number of patients              | 896            |
| Female patients                       | 717 (80)       |
| Male patients                         | 179 (20)       |
| Mean age of females (yr)              | 41.4 ± 21.3    |
| Mean age of males (yr)                | 45.0 ± 21.6    |
| Number of patients underwent LC without MRCP or/and ERCP | 703 (78.5%) |
| Number of patients with abnormal liver functions | 193 (21.5%) |
| Female patients                       | 116 (60)       |
| Male patients                         | 77 (40)        |
| Mean age of females (yr)              | 55.6 ± 19.6    |
| Mean age of males (yr)                | 60.7 ± 19.8    |

**Table 2 Radiological findings in patients with abnormal liver function tests n (%)**

| Findings                | Patient | Stones removed by ERCP | Mean T:Bili (mg/dL) | Mean Al-P (ratio to normal) |
|-------------------------|---------|------------------------|---------------------|-----------------------------|
| Total                   | 193     | 109                    | 3.7                 | 1.7                         |
| Abnormal CBD on USG     | 91 (47.2) | 82 (90)               | 4.2                 | 2                           |
| CBD dilatation          | 28 (30.8) | 24 (85.7)             | 4.5                 | 2                           |
| CBD stones              | 23 (25.3) | 20 (87)               | 4.3                 | 2.2                         |
| Both                    | 40 (43.9) | 38 (90)               | 4                   | 1.8                         |
| Normal CBD on USG       | 102 (52.8) | 27 (26.5)             | 3.3                 | 1.4                         |
| MRCP findings (percent of total) |         |                        |                     |                             |
| Normal MRCP             | 70 (68.6) | 2 (2.9)               | 3.2                 | 1.3                         |
| Stones on MRCP          | 32 (31.4) | 25 (78.2)             | 3.4                 | 1.7                         |

**Table 3 Final endoscopic retrograde cholangiopancreatography findings**

| Presence of stones | Patient | US abnormal | Mean T:Bili (mg/dL) | Mean Al-P (ratio to normal) |
|--------------------|---------|-------------|---------------------|-----------------------------|
| Stones             | 109 (56.5) | 82 (90) | 4.3 ± 2.1 | 1.9 ± 0.8 |
| No stones          | 84 (43.5) | 9 (10)    | 2.9 ± 1.3 | 1.3 ± 0.6 |
| P value            | < 0.001  | < 0.01     | < 0.001            | < 0.001                     |
| Total              | 193     | 91         | 3.7 | 1.7                         |

Data are expressed as absolute numbers (percentage) or mean ± SD. MRCP: Magnetic resonance cholangiopancreatography; Al-P: Alkaline phosphatase; T:Bili: Total bilirubin; US: Ultrasound.

MRCP: Magnetic resonance cholangiopancreatography; Al-P: Alkaline phosphatase; T:Bili: Total bilirubin; USG: Ultrasonography; CBD: Common bile duct; LFT: Liver function test; ERCP: Endoscopic retrograde cholangiopancreatography.
this enzyme level was within the normal range.

In addition, in USG findings that detected CBD dilatation and those that detected stones were both significant predictors for the presence of CBDS found by ERCP. Detection of both dilatation and stones concurrently was a highly significant predictor of the presence of CBDS, which were about 60 times more likely than when USG results were normal.

**DISCUSSION**

CBDS can remain hidden for years, frequently passing undetected into the duodenum. When the symptoms become apparent, the presentation will likely include obstructive jaundice or more serious complications such as acute pancreatitis or cholangitis. Preoperative detection and intervention to remove these stones is vital. An increase in bilirubin and alkaline phosphatase levels may be the only evidence of cholecoldolithiasis. USG examination may confirm the presence of CBDS but cannot definitively exclude them when not detected. The gold standard for treating these stones is ERCP, which has sensitivity and specificity rates both around 95%. However, if the clinical, radiological, and laboratory testing indicates a low probability of cholecolithiasis, less invasive methods such as MRCP should be performed first.

The sensitivity of transabdominal USG is low for detecting CBDS (22%-55%), but it is better at detecting CBD dilatation (sensitivity 77%-87%). For patients with abnormal LFT which USG detects CBDS, successful diagnosis of cholecolithiasis has been reported to be above 80%. Negative CBD detection by ERCP in such patients may be related to the passage of these stones into the duodenum before the procedure.

