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The reliability of liver function tests and ultrasonography in excluding choledocholithiasis

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ABSTRACT

INTRODUCTION Magnetic resonance cholangiopancreatography (MRCP) is not a routine investigation to exclude choledocholithiasis unless there is clinical or biochemical suspicion of common bile duct (CBD) stones. This study attempted to determine which radiological or serological parameters best predicted CBD stones.

METHODS All patients undergoing MRCP from 2005 to 2011 were selected. Patients with pancreatitis were excluded. Liver function tests (LFTs) at admission and prior to MRCP were recorded, as was abdominal ultrasonography and MRCP results. Parameters measured routinely on LFTs included alkaline phosphatase (ALP), alanine transaminase (ALT) and bilirubin. Receiver operating characteristic curve area analysis (area under the curve [AUC]) and chi-squared analysis were undertaken.

RESULTS Overall, 195 patients were identified, 71 of whom had CBD stones on MRCP. Raised ALP levels on admission demonstrated a correlation with CBD stones (AUC: 0.619, odds ratio [OR]: 3.16, p=0.06). At ultrasonography, a dilated CBD (OR: 3.76, p<0.001) and intrahepatic duct dilation (OR: 5.56, p<0.001) were highly significant predictors. However, only 37% of patients had a dilated CBD on ultrasonography. Ongoing elevation of LFT parameters, particularly ALP (AUC: 0.707, OR: 4.64, p<0.001) and ALT (AUC: 0.646, OR: 5.40, p<0.001), displayed a significant correlation with CBD stones.

CONCLUSIONS Ongoing (even if minor) elevations of liver function test parameters should prompt the need to exclude CBD stones even in the presence of a normal CBD diameter on ultrasonography.

KEYWORDS

Common bile duct stone – Magnetic resonance cholangiopancreatography – Liver function test – Ultrasonography

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Magnetic resonance cholangiopancreatography (MRCP) is a not a routine investigation to exclude choledocholithiasis unless there is clinical suspicion of common bile duct (CBD) stones. Intraoperative cholangiography (IOC) also allows for definitive imaging of the biliary tree but is not widely adopted by all cholecystectomy surgeons. MRCP has a high sensitivity and specificity for the detection of CBD stones. However, it is costly and places substantial pressure on resources.[1–4] The advantage of MRCP is that it enables preoperative determination of how best to treat any CBD stones, allowing for better management of elective operating lists. MRCP has superseded endoscopic retrograde cholangiopancreatography (ERCP) as the preoperative investigation of choice for CBD stones. Although ERCP has the benefit of concurrent treatment of CBD stones, it does come with inherent risks.

The prevalence of CBD stones has been estimated at approximately 10% in patients with symptomatic gallstones,[5] and accurate identification of CBD stones is important to avoid the potential morbidity and mortality that can result from missing CBD stones. It is not practical or cost effective to investigate all choledocholithiasis patients with MRCP for potential CBD stones. The clinical suspicion of CBD stones varies widely, and there have been algorithms and predictive models proposed.[6–9] This study attempted to determine which liver function tests (LFTs) or radiological parameters best predicted CBD stones by retrospectively examining MRCP performed for suspected CBD stones.

Methods

This was a retrospective review of patients admitted as an acute admission with symptomatic gallstones (patients with pancreatitis and asymptomatic cholelithiasis were excluded) who underwent MRCP for suspected CBD stones between 2005 and 2011 at two university teaching hospitals. LFTs performed routinely, both on admission and prior to MRCP, were analysed. LFT parameters included bilirubin, alkaline phosphatase (ALP) and alanine transaminase (ALT). Abdominal ultrasonography was performed for all patients. The diameter of the CBD was documented as dilated if over

8mm. The presence of CBD stones and intrahepatic duct dilation (IHDD) was also recorded.

Patients with persistent elevation of LFT parameters, a dilated CBD or CBD stones on ultrasonography underwent MRCP. In this study, all patients were investigated with MRCP and results were recorded as either normal, dilated CBD, CBD stone or stricture. If patients had both a dilated CBD and CBD stone, this was documented as CBD stone. The presence or absence of CBD stones was confirmed by an independent consultant radiologist reporting the MRCP. Those patients who had confirmed CBD stones at MRCP underwent ERCP. All patients underwent a subsequent laparoscopic cholecystectomy. This retrospective study received institutional approval; no ethical approval was required and informed consent was waived.

Statistical analysis

Data were analysed using PASW® Statistics version 20.0 (SPSS, Chicago, IL, US). Receiver operating characteristic curve analysis (area under the curve [AUC]) was performed on LFTs. Chi-squared analysis was performed on individual factors and combination factors. Odds ratios (ORs), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

One hundred and ninety-five patients were selected. There were 81 male (mean age: 60 years) and 114 female patients (mean age: 46 years). One hundred patients had a normal MRCP, twenty-four patients had a dilated CBD and seventy-one patients were found to have a CBD stone. On analysis, there was no significant difference between median LFT parameters on admission and following ultrasonography or the percentage change between those with and without a CBD stone on MRCP. Generally, patients with demonstrable CBD stones on MRCP had a higher median LFT measurement that remained elevated compared with patients without a CBD stone.

AUC and chi-squared analysis was undertaken on LFT and radiological parameters (Table 1 and Fig 1). AUC values demonstrated that the highest predictor was ALP on admission (0.62), and ALT (0.65) and ALP (0.70) prior to MRCP (Table 1). Correlation with CBD stones was demonstrated with ALP on admission (p=0.06). An ALT level over

Table 1 Area under the curve and chi-squared analysis, sensitivity and specificity of individual liver function test parameters at admission and prior to magnetic resonance cholangiopancreatography

	AUC analysis			Chi-squared analysis						
	AUC	*p*-value		*p*-value	OR	95% CI	Sensitivity	Specificity	PPV	NPV
Raised bilirubin on admission (normal: 3–21μmol/l)	0.520	0.637	>100% normal	0.170	1.20	0.64–2.26	53.7%	50.8%	52.4%	52.1%
			If >110μmol/l	0.820	0.85	0.32–2.30	11.3%	87.5%	33.3%	63.4%
Raised ALT on admission (normal: 2–53iu/l)	0.557	0.187	>100% normal	**0.024**	2.39	1.04–5.60	85.9%	28.2%	40.7%	77.8%
			If >750iu/l	0.865	1.08	0.38–2.99	11.3%	89.5%	38.1%	63.8%
Raised ALP on admission (normal: 30–130iu/l)	0.619	0.060	>100% normal	0.540	1.21	0.61–2.40	32.4%	71.8%	39.7%	65.0%
			If >400iu/l	0.072	2.09	0.86–5.10	19.7%	89.5%	51.9%	66.1%
Raised bilirubin prior to MRCP (normal: 3–21μmol/l)	0.591	0.340	>100% normal	0.092	1.68	0.87–3.25	40.8%	71.0%	44.6%	67.7%
			If >100μmol/l	0.122	1.91	0.77–4.79	14.0%	90.0%	16.3%	88.7%
Raised ALT prior to MRCP (normal: 2–53iu/l)	0.646	**0.010**	>100% normal	**0.002**	2.67	1.34–5.34	74.6%	47.5%	44.9%	76.6%
			If >440iu/l	0.063	2.10	0.88–5.01	21.1%	88.7%	51.7%	66.3%
Raised ALP prior to MRCP (normal: 30–130iu/l)	0.707	**0.010**	>100% normal	**0.004**	2.50	1.27–4.95	42.3%	77.4%	51.7%	70.1%
			If >370iu/l	**0.010**	2.66	1.15–6.19	25.0%	90.0%	32.2%	86.3%

AUC = area under the curve; OR = odds ratio; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; ALT = alanine transaminase; ALP = alkaline phosphatase; MRCP = magnetic resonance cholangiopancreatography.