The diameter of a normal bile duct is 3-6 mm. It increases by one mm every 10 years after the age of 60, causing mild dilatation in the elderly. CBD greater than 8 mm in patients with an intact gallbladder is usually indicative of biliary obstruction. Although no single factor strongly predicts cholecolithiasis in patients with symptomatic gallstones, many studies have shown that the probability of CBDS is higher in the presence of multiple abnormal prognostic signs. Patients with such markers are considered to be at high risk, and preoperative ERCP is indicated when there are no available facilities for performing CBD laparoscopic exploration.

In the present study, abnormal LFT results were observed in 21.5% in patients with symptomatic gallstones, a higher incidence than previously reported in the literature (15%). This discrepancy may be related to environmental (Taif is a high-altitude province), cultural or social factors. Our facility is a tertiary hospital serving a widespread rural area.

Therefore, the routine use of MRCP as has been recommended by others for patients with abnormal LFTs is not practical or cost-effective. Among the patients involved in the study, there were 78.5% patients with normal LFT results and no CBD abnormalities detected by USG. They were therefore referred for LC without further workup, consistent with the recommendations made by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (SPC-ASGE). The results of our study, which concluded before the publication of the 2010 guidelines, were similar, patients with symptomatic gallstones but normal LFT and USG are considered to be at low risk for cholecoldolithiasis. For these patients, they recommend, as we do, cholecystectomy, without further evaluation to avoid the cost and risks of additional preoperative biliary evaluation, which are not justified by the low probability of CBDS. Whether or not to perform routine IOC or laparoscopic US during LC remains an area of controversy.

We found (52.8%) patients with abnormal LFT but normal CBD USG results, who were sent for MRCP examination. This group of patients is considered by the SPC-ASGE to be at intermediate risk of cholecoldolithiasis, and their guidelines recommend further evaluation with preoperative EUS or MRC or an IOC, as we do. However, they do recommend that a total bilirubin higher than 4 mg/dL should be considered as a high probability of CBDS. In our study, we found total bilirubin to be not a significant predictor on multivariate analysis. Also, in 17 (58.6%) of the patients with high total bilirubin (>4 mg/dL) and normal USG, CBDS was not detected by IOC in the operating room. Therefore, as per their recommendation ERCP was avoided in this group in our study.

Statistical findings revealed that a rise in bilirubin level was not a significant predictor for detecting CBDS. However, this finding should be reevaluated considering the higher incidences of hepatitis, sickle cell anemia, and secondary polycythemia (related to the high altitude) in our province. Yang et al. found that among the components of the LFTs, alkaline phosphatase was a better indicator for cholecoldolithiasis than bilirubin. However, the SPC-ASGE reported modestly better CBDS positive predictive values for bilirubin. They found choledac...
liver biochemical tests, in particular alkaline phosphatase and γ-glutamyl transpeptidase, increases progressively with the duration and severity of biliary obstruction.

In the present study, MRCP helped avoid unnecessary ERCP in 58.6% of patients with high total bilirubin and normal CBD USG results. It was associated with a false negative rate of 2.96% and false positive rate of 21%, similar to those reported in other studies.[16,17]

Patients with abnormal LFT and USG were classified as a high risk for CBDS. By applying this algorithm, we diagnosed and treated these patients directly with ERCP and avoided the cost of MRCP and stones were extracted in 90%, with a low negative incidence of ERCP of 10%. This led to a shorter hospital stay and was even far better when some patients had the ERCP and the LC in the same setting.

IOC has multiple advantages, as some centers use it routinely to identify the biliary anatomy and others use it for stone detection[15,16]. Its routine use is still controversial; however, in selected cases it is widely adopted. In cases where CBDS are thought of, it can be used with less cost and in the same time as the LC where it will take few minutes. However, not many general surgeons are familiar with this use, making it a less popular procedure. Therefore, its use in selective cases has been accepted. We have recommended its use in patients with negative MRCP or ERCP since these procedures have a false negative rate and discharging these patients with retained CBDS can lead to delayed acute presentation like acute pancreatitis, cholangitis and cystic duct leaks.[23,24]

In conclusion, we recommend the use of this simple algorithm to stratify patients into low risk when LFT and USG are normal. These patients can go for LC with no further work-up. Patients with abnormal LFT or US are stratified as intermediate risk regardless of the total bilirubin level and should undergo MRCP as the risk of ERCP is not justified. Patients with abnormal LFT and USG are stratified as high risk and should undergo ERCP and stone extraction with LC in the same sitting if possible, as the cost of MRCP and the time needed is not justified.