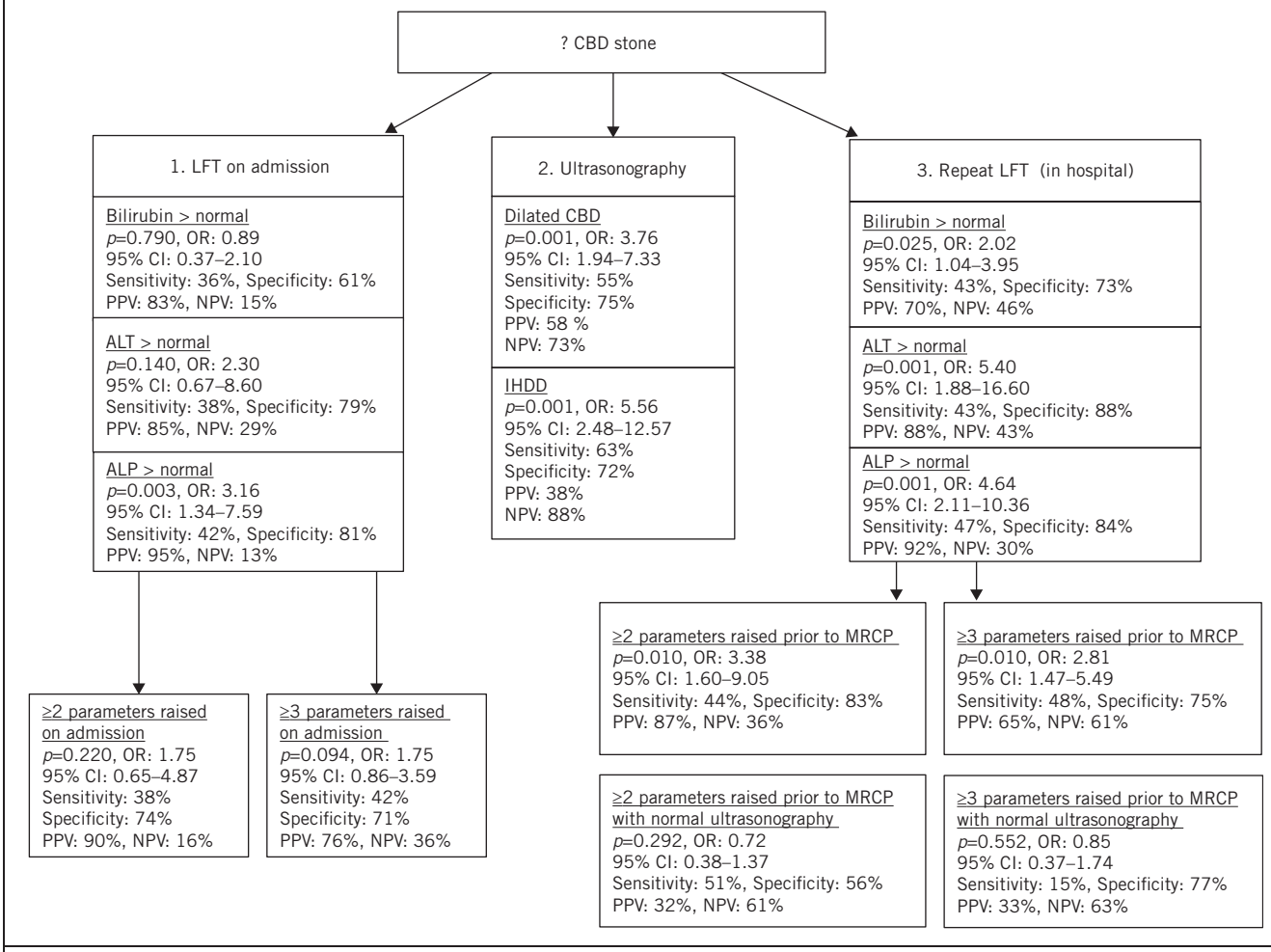

Figure 1 Chi-squared analysis of predictive indicators of common bile duct stones. ALP = alkaline phosphatase; ALT = alanine transaminase; CBD = common bile duct; CI = confidence interval; IHDD = intrahepatic duct dilation; LFT = liver function test; MRCP = magnetic resonance cholangiopancreatography; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.

50% (p=0.011) and 100% (p=0.024) of normal on admission demonstrated a significant correlation. Ongoing elevation of ALP (p<0.01) and ALT (p<0.01) demonstrated statistical significance with CBD stones. However, sustained elevation of bilirubin was only significant if elevated by over 50% of normal (Table 1).

LFTs on admission and prior to MRCP were grouped together and analysed. When two (p=0.223) or three (p=0.094) parameters were elevated on admission, they did not show significant correlation with CBD stones at MRCP (Fig 1). In contrast, two (p=0.01) or three (p=0.01) parameters elevated prior to MRCP did demonstrate a significant correlation with CBD stones on MRCP although this observation was not maintained in the presence of normal ultrasonography (Fig 1).

Seventy-four patients (37.9%) had abnormal ultrasonography findings that demonstrated a dilated CBD and 9 of these had a sonographically identifiable duct stone. The remaining 121 patients had normal ultrasonography. Dilated ultrasonography (p=0.001) and IHDD (p=0.001) showed significant correlation with CBD stones at MRCP. Only two patients with IHDD did not have a dilated CBD. Of the 124 patients who did not have a CBD stone on MRCP, 91 had normal ultrasonography and 33 had abnormal ultrasonography. Of the 71 patients with a CBD stone on MRCP, 30 had normal and 41 had abnormal ultrasonography.

Discussion

Despite the improvement in radiological investigations and the increasing use of MRCP, CBD stones are missed and have the potential to cause significant morbidity. Studies have shown that LFTs and ultrasonography results have low sensitivities, and should not be used in isolation.[11–12] There is a lack of published evidence to support the use of MRCP to exclude CBD stones, prior to laparoscopic cholecystectomy, following normal ultrasonography. This study demonstrates that persistently raised LFT parameters should merit definitive imaging on the biliary tree.

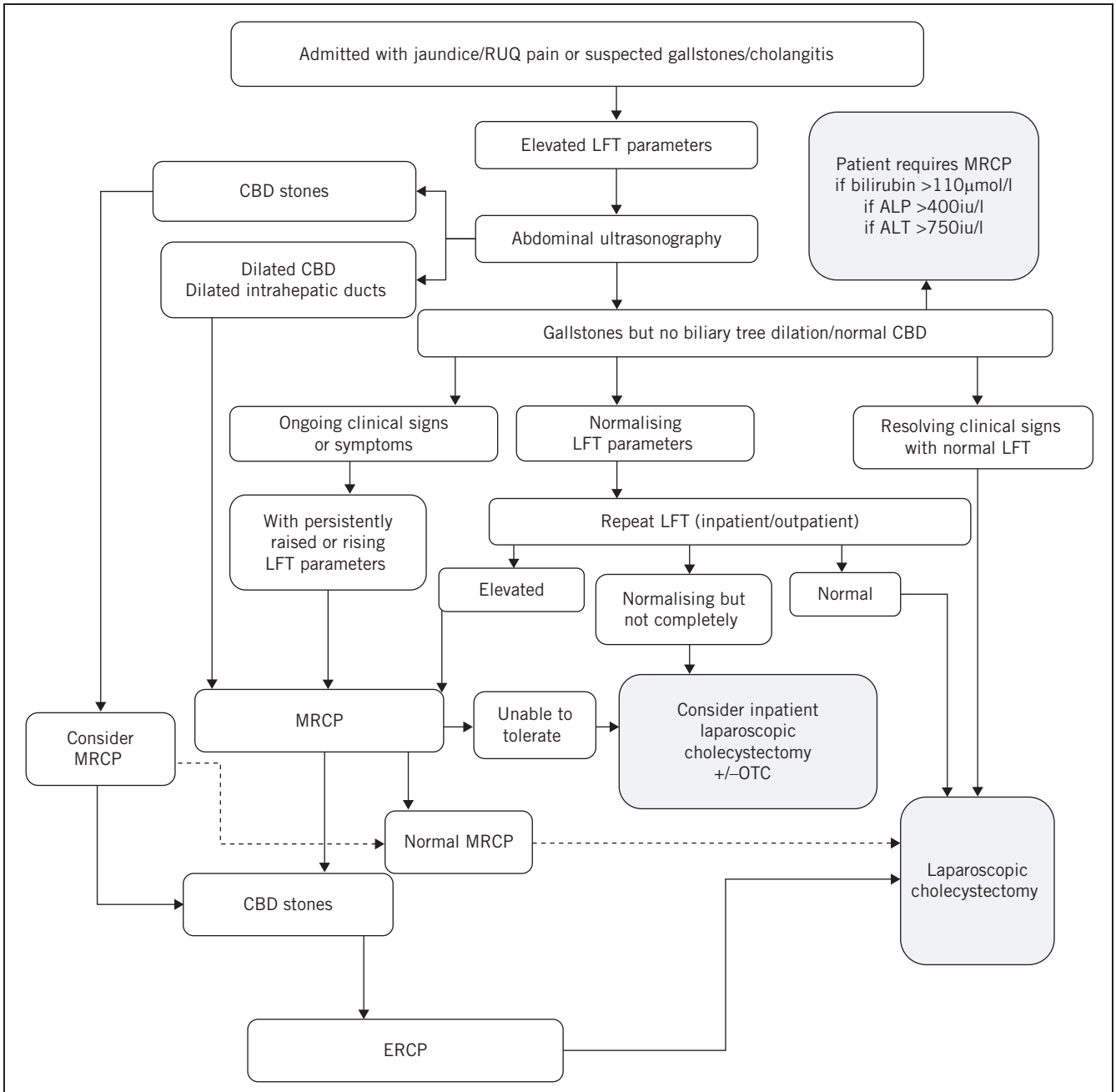

Figure 2 Algorithm for the investigation of common bile duct stones (excluding gallstone pancreatitis). ALP = alkaline phosphatase; ALT = alanine transaminase; CBD = common bile duct; ERCP = endoscopic retrograde cholangiopancreatography; LFT = liver function test; MRCP = magnetic resonance cholangiopancreatography; OTC = on-table cholangiography; RUQ = right upper quadrant.