**REFERENCES**

1. Nakeeb A, Comuzzie AG, Martin L, Sonnenberg GE, Swartz-Basile D, Kissebah AH, Pitt HA. Gallstones: genetics versus environment. *Ann Surg 2002; 235*: 842-849 [PMID: 12035041 DOI: 10.1097/00000658-200206000-00012]
2. Alsaif MA. Variations in dietary intake between newly diagnosed gallstone patients and controls. *Pakistan Journal of Nutrition* 2005; 4: 1-7 [DOI: 10.3922/jpn2005.1.7]
3. Abu-Emsha SA, Mabilouz AA, Badr a, El Gamal MN, Al-Shewri MY, Salati ML, Rabie ME. Prevalence and risk factors of gallstone disease in a high altitude Saudi population. *East Mediterr Health J 2007; 13*: 794-802 [PMID: 17955761]
4. Alam MK. Assessment of indicators for predicting cholelithiasis before laparoscopic cholecystectomy. *Ann Saudi Med 2011; 18*: 511-513 [PMID: 17344723]
5. Moro PL, Checkley W, Gilman RH, Cabrera L, Lescano AG, Bonilla JJ, Silva B. Gallstone disease in Peruvian coastal natives and highland migrants. *Gut* 2000; 46: 569-573 [PMID: 10716689 DOI: 10.1136/gut.46.4.569]
6. Spathis A, Heaton KW, Emmett PM, Norboo T, Hunt L. Gallstones in a community free of obesity but prone to slow intestinal transit. *Eur J Gastroenterol Hepatol 1997; 9*: 201-206 [PMID: 9058635 DOI: 10.1097/00042737-199702000-00018]
7. Browning JD, Horton JD. Gallstone disease and its complications. *Semin Gastrointest Dis 2003; 14*: 165-177 [PMID: 14791767]
8. O’Neill CJ, Gillies DM, Gani JS. Cholelithiasis: overdiagnosed endoscopically and undertreated laparoscopically. *ANZ J Surg 2008; 78*: 487-491 [PMID: 18522571 DOI: 10.1111/j.1445-2197.2008.04540.x]
9. Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, Fisher L, Harrison ME, Fanelli RD, Fukushima N, Ikemurry SO, Jain R, Khan K, Krinsky ML, Strohmeyer L, Dominitz JA. The role of endoscopy in the evaluation of suspected choleclohlitis. *Gastrointest Endosc* 2010; 71: 1-9 [PMID: 20105473 DOI: 10.1016/j.gie.2009.09.041]
10. Freitas ML, Bell RL, Duffy AJ. Cholelithiasis: evolving standards for diagnosis and management. *World J Gastroenterol* 2006; 12: 3162-3167 [PMID: 16718834]
11. Dumot JA. ERCP: current uses and less-invasive options. *Cleve Clin J Med* 2006; 73: 418, 421, 424-425 [PMID: 16708711 DOI: 10.3949/ccjm.73.5.418]
12. Grande M, Torquati A, Tucci G, Rulli F, Adorisio O, Farinon AM. Preoperative risk factors for common bile duct stones: defining the patient at high risk in the laparoscopic cholecystectomy era. *J Laparoendosc Adv Surg Tech A* 2004; 14: 281-286 [PMID: 15630944 DOI: 10.1089/lap.2004.14.281]
13. Charatcharonithaya P, Saitawathiamrong Y, Manasathit S, Tanwandeew T, Leelakulsoong S, Kachintorn U, Leongjukankul P, Boonyapisit S, Pongprasobchai S. Predictive factors for synchronous common bile duct stone in patients with symptomatic cholecystitis. *J Med Assoc Thai* 2004; 87: 131-136 [PMID: 15061295]
14. Mori T, Sugiyama M, Aomi Y. Gallstone disease: Management of intrahepatic stones. *Best Pract Res Clin Gastroen*