Guidelines assisting the triaging of patients have been developed. Nevertheless, inconsistency does persist.[6,10–12] Figure 2 shows an investigatory algorithm used by the authors. Some studies have shown that gamma-glutamyltransferase (GGT) has the highest sensitivity of available LFT parameters in predicting CBD stones.[13] Others use bilirubin in their risk prediction models.[10] Our trust does not screen routinely for GGT. Our results demonstrate that raised ALP (OR: 3.16, p=0.006) on admission blood tests was a superior indicator to ALT (OR: 2.30, p=0.187) and bilirubin (OR: 0.89, p=0.637) for CBD stones although all had low sensitivity. Overall, LFTs are a poor predictor of CBD stones. However, if admission bilirubin is >110μmol/l (specificity 87.5%), ALP is >400iu/l (specificity 89.5%) or ALT is >750iu/l (specificity 89.5%), even in isolation, MRCP is required to exclude a CBD stone.

This study shows that in cases of suspected CBD stones, ongoing elevation of LFT parameters can provide support when deciding on further imaging of the biliary tract.

A sustained elevation of ALP (AUC: 0.70, p=0.01) or ALT (AUC: 0.64, p=0.01) had a significant correlation with CBD stones on MRCP. They were more sensitive than persistently raised bilirubin levels, which is used in many published algorithms. The sustained elevation of LFT parameters should prompt clinicians to image the biliary tract prior to laparoscopic cholecystectomy. Although this proposal does have associated cost implications, this study provides evidence to support this change in practice. The main limitation to this study is the use of a biased cohort of selected patients who have had MRCP and retrospective interpretation of their LFTs and ultrasonography results.

Some cholecystectomy surgeons assess patients prior to surgery and repeat LFTs at this point. A continued elevation of LFT parameters should prompt re-evaluation and consideration for definitive imaging of the biliary tree to exclude choledocholithiasis. Repeating LFTs can assist in reducing the number of unnecessary MRCPs performed and normal LFTs can reassure the surgeon. Yang *et al* examined LFTs in 1,002 patients undergoing laparoscopic cholecystectomies and found that completely normal LFTs had a negative predictive value of up to 97.9% (GGT), with the lowest at 94.7% (bilirubin).[14]

Ultrasonography is a poor at detecting CBD stones but relatively reliable at detecting a dilated CBD with a sensitivity of up to 87%.[15] Unsurprisingly, there was significant correlation with CBD stones when ultrasonography demonstrated a dilated CBD or IHDD. Interestingly, of the 71 patients with a CBD stone on MRCP, 30 had normal and 41 had abnormal ultrasonography. This demonstrates that normal ultrasonography can be falsely reassuring. An increase in LFT derangement will generally correspond to an increase in biliary obstruction. However, LFTs do not have very good predictive values, as demonstrated by our findings. Repeating the LFT after ultrasonography does provide a quick method of determining whether further tests are required. If LFT parameters are elevated persistently, clinicians should consider further investigations.

Not all cholecystectomy surgeons favour MRCP, with some preferring IOC or ERCP. Nugent *et al* demonstrated a low incidence of retained CBD stones using selective biliary imaging.[16] They performed ERCP in patients who had persistently elevated LFT parameters and dilated CBD stones, and IOC if LFT parameters returned to normal.

MRCP has up to 97% specificity for detecting choledocholithiasis although its accuracy is reduced when a small stone (<5mm) is present.[17,18] Given its increasing availability and accuracy, the European Association for Endoscopic Surgery considers MRCP the most appropriate investigation for patients with an intermediate probability of CBD stones.[19] There is a risk of becoming overly reliant on MRCP; while it provides accurate detection of CBD stones, it is expensive and time consuming. In our trust, MRCP costs approximately £650 and any reduction in unnecessary imaging can render a substantial saving. There are useful and established guidelines on managing suspected choledocholithiasis.[9,10] Nevertheless, several grey areas exist and clinicians need to consider all factors in difficult cases, including the patient's clinical signs and symptoms.

Furthermore, MRCP is not suitable for all patients (those with allergies to gadolinium, morbid obesity, claustrophobia, pacemakers, intracranial and some intravascular metallic clips). In this case, other forms of investigation and exclusion of CBD stones are required. A number of doctors will perform ERCP, endoscopic ultrasonography, intraoperative ultrasonography or IOC with the option of exploration in cases where there is a possibility of a CBD stone.

Conclusions

This study confirms that in the management of suspected symptomatic choledocholithiasis in patients without pancreatitis with persistently elevated LFT parameters should merit definitive imaging of the biliary tree.

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